Coronary artery stents:

a systematic review & economic evaluation

3′

Appraisal Committee Version

Addendum

Confidential: not for release

The full **report** prepared for the Appraisal Committee should be considered with this addendum

Review aims:

To assess the effectiveness and cost effectiveness of the use of coronary artery stents in patients with coronary artery disease (CAD).

Specifically the clinical review compares the use of:

- Stent versus Percutaneous Transluminal Coronary Angioplasty (PTCA)
- Stent versus Coronary Artery Bypass and Graft (CABG)
- Stent versus drug-eluting stent (DES).

The economic analysis compares the cost effectiveness of:

- Stent versus DES
- Stent versus CABG.

Report commissioned by: NHS R&D HTA Programme

On behalf of: The National Institute for Clinical Excellence

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Addendum 1

Clinical effectiveness: selected drug-eluting stents

1. Introduction

This addendum has been prepared following a first meeting of the Appraisal Committee to consider the original Liverpool Reviews and Implementation Group (LRiG*)* report on the effectiveness and cost effectiveness of the use of coronary artery stents in patients with coronary artery disease, and in particular of drug eluting stents (DES). It deals with specific requests from the Appraisal Committee for further consideration of aspects of the original report, but more importantly, it deals with new information which became available only after the submission of the original report and further analysis arising from that information. This new information has allowed us to consider such aspects as subgroup analysis, not previously possible.

As such it is not intended as a standalone document, but does supercede elements of the original report.

Five DES have been awarded the CE Marking. Only the CYPHER™ sirolimus-eluting stent from Cordis, the TAXUS™ paclitaxel-eluting stent from Boston Scientific and the Dexamet™ dexamethasone-eluting stent from Abbott are anticipated to be available as commercial products in the near term.

New information has been provided on two of these, the CYPHER™ and TAXUS™ stents.

2. Evidence on the clinical effectiveness of selected drug-eluting stents

There remain no direct comparisons of different DES, and therefore the data are presented independently.

For this summary of selected DES, data from print journals or submitted by manufacturers were included. Data from other sources, such as conference presentations or reports were not sufficiently detailed and therefore were not considered eligible for inclusion in the analyses. (Most such presentations have been well covered by the manufacturers' reports).

Data regarding Dexamet™ are based on single report of non-randomised registry data. No new information has been provided on this.

The CYPHER™ and TAXUS™ DES have been evaluated within randomised controlled trials (RCTs). Data from these trials are presented in the form of meta-analysis forest plots for a range of outcomes including major adverse cardiac events (MACE), all cause mortality, myocardial infarction (MI) and binary restenosis rate (BRR).

Table 1: Drug-eluting stents with CE Marking intended for commercialisation

System name	Agent -stent	Manufacturer	Study name & design	Data available up to:
TAXUS™	**Paclitaxel NIRx**	**Boston**	TAXUS I RCT TAXUS II RCT	1 year 1 year
CYPHER™	**Sirolimus Bx Velocity**	**Cordis**	RAVEL RCT SIRIUS RCT E-SIRIUS RCT	2 years 1 year 9 months
Dexamet™	**Dexamethasone Biodiv*Ysio* DD PC**	**Abbott**	STRIDE Registry	Short-term - Abbott

TAXUS™

There have been two trials of the TAXUS stent, TAXUS I and II. However TAXUS II is perhaps best considered as two separate trials, one of a moderate release stent and the other of a slow release stent (also used in TAXUS I). Recruitment to the moderate release element of TAXUS II followed completion of recruitment to the slow release element. Data up to 1 year are now available from these trials. These stents are of identical design and drug dose density (1.0µg/mm^2 of paclitaxel), but have different polymer to drug ratios to mediate the rate of release of the drug. The current CE Marking applies only to the slow release (SR) TAXUS™ stent.

In the earlier report, it was not possible to separate out the two elements of TAXUS II. We now present the results of each element of TAXUS II separately with their controls, and then proceed to meta-analysis with TAXUS I.

Sources of data on the evaluation of TAXUS™ stents (compared with non-eluting controls) are restricted to manufacturer reports, provided in the initial submission to NICE, and reports provided to the Review Team by Boston Scientific in March 2003. The published article on TAXUS I (Grube *et al*., 2003) was also used for reference.

Reporting of mortality in the TAXUS studies was limited to cardiac death although details of all deaths were noted within patient flow tables and patient level data. Using this additional information, the Review Team present 'all deaths' in the analyses of mortality outcomes.

The combined event rate used in the TAXUS studies was MACE. This included specifically cardiac death, myocardial infarction (Q or Non-Q wave) or 'clinically driven' target vessel revascularisation (repeat PCI or CABG performed on the vessel previously treated by stenting), as defined by the FDA. It should be remembered that this definition includes the possibility of a solely angiographic criterion of revascularisation.

The definition is mandated by the US FDA and states that the procedure was considered clinically driven if the patient had 'a positive functional study, ischaemic ECG changes at rest in a distribution consistent with the target vessel, or ischaemic symptoms and an in-lesion diameter stenosis greater than 50 percent. Revascularisation of a target lesion with an in-lesion diameter stenosis greater than 70 percent in the absence of the above mentioned ischaemic signs or symptoms was also considered clinically driven'.

A 'functional test' refers to a positive exercise ECG or nuclear perfusion scanning. The key point here is that even by this definition, 'clinically driven events' can be defined by angiographic indices alone. It assumes that with a stenosis greater than 70 percent, even if the patient is not symptomatic at the time, it is highly likely that they will soon 'tip over' into a symptomatic state and require a repeat revascularisation soon after.

Non-cardiac death or revascularisation (e.g. other than target vessels or lesion) outside the definition of 'clinically driven' would not contribute to MACE.

The binary restenosis rates used in the meta-analysis are for the in-stent region only.

CYPHER™

Data on the CYPHER™ stent are currently available from three RCTs, with RAVEL reporting up to two years follow up. Design of the CYPHER™ stent did not differ between trials (dose density 1.4μg/mm^2 in all three studies), although only 18mm stents where used in RAVEL, a combination of 18mm, 18 and 8mm or two 18mm stents could be deployed and overlapped in the SIRIUS trials. Over a quarter of participants in SIRIUS received overlapping stents.

Sources of data on the evaluation of the CYPHER™ stent (compared with non-eluting controls) are restricted to manufacturer reports, which were provided in the initial submission to NICE, and reports (on RAVEL, SIRIUS and E-SIRIUS) provided to the Review Team by Cordis in February 2003. The published paper on RAVEL (Morice *et al*., 2002) was used for reference.

As for TAXUS, all cause mortality was recorded for the CYPHER™ trials considered in this Addendum.

The definition of MACE varied slightly between the CYPHER™ stent trials. Both RAVEL and SIRIUS defined MACE as all cause death, myocardial infarction (Q or non Q-wave), and target lesion revascularisation (TLR by PCI or TLR by CABG). The E-SIRIUS trial rate includes 'emergent CABG' – where emergency surgical invention may have been necessary (in fact there were no such events in E-SIRIUS). A further variation is that only events determined to be 'clinically driven' (FDA definition) in SIRIUS, E-SIRIUS and RAVEL at 2 years were provided within items submitted by Cordis, whereas the original submission to NICE and published paper on RAVEL at 1 year appear to report a amalgamation of both clinically driven and non-clinically driven events. In order to resolve this disparity, only events determined to be 'clinically driven' at 1 year have been provided for RAVEL and are utilised in the analyses.

Another composite event rate, target vessel failure (TVF), is presented within reports of the CYPHER™ studies. Target vessel failure comprised: Cardiac death, MI which could not be

clearly attributed to a vessel other than the target vessel, or target vessel revascularisation (TVR) by PCI or CABG.

Binary restenosis rate considered is in stent, at 8 months.

Presentation of alternative event rates for CYPHER™ trails

Analyses in this addendum will be of TVF and MACE for the CYPHER™ trials. The reason for this is that the composition of MACE in the TAXUS studies seem closer to the TVF in the CYPHER studies than MACE as defined in SIRIUS or RAVEL. The composition of 'MACE' in the TAXUS studies and the 'TVF' in the CYPHER™ trials would appear would appear to be comparable. Both event rates specify cardiac death, MI, TVR ('clinically driven', reinvention of the vessel by PCI or CABG).

3. Meta-analysis of clinical data on drug-eluting stents

Event Rate – TAXUS MACE, CYPHER™ MACE and CYPHER™ TVF

Event rates were reduced significantly by the use of either TAXUS™ or CYPHER™ stents at six and twelve months. The results were broadly similar for both types of stent, with a reduction in events by approximately 2/3 compared to bare metal stents (BMS) (Figure 1). Most events occur within the first 6 months. There are now data up to two years for CYPHER™ in the RAVEL study: this shows that the event rate remains reduced.

Odds ratios and 95% Confidence Internals for pooled estimates appear similar for CYPHER™ MACE and CYPHER™ TVF.

Within the RAVEL trial, a reduced event rate in the CYPHER™ arm and increase in the control arm is observed when TVF is substituted for the CYPHER™ defined MACE. Odds ratios decrease from 0.46 [95% CI: 0.22-0.97] (MACE) to 0.23 [95% CI: 0.10-0.56] (TVF) in RAVEL at 2 years.

Mortality

There were no significant differences in mortality rates between DES and BMS at any time point (Figure 2).

MI (any reported)

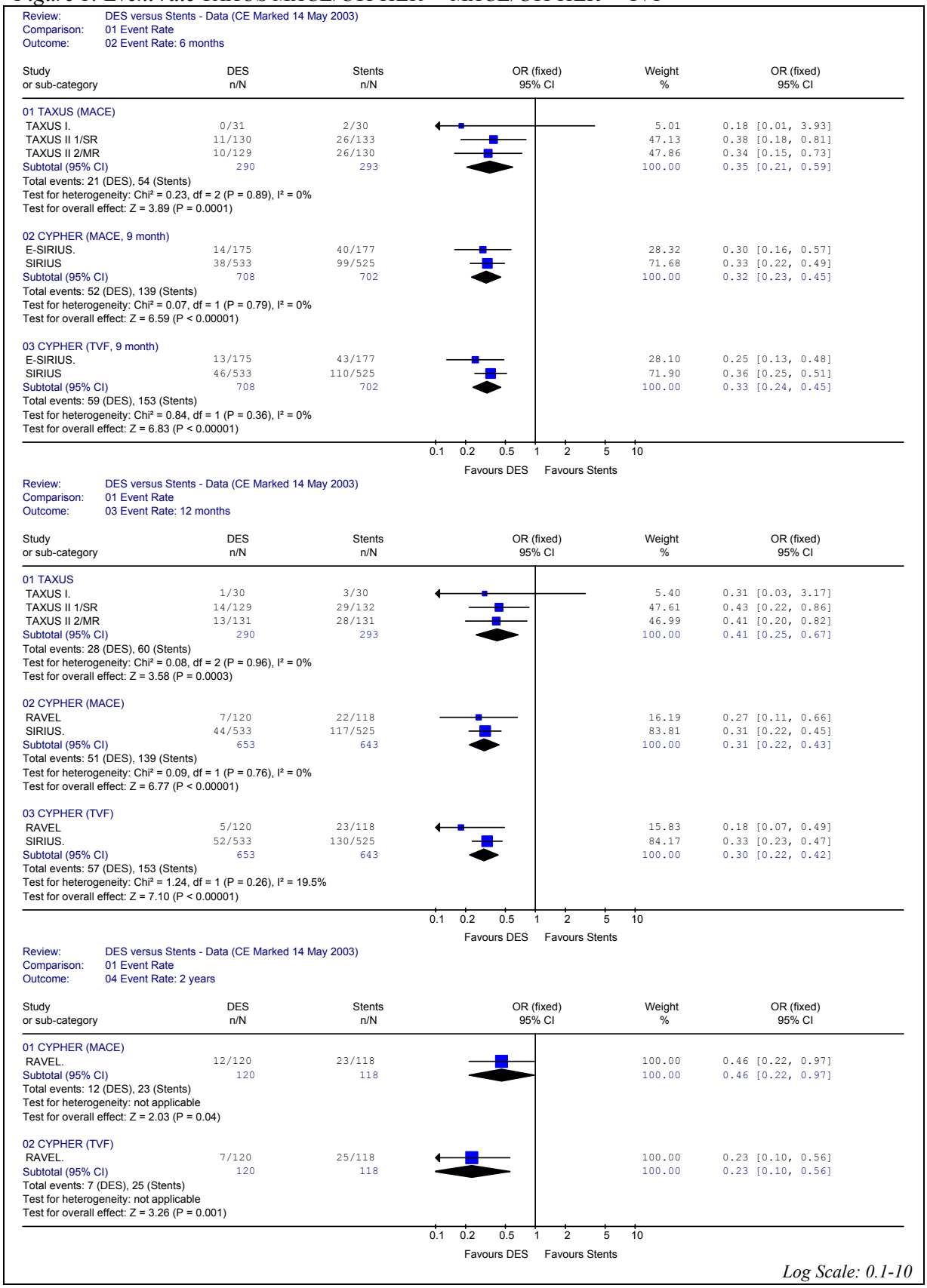
Myocardial infarction was significantly reduced in the TAXUS meta-analysis at six months but not at 12 months. There was no difference for CYPHER™ at any time point (Figure 4).

Restenosis (in the range of 6 or 8 months)

There was a marked reduction in binary restenosis rates at 6 to 8 months as detected by angiography. Since these studies do not have a further protocol driven angiography, there are no later data on this (Figure 5).

There was no heterogeneity of results and therefore random effects models were not used.

Figure 1: Event rate TAXUS MACE/CYPHER™ MACE/CYPHER™ TVF



Footnote: Event rate for RAVEL at one year is represents only clinically driven events. Cordis provided these data at our request. TVF data at 1 year for SIRIUS provided by Cordis at our request.

Figure 2: All cause mortality

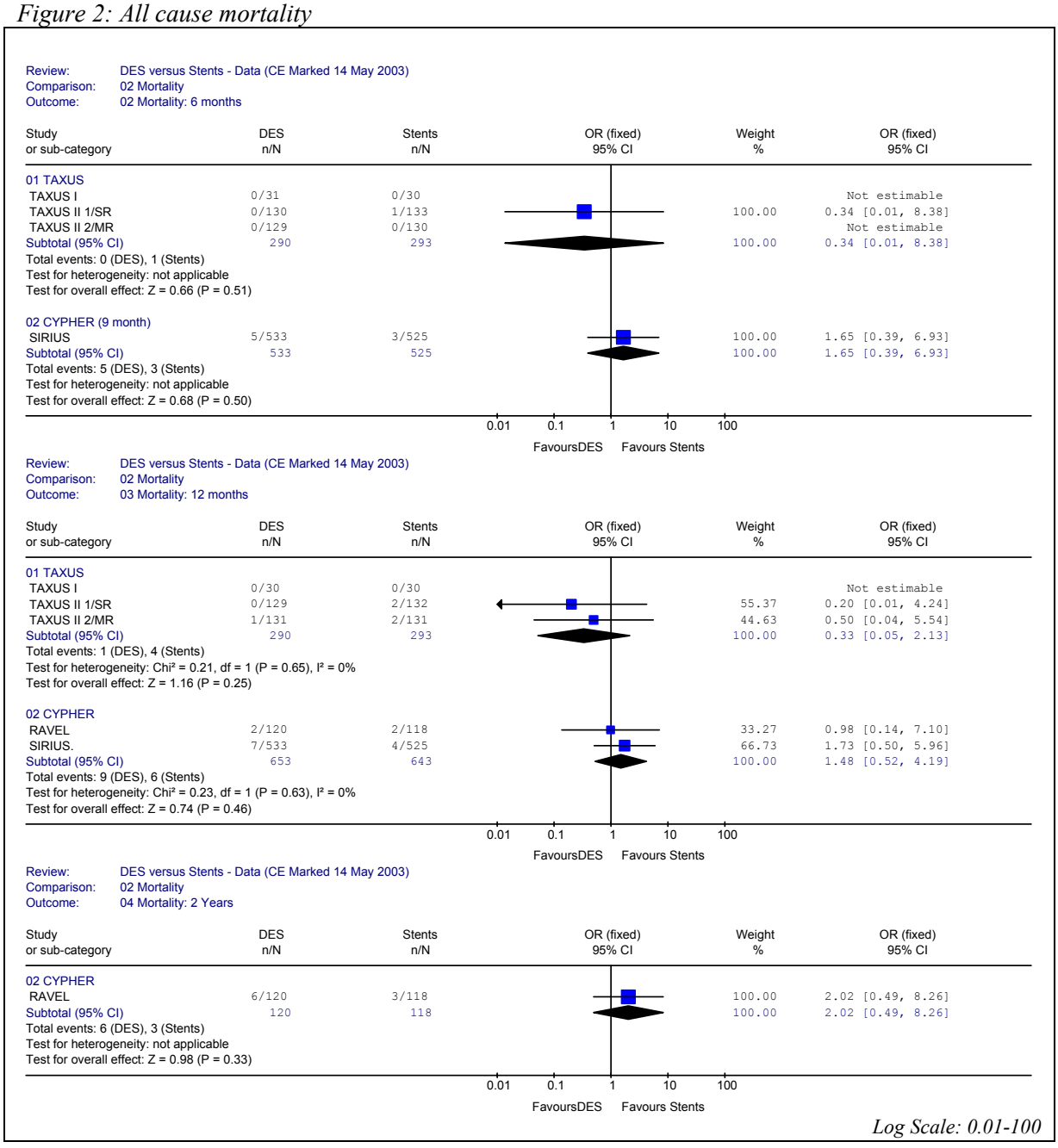
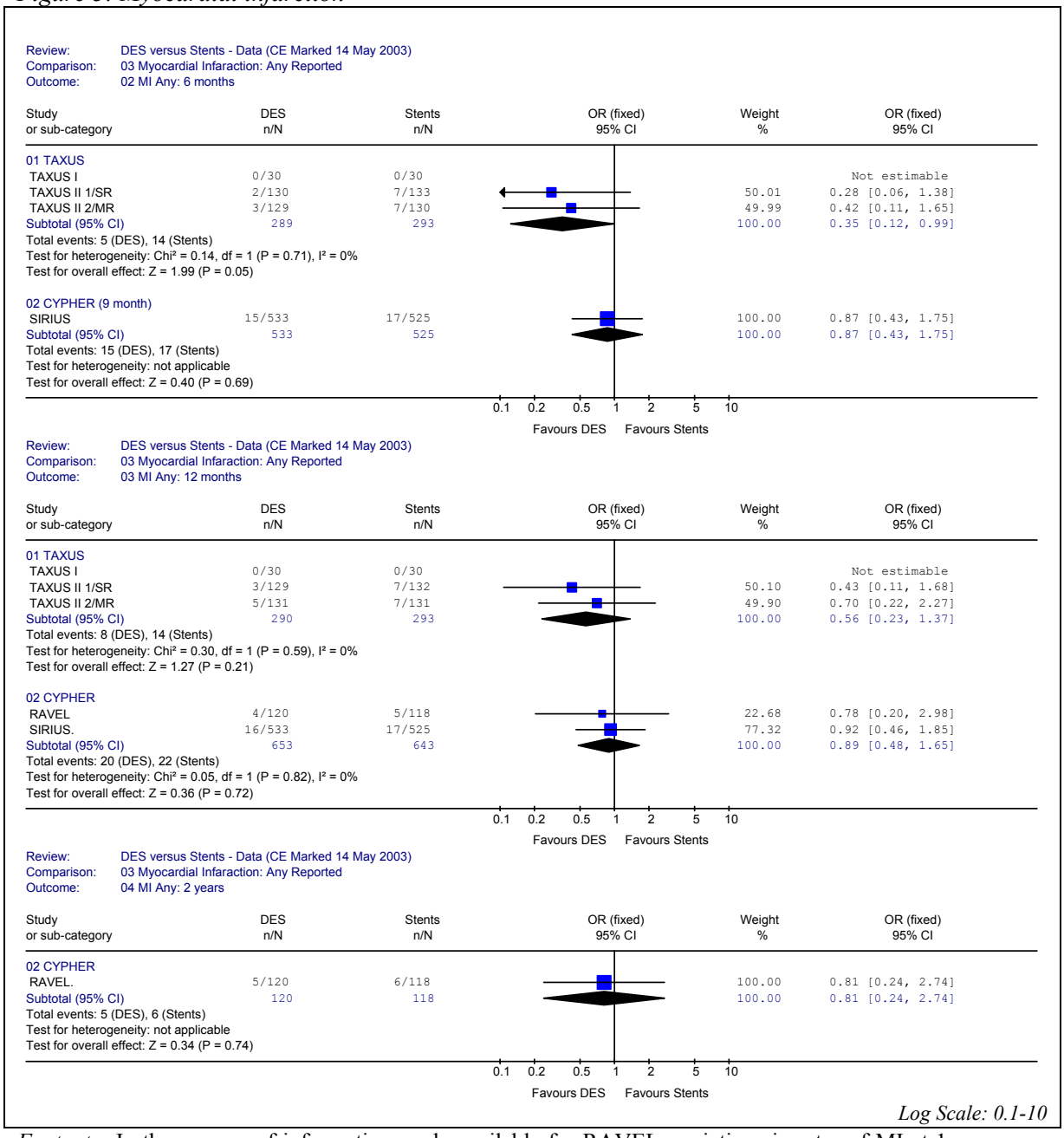
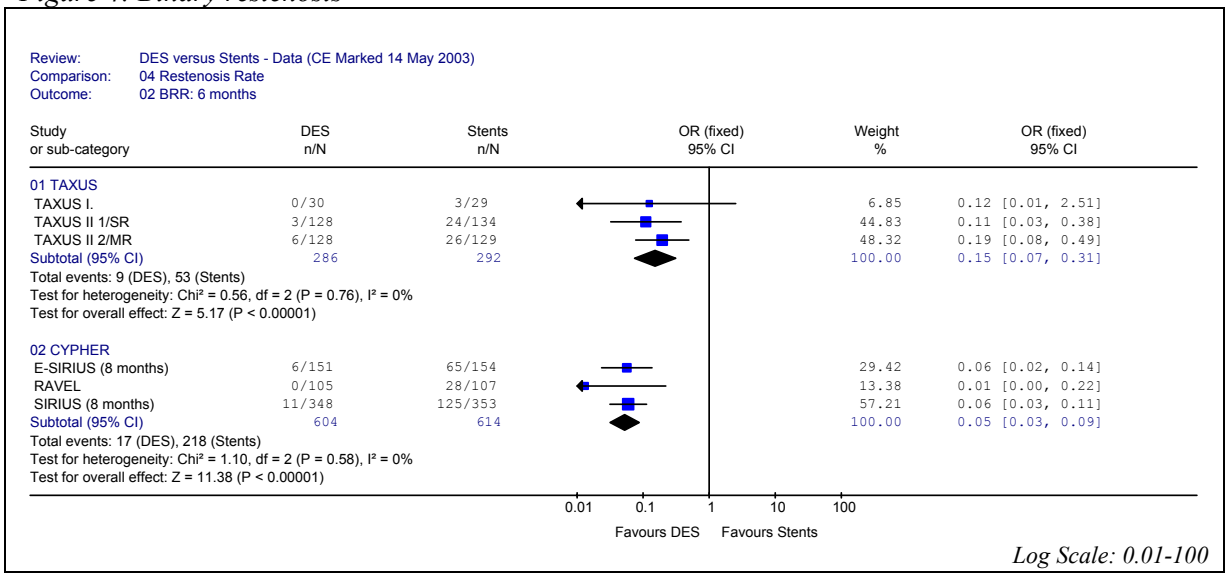


Figure 3: Myocardial infarction



Footnote: In the sources of information made available for RAVEL, variations in rates of MI at 1 year were noted. The values reported in Morice *et al*.,2002 are used in the meta-analysis.

Figure 4: Binary restenosis



4. Discussion

The data presented here are a large expansion in those previously considered for DES versus non drug-eluting stents: these were limited before to the RAVEL and TAXUS I studies (total 297 patients), but now extend to SIRIUS, E-SIRIUS and TAXUS II (total 2,230 patients).

The results show a marked decrease in events up to12 months and in the case of RAVEL, up to 2 years.

Issues around the outcomes reported were discussed before in the main report and persist to some extent. Kaplan Meier plots of each of the trials shows a marked increase in number of revascularisations at the time of the protocol driven angiogram – this continues concerns about the extent to which the events reported are based on the appearance at angiogram and would not reflect real clinical practice. Furthermore, the use of FDA definitions of clinically driven revascularisations include an angiographic component, although we are told by companies that in practice this was rarely invoked in the absence of other criteria. For instance: *"the 9m SIRIUS report to the FDA …showed that of the 87 patients in the control group who had repeat revasc(ularisation) at 9m, 71/87 had recurrent angina, 16/87 had a positive functional study and 47/87 had stenosis >/= 70%. …(This) shows that 70% stenosis only as a criterion could have had only minimal impact because of the proportion with angina and/or positive functional study"* (S.Fearns, Cordis: communication to LRiG & NICE).

One reason for the sharp increase in revascularisations at the protocol driven angiograms maybe that there was an accumulation of truly clinical indications which waited until the angiogram for action. Even in the case of true clinically indicated angiograms, the decision to revascularise or not is still angiographic as it depends on the results of the angiogram: this distinction is clear in BENESTENT II where the rate of revascularisation in the protocol-angiogram arm was higher than in the arm where angiograms were clinically driven. We believe that this issue is unresolved and that the extent of the favourable results here might not therefore be repeated in common clinical practice. In calculating the cost effectiveness of stenting later, we have adopted a BENESTENT II type correction for rates of

revascularisation, as we think this is a conservative and the most appropriate approach (see section 4.3.3.)

It should also be remembered that meta-analysis as conducted here will tend to hide important differences which may become apparent with more detailed study of subgroups.

The 'life expectancy' of the current data needs to be considered: the TAXUS IV trial (slow release, single stents in vessels 2.5-3.5 diameter, up to 28mm long, approximately 1350 patients) is due to report its 9 month data on 15th September 2003. The Canadian arm of the SIRIUS trial family, C-SIRIUS, but with only 100 patients, has already reported its 9 month data in conferences (presented at ACC April 2003). Although not included in the analysis here, as it is only available as a conference presentation, the results are consistent with those of the studies considered here. In addition there will of course be regular updates of the results of the other studies. The SIRIUS trial itself has been submitted for publication.

These results are therefore probably the most reliable available for the next 4 months, but may require reconsideration depending on the results of TAXUS IV**.**

Subgroups

In addition to summary data, for TAXUS II we were also supplied with patient level data which has allowed us to consider subgroups. These are explored more fully in Section 4.6 of this report.

This information is used in the economic evaluation of subgroups to try to help define where DES may be most cost-effectively deployed.

There are several caveats to this:

- None of the studies have been powered to examine subgroups and therefore the results in subgroups can only be considered tentative.
- The results in trials are usually reported in an intention to treat manner - entirely appropriate for clinical trials but less useful than an on treatment analysis for economic review. Our analysis in Section 6 is based on the latter.
- The data is also patient driven rather than event driven: each patient is therefore recorded as having or not having a MACE/TVF endpoint. The hierarchical nature of these event rates (i.e. patients can only be recorded as having one MACE/TVF event, and are documented as having the most important event – e.g. a patient who dies will be recorded as a death, but the number of revascularisations such a patient may have had may not be so well captured).

Despite these limitations, we believe that useful conclusions can be drawn from this and these are presented in Addendum 6.

Addendum 2

Economic modelling: Exploration of the sources of differences between cost-effectiveness models of coronary stenting prepared in evidence for the NICE Appraisals Committee

1. Introduction

This section details an investigation into the sources of apparently large differences in incremental cost-effectiveness ratios (ICERs) between the two industry 2 models submitted in evidence to NICE, and the model prepared by the Liverpool appraisals group (LRiG) for assessing drug-eluting stents (DES) in comparison to bare metal stents (BMS).

2. Boston Scientific Ltd. - TAXUS model

The Boston Scientific economic model is based on the results of TAXUS II using clinical results after 6 months. The model can be run with five distinct patient subgroups:

- all TAXUS II patients (single vessel de novo disease)
- diabetic patients
- patients with a small diseased vessel 2.5-3 mm
- patients with a small diseased vessel <2.5 mm
- patients with long lesions.

To permit a direct comparison between the results of this model with those of the LRiG model, it is necessary to modify the input parameters of the 'patients' scenario to match the basic uncomplicated single vessel option in the LRiG model. It is also necessary to limit the model outputs to 6 months follow-up only.

2.1 Outcomes

The most important differences between the model outputs are in the health related utility outcomes.

In the Boston model, for bare metal stenting (**BMS**) a cohort of 1000 revascularised patients experience a total of **419.70 QALYs** in the first 6 months of follow-up i.e. **0.41970 per patient**.

However, in the case of **TAXUS** stenting, this rises to **426.57 QALYs** (or **0.42657 per patient**), giving a net incremental **gain of 6.87 QALYs /1000 patients** (or **+0.00687 per patient**).

i) *Procedural mortality*

The first element of difference between the TAXUS and LRiG models involves mortality assumptions. LRiG assumes that there are no differences at all between BMS and TAXUS, but the Boston model employs the TAXUS II mortality figures directly based on a single death in the BMS trial arm, suggesting an apparent (non-significant) difference in procedural mortality of 0.4% in favour of TAXUS.

This accounts for a difference of +0.86 QALYs /1000 patients.

ii) *Procedural complications*

In the TAXUS model, differences in the incidence rates of Stroke and AMI recorded in the trial data are used directly, and lead to differences in the QALYs attributable to BMS and

DES in the model. The difference for stroke (0.8% versus 0.4%) is non-significant. In the case of AMI, there appears to be a benefit for DES over BMS (1.5% versus 5.4%), but this effect is not sustainable in the context of the LRiG meta-analysis of taxane eluting stents. Therefore in both instances, the LRiG model assumes that no difference exists.

These account for a difference of +0.34 QALYs /1000 patients.

iii) *Disutility of recurring symptoms*

In the TAXUS model, all patients who require a repeat revascularisation within 6 months of the index procedure are assumed to suffer loss of health-related quality of life for an average period of 4.5 months while waiting for the second intervention, irrespective of the type of repeat revascularisation carried out (i.e. no differential in waiting times is assumed). This is unrealistic since it requires virtually all second interventions to take place in the last few weeks of the period, contrary to the evidence of virtually all studies that these events are spread fairly evenly over the first 6-9 months. By contrast, the LRiG model is based on Kaplan-Meier event-free survival plots, yielding realistic incidence rates for each week. Moreover, for those patients revascularised in the earlier part of the period, their waiting time is necessarily limited to the maximum time since the index procedure, so that a blanket application of an average waiting period to all patients is incorrect.

In the LRiG model, a typical waiting time of 6 weeks was assumed. This translates into an average time of 1.205 months for use in the TAXUS model.

This accounts for a difference of +0.04805 QALYs per patient with a 2nd procedure

iv) *Disutility of repeat procedure*

The TAXUS model makes no allowance for any disutility associated with recovery following a second intervention. However, in the LRiG model it is assumed that each CABG causes a quantum of disutility of 0.012 QALYs spread over 13 weeks, and each PCI a quantum of 0.0035 over 6 weeks.

This accounts for a difference of -0.00350 QALYs per patient with a 2nd procedure

v) *Repeat revascularisation rates*

The main source of outcome differences between the TAXUS and LRiG models is the estimated rate at which repeat revascularisations occur. This is generated by two elements: the baseline risk for patients receiving BMS in their index procedure, and the proportionate reduction in this risk assumed to arise from substitution by DES.

In the TAXUS model the 'All Patients' scenario assumes that 14.1% of BMS patients undergo a 2nd intervention within 6 months, but only 5.4% of DES patients do so (equivalent to a relative reduction of 61.7%). By contrast the LRiG base case scenario is based on 7.4% of uncomplicated single vessel PCIs having another procedure in 12 months (equivalent to 5.0% at 6 months), and a relative risk reduction of 30% due to substitution with DES (30% was chosen to represent a more realistic figure of what reduction might actually be seen in clinical practice, based on the type of outcomes seen in the BENESTENT II study).

None of these values are directly comparable, due to different definitions of both revascularisation and patient groups. The TAXUS patients include a mixture of patients with known risk factors for repeat intervention (diabetes, small vessels, long lesions, etc.), whereas the LRiG base case includes only patients without predisposing factors (diabetes, history of heart failure, low ejection fraction, etc.). Thus the LRiG baseline would be

expected to be lower than that used in TAXUS. In the TAXUS model only Target Lesion Revascularisations (TLRs) are used (though there appears to be some ambiguity concerning Target Vessel Revascularisations (TVRs)), whereas the LRiG model is concerned with any revascularisation required by a patient, regardless of its origin. Since additional non-TLR non-TVR interventions are not counted by TAXUS, the quoted risk reduction is likely to be diluted in the LRiG context, depending on the balance of new lesion type.

Within the TAXUS model the incremental utility benefit attributable to DES due to reduced risk of repeat revascularisation can be estimated as:

65.6 QALYs * (Baseline Rate) * (% reduction due to DES)/1000 patients

2.2 Summary for TAXUS™ model outcomes

Table 1 shows the outcome gains to be expected within the original TAXUS model for a range of combinations of baseline revascularisation risk, and the efficacy rate of DES in reducing the need for reintervention. The bold figures indicate the scenarios preferred by **Boston Scientific Ltd**. and **LRiG**.

Table 1: Unadjusted Incremental QALYs gained/1000 patients

	Baseline revascularisation rate (6 months)			
DES efficacy	5%	10%	14.1%	20%
30%	**+2.15**	+3.13	+3.94	+5.10
40%	+2.48	+3.79	+4.86	+6.41
50%	+2.80	+4.44	+5.79	+7.72
61.7%	+3.19	+5.21	**+6.87**	+9.26
70%	+3.46	+5.76	+7.64	+10.35

In Table 2, the changes described above have been implemented to obtain net outcome results from the TAXUS model using LRiG assumptions.

Table 2: Incremental QALYs gained/1000 patients on LRiG assumptions

	Baseline revascularisation rate (6 months)			
DES efficacy	5%	10%	14.1%	20%
30%	**+0.28**	+0.60	+0.85	+1.23
40%	+0.39	+0.81	+1.15	+1.65
50%	+0.49	+1.02	+1.45	+2.07
61.7%	+0.61	+1.26	**+1.80**	+2.56
70%	+0.70	+1.44	+2.04	+2.91

By comparing the TAXUS scenario in Table 1 (+6.87) with the LRiG scenario in Table 2 (+0.28), it can be seen that the Boston incremental gain is 24.5 times the size of that obtained with LRiG assumptions. Thus the ICER for DES vs. BMS increases from £55,438/QALY gained in the LRiG model to £1,359,659/QALY gained in the Boston model, on the basis of differences in the estimation of health-related quality of life alone.

2.3 Costs

Differences in incremental costs are more difficult to reconcile accurately since they occur via several mechanisms within the model: the clinical assumptions (as described above for

outcomes), resource use assumptions, unit costs and costing methodology differences. Indeed, it is not possible to reflect all differences by simply replacing parameter values within one model.

Table 3 shows the TAXUS model incremental costs per 1000 patients for a range of baseline revascularisation rates and DES efficacy, corresponding to the incremental outcomes shown in Table 1.

Table 3: Unadjusted Incremental Cost /1000 patients

	Baseline revascularisation rate (6 months)			
DES efficacy	5%	10%	14.1%	20%
30%	**£653,132**	£609,980	£574,595	£523,676
40%	£631,476	£566,668	£513,526	£437,052
50%	£609,820	£523,357	£452,456	£350,429
61.7%	£584,483	£472,682	**£381,005**	£249,079
70%	£566,509	£436,733	£330,317	£177,182

Some of the main sources of cost difference between the TAXUS model and the LRiG model have been identified as follows:

Procedure costs - Although both models use identical unit costs per stent, the average number of stents used per patient differs: 1.035 in TAXUS and 1.3 in LRiG. This leads to an additional net cost of £137,800 /1000 patients in the LRiG model.

Procedural complications costs - In the same way that TAXUS model differences in outcomes all derive from non-significant trial differences, so also the TAXUS cost differences for procedural complications are all ignored in the LRiG model. In addition to Stroke and AMI (discussed above), this also includes vascular bleeding where the trial incidence for BMS 3.3% is very similar to that for DES (3.1%). All procedural complications account for a difference of £31,067 /1000 patients.

Revascularisation costs - A complex interaction between several factors contributes to differences in repeat revascularisation costs:

- baseline risk of repeat intervention
- reduction in risk attributable to use of DES
- distribution of patients between different types of repeat revascularisation
- number of stents used per intervention
- unit costs of procedures
- frequency of angiography
- out-patient consultations prior to reintervention

2.4 Summary for TAXUS™ model costs

Aggregating all these readily identifiable differences between the TAXUS and LRiG models leads to adjusted estimates of incremental cost, based wherever possible on LRiG assumptions. These are shown below in Table 4, allowing comparison with Table 2.

Table 4: Incremental costs /1000 patients on LRiG assumptions

	Baseline revascularisation rate (6 months)			
DES efficacy	5%	10%	14.1%	20%
30%	**£771,468**	£713,582	£653,183	£583,537
40%	£757,770	£665,538	£591,008	£490,515
50%	£724,814	£618,331	£527,368	£397,889
61.7%	£694,477	£561,060	**£451,773**	£289,597
70%	£678,538	£524,953	£396,305	£213,137

2.5 Incremental Cost-Effectiveness Ratios

From Tables 1-4 we can calculate ICERs for the original TAXUS, and the adjusted model, taking account of LRiG values and assumptions wherever possible. These are set out in Tables 5 and 6.

Table 5: Unadjusted Incremental Costs / QALY gained

	Baseline revascularisation rate (6 months)			
DES efficacy	5%	10%	14.1%	20%
30%	**£304,005**	£194,731	£145,862	£102,673
40%	£254,995	£149,579	£105,571	£68,157
50%	£217,449	£117,756	£78,155	£45,366
61.7%	£183,328	£90,692	**£55,448**	£26,900
70%	£163,711	£75,869	£43,240	£17,122

Table 6: Adjusted Incremental Costs / QALY gained with LRiG assumptions

	Baseline revascularisation rate (6 months)			
DES efficacy	5%	10%	14.1%	20%
30%	**£2,755,244**	£1,189,304	£768,451	£474,420
40%	£1,943,000	£821,652	£513,920	£297,282
50%	£1,479,212	£606,207	£363,702	£192,217
61.7%	£1,138,487	£445,286	**£250,985**	£113,124
70%	£969,340	£364,551	£194,267	£73,243

The ICER generated by the LRiG model directly is £1,891,326 / QALY gained, which though different from the corresponding estimate in Table 6 (£2.76m) is of similar magnitude. In conclusion, we conclude that the major part of the apparent difference in ICER between the Boston Scientific and LRiG models is attributable to varying assumptions relating to health-related utility, especially to different baseline risks of repeat revascularisation, and the efficacy of DES in avoiding such reinterventions. Differences in costs, though important, contribute much less to the apparent difference.

3. Cordis – CYPHER™ model

The Cordis economic model is used to present results in respect of four patient sub-groups:

- patients with single small vessel disease
- patients with long lesions
- diabetic patients
- patients with multi-vessel disease

Analysis for the first group is based on RAVEL clinical results, for the second and third groups on SIRIUS and BENESTENT II results, while ARTS is used in the case on multi-vessel disease.

Since the model structure is common to the analyses presented, we have carried out a comparison between the results of the multi-vessel version of the model and the LRiG model by modifying the input parameters of the Cordis scenario to match the basic uncomplicated double vessel option in the LRiG model. It is also necessary to limit the model outputs to 12 months follow-up only.

3.1 Outcomes

In the Cordis model, differences in health-related utility outcomes are solely generated by the delay between recurrence of angina symptoms and the timing of the repeat procedure i.e. the waiting time. In contrast to the LRiG formulation no disutility is assigned to the repeat procedure itself. However, different assumptions are made in the Cordis models concerning the proportion of repeat revascularisations which would require a CABG, and this impacts on the incremental utility calculation.

There is an anomaly in the Cordis model in that an assumed average waiting time for CABG interventions is applied to patients identified with recurrent symptoms in the first year, truncated since most such patients are not expected to receive the intervention within 12 months. Yet, it appears that the full cost of these repeat procedures is attributed to the first year of follow-up. This discrepancy has the effect of overstating the costs in the initial period.

Table 7 shows the outcome gains to be expected within the original Cordis model for a range of combinations of baseline revascularisation risk, and the efficacy rate of DES in reducing the need for reintervention. The bold figures indicate the scenarios preferred by **Cordis** (for multi-vessel disease) and **LRiG** (for uncomplicated 2 vessel disease).

Table 7: Unadjusted Incremental QALYs gained /1000 patients

	Baseline revascularisation rate (12 months)			
DES efficacy	10%	15%	22.3%	30%
30%	**+1.36**	+2.05	+3.04	+4.09
50%	+2.20	+3.30	+4.91	+6.60
70%	+3.04	+4.55	+6.77	+9.11
82.2%	+3.55	+5.32	**+7.91**	+10.64

In Table 8, the amendments described above for disutility of repeat procedures, type of repeat procedure, and the LRiG assumptions of equal waiting times for PCI and CABG are

exemplified within the Cordis model to obtain net outcome results from the Cordis model using LRiG assumptions.

Table 8: Incremental QALYs gained /1000 patients on LRiG assumptions

	Baseline revascularisation rate (12 months)			
DES efficacy	10%	15%	22.3%	30%
30%	**+0.73**	+1.09	+1.63	+2.19
50%	+1.16	+1.74	+2.59	+3.48
70%	+1.59	+2.39	+3.55	+4.77
82.2%	+1.85	+2.78	**+4.13**	+5.56

By comparing the Cordis scenario in Table 7 (+7.91) with the LRiG scenario in Table 8 (+0.73), it can be seen that the Cordis incremental gain is 10.8 times the size of that obtained with LRiG assumptions. Thus the ICER for DES vs. BMS increases from £54,237 / QALY gained (after adjusting the mean number of stents per patients for 2 vessel disease) to £587,659 / QALY gained on the basis of differences in the estimation of incremental changes in health-related quality of life alone.

3.2 Costs

Differences in incremental costs are more difficult to reconcile accurately since they occur via several mechanisms within the model: the clinical assumptions (as described above for outcomes), resource use assumptions, unit costs and costing methodology differences. Indeed, it is not possible to reflect all differences by simply replacing parameter values within one model.

Table 9 shows the Cordis model incremental costs per 1000 patients for a range of baseline revascularisation rates and DES efficacy, corresponding to the incremental outcomes shown in Table 7.

Table 9: Unadjusted Incremental Cost /1000 patients (for 2 vessel disease)

	Baseline revascularisation rate (12 months)			
DES efficacy	10%	15%	22.3%	30%
30%	**£1,317,511**	£1,229,607	£1,101,268	£965,896
50%	£1,201,988	£1,056,323	£843,653	£619,328
70%	£1,086,466	£883,040	£586,037	£272,761
82.2%	£1,015,997	£777,336	**£428,892**	£61,354

An indication of the impact of differences in prices on the incremental cost can be gauged by substituting LRiG prices for the most important resources in the model. This leads to a net reduction in the incremental cost for the Cordis preferred scenario of £70,000 per 1000 patients.

Table 10 shows adjusted estimates of incremental cost using wherever possible LRiG assumptions within the Cordis model. These may be compared with those shown in Table 8.

Table 10: Incremental costs /1000 patients on LRiG assumptions

	Baseline revascularisation rate (12 months)			
DES efficacy	10%	15%	22.3%	30%
30%	**£1,110,002**	£1,039,610	£936,836	£828,431
50%	£1,025,520	£912,886	£748,441	£574,985
70%	£941,038	£786,163	£560,046	£321,538
82.2%	£889,504	£708,862	**£445,124**	£166,936

3.3 Incremental Cost-Effectiveness Ratios

From Tables 7-10 we can calculate ICERs for the original Cordis model, and the adjusted model taking account of LRiG values and assumptions wherever possible. These are set out in Tables 11 and 12.

Table 11: Unadjusted Incremental Costs / QALY gained (for 2 vessel disease)

	Baseline revascularisation rate (12 months)			
DES efficacy	10%	15%	22.3%	30%
30%	**£965,883**	£600,977	£362,059	£236,050
50%	£546,337	£320,091	£171,962	£93,837
70%	£357,846	£193,899	£86,559	£29,947
82.2%	£286,511	£146,141	**£54,237**	£5,767

Table 12: Adjusted Incremental Costs / QALY gained with LRiG assumptions

	Baseline revascularisation rate (12 months)			
DES efficacy	10%	15%	22.3%	30%
30%	**£1,520,992**	£949,691	£575,655	£378,389
50%	£884,131	£524,684	£289,351	£165,237
70%	£591,829	£329,618	£157,946	£67,406
82.2%	£480,182	£255,111	**£107,754**	£30,039

The ICER generated by the LRiG model directly is £1,529,445 / QALY gained, which is very similar to the corresponding figure in Table 12. In summary, we conclude that the major part of the apparent difference in ICER between the Cordis and LRiG models is attributable to varying assumptions relating to health-related utility, especially to different baseline risks of repeat revascularisation, and the efficacy of DES in avoiding such reinterventions. Differences in costs, though important, contribute much less to the apparent difference.

4. Summary

Though it is not feasible to provide a complete reconciliation between either of the submitted models and the LRiG model, due to the contrasting model architectures, a good degree of agreement has been demonstrated if common costs and assumptions are employed, particularly relating to the baseline risk of repeat revascularisation, and the relative efficacy of DES over BMS. In general, the majority of apparent differences arise in relation to the estimation of incremental outcomes, rather than cost effects.

Addendum 3

Economic evaluation: further consideration of differential waiting times

1. Introduction

Use of much longer waiting times (approximately 3-fold) for elective treatment by CABG compared to PCI is a major source of utility benefit in the submitted models. This is especially the case when considering PCI with DES as an alternative to CABG, but also applies to a lesser extent when comparing DES and BMS.

Clearly, this does not constitute an inherent feature of the technologies, as a scenario can be readily be envisaged in which the relative supply of service capacity was changed to favour CABG (e.g. too few trained cardiologists, inadequate radiology facilities, or a shortage of specialist consumables). In such an environment it can be anticipated that the advocates of PCI would be arguing that present constraints should not be allowed to bias a comparison, so as to inhibit the future development of the new technology.

Thus the only argument that may be advanced in favour of including an estimated disutility arising from differential waiting times in our economic evaluation is a pragmatic one. This rests on the contention that the nature of the supply constraints on CABG in the UK are sufficiently severe and likely to be of sufficient duration to render the current imbalance of supply and demand in CABG interventions irremediable, so that extended waiting is effectively inevitable for the type of patient currently assigned to elective CABG treatment.

There are two grounds on which we believe that the argument that differential waiting time should be allowed in the economic evaluation of drug-eluting stents fails on two counts: one based on recent evidence of waiting times in the NHS, and the other concerning the legitimacy of implicitly endorsing an imbalance which is both contrary to government policy, and is probably untenable in European law.

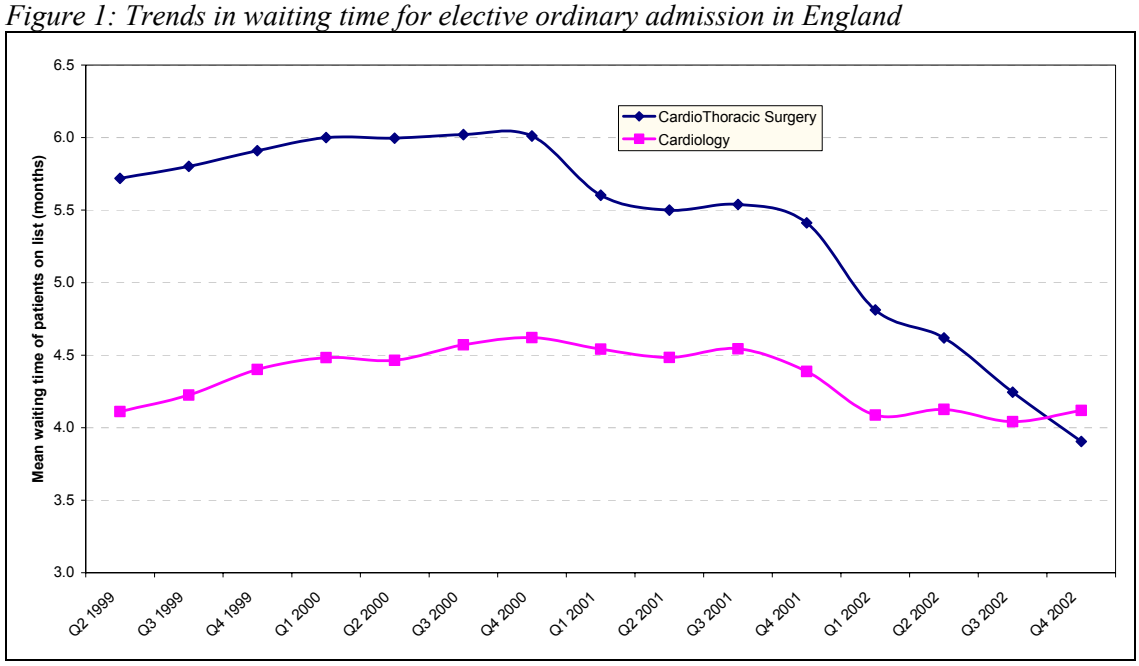
2. Waiting Time trends

In historic research studies and clinical trials the time spent by elective patients on the waiting list for CABG is generally considerably longer than that for angioplasty and similar procedures. However, the impact of recent government initiatives to reduce waiting times, improve access to priority services and to expand service capacity toward typical European levels, suggest that some equalisation of these disparities is to be expected. Accurate information on completed waiting time episodes is only available some time after the event, and is therefore unable to reflect recent changes in waiting time trends. However, the quarterly information on the number and duration of wait of people currently awaiting admission is more easily obtained. The following chart shows the mean waiting time for the specialties of Cardiology and Cardio-Thoracic surgery, using the NHS quarterly statistics since 1999.

It is clear that the historic difference between the specialties is indeed present at the beginning of this period. However, there follows a steady reduction in average surgical waiting times until 2003 when the two trends converge. The patients in these specialities are not exclusively waiting for coronary artery revascularisation. Nonetheless, CABG and PCI does constitute a substantial proportion of their caseload, and it is likely that the general trend is also reflected in these specific procedures. It therefore follows that the argument for

use of differential waiting times in PCI and CABG is probably now redundant since experience has largely converged for the two groups of patients.

Figure 1: Trends in waiting time for elective ordinary admission in England



3. Patient Access, Public Policy and European Law

We believe it can also be established on grounds of legality, public policy, and economic reality that the argument for using differential waiting times is false, and that if a significant difference in waiting times still exists in favour of PCI it is completely feasible within a short period of time to expand the volume of elective CABG treatment undertaken for the benefit of NHS patients so as to reduce waiting times to comparable levels currently experienced by those undergoing PCI. If this point is conceded, then there are no legitimate grounds for considering treatment delays in the economic assessment of revascularisation procedures.

3.1 Legal position

In July 2001 the European Court of Justice ruled that patients in the UK are entitled to receive hospital care in other countries in the European Economic Area. In effect this means that where a need for an intervention is established on clinical grounds, it is not acceptable to withhold or unreasonably delay treatment on the grounds that there are insufficient facilities or capacity locally or in the UK to provide them, if capacity to provide the service is available elsewhere in Europe. This ruling has been accepted by the UK government, which has undertaken pilot projects to explore the practical issues involved in offering overseas treatment to UK residents who would otherwise be denied treatment within a reasonable time, with a view to providing guidance to the NHS.

3.2 Public Policy

Current government policy on waiting times and the development of services for treatment of CHD is clearly set out in the three-year Priorities and Planning Framework 2003-2006 (Improvement, Expansion and Reform) published in October 2002. This sets targets for "maximum waits of 3 months for revascularisation by March 2005, or sooner if possible."

To achieve this it assumes there will be "increased access to diagnostic and surgical capacity to enable waiting times to be met."

A key element in meeting these targets involves "increasing the total numbers of cardiologists to 685 and cardiothoracic surgeons to 217 by 2004." In addition, the plan confirms the need to "establish additional inpatient beds and hospital capacity to meet access and clinical priority targets." Moreover, there is a general commitment to "introduce new providers from the independent sector and overseas to offer patients a greater choice over where they obtain diagnosis and treatment."

Clearly, there is every intention on the part of the UK government to bring the maximum waiting time for elective revascularisation (regardless of mode of treatment) to 13 weeks within the timescale of applicability of this NICE appraisal. That policy target maximum wait is also consistent with an average waiting time of 6-8 weeks, as used in the LRiG economic evaluation.

3.3 Economic reality

The patients currently waiting for CABG have been assigned to this mode of treatment as clinically most appropriate, notwithstanding the widespread availability of conventionally stented PTCA. Since, in the submissions made to NICE it is only suggested that a minority of these could be considered appropriate for PCI using DES, regardless of anticipated use of DES, there may remain a need to expand services in the UK for cardiac surgery. The size of any differential in waiting times would merely be a strong indicator of the urgency of the need for this expansion in capacity if public policy targets are to be achieved.

In the meantime the only way to meet the identified need may be to seek additional service capacity from other sources, as envisaged in the policy framework. This could be from the UK private sector, or from other health economies. Although the government has sanctioned arrangements with the private sector for some treatment, there are limitations on this option in that in many cases the private sector is using or sharing the same resources (i.e. skilled staff) available to the NHS, so that the net additional capacity available within the UK is probably quite limited.

By contrast, evidence from the NHS pilot projects and also from larger schemes undertaken in Norway indicates that there is substantial spare surgical capacity available in Europe which can be purchased at prices comparable to the average cost per case incurred by the UK. Most patients who have been so treated have had good outcomes and indicated a high level of satisfaction with their treatment. The main barriers identified in the evaluation if the UK pilots was the evident reluctance and even non co-operation of some GPs and specialists in accepting that patients could receive care from another consultant based in another unit, despite the clear benefits to patients suffering on the waiting list.

4. Summary

Recent evidence from NHS statistics suggests that the historic differences in waiting times for PCI and CABG may be diminishing rapidly, or even have disappeared already. Where differences persist it is both desirable and practical to employ available capacity elsewhere than in the NHS to remedy any existing service deficiency in the timely treatment of NHS patients requiring elective CABG. This may be appropriate in the short and medium term until investment within the UK comes to fruition, allowing all patients to receive care promptly in local facilities. Moreover, there is evidence that this can be achieved at

comparable cost to conventional NHS treatment. Therefore, it appears that the pragmatic argument that differential waiting times are effectively unavoidable is untenable, and should not be allowed to distort considerations of relative cost-effectiveness between the two available technologies.

Addendum 4

Analysis of subgroups from the clinical trials

1. Objective

Clinically and economically relevant subgroups of patients for whom an intervention is more effective and cost-effective is dependent on the availability of detailed information from clinical trials or patient registries, ideally at the level of the individual patient. The primary objective of this exercise is to consider whether any evidence exists from the trials so far reported, to indicate that differentiation of patients by sub-groups of efficacy is both possible and desirable. For this purpose, it is necessary to estimate both the current risk of repeat revascularisation in patients receiving uncoated (bare-metal) stents (BMS), and the reduction in risk which is attributable to use of drug-eluting stents (DES).

2. Data Sources

Some useable information exists in published trial papers, but there are currently only three trials for which such information is available:

- The RAVEL trial was restricted to patients with single lesions in small vessels (reference vessel diameter or RVD between 2.5mm and 3.5mm), so that the trial as a whole relates to a distinct specific subgroup, though any further detail of these patients is missing.
- The SIRIUS trial enrolled patients with longer lesions in a single vessel. Outcome information after 12 months of follow-up has been made available by Cordis, and this allows consideration of patients with and without diabetes, and also results for patients receiving two overlapping stents.
- The TAXUS II trial investigated use of a drug-eluting stent in patients with a lesion in a small artery (RVD < 3.0mm). The recently received detailed clinical trial reports on both cohorts (slow-release and moderate-release formulations) include patient level demographic, procedure and outcome data. This has been subjected to detailed analysis in search of insights to help in defining subgroups relevant to economic analysis.

3. Analytical methods and objectives

3.1 Risk measurement

It is common practice in clinical trials to measure efficacy and effectiveness in terms of relative measures; changes in relative risk, or relative improvement in performance/function. This approach is mediated through the use of proportional hazards models and related statistical procedures. However, there are circumstances where relative measures are inappropriate and indeed may be misleading. All the economic models considered in our main report, including our own have expressed benefit in terms of the relative reduction in the risk of restenosis or repeat revascularisation, following closely the pattern of published trial reports. However, as can readily be seen in the simplified model set out in Addendum 5, for the purposes of economic assessment the critical statistic is the *absolute* risk reduction since this converts directly into the expected number of additional procedures avoided. For this reason, we have re-expressed all results as absolute risk changes, to avoid the implicit temptation to apply a relative risk change to a different group of patients without justification.

3.2 Outcome measurement

For economic analysis the prime concern is the expected cost of repeated revascularisation. This means that the key outcome variable is the number of revascularisation events that occur, regardless of whether they occur in separate patients or involve some patients undergoing several procedures. Once again this is different from the traditional perspective of clinical researchers who generally report the number of patients affected (or equivalently the number of patient free of an event). Unfortunately, where the source of information is published papers or synopses of clinical trial reports, we are restricted to those outcome measures considered important by the authors. Thus in such cases we are obliged to rely on patient (rather than intervention) findings, using these cautiously as proxies for revascularisations.

As stated in our main report, for economic analysis we are concerned primarily with identifying *any* coronary arterial revascularisation carried out, regardless of the site of the lesion or the specific vessel involved. This focuses attention on the overall consumption of healthcare resources and avoids any subjective judgements about which interventions are to be considered 'relevant'. Unfortunately, this statistic is rarely if ever reported in the literature or in trial report, which employ a range of anatomical/angiographically-oriented definitions - target-lesion revascularisation (TLR), target-vessel revascularisation (TVR), and target-vessel failure (TVF), among others. These different measures involve various overlaps and exclusions, which makes direct comparison difficult and confusing, both within and between trials. Where no access is available to individual patient data we are obliged to interpret these measures as best we can, recognising that any inferences drawn are necessarily tentative rather than definitive.

3.3 Correcting for protocol-driven excess interventions

In all of the trials of drug-eluting stents for which results are available, a key focus has been anatomical outcomes, which can only be determined accurately by angiography. This means that trial protocols include provision for a follow-up invasive investigation 6 or 8 months following the index procedure. It was recognised in the early BENESTENT trials that this led to a sudden increase in repeat revascularisations occurring around the time of the follow-up angiography. This phenomenon is understood to result from the clinicians reaction to visual evidence of significant restenosis at angiography, despite minimal or even absent patient symptoms. Clinicians feel obliged to intervene in a precautionary role when they are confronted with a restenotic lesion which appears to put their patient at risk. Though completely understandable, this pattern of response is completely atypically of service environments (such as the NHS) where follow-up does not normally involve angiography, and the decision to carry out a second intervention is judged primarily on symptoms of angina and limitations to a patient's normal activity. This phenomenon seriously undermines the reliability of estimates of the risk of revascularisation in both arms of a trial, and hence calls into question claims for the additional efficacy of drug-eluting stents.

Attempts have been made to avoid these problems by distinguishing between clinically-driven and angiographically driven reinterventions, particularly in the FDA statement of definitions. However, even the FDA formulation includes angiographic measurements and there is sufficient scope for subjective interpretation in this exercise to bring it into serious question. Ultimately, the acid test is the time plot of survival free of revascularisation, and in all the available trials this continues to show a sharp dip in trend around the time of the protocol angiography. By contrast, some pragmatic trials of stent use (notably SOS) show

no such dip, implying that where angiography is not routinely used as part of patient follow-up, the clinical need for early intervention is represented by a relatively constant "smooth" risk function.

The first attempt to correct for this phenomenon was using information from BENESTENT II to adjust the outcomes of the RAVEL trial, which was employed by van Hout in his economic analysis (Cordis submission). This was made possible because in BENESTENT II angiographic follow-up was only carried out on a subset of patients so that a direct comparison of reinterventions was possible. An alternative approach to correcting trial outcomes involves estimating a single correction to the survival curve of each trial arm in order to bring the trend after angiography into line with that applying before. Either approach has the effect of reducing the apparent rate of repeat revascularisation in both arms of a trial, and usually also reduces the estimated additional benefit attributable to drug-eluting stents. In the cases considered here, we have used the BENESTENT-II method but have confirmed that the trend adjustment approach produces broadly similar results.

3.4 Analysis of individual patient data

Our analysis of TAXUS II individual patient data has been carried out on the basis of the actual treatment received, rather than intention-to-treat, since within an economic model we need to know the expected outcome conditional on a particular treatment having been undertaken, which may be partially obscured by post-randomisation variations from protocol. The main analysis was carried out using univariate analysis of variance to assess the nature and size of differences that might be related to specific factors. Subsequently, where sufficient data was present two-way analysis were undertaken to confirm and clarify the nature of the apparent differences. We combined the two TAXUS II cohorts (slow-release and moderate-release) in order to assemble sufficient records to allow meaningful analysis to be carried out. However, we also compared results from the two sub-studies to assess the homogeneity of the data, and any implications for our conclusions.

4. RAVEL

The RAVEL trial compared the use of CYPHER stents in 120 patients with single lesions in a small vessel (RVD between 2.5mm and 3.5mm) with 118 patients receiving BMS. At 12 months follow-up, 3 repeat revascularisations were recorded in the DES arm (2.5%) compared to 19 (16.1%) in the BMS arm, suggesting an absolute risk reduction in TLR of 13.6% and relative risk reduction of 84.5%. The corresponding figures for TVF at 12 months are 15.3% (absolute risk reduction) from 19.6% BMS to 4.2% for DES.

In RAVEL, patients were reviewed by angiography about 6 months following the index procedure so that an excess of repeat revascularisations compared to normal practice is to be expected. Applying a rate adjustment based on BENESTENT II experience reduces these estimates considerably: the revascularisation rates (TLR) are then 1.5% for DES and 9.4% for BMS, giving a revised absolute risk reduction of 7.9%. For TVR the adjusted absolute risk reduction is 8.9%.

No results for sub-groups are available for RAVEL.

5. SIRIUS

The SIRIUS trial was carried out in the USA in a population of patients requiring stenting of a single long lesion. In all 533 patients were randomised to use of CYPHER, and 525 to BMS. Angiographic follow-up occurred at about 8 months in this trial.

Assessment of revascularisation rates is more complex for this trial, due to the way results are reported in the 12 month update report submitted. Freedom from TVR is estimated at 77.6% for BMS and 93.4% for DES. There is evidence that some patients received further treatment to more than one lesion/vessel, but it is not possible to estimate how many of these occurred on separate occasions. Thus only patient-based rates are available, and event rates cannot be determined.

Although the authors report only clinically driven repeat intervention rates, it is clear from the K-M survival plots that an important angiography-related effect remains in the outcomes reported. Correcting for this effect by trend displacement, we estimate the underlying 12 month risk in the BMS arm to be 16.0%, and in the DES arm to be 5.0%, giving an absolute risk reduction of 11.0% (68.8% relative risk reduction).

Applying similar assumptions to the outcomes reported for the diabetic sub-group implies that patients with long lesions and diabetes gain a mean beneficial absolute risk reduction of 12.6% (61.2% relative), whereas those without diabetes achieve an absolute reduction of just 10.1% (71.6% relative).

According to an additional analysis of outcomes from SIRIUS at 9 months, approximately one-third of patients in this trial required two overlapping stents to cover the lesion. However, the reported absolute risk reduction in TLR due to use of CYPHER was very similar between the two sub-groups. This suggests that the only important distinction to be made for the purposes of economic analysis is the cost of implanting an additional stent.

6. TAXUS II

6.1 Analysis Outline

The individual patient information available offers the prospect of greater insight into the impact of the TAXUS stent, but at the same time poses some additional problems in analysis and interpretation. Initially, we carried out a simple univariate comparison of revascularisation rates within each category of each relevant risk-related variable. These results are presented in Tables 1-7, and revealed important findings concerning the type of vessel stented, vessel size, and the number of vessels used. In addition, a similar univariate analysis of trial cohorts indicated that the currently marketed slow-release formulation seems to deliver much less benefit than the moderate-release TAXUS stent. It is possible that these differences are the consequence of casemix differences and statistical variation, rather than differential efficacy.

A further difficulty was identified by examining the Kaplan-Meier plots for survival free from repeat revascularisation. This showed a very strong trend deviation around the time of the protocol angiography at 6 months, indicating that estimates of baseline risk and risk reduction based on the reported data would almost certainly be overstated.

We identified problem categories as defined below (i.e. LCX target vessel, multiple stent use, and RVD > 3.5mm), and decided therefore to repeat the analysis excluding these cases. In addition, we also applied an adjustment based on BENESTENT II similar to that used by van Hout, in order to approximate the results that could be expected in normal clinical practice in the UK.

6.2 Initial Univariate Analysis

a) Vessel type: three types of artery were stented in the trial - left anterior descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA). Table 1 shows the results of analysis by these categories for patients after 12 months follow-up.

Table 1: TAXUS II revascularisation changes due to DES at 12 months by Vessel type

	Patients affected			Events occurring		
Vessel stented	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
LAD						
LCX						
RCA						

Commercial in confidence: figures in Table 1.

One-way ANOVA showed ***[Commercial in confidence]*** in DES outcome between LCX and LAD/RCA, which was subsequently confirmed in mulitvariate analysis. LAD and RCA were ***[Commercial in confidence]***. It appears that using a drug-eluting stent for stenting a single lesion in a narrow segment of the LCX, ***[Commercial in confidence]***

b) Reference Vessel Diameter: target vessel are classified in TAXUS into three groups for very small vessels (less than 2.5mm), small vessels (2.5 - 3.5mm) and normal (3.5+mm). Only a few patients (7%) fell into the last group, which technically is outside the scope of the trial protocol. Table 2 shows the results of analysis by these categories for patients after 12 months follow-up.

Table 2: TAXUS II revascularisation changes due to DES at 12 months by RVD

	Patients affected			Events occurring		
RVD	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
<2.5mm						
2.5-3.5mm						
>=3.5mm						

Commercial in confidence: figures in Table 2.

In view of the very small number of cases involved and the consequent risk of anomalous results, it appeared prudent in this case to exclude the non-protocol 'normal' vessel size patients from multi-variate analysis.

c) Lesion length: here patients were grouped into approximate quartiles by length of lesion to be stented, in order to assess whether there is any evidence of differential benefit. Table 3 shows the results of analysis by these categories for patients after 12 months follow-up.

Table 3: TAXUS II revascularisation changes due to DES at 12 months by Lesion length

	Patients affected			Events occurring		
Lesion length	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
< 8mm						
8 - 10mm						
11 - 12mm						
>12mm						

Commercial in confidence: figures in Table 3.

[Commercial in confidence] ……DES outcome effect was found for length of lesion.

d) Diabetes: about 16% of the combined cohorts were identified as suffering from diabetes mellitus. Table 4 shows the results of analysis by diabetes status for patients after 12 months follow-up.

Table 4: TAXUS II revascularisation changes due to DES at 12 months by Diabetes status

	Patients affected			Events occurring		
Diabetes status	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
Absent						
Present						

Commercial in confidence: figures in Table 4.
In this one-way analysis ***[Commercial in confidence]***

e) Number of Stents: although the trial was designed to consider the use of a single stent in a small vessel, a number of patients received more than one stent (up to 5) at their index procedure. Two-thirds of these received an additional stent at the test lesion, the remainder involving other diseased locations/vessels. Table 5 shows the results of analysis by number of stents used for patients after 12 months follow-up.

Table 5: TAXUS II revascularisation changes due to DES at 12 months by number of stents used

	Patients affected			Events occurring		
Stents used	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
1						
2+						

Commercial in confidence: figures in Table 5.
Here the need to use more than one stent ***[Commercial in confidence]***

f) Gender: a minority (24%) of the combined cohorts were female. Table 6 shows the results of analysis by diabetes status for patients after 12 months follow-up.

Table 6: TAXUS II revascularisation changes due to DES at 12 months by Gender

	Patients affected			Events occurring		
Gender	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
Female						
Male						

Commercial in confidence: figures in Table 6.
Women appear to have ***[Commercial in confidence]***

g) Age: here patients were grouped into approximate quintiles by age when first stented, in order to assess whether there is any evidence of differential benefit. Table 7 shows the results of analysis by these categories for patients after 12 months follow-up.

Table 7: TAXUS II revascularisation changes due to DES at 12 months by Age

	Patients affected			Events occurring		
Age	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
<52						
52 - 58						
59 - 62						
63 - 69						
70+						

Commercial in confidence: figures in Table 7.
Commercial in confidence trend in DES outcome effect ***Commercial in confidence***.

6.3 Revised Univariate Analysis

The one-way comparison of sub-groups was repeated following exclusion of the identified extreme categories, and adjustment for angiography associated event inflation.

a) Vessel type: Table 8 shows the results of the revised analysis by vessel categories for patients after 12 months follow-up. ***[Commercial in confidence]***

Table 8: TAXUS II revascularisation changes due to DES at 12 months by Vessel type

	Patients affected			Events occurring		
Vessel stented	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
LAD						
RCA						

Commercial in confidence: figures in Table 8.
b) Reference Vessel Diameter: Table 2 shows the results of the revised analysis by vessel diameter categories for patients after 12 months follow-up. ***[Commercial in confidence]***

Table 9: TAXUS II revascularisation changes due to DES at 12 months by RVD

	Patients affected			Events occurring		
RVD	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
<2.5mm						
2.5-3.5mm						

Commercial in confidence: figures in Table 9.
c) Lesion length: Table 10 shows the results of the revised analysis by length of lesion for patients after 12 months follow-up. ***[Commercial in confidence]***

Table 10: TAXUS II revascularisation changes due to DES at 12 months by Lesion length

	Patients affected			Events occurring		
Lesion length	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
< 8mm						
8 - 10mm						
11 - 12mm						
>12mm						

Commercial in confidence: figures in Table 10.

d) Diabetes: 14% of the moderate-release cohort was identified as suffering from diabetes mellitus. Table 11 shows the results of the revised analysis by diabetes status for patients after 12 months follow-up.

Table 11: TAXUS II revascularisation changes due to DES at 12 months by Diabetes status

	Patients affected			Events occurring		
Diabetes status	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
Absent						
Present						

Commercial in confidence: figures in Table 11.
In the revised analysis diabetes appears to be ***[Commercial in confidence]***

f) Gender: 27% of the moderate-release cohort was female. Table 12 shows the results of the revised analysis by diabetes status for patients after 12 months follow-up.

Table 12: TAXUS II revascularisation changes due to DES at 12 months by Gender

	Patients affected			Events occurring		
Gender	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
Female						
Male						

Commercial in confidence: figures in Table 12.
[Commercial in confidence]

g) Age: Table 13 shows the results of the revised analysis by age categories for patients after 12 months follow-up. ***[Commercial in confidence]***

Table 13: TAXUS II revascularisation changes due to DES at 12 months by Age

	Patients affected			Events occurring		
Age	BMS risk	Absolute risk change	Relative risk change	BMS risk	Absolute risk change	Relative risk change
<52						
52 - 58						
59 - 62						
63 - 69						
70+						

Commercial in confidence: figures in Table 13.

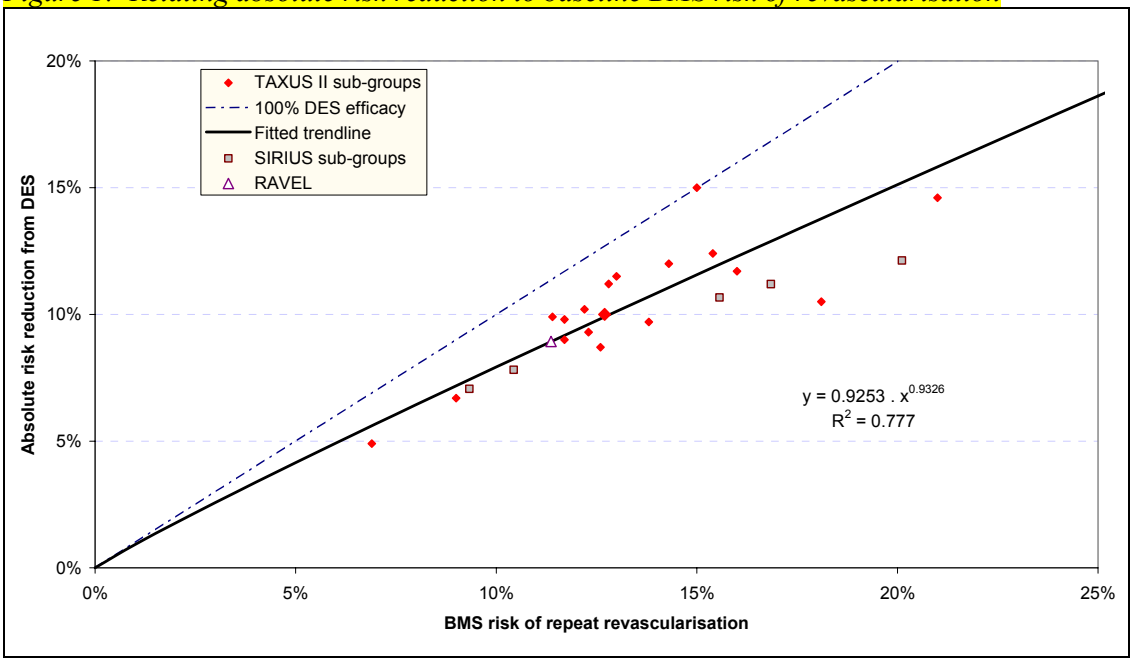
6.4 Multivariate Analysis

A general linear model of the number of episodes of repeat revascularisation was analysed based on main effects and first-order interactions. After allowing for the contrast between the control and intervention arms of the TAXUS II trial, none of the available factors were found to be significant predictors, either as main effects or as first-order interactions. This confirms that the only basis on which to distinguish between patients with single lesions in small vessels is on the number of stents required to complete the procedure.

6.5 Relationship between Baseline Risk and Absolute Risk Reduction

Although the primary outcome measure for economic analysis is the reduction in absolute risk of repeat revascularisation associated with use of DES, it may also be helpful to relate this parameter to the baseline risk for any patient group when using bare metal stents. A simple power function model was derived from the TAXUS II analyses as illustrated in Figure 1. In addition to the various TAXUS II sub-groups, Figure 1 also shows corresponding results for RAVEL (all patients) and SIRIUS, indicating that the power function provides a good approximation across all three studies.

Figure 1: Relating absolute risk reduction to baseline BMS risk of revascularisation



7. Summary

The evidence available of the effectiveness of DES in specific groups of patients is severely limited at present. Table 14 summarises the results for five types of patient where some figures can be estimated, following adjustment of rates to conform to routine clinical practice in the UK. These are used in the simplified economic model to derive estimates of relative cost-effectiveness.

Table 14: DES effectiveness for patient groups in an NHS setting

Patient type	Absolute risk reduction	Source
Single vessel, non-diabetic	6.0%	CTC, LRiG report*
Single vessel, small diameter	10.0%	TAXUS II / RAVEL
Single vessel, long lesion, non-diabetic	10.1%	SIRIUS
Single vessel, long lesion, diabetic	12.6%	SIRIUS
Two vessel, non-diabetic	7.9%	CTC, LRiG report*

*scenarios used in previous LRiG report

Addendum 5

Economic modelling: simplified model for non-drug eluting versus drug-eluting stents

1. Rationale for a simplified model

The model developed for our appraisal was designed to address two issues using a single model structure: whether DES may be considered a cost-effective alternative to CABG in patients with multiple-vessel disease, and whether DES is a cost-effective alternative to BMS in single vessel disease. Since the former comparison could involve the possibility of differential survival over extended time periods, it proved necessary to employ a complex model architecture. However, the comparison of DES and BMS for single vessel disease does not involve any question of mortality and therefore can easily be represented in a much simpler way.

In this addendum we introduce a simplified model for this purpose, which can be presented on a single Excel worksheet and encapsulates virtually all the detail of the original LRiG model for comparison of stents.

2. Model structure and assumptions

The principal limitation in the simplified model is that imposed by the clinical evidence available to populate it. Since none of the clinical trials provide follow-up outcomes beyond 12 months, we restricted attention to this period, and therefore considered that the question of discounting costs and outcomes was redundant.

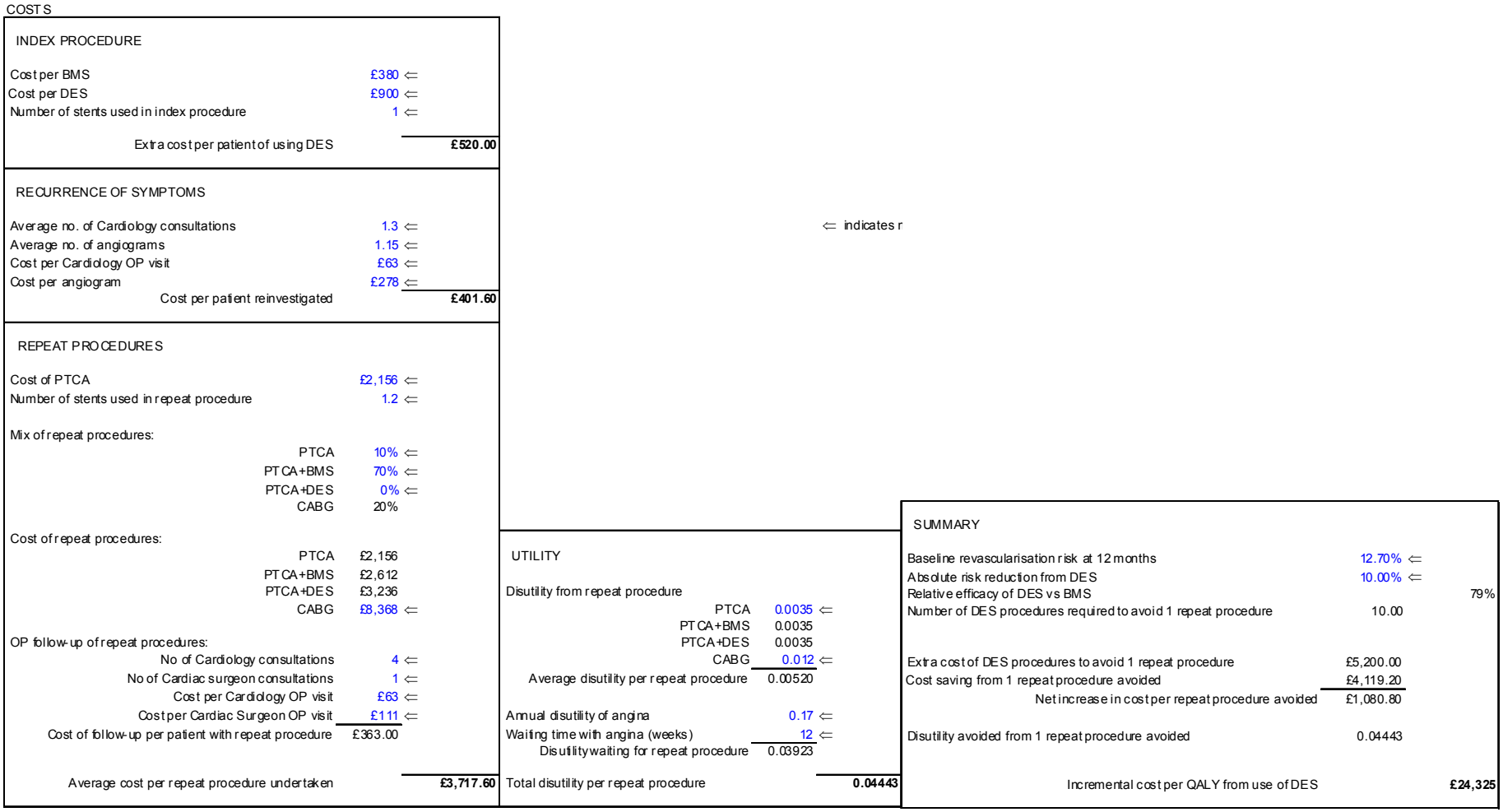
The one-page printout from the Excel spreadsheet below encompasses the whole of the simplified model, which accounts for all relevant outcome elements and more than 99% of the cost elements in the original model. Model parameters are identical to those previously used, with the exception of the average waiting time prior to undergoing a repeat procedure, which has been increased from 6 to 12 weeks.

The left-hand column of the worksheet includes all incremental costs affected by the choice of stent. A simple calculation (top box) presents the additional cost per patient from substituting DES for BMS. The middle box estimates the cost of reinvestigating a patient representing with recurrent symptoms, including out-patient visits and angiography. The bottom box estimates the average cost of a repeat revascularisation procedure based on the mix of procedures used and the costs of each type of procedure, added to the cost of out-patient follow-up.

The central column estimates the incremental disutility associated with a repeat revascularisation, comprising a quantum related to the procedure undergone added to a time-dependent disutility from angina symptoms suffered whilst awaiting the repeat intervention.

Finally incremental cost and utility are combined in the right-hand column. The absolute reduction in revascularisation risk associated with use of DES is used to estimate the net incremental costs incurred to avoid one repeat revascularisation. This is then combined with the corresponding disutility to arrive at the incremental cost per QALY gained.

Figure 1: Cost effectiveness of drug-eluting stents versus non drug-eluting stents



COSTS

INDEX PROCEDURE

Cost per BMS	£380 ⇐	
Cost per DES	£900 ⇐	
Number of stents used in index procedure	1 ⇐	
Extra cost per patient of using DES		**£520.00**

RECURRENCE OF SYMPTOMS

Average no. of Cardiology consultations	1.3 ⇐	
Average no. of angiograms	1.15 ⇐	
Cost per Cardiology OP visit	£63 ⇐	
Cost per angiogram	£278 ⇐	
Cost per patient reinvestigated		**£401.60**

⇐ indicates r

REPEAT PROCEDURES

Cost of PTCA	£2,156 ⇐	
Number of stents used in repeat procedure	1.2 ⇐	
Mix of repeat procedures:		
PTCA	10% ⇐	
PTCA+BMS	70% ⇐	
PTCA+DES	0% ⇐	
CABG	20%	
Cost of repeat procedures:		
PTCA	£2,156	
PTCA+BMS	£2,612	
PTCA+DES	£3,236	
CABG	£8,368 ⇐	
OP follow-up of repeat procedures:		
No of Cardiology consultations	4 ⇐	
No of Cardiac surgeon consultations	1 ⇐	
Cost per Cardiology OP visit	£63 ⇐	
Cost per Cardiac Surgeon OP visit	£111 ⇐	
Cost of follow-up per patient with repeat procedure	£363.00	
Average cost per repeat procedure undertaken		**£3,717.60**

UTILITY

Disutility from repeat procedure		
PTCA	0.0035 ⇐	
PTCA+BMS	0.0035	
PTCA+DES	0.0035	
CABG	0.012 ⇐	
Average disutility per repeat procedure	0.00520	
Annual disutility of angina	0.17 ⇐	
Waiting time with angina (weeks)	12 ⇐	
Disutility waiting for repeat procedure	0.03923	
Total disutility per repeat procedure		**0.04443**

SUMMARY

Baseline revascularisation risk at 12 months	12.70% ⇐	
Absolute risk reduction from DES	10.00% ⇐	
Relative efficacy of DES vs BMS		79%
Number of DES procedures required to avoid 1 repeat procedure	10.00	
Extra cost of DES procedures to avoid 1 repeat procedure	£5,200.00	
Cost saving from 1 repeat procedure avoided	£4,119.20	
Net increase in cost per repeat procedure avoided	£1,080.80	
Disutility avoided from 1 repeat procedure avoided	0.04443	
Incremental cost per QALY from use of DES		**£24,325**

Of the 23 input parameters, just five can be considered to influence the final result significantly:

- the unit price per BMS;
- the unit price per DES;
- the number of stents used per patient;
- the average waiting time of patients requiring a repeat procedure, and
- the absolute risk reduction produced by use of DES in place of BMS in the index procedure.

Addendum 6

Economic modelling: evaluation of drug-eluting stents for single vessel disease

1. Main analysis

The simplified LRiG model was populated with the efficacy estimates for patient sub-groups detailed in Addendum 4. We have diverged from previous modelling practice in presenting results separately by the number of stents employed, since this is probably the single most important parameter in the model. The previous approach used an average number of stents (between 1 and 2), which may have been appropriate in some trial situations where information on anatomical detail may not have been available at randomisation. However, in most clinical situations this is not the case, and the interventional cardiologist will have a very good idea of how many stents will be required by any patient. This is borne out by experience in the TAXUS II trial where only 3.5% of patients required more than one study stent.

Figure 1 and Table 1 show the results obtained. Results for patient groups assessed using direct trial or registry evidence are indicated in the chart by circles, and in the table by emboldened figures. Other results (triangles in the chart, and normal text in the table) assume the same efficacy gain, but using additional drug-eluting stents. The three sub-groups identified from trial evidence appear to be acceptable in terms of relative cost-effectiveness. By contrast, the two broader classifications identified from the Liverpool registry do not produce sufficient benefit to justify use of DES.

In general, it is clear that treating patients with more than a single drug-eluting stent is unlikely to prove cost-effective unless the likely risk reduction in the first 12 months were as high as 19% (2 stents) or 29% (3 stents). This is equivalent to risks of revascularisation at 12 months using BMS of 25% and 40% respectively. On the basis of evidence currently available it is difficult to envisage well-defined patient sub-groups currently treated which would fall within this extreme range.

Table 1: Results of cost-utility analysis for specific patient sub-groups

Patient type	Risk reduction	Incremental cost per QALY gained		
		1 stent	2 stents	3 stents
Single vessel, non-diabetic	6.0%	**£94,179**	£289,239	£484,300
Single vessel, small diameter	10.0%	**£16,155**	£133,191	£250,227
Single vessel, long lesion, non-diabetic	10.6%	**£9,531**	£119,942	£230,353
Single vessel, long lesion, diabetic	12.1%	**-£4,157**	£92,567	£189,291
Two vessels, non-diabetic	7.9%	-	**£195,413**	£343,560

Figure 1: Cost-utility ICERs for drug-eluting stents versus non drug-eluting stents in trial subgroups

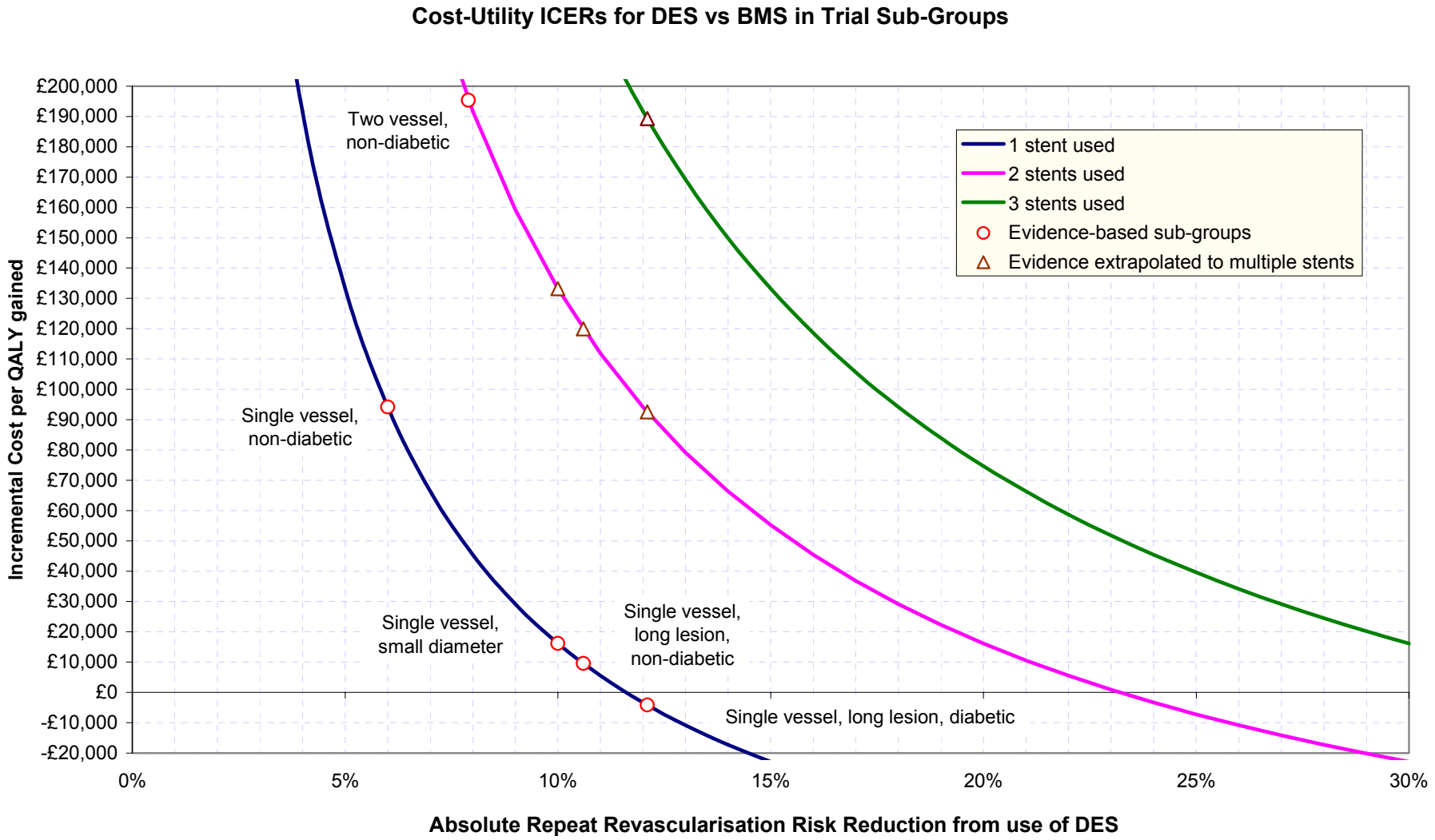


Table 2: One-way sensitivity analysis of simplified model results

Sensitivity Analyses

		Patient Group				
Model parameter	Limits	A	B	C	D	E
Excess cost per DES vs BMS	-£20	£86,299	£11,276	£10,162	-£11,945	£183,639
	+£20	£102,060	£21,035	£19,832	-£4,044	£207,187
Price of BMS	-£100	£96,070	£18,046	£16,887	-£6,104	£197,304
	+£100	£92,289	£14,265	£13,106	-£9,885	£193,523
OP reinvestigation visits	1.0	£94,605	£16,581	£15,422	-£7,569	£195,839
	1.5	£93,896	£15,872	£14,713	-£8,278	£195,130
Angiograms per patient	1.0	£95,118	£17,094	£15,935	-£7,056	£196,352
	1.3	£93,241	£15,217	£14,058	-£8,933	£194,475
Cost per cardiology OP visit	£55	£94,886	£16,862	£15,703	-£7,288	£196,120
	£70	£93,097	£15,073	£13,914	-£9,077	£194,331
Cost per angiogram	£250	£94,904	£16,880	£15,721	-£7,270	£196,138
	£300	£93,610	£15,586	£14,427	-£8,564	£194,844
Cost per PTCA	£1,940	£98,069	£20,045	£18,886	-£4,106	£199,302
	£2,372	£90,290	£12,266	£11,108	-£11,884	£191,524
No. of stents used in repeat PCI	1.0	£95,377	£17,353	£16,194	-£6,797	£196,611
	1.4	£92,982	£14,958	£13,799	-£9,192	£194,216
Case-mix of repeat revasc.(PTCA/BMS/DES/CABG)	0/75/0/25	£85,854	£8,570	£7,422	-£15,352	£186,129
	20/65/0/15	£102,665	£23,888	£22,718	-£496	£204,877
Cost per CABG	£7,531	£97,947	£19,923	£18,764	-£4,227	£199,181
	£9,205	£90,412	£12,388	£11,229	-£11,762	£191,645
Follow-up OP cardiology visits	3	£95,597	£17,573	£16,415	-£6,577	£196,831
	5	£92,762	£14,738	£13,579	-£9,413	£193,995
Follow-up OP cardiac surgery visits	0	£96,678	£18,654	£17,495	-£5,497	£197,911
	2	£91,681	£13,657	£12,498	-£10,493	£192,915
Cost per cardiac surgery OP visit	£100	£94,427	£16,403	£15,244	-£7,747	£195,661
	£122	£93,932	£15,908	£14,749	-£8,242	£195,166
Disutility of PTCA procedure	0.003	£95,035	£16,302	£15,133	-£8,067	£197,188
	0.004	£93,339	£16,011	£14,863	-£7,923	£193,670
Disutility of CABG procedure	0.010	£95,035	£16,302	£15,133	-£8,067	£197,188
	0.014	£93,339	£16,011	£14,863	-£7,923	£193,670
Annual disutility of angina	0.15	£105,097	£18,028	£16,735	-£8,922	£218,065
	0.19	£85,317	£14,635	£13,585	-£7,242	£177,024
Average waiting time for reintervention (weeks)	10	£110,431	£18,943	£17,584	-£9,374	£229,132
	14	£82,098	£14,083	£13,073	-£6,969	£170,345
Absolute risk reduction	-1%	£133,191	£29,159	£27,730	£13	£238,354
	+1%	£66,314	£5,516	£4,557	-£14,825	£162,122
Central estimate of ICER	-	£94,179	£16,155	£14,997	-£7,995	£195,413

A	Single vessel, non-diabetic
B	Single vessel, small diameter
C	Single vessel, long lesion, non-diabetic
D	Single vessel, long lesion, diabetic
E	Two vessel, non-diabetic

2. Sensitivity analysis

The model results have been subjected to full one-way sensitivity analysis, with results shown in Table 2. As expected the model responds most strongly to uncertainty in the extra cost of drug-eluting stents, the absolute risk reduction attributable to drug-eluting stents, and factors influencing the loss of utility for patients awaiting a revascularisation procedure. In addition the proportion of repeat procedures requiring CABG is also influential. For all other model inputs the model results are very insensitive to variation. Despite these findings it appears that uncertainty in any single variable is unlikely to materially alter the inferences made concerning cost-effectiveness for the five patient groups assessed.

The influence of price on cost-effectiveness can be judged by considering the price premium which corresponds to breakeven (i.e. zero net difference in costs at 12 months) for each patient group shown in Table 3.

Table 3: Additional price of DES vs. BMS required to achieve zero net change in cost of treatment at 12 months

	Patient sub-group	Breakeven DES price premium
A	Single vessel, non-diabetic	+£269
B	Single vessel, small diameter	+£448
C	Single vessel, long lesion, non-diabetic	+£453
D	Single vessel, long lesion, diabetic	+£565
E	Two vessel, non-diabetic	+£177

Our base case assumed a difference in cost between BMS and DES of £520, as in the original LRiG report. NICE asked for specific comparisons of ICER using DES list prices. Tables 4 and 5 illustrate this.

Table 4: CYPHER™ - differences in cost between BMS and DES £525

Single vessel, non-diabetic	6.0%	**£96,150**	£293,085	£490,021
Single vessel, small diameter	10.0%	**£17,375**	£135,537	£253,698
Single vessel, long lesion, non-diabetic	10.1%	**£16,205**	£133,197	£250,188
Single vessel, long lesion, diabetic	12.6%	**-£7,007**	£86,772	£180,551
Two vessel, non-diabetic	7.9%	-	**£198,357**	£347,928

Table 5: TAXUS™ - differences in cost between BMS and DES £500

Single vessel, non-diabetic	6.0%	**£86,299**	£273,857	£461,414
Single vessel, small diameter	10.0%	**£11,276**	£123,811	£236,345
Single vessel, long lesion, non-diabetic	10.1%	**£10,162**	£121,582	£233,003
Single vessel, long lesion, diabetic	12.6%	**-£11,945**	£77,368	£166,681
Two vessel, non-diabetic	7.9%	-	**£183,639**	£326,088

Addendum 7

Likely use & budget impact of drug-eluting stents

To estimate the cost of using DES in the manner suggested in section 6, we needed data on the frequency of single vessel stenting in patients with small vessels, with long lesions and in diabetic patients. We understand that such data is currently being collected by BCIS but is not yet available (de Belder, M. Communication to NICE: 28 March 2003). Therefore we have had to use the only other source from which we could extract some of this data rapidly, i.e. the BCIA submission to NICE in November 2002 (table 8, p10).

This submission quotes data from the EUROHEART STUDY. We understand that this is only a preliminary analysis and that much more complete data will be available later. It is not clear when the data was collected, and practice may have changed since. At present, the data is crude - in particular, figures which should sum to 100% generally do not! The number of patients in this dataset is small for the UK (only 87). We have therefore viewed the wider database for the NW WHO region, allowing consideration of 1259 patients but it should be borne in mind that the indications considered for coronary interventions may differ in different countries.

Despite these limitations, these data allow us to do some simple calculations as follows:

Calculations
PATIENT NUMBERS

- Of 100 PCI patients, 74 are stented & 26 get PTCA only (row 29)
- Of these 56.24 (74 * 76%) get 2+ stents, and 17.76 get 1 stent (row 31)
- If 52% of stented patients have multivessel disease (row 26), then we guess that there
- are 38.48 multivessel disease stented patients (52% x 74) all having 2+ stents
- This means that 17.76 single vessel disease patients (56.24 - 38.48) get 2+ stents, and
- 17.76 SVD patients get 1 stent, i.e. a 50:50 split.

Only 83% of SVD patients (100% - row 19) would eligible for stenting according to the suggestions in section 6, i.e. 14.74 (83% * 17.76)

Hence - about 15% of all PCI patients would get a single DES

STENT NUMBERS

- Of 100 PCI patients, 74 are stented & 26 get PTCA only (row 29)
- Mean number of stents per patient stented is 1.28 (row 30), giving a total of 94.72 stents used
- We estimate that 14.74 patients are eligible for a single DES
- This is equivalent to 15.56% of all stents used (14.74 / 94.72)

An alternative calculation using the same table:

1) Approximately 50% of single vessel disease involves small vessels (<3.0mm)
2) Approximately 50% of single vessel disease involves long lesions (>16mm)
3) Approximately 18% of single vessel disease does not involve either small vessels or long lesions, i.e. 82% of patients may be eligible for DES. This is equivalent to about 39% of all PCIs currently done (including PTCAs & multi-vessel disease).

4) About 76% of all stented patients receive more than one stent (row 29), and 52% of patients have multivessel disease (row 26). Assuming that all multi-vessel stented patients get 2 or more stents, this implies that about half of single vessel stented patients get more than one stent (i.e. approx 25% of all PCI patients).

5) 17% of patients do not have long or small diameter lesions (row 19), so 83% do. We can therefore estimate that about 20% (25% x 83%) of all PCI patients have single vessel disease in one of the appropriate categories and could currently receive only one stent.

6) The EUROHEART figures also show that only 74% of PCI patients receive any stent (i.e. 26% get PTCA only), implying that the likely take-up of DES would be around 15% (20% x 75%) of patients.

7) Converting this into numbers of stents used (rather than patients): 76% receive more than 1 stent, 25% receive 1. Total stent use in 100 patients is therefore 175 stents or so 15-25 of these would be displaced by DES, i.e. 8.5%-14.5%.

Both calculations come to approximately 15% of all stents but these are extremely crude figures, of uncertain relevance to NHS practice. Specific UK data should be sought from BCIS when available to allow a more accurate prediction.

The cost implications of this can be considered using the data presented previously in the main report. Use outside these categories will, of course, be more expensive and far less cost effective.

Table 1 Budget impact estimates: cost of DES

Scenario	Total additional cost (£ 000,000) Current Service Levels	Total additional cost (£ 000,000) NSF Service Levels
15% of total stenting (favoured scenario)	3.51	4.26
50%	11.72	14.92
75%	17.58	22.38
100%	23.44	29.84

There will be cost offsets if DES are used in manner suggested: these will be particularly large for instance for diabetic patients with long lesions, such that the use of DES in these patients may be cost saving.

Addendum 8

Other work

Other work planned but incomplete for this report and a lower priority for the Appraisals Committee than that already described in this report included a reconsideration of differences in mortality in patients receiving stents or CABG based on long-term (3 year) data from the ARTS trial, with extensive sensitivity analysis.

Addendum 9

Addendum discussion & summary

1. Discussion

This work updates the available clinical evidence previously presented by including the large SIRIUS, E-SIRIUS and TAXUS II studies. These results provide considerably more data than was previously available – for instance the total number of patients has risen from 297 available in the previous report where the only trials were TAXUS I and RAVEL to 2230 by pooling the results of newer trials. These results largely confirm the previous results and give greater confidence in them.

The extent of the reduction is approximately 2/3 in the randomised clinical controlled trials, but there is some evidence that this is exaggerated by the trial protocols including angiography. A more realistic expectation might be reduction of the order of approximately half of this.

More importantly perhaps, access to individual patient data for one of the trials, TAXUS II, has allowed us to explore sub-groups. TAXUS II however represents a relatively small proportion of the total number of patients involved (less than 20%) and if individual patient data in a similar fashion were available for SIRIUS and for RAVEL, then a further subgroup analysis could be undertaken. This subgroup analysis raises some important issues. Firstly, it was always thought that DES would be more cost-effective in certain patient subgroups that were at higher risk of restenosis. Early data suggested that the relative reduction in risk of restenosis would be similar across all groups, implying greater benefit in those groups at highest risk of restenosis, e.g. diabetics. The subgroup analysis however suggests that the absolute benefit is relatively constant across all subgroups and it is this figure that is most influential in determining the economic efficiency in each case.

A criticism of this work might be that we have extrapolated from subgroups in one study to the whole group: however, this is all that is possible with the data available at the present time. We can only assume at present that subgroup results from SIRIUS would be broadly similar to those in TAXUS II.

The next major expansion in data in this regard will be when TAXUS IV reports its first results in September this year: this will increase the numbers of patients exposed to DES in randomised controlled trials by a further 1300.

A key change in the economic evaluation was to move away from the population average number of stents (e.g. 1.4 or 1.7) to consider the effects of putting one or two discreet stents in an individual patient – which is, of course, clinical reality. This has a substantial effect on the cost effectiveness of the interventions and the differences between using one and two stents are graphically illustrated in Section 6. This allows definition of patients in whom DES may be considered cost effective at a conventional threshold, or even cost saving. These patients are now defined as diabetics with a long lesion in a single vessel, non-diabetics with a long lesion at single vessel or patients with a single vessel with a small vessel diameter, i.e. less than 3mm. This will account for approximately 30% of stenting procedures and about 19% of all stents used in the UK leading to an increased expenditure of between £4 to £6 million pounds depending on the level of service provision. This cost will be offset against reduced reinterventions.

The subgroups identified as benefiting are perhaps not those that would have been predicted, for instance, from the Cutlip or Sheffield analysis considered in the earlier report. Clearly substantially more work on this area needs to be done using wider patient databases. The data for the CYPHER studies (SIRIUS, RAVEL, & E-SIRIUS) are potentially available now.

The issue around the effects of the protocol driven angiograms and to what extent this influences the results of these studies will only be resolved by a large pragmatic study comparing DES to BMS which does not involve such an angiogram – similar to the design of the SOS study in BMS versus CABG.

In conclusion, DES reduce the need for reintervention after PTCA to a greater extent than bare metal stents. The use of a single DES may be cost saving with an improvement in quality of life in some patients, but DES will achieve an acceptable incremental cost per QALY in some other patients. The use of more than one DES gives rise to much higher ICERs per QALY gained.

2. Addendum summary

1. This report updates the previous LRiG report on the effectiveness and cost-effectiveness of coronary artery stenting in coronary heart disease. It focuses particularly on the effectiveness and cost-effectiveness of drug eluting stents versus bare metal stents.
2. New results from three studies - SIRIUS, E-SIRIUS, and TAXUS II have now become available. In addition to summarised results, original patient level data was made available for TAXUS II.
3. This expands the total volume of patient information available from the 297 considered in the previous report to 2230.
4. The key clinical conclusions are:
   a. Drug-eluting stents reduce the risk of further coronary 'events' by approximately 66% compared to than that of BMS in the randomised controlled trials over 12 months.
   b. There is no difference in the incidence of myocardial infarction or death up to 12 months.
   c. Data from one trial, RAVEL (238 patents) are now available for up to 2 years and demonstrate maintenance of the advantage of DES over BMS.
5. The nature of the trial protocols in these studies may exaggerate the apparent benefits of DES over BMS due to the presence of a protocol driven angiogram. This has previously been clearly observed in other studies of BMS.
6. Differences between industry models and the original model submitted by LRiG to the NICE Appraisal Committee are considered at length: the key differences are in the underlying assumptions with regard to baseline risk and extent of reduction in revascularisation procedures. There are other lesser differences arising from differences in costing and in the evaluation of a reduction of quality of life mainly due to differences in waiting time.
7. A previous criticism of the LRiG model was the use of similar waiting times for revascularisation procedures, either PCI with stenting or CABG. The justification for this position is presented and our view on this remains unchanged.
8. Access to TAXUS II original patient data has allowed evaluation of subgroups. This trial was not powered to produce definitive results in subgroups and therefore the results must be considered tentative. To achieve reasonable patient numbers we have merged the results of the two elements of this study. Furthermore, given differences in the nature of the patient populations considered in each study, it may not be appropriate to extrapolate from the study of the TAXUS stents to other DES. Despite these limitations, these data allow identification of key risk factors which determine the risk of revascularisation. These data are subsequently used in the economic evaluation.
9. There are two key conclusions from this analysis
   a. The key risk factors identified are: diabetes, long lesion, small vessel.
   b. Unexpectedly, absolute risk reduction is remarkably similar across all subgroups.
10. A simplified model of the cost effectiveness of DES versus BMS was developed and is presented.

11. A conceptual change in the economic model was the move from considering the average number of stents inserted per patient to considering the use of one or more stents, as would happen in the case of the individual patient.

12. Economic modelling was conducted using data from the subgroup analysis and the simplified model. The results are presented graphically. Key conclusions are when one stent is used in a single vessel with long lesion in a diabetic patient the absolute risk reduction is 12.6%, and the use of DES is cost saving compared to a BMS. For non-diabetic patients with a long lesion the risk reduction for revascularisation is 10.1% and the incremental cost per QALY gained is £15,000. For a patient with a small vessel, the risk reduction is 10% and the incremental cost per QALY gained is £16,000. However for use in a small single vessel non-diabetic patient, not fitting into either the category of long lesion or small vessel, the cost per QALY gained is £94,000. These ICERs deteriorate rapidly if two stents are used – for example in the case of a diabetic with a long lesion in a single vessel, the incremental cost per QALY is £85,000.

13. Sensitivity analysis shows that the key parameter is the extra cost of DES over and above BMS, the number of stents used per patient, and also the waiting time of patients for a repeat procedure and the absolute risk reduction attributable to drug eluting stents.

14. If DES were limited to one per patient in the subgroups identified, this would lead to a 19% switch from BMS to DES, which would increase NHS costs for stents by £4-6 million. There would be some cost offsets against this due to decreased revascularisations.

15. A proposal to re-examine mortality differences after CABG and stenting was not possible within the time available.

16. Further research is required. This could include subgroup analysis using individual patient data from existing trials such as SIRIUS and RAVEL and in the future from TAXUS IV. However, there is a need for a large pragmatic randomised controlled trial of DES versus BMS that would not involve a protocol driven angiogram.