Evidence Review Group's Report

Title: Bivalirudin for the treatment of ST-segment elevation myocardial infarction

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Declared competing interests of the authors

Dr Bakhai has a personal pecuniary interest with Eli Lilly, as declared to NICE

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Abbreviations

ACS	Acute coronary syndrome
AE	Adverse event
AMI	Acute myocardial infarction
BCIS	British Cardiovascular Intervention Society
BNF	British National Formulary
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
CCU	Coronary care unit
EMA	European Medicines Agency
ERG	Evidence review group
ESC	European Society of Cardiology
GPI	Glycoprotein IIb/IIIa inhibitors
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
HORIZONS-AMI Trial	Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction Trial
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ITT	Intention to treat
MACE	Major adverse ischaemic cardiac events
MI	Myocardial infarction
MS	Manufacturer's submission
NIAP	National Infarct Angioplasty Project
NICE	National Institute for Health and Clinical Excellence
NSTEMI	Non-ST-segment elevation myocardial infarction
OS	Overall survival
PCI	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RAA	Radial artery access
RCT	Randomised controlled trial
SPC	Summary of Product Characteristics

STEMI	ST-segment elevation myocardial infarction
UA	Unstable angina

1 SUMMARY

1.1 Scope of the manufacturer submission

The manufacturer's submission (MS)[1] reflects the scope of the appraisal issued by NICE,[2] in terms of population, intervention and outcomes. However, the comparator differs. In the final scope issued by NICE the comparator was stated as "Anticoagulants, with or without glycoprotein IIb/IIIa inhibitors, in combination with aspirin and clopidogrel". The manufacturer considers heparin with glycoprotein IIb/IIIa inhibitors as the comparator (in combination with aspirin and clopidogrel). The use of heparin alone is not considered as a comparator within the manufacturer's submission (MS), however our clinical advisors agree that the use of heparin alone for percutaneous coronary intervention (PCI) is not common practice.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

Results were provided from one RCT. Treatment with bivalirudin was associated with a significant reduction in cardiac mortality and major bleeding compared with the comparator at 30-days and one-year follow-up. Stent thrombosis up to 24 hours following PCI was more common with bivalirudin than heparin with glycoprotein IIb/IIIa inhibitors (GPI), however there was no significant treatment effect for stent thrombosis from one to 30 days, or at one-year follow-up. There were no significant treatment group differences in non-haemorrhagic stroke, myocardial infarction, or need for revascularisation at 30 days or one year follow-up. In addition, the manufacturer's submission reports the findings of one retrospective database study; this study found no significant difference between treatment with bivalirudin alone and non-bivalirudin treatment for an outcome of death, stroke or bleeding.

1.3 ERG's comment on clinical effectiveness evidence submitted

Only one randomised controlled trial (RCT) was available – the HORIZONS-AMI. The MS does not seem to have missed any studies meeting the inclusion criteria. The RCT, while having a low proportion of UK participants, was relevant to UK practice in terms of the population recruited. The RCT administered bivalirudin at the licensed dose for PCI, of intravenous bolus of 0.75 mg/kg body weight followed immediately by an intravenous infusion at a rate of 1.75 mg/kg body weight/hour. The comparator was heparin with glycoprotein IIb/IIIa inhibitors, which is authorised for use in UK practice.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer submitted two decision-analytic models: one represented the base case scenario using 1-year follow-up data from the HORIZONS-AMI trial whilst the other presented a sensitivity analysis using 3-year follow-up data from this trial. Both models are

used to evaluate the incremental costs and outcomes of bivalirudin treatment compared against a heparin plus GPI strategy for patients with ST-segment elevation myocardial infarction (STEMI) intended for primary percutaneous coronary intervention (PPCI). The model adopts a decision tree structure to reflect initial events for this initial period (stroke, re-MI, minor/major bleeding events, repeat revascularisation, and death) and a two-state Markov component to simulate longer-term survival. Health-related quality of life was not an endpoint within the HORIZONS-AMI trial. HRQoL estimates were instead drawn from a single UK study which followed a cohort of patients for 1-year after they were diagnosed with an acute MI. Resource use was primarily drawn from the HORIZONS-AMI trial and augmented using other external data sources.

The economic analysis suggests that bivalirudin is expected to dominate the heparin plus GPI strategy. This finding is consistent across the probabilistic analysis and the vast majority of deterministic sensitivity analyses undertaken. Three exceptions to this finding were observed for the following sensitivity analyses:

- the exclusive use of eptifibatide as the GPI (ICER = £1,764),
- the combination of 100% eptifibatide use, 100% RAA, and no differential length between strategies for initial hospital stay (ICER = £4,106)
- a longer length of ward stay (increase of 0.33 days) for the initial hospitalisation (ICER = £415)

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic analysis presented by the manufacturer appears generally robust and represents an appropriate means by which to address the decision problem specified in NICE's scope.[2] The structure of the model does not appear to omit any relevant clinical outcomes in the short-term, however the long-term model is "blunt" due to an absence of evidence concerning the long-term prognosis, costs and outcomes for this population. The implemented model was more complex than was necessary, however this issue does not influence the model results. The ERG noted that a number of parameter values used in the model do not exactly match the values presented in MS.[1] The effect of these discrepancies on the results of the economic analysis is however minor. Some model parameter values within the model were not described in the submission report. The choice of several distributional forms within the probabilistic sensitivity analysis was dubious. Finally, a number of uncertain parameters within the model were held fixed within the probabilistic sensitivity analysis. As such the level of uncertainty within the model is under-represented; however this additional uncertainty is unlikely to influence the ICER.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

It is unlikely that there any additional trials meeting the inclusion criteria in the MS.[1]

The identified RCT, which represents the main clinical effectiveness evidence, was thoroughly described in the MS, and was of good methodological quality. It administered bivalirudin in line with UK marketing authorisation, and measured appropriate and clinically relevant outcomes.

1.6.2 Weaknesses and areas of uncertainty

The identified randomised controlled trial (RCT), which represents the main clinical effectiveness evidence, had some differences from standard UK practice, in terms of pre-procedural heparin administration, which was common in the RCT but rare in UK practice, and access site, which was predominantly femoral in the RCT but with radial access becoming increasingly common in UK practice.

1.7 Summary of additional work undertaken by the ERG

Summary of additional work undertaken by the ERG

The ERG undertook a number of additional analyses to ensure that the manufacturer's model was robust. In particular this additional work included:

- Checking consistency of all model parameter values between the model and the submission report
- Double-programming of the manufacturer's model within Excel to understand and verify the TreeAge model
- Further sensitivity analysis to examine the impact of the long-term Markov model on the model results

The checking activities undertaken by the ERG did not identify any significant errors that have a marked impact upon the conclusions of the manufacturer's economic analysis. Despite the excessively complicated implementation of the model, the ERG believe that the economic analysis produced is robust. The additional sensitivity analysis undertaken by the ERG highlights that the extrapolation of 1-year trial-based results to a lifetime horizon increases the incremental QALY gain for bivalirudin considerably. However, bivalirudin is expected to remain dominant even when the time horizon is truncated to reflect the HORIZONS-AMI follow-up duration currently reported in peer-reviewed publications..

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The description of the underlying health problem in Section 2 of the MS[1] is adequate and relevant.

The MS section 2.2[1] reports the Myocardial Ischaemia National Audit Project (MINAP) report[3] which found 14,149 patients with STEMI referred for PPCI, in England and Wales between 2009/2010. The MS[1] also point out that the NHS strategy to increase the availability of PPCI will lead to an increase in its use. The British Cardiovascular Intervention Society (BCIS) submission[4] reports the estimate from the Department of Health that approximately 20,000 patients each year will undergo PPCI in England and Wales.

2.2 Critique of manufacturer's overview of current service provision

Section 1.3 of the MS[1] states that bivalirudin was approved, by the European Medicines Agency (EMA), for use in patients with ST-segment elevation myocardial infarction (STEMI) undergoing PPCI.[5] Section 1.5 gives the indications for the UK. Sections 1.3 and 1.5 of the MS also state that bivalirudin is licensed for other indications, non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). Doses and indications concord with information on bivalirudin from the British National Formulary (BNF) and EMA.[6]

The MS section 2.4[1] gives the patient pathway for STEMI. Section 2.5 of the MS[1] describes current variation in UK practice from geographical availability of PPCI, and variation in choice of glycoprotein IIb/IIIa inhibitors (GPIs). The BCIS submission[4] agrees that abciximab is the most commonly used GPI.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

Table 1 shows the decision problem outlined the scope,[2] and that addressed in the MS.[1]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the manufacturer's submission
Population	Adults with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention	As scope
Intervention	Bivalirudin in combination with aspirin and clopidogrel	As scope
Comparator(s)	Anticoagulants, with or without glycoprotein IIb/IIIa inhibitors, in combination with aspirin and clopidogrel	Heparin with glycoprotein IIb/IIIa inhibitors, in combination with aspirin and clopidogrel
Outcomes	Mortality Non-haemorrhagic stroke Myocardial infarction Early and late stent thrombosis Need for revascularisation Complications related to bleeding Health related quality of life	As scope
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The cost effectiveness analysis was conducted and reported in accordance with the agreed scope. Costs were considered from an NHS perspective, as per the agreed scope. The implemented life-long time horizon, and detailed modelling of adverse events and associated costs of during 1 year (3 years as sensitivity analysis) were considered adequate for the technologies and outcomes being considered.

3.1 Population

The manufacturer's statement of the decision problem appropriately defines the population as adults with STEMI intended for PPCI.

3.2 Intervention

Section 1.3 of the MS[1] states that bivalirudin was approved, by the EMA, for use in patients with ST-segment elevation myocardial infarction (STEMI) undergoing PPCI.[5] Section 1.1 of

the MS gives the dose of bivalirudin for PCI as an intravenous bolus of 0.75 mg/kg body weight followed immediately by an intravenous infusion at a rate of 1.75 mg/kg body weight/hour for at least the duration of the procedure. The infusion may be continued for up to 4 hours post-PCI as clinically warranted. After cessation of the 1.75 mg/kg /h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4 – 12 hours as clinically necessary. This concords with the licensed dose as stated by the BNF and EMA.[6,5] The intervention is delivered in combination with aspirin and clopidogrel.

3.3 Comparators

In the final scope issued by NICE the comparator was stated as "Anticoagulants, with or without glycoprotein IIb/IIIa inhibitors, in combination with aspirin and clopidogrel". The manufacturer considers heparin (an anticoagulant) with glycoprotein IIb/IIIa inhibitors as the comparator (delivered in combination with aspirin and clopidogrel), and does not consider heparin alone, or alternative anticoagulants.

Our clinical advisors agree that it is not standard UK practice to use heparin alone for PCI. The BCIS submission[4] reports from their audit data that in 2009 72% of STEMI patients received a GPI, and that a minority of units use bivalirudin instead of GPIs.

3.4 Outcomes

The manufacturer's statement of the decision problem appropriately defines the outcomes relevant to this appraisal. The clinical and economic analysis is based primarily on evidence reported within the HORIZON-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction Trial) trial. The main clinical endpoints reflected in the submission are consistent with those reported within this trial.

3.5 Other relevant factors

The manufacturer's decision problem, in general, adheres to NICE's Reference Case. However, the direct evidence of clinical benefit for this appraisal is based upon 1-year follow-up data from a single RCT. 3-year follow-up data were also examined within the manufacturer's model. In order to meet the Reference Case, the manufacturer has extrapolated short-term results out to a 40-year time horizon. Whilst little is known about the costs and outcomes of bivalirudin over this longer time frame, this extrapolation does have a substantial impact upon the incremental QALY gain between the treatment groups. The ERG undertook an additional analysis which examines the impact of this element of the decision problem (see Section 6.3).

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

The objective of the review was to address the decision problem, to appraise the effectiveness of bivalirudin within its licensed indication for PCI in patients with STEMI.

4.1.1 Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The searches undertaken by the manufacturer to identify all RCTs were conducted in January 2011. The search strategy utilises terms to identify the condition (coronary artery balloon angioplasty after myocardial infarction), the intervention (bivalirudin) and the type of evidence (RCTs, economic analyses). The searches were restricted to English language studies only. There were issues with consistency (detailed below) and some data may have been missed by not searching Web of Science or BIOSIS. Whilst the International Standard Randomised Controlled Trial Number Register (ISRCTNR) and clinical trials.gov were searched, they were not reported.

From the varying search strategies a general search strategy was devised and where possible the same filters were used. To create consistency between searches all the synonyms for bivalirudin were used, the population was not limited to STEMI, and the same comparators applied to each database (Table 2).

The main problem with the searches was a lack of consistency of search strategies between databases, with search terms varying in all sections: population, intervention and comparators. A major cause for concern was the search conducted in Embase where Hirulog (a synonym for bivalirudin) was combined with the other intervention terms with AND limiting the results to those papers which explicitly mentioned both names for the drug. The manufacturer's searches were replicated as closely as possible from the information provided, however it was not always clear which filters had been used, resulting some in discrepancies in results, shown in brackets (Table 3).

Table 2: Search Strategy

Angiox or Angiomax or Bivalirudin or Hirulog	Intervention
(Angioplasty, balloon, coronary/ or Percutaneous coronary intervention) and Myocardial infarction	Population
AND either	
Anticoagulant or platelet glycoprotein or heparin	Comparator
OR	
Economics filter	Health economics

The results were as follows, after the new results were compiled and de-duplicated, 213 additional individual results were found, extra to the 92 from the de-duplicated MS search with reviews removed (Table 3):

Table 3: Search results

	MS search	General search
PubMed	30	104
PubMed (Economics filter)	16 (re- run of the manufacturer's search found 18)	22
Cochrane CCT	13	53
Cochrane reviews	2	3
Cochrane DARE	0	4
Cochrane NHS EED	Not reported	5
Cochrane HTA	Not reported	1
NHS Evidence	9	9
Embase	50 (47)	158
Embase (Economics filter)	16	34
EconLit	0	0

4.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Inclusion criteria for the intervention and outcomes, from Section 5.2.1 of the MS,[1] were appropriate and reflected the scope. The population was restricted to studies with at least 50% of STEMI patients. A broadened search by the ERG did not identify any additional RCTs with data for STEMI patients.

The comparator in the MS[1] was "anticoagulants, with glycoprotein IIb/IIIa inhibitors, in combination with aspirin and clopidogrel." Heparin alone was not considered within the searches. Our clinical advisors agree that it is not standard UK practice to use heparin alone for PCI.

4.1.3 What studies were included in the clinical effectiveness review and what were excluded?

Studies included in the clinical review are shown in Table 4. One RCT, the HORIZONS-AMI trial with data published in 7 articles,[7,8,9,10,11,12,13] and one observational study, with one publication,[14] were included.

Table 4: Included studies of bivalirudin

Study	Design	Participants	Intervention(s)	Primary outcomes
HORIZONS-AMI.[7;8]	RCT	Patients with protocol defined STEMI, new left bundle-branch block, or true posterior myocardial infarction intended for PPCI (n=3602)	1: Bivalirudin with provisional use of a GPI, with aspirin and clopidogrel (n=1800) 2:Heparin and GPI, with aspirin and clopidogrel (n=1802)	Net Clinical Benefit (combination of adverse clinical events: including major bleeding or a composite of MACE* Non-CABG major bleeding
Dauerman *et al.*[14]	Observational Study-Retrospective database analysis	Patients with STEMI, treated with PPCI (n=7629)	1: Bivalirudin +/- GPI (n=177); 2: bivalirudin alone (n=143) 3: No bivalirudin (n=7309)	Antithrombotic strategies Major hospital outcomes (death, major bleeding, stroke, re-infarction)

*MACE (Major adverse ischaemic cardiac events) includes: death, re-infarction, target vessel revascularisation for ischaemia, and stroke

Figure 9 of the MS (Section 5.2.3)[1] indicates that 71 articles were excluded at screening stage, but no records retrieved for eligibility assessment were excluded, thus, reasons for exclusion of articles were not given.

The trial design of the included RCT the HORIZONS-AMI trial was presented in section 5.3 of the MS.[1] This was a multi-centre international trial which contained two randomisations. The first randomisation, of relevance to the decision problem considered here, was to treatment with either bivalirudin or unfractionated heparin plus GPI. The second randomisation was to either paclitaxel-eluting stents or bare-metal stents.[8] This second randomisation was not of direct relevance to the decision problem and is not considered further in this report. Results of the RCT are presented in MS section 5.5,[1] with results from peer-reviewed journal articles containing 30 day follow-up data (Stone *et al.*[8]) and one year follow-up data (Mehran *et al.*[7])

The included observational study, Dauerman *et al.*,[14] was a retrospective database study that examined the pattern of use of antithrombotic agents, including bivalirudin. It also examined the association between antithrombotic agent used and hospital outcomes, adjusting for differences in baseline characteristics.

4.1.4 Provide details of any relevant studies not discussed in the submission? Why were these studies excluded and how were these studies identified by the ERG?

The ERG is confident that there are no additional studies available meeting the inclusion criteria in the MS,[1] and no additional RCTs meeting the inclusion criteria in the final scope from NICE.[2]

One study comparing bivalirudin with heparin alone (in combination with aspirin and either clopidogrel or ticlopidine) in STEMI patients was identified, Bonello *et al*.[15] This study was in the reference list of the MS, but not discussed in the MS.[1] This was a retrospective, observational study from a single centre in the USA, looking at STEMI patients that had undergone PCI. Of 566 patients given bivalirudin, and 333 patients treated with unfractionated heparin, there were no significant treatment differences for in-hospital outcomes, death, stroke, stent thrombosis, MACE (including death, stroke, urgent repeated revascularisation), or major bleeding.[15] However, these were based on low numbers of events and with a follow-up confined to in-hospital treatment (mean fewer than 5 days).[15] The Chu *et al.* study of heparin versus bivalirudin did not present separate data for STEMI patients, and so was not relevant to this review.[16]

4.2 Summary and critique of submitted clinical effectiveness evidence

4.2.1 Summary of results

This section presents the main clinical effectiveness evidence, from the RCT and observational study reported in the MS,[1] considering the outcomes included in the final scope. Data presented from the included RCT in Tables 5 and 6 are intention to treat data (bivalirudin n=1800, heparin plus GPI n=1802). All patients received clopidogrel and aspirin.

Table 5: Summary of outcomes at 30 days as reported by Stone *et al.* 2008[8]

Outcome at 30 days	Bivalirudin	Heparin plus GPI
Mortality (overall)*	2.1%	3.1%
Stroke	0.7%	0.6%
Myocardial infarction	1.8%	1.8%
Stent thrombosis, acute (within1 day)*	1.3%	0.3%
Stent thrombosis, early (>1 day - 30 days)	1.2%	1.7%
Revascularisation of target vessel for ischaemia	2.6%	1.9%
Major bleeding (trial protocol defined excluding CABG-related)*	4.9%	8.3%

*significant difference between treatment groups

Table 6: Summary of outcomes at 1 year as reported by Mehran *et al.* 2009[7]

1 year	Bivalirudin	Heparin plus GPI
Mortality (overall)*	3.5%	4.8%
Stroke**	1.1%	1.2%
Myocardial infarction	3.6%	4.4%
Stent thrombosis, late (31 days to 1 year, excludes early stent thrombosis)	1.0%	1.1%
Revascularisation of target vessel for ischaemia	7.2%	5.9%
Major bleeding (trial protocol defined excluding CABG-related)*	5.8%	9.2%

*significant difference between treatment groups

**the MS reports only one case of stroke was haemorrhagic (in the bivalirudin arm), this did not alter percentages; thus these figures apply to non-haemorrhagic stroke as well as all stroke

Mortality

The included RCT reported all-cause mortality at 30 days and 1 year. Section 5.5 of the MS[1] reports all-cause mortality at 30 days as 2.1% for bivalirudin, and 3.1% for the comparator (heparin plus GPI). This was a borderline significant advantage for bivalirudin over the comparator (p=0.0465). This was based on a small number of events. Most mortality was cardiac-related in both treatment groups (32/37 for bivalirudin; 52/56 for comparator), with the difference between treatment groups being significant for cardiac mortality (p=0.0276) but not for non-cardiac mortality (p=0.7535).

At 1 year follow-up, all-cause mortality was 3.5% for bivalirudin and 4.8% for the comparator, significantly favouring bivalirudin (p=0.037). Most mortality was cardiac-related in both groups (38/61 for bivalirudin; 67/86 for comparator), with the difference between treatment groups being significant for cardiac mortality (p=0.0042) but not for non-cardiac mortality (p=0.5323). Considering only events that occurred between day 31 and one year follow-up in the ITT population,[7] there were no significant treatment group differences for all-cause mortality (p=0.38) or non-cardiac mortality (p=0.63), but a borderline significance for cardiac mortality (p=0.046) favouring bivalirudin (0.4%) over the comparator (0.9%). Various subgroup analyses of mortality were presented (MS Figure 12)[1] but no significant interactions with treatment group were found. For two of the subgroups, it appeared that bivalirudin fared worse than the comparator, however the subgroup radial arterial access had only 214 participants, and the subgroup no thienopyridine use (that is, neither clopidogrel or ticlopidine) only 112 participants, and as with other subgroups presented, no significant interactions with treatment group were found.

Three-year all-cause mortality for the ITT population (taken from Stone 2010, a conference presentation provided by the manufacturer) was significantly lower (p=0.03) for bivalirudin (5.9%) than comparator (7.7%).

Non-haemorrhagic stroke

The included RCT reported stroke rates at 30 days and 1 year. Section 5.5 of the MS[1] reports all strokes for bivalirudin within 30 days as n=14, of which n=1 was a haemorrhagic stroke, thus the rate of non-haemorrhagic stroke was 0.72% for bivalirudin at 30 days. For the comparator the rate of non-haemorrhagic stroke at 30 days was 0.67%. At follow-up of one year, rates were 1.1% for both bivalirudin and comparator groups (p=0.9972).

Myocardial infarction

Section 5.5 of the MS[1] reports re-infarction at 30 days as 1.9% for bivalirudin and 1.8% for the comparator (p=0.8003). When considering Q-wave and non-Q-wave infarction separately, these did not differ between groups (p=0.5585 and p=0.3711 respectively).

At one year follow-up rates of re-infarction were 3.6% for bivalirudin and 4.4% for the comparator (p=0.22). Q-wave infarction did not differ between groups (p=0.8105). Non-Q-wave infarction significantly favoured bivalirudin (p=0.0108), based on 24 patients (1.3%) in the bivalirudin group and 45 (2.5%) in the comparator group.

Three-year re-infarction for the ITT population (taken from Stone 2010, a conference presentation provided by the manufacturer) was significantly lower (p=0.04) for bivalirudin (6.2%) than comparator (8.2%).

Early and late stent thrombosis

From the ITT population, acute stent thrombosis (within one day) was significantly (p<0.001) more common in the bivalirudin (1.3%) than the comparator (0.3%) group.[8] Between 1 and 30 days, there was no significant difference (p=0.28) between bivalirudin (1.2%) and comparator (1.7%) groups.[8] Section 5.9.2 of the MS gives stent thrombosis for the safety population of the RCT (bivalirudin n=1749, heparin plus GPI n=1818). Within one day of PCI, there were more stent thromboses in the bivalirudin (24/1749) than the comparator group (4/1818). Between 1 and 30 days, rates between groups were more similar (bivalirudin n=20; comparator n=33). The MS[1] states that there was a lower risk of death from stent thrombosis 1 day after the procedure, than between 1 and 30 days.

From the ITT population, stent thrombosis from day 31 to one year follow-up did not differ significantly (p=0.66) between bivalirudin (1.0%) and comparator (1.1%) groups.[8] Late stent thrombosis, the safety population (bivalirudin n=1749, heparin plus GPI n=1818) section 5.9.2 of the MS, occurring after 30 days and within one year follow up was 3.3% for each treatment group (p=0.9789).

Three-year stent thrombosis for the safety population (bivalirudin n=1611; comparator n=1591) (taken from Stone 2010, a conference presentation provided by the manufacturer) did not differ significantly between treatment groups (bivalirudin 4.5%; comparator 5.1%).

Need for revascularisation

The rates of target vessel revascularisation (TVR), reported in Section 5.5 of the MS,[1] were 2.5% for bivalirudin and 1.9% for the comparator at 30 days (p=0.2561). At one year, these rates were 6.8% and 5.5% (p=0.1099) respectively.

Complications related to bleeding

Major bleeding (MS section 5.9.2)[1] defined by the RCT protocol, and excluding CABG bleeding (MS section 9.1.4 and Table 26) was significantly lower in the bivalirudin group than the comparator at 30 days (p<0.0001) for both the ITT population (bivalirudin 92/1800; comparator 159/1802) and the safety population (bivalirudin 88/1749; comparator 162/1818).

Radial arterial access is associated with a lower risk of access-site bleeding than femoral arterial access, as reported in the BCIS submission.[4] Data from the RCT, at 30 days follow-up, restricted to non-access site major bleeding is reported by the EMA.[5] Non-access site major bleeding was significantly lower in the bivalirudin group than the comparator for both the ITT population (bivalirudin 45/1800; comparator 79/1802; p=0.0019) and the safety population (bivalirudin 43/1749; comparator 80/1818; p=0.0015).[5]

Results at one year follow up also showed lower rates of major bleeding for the bivalirudin group, p<0.001 for both the ITT (bivalirudin 103/1800; comparator 165/1802) and safety (bivalirudin 99/1749; comparator 169/1818) populations. Various subgroup analyses of major bleeding were presented (MS Figure 21 Section 9.1.7) but no significant interactions with treatment group were found. Considering only events that occurred between day 31 and one year follow-up in the ITT population,[7] there was no significant treatment group difference (p=0.55) for non-CABG protocol defined major bleeding (bivalirudin 0.8%; comparator 0.6%).

By the GUSTO criteria,[17] the safety population of the RCT at 30 days showed similar rates of severe or life-threatening bleeding in the bivalirudin (n=5, 0.5%) and comparator (n=12, 0.7%) groups p=0.4177. This was based on a small number of events. There was a lower rate of GUSTO criteria[17] moderate bleeding (p=0.0010) in the bivalirudin (3.0%) than the comparator group (5.2%), and similarly for GUSTO criteria[17] mild bleeding (bivalirudin 3.2%; comparator 6.1%; p<0.0009).

The safety population of the RCT at 30 days reported significantly lower bleeding in the bivalirudin than comparator group for TIMI[18] defined major bleeding (bivalirudin 1.8%; comparator 3.2%; p=0.0096), and TIMI[18] defined minor bleeding (bivalirudin 2.9%; comparator 4.4%; p=0.0005).

Two-year major bleeding (protocol defined non-CABG) for the ITT population (taken from Stone 2009, a conference presentation provided by the manufacturer) was significantly lower (p<0.001) for bivalirudin (6.4%) than for comparator (9.6%).

Adverse events

The RCT reported MACE outcomes (MS Section 5.5[1]), which is a composite measure of death, re-infarction, TVR for ischemia, or stroke (which are considered separately above). There was no significant treatment group difference for this outcome at 30 days (ITT

population p=0.8901, per protocol population p=0.7143) or 1 year follow-up (ITT population p=0.9682).

Thrombocytopenia (including heparin induced thrombocytopenia) as reported in MS section 5.9.2[1] had a significantly lower rate in the bivalirudin than the comparator group. As reported by Stone *et al*[8] from a safety population, bivalirudin n=1665, comparator n=1653, most cases were moderate (19/24 bivalirudin; 48/69 comparator) with a treatment group difference p=0.003. There was a significantly ($p<0.02$) lower rate of severe and profound cases in the bivalirudin group (0.3% and 0% respectively) than the comparator group (0.9% and 0.4% respectively).

The RCT safety population (bivalirudin n=1749; comparator n=1818), as reported by the EMA[5] (differed in minor respects from Table 32 in the MS), [1] did not report any significant differences between groups for serious AEs (p=0.1358), serious AEs thought to be related to study drug (p=0.0673), serious AEs leading to study discontinuation (p=0.6137), or total AEs (p=0.0961). AEs thought to be related to study drug by the investigator were lower ($p<0.0001$) in the bivalirudin group (8.6%) than the comparator group (15.1%). These were assessed without blinding.

4.2.2 Describe and critique the manufacturer's approach to validity assessment for each relevant trial.

The criteria chosen for validity assessment of the included RCT, based on CRD guidance,[19] as detailed in Table 18 of the MS (Section 5.4),[1] were appropriate.

Question 1 from Table 18 "Was randomisation carried out appropriately?" referred to sequence generation. The MS conclude that this was appropriate, MS Section 5.3.2.[1] The randomisation sequence generation described for the trial was adequate, being computerised, using the minimisation method to stratify for pre-procedural heparin, pre-catheterisation drug, planned choice of GPI for the comparator, and location.[8]

Question 2 from Table 18 asked the question "Was the concealment of treatment allocation adequate?" The MS[1] states that concealment was adequate, however the manufacturer's response that the trial was single-blind suggests that they have interpreted the question as referring to blinding. Concealment of treatment allocation, when used in quality assessment of randomised trials, indicates that the treatment group that will be allocated cannot be known in advance of assignment.[19] Treatment allocation needs to be concealed to prevent selection

bias, as explained in CRD guidance, so that investigators cannot predict the treatment group to which the next patient will be allocated.[19] As Stone[8] states that a centralised telephone randomisation service was used, this means that concealment of treatment allocation was adequate for the HORIZONS-AMI trial.

For question 3 "Were the groups similar at the outset of the study in terms of prognostic factors?" the MS[1] concludes that treatment groups were similar at baseline. The groups were well balanced, with the exception of a significantly (p=0.04) lower rate of hypertension in the bivalirudin group (51.8%) than the comparator group (55.2%).[8]

For question 4, "Were the care providers, participants and outcome assessors blind to treatment allocation?", the MS[1] states that participants and outcomes assessors were masked. Trial clinician investigators were not blinded. As described by Stone,[8] non-blinding of clinicians was addressed by the use of a blinded clinical event adjudication committee that had access to medical records for event verification, and assessed the endpoints of MACE, major bleeding and stent thrombosis. Follow-up visits were conducted by personnel other than those that conducted the procedure, where possible.

Question 5 asks the question "Were there any unexpected imbalances in drop-outs between groups?. The MS[1] states that there were not.

For question 6 "Is there any evidence to suggest that the authors measured more outcomes than they reported?" the MS[1] concludes that there is not.

In response to Question 7 in Table 18 "Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?." the MS[1] reports that ITT analyses were available from HORIZONS-AMI. From the HORIZONS-AMI publications,[8,7] ITT analyses were available at 30 days and one year follow-up.

The validity assessment for the observational study, Dauerman *et al*[14] Table 69 of the MS, was based on the Downs and Black checklist,[20] which is appropriate. For a non-randomised study, this was of reasonable methodological quality. However, as a retrospective, observational study with a small sample size of bivalirudin treated patients, results are not as substantial as for an RCT.

4.2.3 Describe and critique the statistical approach used within each relevant trial.

The MS section 5.3.6[1] describes how, for the RCT, the comparison of bivalirudin versus heparin plus GPI was powered at 80% to test the non-inferiority hypothesis for the outcome of net clinical benefit (major bleeding or MACE, includes death, re-infarction, target vessel revascularisation, and stroke) at 30 days. The study was also powered at 99% to show non-inferiority for major bleeding at 30 days. For testing superiority, the RCT was powered at 80% to assess net clinical benefit and 90% for major bleeding. While adequately powered for major outcomes, the trial was underpowered for lower frequency events at 30 days, including death, as acknowledged by Stone *et al.*[8] There was an imbalance in hypertension at baseline (bivalirudin group 51.8%, comparator group 55.2%, p=0.04). Bleeding risk is higher in individuals with higher blood pressure, so it might be expected that this would contribute to the higher rate of major bleeding in the comparator group than in the bivalirudin. The MS Section 5.3.4 states that hypertension did not have a positive interaction with any of the primary endpoints and Figure 21 states a lack of interaction between hypertension and major bleeding. While it was not clear from journal articles that any attempt had been made to adjust outcomes to reflect this difference between treatment groups at 30 days follow-up,[8] at one year follow-up an analysis of mortality was conducted that adjusted for differences in baseline covariates[7] and found lower mortality for bivalirudin than comparator (p=0.04, similar to the unadjusted p=0.037). For the observational study, the MS[1] Table 25 states that there were too few patients for statistical comparisons to be valid. The Dauerman *et al* study used a logistic regression model to test for associations between treatment and outcomes, controlling for baseline differences in demographics, clinical history and clinical presentation including time to procedure, but acknowledges the smaller bivalirudin cohort than non-bivalirudin cohort limits the statistical strength of comparisons.[14]

4.2.4 Describe and critique the manufacturer's approach to outcome selection within each relevant trial.

The ERG judged this to be an appropriate approach, reflecting the outcomes in the final scope provided by NICE.[19]

4.2.5 To what extent does each relevant trial include the patient population(s), intervention(s), comparator(s) and outcomes as defined in the final scope?

The one available RCT, HORIZONS-AMI,[8,7] reflected the decision problem. The population was adults with STEMI indicated for PPCI. The intervention drug, bivalirudin, was administered within UK marketing authorisation. The comparator was heparin plus GPI. GPI used was either abciximab (52%) or eptifibatide (45.6%), with randomisation balanced for choice of GPI.[7] The trial did not include heparin alone as a comparator. Aspirin and clopidogrel were utilised in both intervention and comparator groups, consistent with

licensing and UK practice. In the RCT, radial arterial access was used in 5.9% of patients with the majority of procedures using femoral arterial access. As reported in the BCIS submission, 42.8% PCI in the UK in 2009 used radial arterial access, and this is increasing, as radial access is associated with reduced access site bleeding. In the RCT, 71% of participants received pre-procedural heparin.[8] It is not standard UK practice to administer pre-procedural heparin, as noted in the BCIS submission.[4] The RCT balanced pre-procedural heparin between treatment arms at randomisation. The outcomes reported reflect those in the final scope,[19] with the exception of HRQoL (which is considered in the cost effectiveness section of the MS).[1]

The retrospective database study, reported by Dauerman *et al*,[14] reflected the decision problem in terms of population, which was adult STEMI patients treated with PPCI. The study compares those treated with bivalirudin, to those not given bivalirudin most of whom had treatment including GPI. Most patients in the trial additionally had clopidogrel. Doses of drugs are not stated. Outcomes of relevance to the final scope were death, stroke, recurrent myocardial infarction and major haemorrhage.

4.2.6 Where appropriate, describe and critique any meta-analysis, indirect comparisons and/ or mixed treatment analysis carried out by the manufacturer.

No meta-analysis was presented as there was only one relevant RCT.

4.3 Conclusions

The manufacturer's search strategies had inconsistencies between databases, and a number of key databases were overlooked. However, additional records identified from a broader search by the ERG did not identify any additional RCTs which met the inclusion criteria. Processes and validation of study screening and data extraction were appropriate. Data provided in the MS[1] are relevant to the decision problem. There is a lack of comparison of bivalirudin with heparin alone, but heparin alone is not common UK practice. The MS[1] provided a thorough account of the only available RCT.

The RCT reported data on the licensed dose of bivalirudin in patients undergoing PCI for STEMI. Compared with heparin plus GPI, there was significant benefit for bivalirudin in cardiac mortality and major bleeding at one year follow-up. The RCT differed from standard UK practice in that pre-procedural heparin was used for the majority of participants, whereas this would not be used in standard UK practice. Within the RCT bivalirudin group, patients treated with pre-procedural heparin had a lower rate of MACE than those that did not receive

pre-procedural heparin.[5] This pattern was not seen in the comparator group, however there was no significant interaction between treatment arm and pre-procedural heparin (p=0.1060).[5] It is unclear how the RCT results would be reflected in practice given the lack of pre-procedural heparin in standard UK practice. The RCT differed from standard UK practice in using predominantly femoral arterial access, whereas radial arterial access is more common in the UK. Access site bleeding is less common with radial than femoral arterial access, and so the benefit in reduced bleeding from bivalirudin is likely to be lower in practice than in the RCT.

5 ECONOMIC EVALUATION

This chapter provides a critical assessment of the economic evaluation submitted by the manufacturer. Section 5.1 presents a brief critique of the manufacturer's review of existing economic evidence concerning the cost-effectiveness of bivalirudin treatment for a STEMI population intended for PPCI compared to a GPI-based strategy. Section 5.2 presents a summary and critique of the manufacturer's model and the economic analysis presented in the MS.

5.1 ERG view of manufacturer's review of cost-effectiveness evidence

The manufacturer's submission includes the methods and results of a search and review of economic evaluations of bivalirudin treatment for a STEMI population intended for PPCI compared to a GPI-based strategy. Section 5.1 of the MS includes a list of databases searched for this purpose. This list appears to be fairly complete: Pubmed; Medline; Medline- In progress (MEIP); Econ-lit, EMBASE, NHS Evidence and the Cochrane Library. The search strings used were the same as those used to identify evidence relating to the clinical effectiveness of bivalirudin. The reader should note the limitations of the clinical search (see Section 4.1.1) also apply to the manufacturer's economics review, however it is unlikely that any relevant economic studies have been missed.

5.1.1 State objective of cost effectiveness review.

The cost-effectiveness review was undertaken to identify existing studies which evaluated the cost-effectiveness of bivalirudin within a STEMI population intended for PPCI.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

- A list of eligibility criteria used within the manufacturer's economic search strategy is presented within Table 35 of the submission. This consists of the following inclusion criteria:
    - Population: (1) adults with STEMI intended for PPCI or (2) UK based PPCI setting of cost-effectiveness analysis

- Interventions: (1) bivalirudin in combination with aspirin and clopidogrel or (2) anticoagulants, with glycoprotein IIb/IIIa inhibitors, in combination with aspirin and clopidogrel
- Outcomes: mortality, non-haemorrhagic stroke, myocardial infarction, early and late stent thrombosis, need for revascularisation, complications related to bleeding, adverse effects of treatment, health-related quality of life
- Study design: (1) randomised controlled trials or (2) non-randomised trials or (3) observational trials
- Restrictions: English language , economic studies filter (if available)

This list appears to be appropriate for the specified decision problem.

5.1.3 What studies were included in the cost effectiveness review and what were excluded?

Figure 9 in the MS (Section 5.2.3) provides a schema of the search results based on PRISMA (www.consort-statement.org/?o=1065). Within this schema, only a subset of the studies considered are identified by authors' names; as a consequence, it is difficult to establish whether studies have been intentionally excluded from the review or missed by the searches. Only two economic studies included in the manufacturer's review were identified by this search (MS Table 36):

(1) Olchanski N, Slawsky KA, Plent S, Kado C, Cyr PL. Economic impact of switching to bivalirudin for a primary percutaneous coronary intervention in a US hospital. Hosp Pract (Minneap). 2010 Nov; 38(4):138-46.
(2) Schwenkglenks M, Brazier JE, Szucs TD, Fox KAA. Cost-effectiveness of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor in the treatment of non-ST-segment elevation acute coronary syndromes. Value Health 2011;14:24-33.

The MS refers to the study reported by Olchanski *et al*[21] as a US budget-impact model based on the HORIZONS-AMI trial. Strictly speaking, this study would be more accurately referred to as a cost consequence analysis as both clinical and cost outcomes are presented in the original publication. The MS suggests that whilst this study represents a non-UK based cost analysis, it may be reasonable to assume that comparisons of costs and cost-savings between treatment strategies are transferable between the US and the UK. However, no evidence is provided to support this assertion and such interpolation should be treated with caution.

The second economic study, reported by Schwenkglenks *et al*,[22] presents a cost-effectiveness analysis based on data from the ACUITY study[23] and GRACE UK registry populations, in non-STEMI/unspecified angina patients from the perspective of the NHS. It should be noted that this population differs from the patient group specified in the decision problem. The analysis based on the ACUITY study suggested that bivalirudin yields an ICER of £9,906 per QALY gained as compared against heparin plus GPI. The analysis based on the GRACE study suggested that the ICER for bivalirudin versus heparin plus GPI is £12,276 per QALY gained. The MS states that "based on probabilistic sensitivity analysis, 72.1% and 67.0% of simulation results were more cost-effective than £20,000 per QALY gained for the bivalirudin-based strategy, in the ACUITY-based and GRACE-based analyses, respectively." The *de novo* economic analysis presented later in the submission is an adaptation of this model.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details

Additional searches by the ERG found 18 publications which were not identified in the manufacturer's submission. It is possible that some of these were among those intentionally excluded by the manufacturer with reasons, or as duplicates, by the selection process illustrated in Figure 9 of the submission. A brief review of the additional 18 abstracts and relevant publications by the ERG indicates there was no major omission of relevant economic evidence within the manufacturer's submission.

The included studies were reviewed for quality based on guidelines produced by Drummond.[24] The results of this quality assessment appear to suggest that the methodological quality and robustness of the conclusions of these studies are reasonable. However, as the *de novo* analysis presented within the MS is the only full economic evaluation of bivalirudin in a STEMI population, the ERG agrees with the MS that the relevance of existing studies is limited.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 7 summarises the adherence of the manufacturer's model to NICE's reference case.

Table 7: Summary of manufacturer's economic analysis with respect to NICE's Reference Case

Element of health technology assessment	Reference case	Comments
Defining the decision problem	The scope developed by the Institute	The scope of the economic analysis is generally in line with that developed by NICE
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	Heparin alone is not included in the economic analysis, however this treatment strategy would not be considered usual/best practice in the UK.
Perspective on costs	NHS and PSS	An NHS perspective was adopted which reflects costs over a lifetime horizon
Perspective on outcomes	All health effects on individuals	Direct health benefits for patients are measured and valued over a lifetime horizon
Type of economic evaluation	Cost-effectiveness analysis	The economic analysis takes the form of a cost-effectiveness analysis
Synthesis of evidence on outcomes	Based on a systematic review	The economic analysis is based on one RCT (HORIZONS-AMI)
Measure of health effects	QALYs	Health outcomes are valued using QALYs
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Health utilities are derived from an EQ-5D study of patients following acute myocardial infarction
Source of preference data for valuation of changes in HRQL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects	Costs and health outcomes for the long-term model are discounted at 3.5%
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to QALY gains

5.2.2 Model structure

The manufacturer's submission includes the following files relevant to the assessment of the economic evaluation:

- Word document manufacturer's submission of evidence - main report
- TreeAge® (TreeAge Software, Inc, Massachusetts) fully executable model file based on 1-year follow-up data from HORIZONS-AMI– base case economic scenario
- TreeAge® fully executable model file based on 3-year follow-up data from HORIZONS-AMI – sensitivity analysis

The base case cost-effectiveness results were generated from a *de novo* decision-analytic model based primarily on an analysis of patient-level data from the HORIZONS-AMI clinical trial (Stone *et al*,[8]). The model also draws together other evidence sources to inform parameters relating to long-term prognosis, valuation of health outcomes, certain resource components and unit costs. As noted in Section 5.1, the same structural approach has been used in a recent economic analysis of a bivalirudin-based strategy versus heparin plus GPI in non-ST elevated acute coronary syndrome patients.[22]

UK data were used to generate model inputs that were not available from the HORIZONS-AMI trial. In particular, these relate to assumptions concerning radial artery access rates, proportion of use of different GPIs, and initial hospital length of stay. This also applies to all costs and consequences for patients who survive the initial reperfusion procedure.

The base case model adopts a cohort-based decision tree structure which covers the initial reperfusion until the end of a specified follow-up period (hereafter referred to as the "initial period" - 1-year in the base case), coupled with a two-state (alive/dead) Markov model to account for subsequent survival over a 39-year horizon using an annual cycle length. The decision tree structure (illustrated in Figure 15 of the MS) is identical to that presented in Schwenkglenks *et al*[22] A sensitivity analysis is also presented using an initial period follow-up duration of three years from the HORIZONS-AMI data together with a 37-year long-term Markov component.

The main clinical pathways modelled within the economic analysis are presented in Figure 1, according to the time periods defined in the submission. There are essentially three initial stages: (1) an index hospital-based stage when the initial treatment is performed (PPCI, CABG or conservative management); (2) the incidence and management of sequelae occurring within the initial period, and; (3) the incidence and management of further sequelae arising in patients undergoing repeat revascularisation. During each of these stages, patients may die, according to the rates observed in the HORIZONS-AMI trial. Despite the bushy structure of the decision tree, total QALYs gained in each treatment group are simply calculated as the sum of three components:

(1) (1-probability death in initial period) *x* duration of initial period *x* health utility for initial period

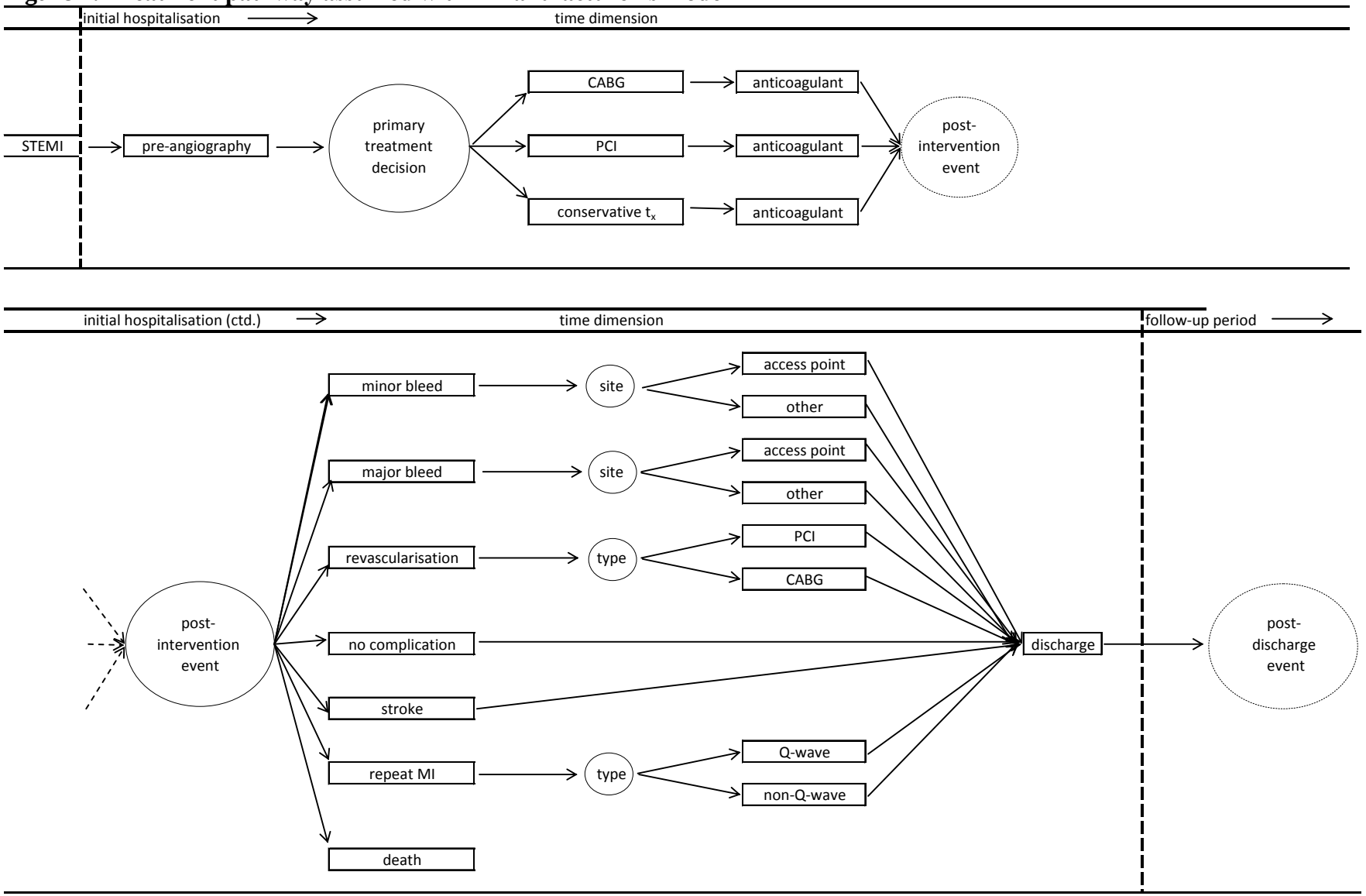
(2) probability death in initial period *x* survival duration in those dying during initial period *x* health utility for initial period

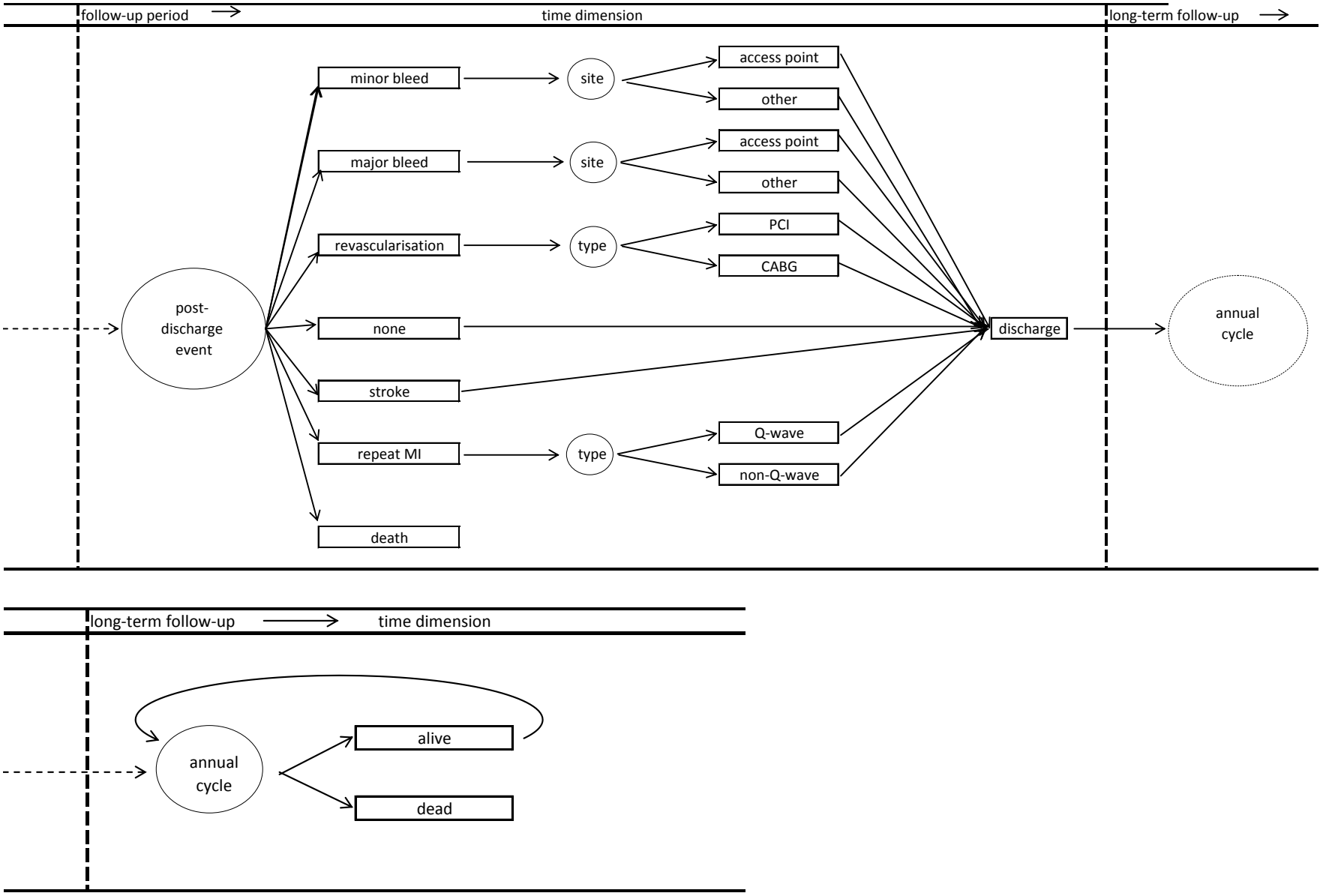
(3) (1-probability death in initial period) *x* survival duration for subsequent years post STEMI event *x* health utility for subsequent years post STEMI event. This component is half-cycle corrected.

Overall the relevance of the model structure employed by the manufacturer appears to be a satisfactory means through which to address the scope of the decision problem. The use of a decision tree to simulate the initial complications and a long-term Markov component to simulate prognosis and costs for those surviving has been used in other economic assessments of treatments for patients with NSTEMI (see, for example, Palmer *et al*[25]). Given the clinical evidence available for bivalirudin in the STEMI PPCI indication, this same general modelling approach appears to also be appropriate here. As shown in Figure 1, the short-term model includes seven possible initial outcomes following reperfusion therapy: (1) no relevant complications, (2) minor bleed, (3) major bleed, (4) stroke, (5) (re-)MI, (6) repeat revascularisation and (7) death. This set of possible events appears to cover main clinical complications arising from the use of bivalirudin and heparin+GPI in the PPCI setting.

The ERG noted a minor issue in that whilst the model structure treats these clinical events as being mutually exclusive (see also Section 5.2.3 below), in reality they are not. For example, some patients could experience both a bleed and a stroke during the initial post STEMI period. The manufacturer however clarified that the HORIZONS-AMI data were analysed such that the probabilities of experiencing each event were analysed independently. The impact is that the costs and consequences of all observed events are counted but the proportion of patients who experience "no relevant complications" will be underestimated. Given that the health gains attributable during the initial model period are common across all outcomes (i.e. a single utility value is used), *and* the probability of having no relevant complications is substantial in both treatment groups, *and* prognosis and health outcomes are identical for all patients surviving the initial period, this structural approach is not expected to bias the model results. The manufacturer produced estimates of the numbers of patients who experienced more than one event during years 1-3 of HORIZONS-AMI (for year 1, bivalirudin n=104, heparin + GPI n = 143). Given the short-term nature of the clinical evidence available for bivalirudin, the use of a simple Markov component for survivors, which is independent of initial treatment received, also appears generally reasonable (see Section 6.3 additional work undertaken by the ERG).

Figure 1: Treatment pathway assumed within manufacturer's model





Whilst the manufacturer's submission was very clear regarding the model structure, the implementation of this structure within the quantitative model was problematic for two reasons:

(1) Redundant portions of the model structure

The simple model structure illustrated in Figure 15 of the MS did not match the actual implemented structure within the executable TreeAge model. In contrast to the model description provided in the MS, the TreeAge model includes *two* initial time periods (1) risk of complication events following reperfusion and (2) subsequent risk of complication events conditional on previous complication events in Period 1. Whilst the duration and event risks for Period 2 were set to zero in the model, this led to an excessively complex model in which a significant proportion of the model structure and code was entirely redundant.

(2) Repetition of redundant code throughout the model

The programming approach within the model was also unnecessarily complex and ran the risk of introducing errors by using formulae which were unnecessarily repeated across conditional chance nodes and by (purposefully) referencing zero values within tables to ensure that these did not influence the model results. This led to an increased burden for model checking by the ERG.

Following the scrutiny of the model by the ERG, these issues do not appear influence the model results (see Section 5.3). It is worth noting however that the manufacturer took a very simple mathematical structure and made it unnecessarily complicated, and more difficult to interpret and verify. Given this lack of transparency, the ERG redeveloped the deterministic model in Excel, firstly to understand the operation of the model logic, and secondly to ensure that the model had been implemented as detailed within the submission report. The results of this exercise are presented in Section 5.3.

5.2.3 Population

With respect to the initial period, the population included in the model is consistent with the specified description of the decision problem. This population is defined as adults with STEMI intended for primary percutaneous coronary intervention. The characteristics of the model population reflect those of the HORIZONS-AMI trial; the characteristics of this population are subsumed within the mean event probabilities applied within the model.

A mean age of 60.9 years was assumed for the cohort based on HORIZONS-AMI; this assumption influences the expected survival duration of those entering the long-term model and the duration over which the long-term Markov model is evaluated. Long-term survival after the follow-up period was modelled by projecting outcomes to an estimated life-expectancy, to reflect average age of patients in the HORIZONS-AMI trial. In addition, a constant estimated annual mortality risk which is applied during the long-term stage was used. Central to this calculation is the inverse relationship between mean survival time and the mean transition probability of death; the MS assumes that the life-expectancy for 1-year survivors of the HORIZONS-AMI trial is 11.26 years. An assumptions underlying this calculation is that 1/3 of cardiovascular patients are women. This assumption was the subject of a request by the ERG for additional information from the manufacturer on the source of this claim (see response to clarification question B12). The response provided examples from three UK cardiovascular research data collections which give percentages of women ranging between 26% and 36%, which appears to support the original claim. Whilst the ERG are satisfied with how this parameter has been derived, the double-programming exercise highlighted an error with respect to its application within the model itself (see Section 5.3). Whilst the use of an exponential distribution to describe long-term survival is unlikely to be appropriate, this is highly unlikely to influence the conclusions of the economic analysis.

5.2.4 Interventions and comparators

The intervention of interest is bivalirudin as anticoagulant therapy during a primary PCI intervention for a STEMI. Heparin with GPI is the only comparator included in the economic analysis. The choice of intervention and comparator is appropriate for the decision problem under consideration. The use of heparin alone was specified in the decision problem scope[2] but was not included in either the clinical or economic analysis. Given that heparin alone is rarely indicated in the treatment of this population, this exclusion appears reasonable.

5.2.5 Perspective, time horizon and discounting

The economic analysis was conducted from the perspective of the NHS. Where a UK setting was required but unavailable for a parameter directly, available values were modified to achieve a suitable approximation.

The decision-analytic model includes an extrapolation to 40 years from the initial PCI intervention; this is intended to reflect a lifetime horizon. However when the long-term model is terminated (when patients reach 100 years of age), a small proportion of patients (<3%) are still alive.

In accordance with the NICE Reference Case,[26] costs and health outcomes are discounted at 3.5%. A half-cycle correction is used to adjust costs and outcomes simulated within the long-term model. The correction of modelled outcomes for the decision tree portion of the model is unnecessary because the model includes survival gains in those who die during this period.

5.2.6 Treatment effectiveness

The modelling approach assumes that all patients receive initial angiography for diagnostic purposes and are then allocated to a primary treatment intervention (around 93% undergo PPCI). Post-intervention follow-up is then modelled according to the two treatment strategies of interest: bivalirudin or heparin-with-GPI.

Differences in event rates between the two strategies were modelled using relative risk parameters estimated from a re-analysis of the ITT population within the HORIZONS-AMI trial. The treatment effect of any GPI type was assumed to be identical for the purposes of evaluation.

The baseline risks of experiencing clinical events (stroke, MI, bleeds, repeat revascularisation and death) were derived from a re-analysis of patient-level data from the HORIZONS-AMI trial. These event risks are applied uniformly to patients irrespective of whether they actually undergo PPCI. In reality, the risks of bleeds, stroke, MI are likely to differ depending on whether the patient undergoes PCI, CABG or conservative treatment; however representation of the latter two patient groups was small within HORIZONS-AMI was very small (bivalirudin arm = 7.6% patients, heparin + GPI = 6.5% patients).

The relative benefits of bivalirudin are modelled by simply applying the relative risks of experiencing clinical complications from the patient-level HORIZONS-AMI clinical trial data (ITT) for the bivalirudin arm, to the baseline event risks for the heparin with GPI arm. As with the baseline event probabilities, these relative treatment effects are applied to *all* patients in the bivalirudin arm irrespective of whether they actually undergo PPCI. At face value, this appears inappropriate as the consequence is that some patients within the model accrue benefits due to bivalirudin treatment despite never actually undergoing PPCI. However, as the baseline event rates for CABG and conservative treatment subgroups were also calculated on an ITT basis, *and* because health outcomes are not differentiated by the incidence of non-fatal complications, *and* because subsequent prognosis is the same for all 1-year survivors, this structural issue does not alter the model's conclusions. Therefore, whilst the event risks for bivalirudin and heparin with GPI may be wrong at each individual chance node, they should be correct overall (refer back to the methods by which QALYs are calculated in Section

5.2.2). The joint implication of these issues is that the implemented model structure used to estimate QALYs is far more complicated than was actually required - the model could have been simply simulated using a single chance node (alive or dead) and then a two-state Markov model for survivors. This would have produced the same result.

The model assumes that life-expectancy for those surviving the initial period was identical for both bivalirudin and heparin with GPI (i.e. long-term prognosis is not conditional on the initial reperfusion strategy).

5.2.7 Health related quality of life

The HORIZONS-AMI trial did not collect direct evidence relating to HRQoL. Instead, evidence was indirectly sourced from a literature search and systematic review of HRQoL studies.

Within the model, health utility values were selected from a single UK study which followed a cohort of patients for 1-year after they were diagnosed with an acute MI (Lacey *et al*[27]). The submission notes that the resulting utilities (0.683 for the initial period and 0.718 for the long-term model) are lower than those reported within other studies identified within the review. However, the MS states that the values accurately reflect the severity of the condition and the potential impact on HRQoL.

These utility values were applied as a constant over lifetime duration in the model independent of the age of the model cohort. Following a request for clarification, the manufacturer stated that the sources of the values were registries in which patients were of various ages, hence the summary statistics have an inherent ageing process component which also reflects associated disease processes. This is actually incorrect as the Lacey study reports outcomes at 6-weeks (applied in the initial period of the model) and 1-year (applied in the long-term Markov model) for the same sample of patients. The main assumption underpinning this approach is that the age distribution in the registries reflects that in HORIZONS-AMI.

The same values were applied in the model to both treatment strategies, such that any difference in HRQoL is primarily driven by differences in survival between the treatment groups. Further time-limited utility decrements or QALY losses arising from the incidence of complications following reperfusion are not included in the base case analysis. Whilst this is a simplistic approach, the impact of including differential health valuations for each complication on the model results is unclear. Given the clinical outcomes at 1-year, only

negative health effects associated with stroke events and/or repeat revascularisation would have an unfavourable impact upon the cost-effectiveness of bivalirudin.

5.2.8 Resources and costs

Estimates of resources and costs were based on NHS perspective and reflect the values used in the Schwenkglenks *et al.* study.[22] Unit costs were based on 2009-10 prices. Where necessary, unit costs were inflated using the hospital and community health services inflation index of the Personal Social Services Research Unit (PSSRU) for 2009-10.[28]

Costs of the following resources were included in the model (Section 6.5.3 in the MS):

- Initial angiography
- Initial revascularisation intervention and associated hospital care
- Anticoagulant intervention medications
- Management of clinical and treatment-related adverse events
- Long-term follow-up costs

The major resources and associated costs are outlined below.

5.2.8.1 Initial angiography

The assumed unit cost for any angiography is £282.88 (Table 45 in MS) based on NHS 2006 HRG RBF2, inflated to 2009-2010 values. As all patients were assumed to undergo initial diagnostic angiography post-admission, this cost parameter has no impact upon the model results whatsoever.

5.2.8.2 Initial reperfusion intervention and associated hospital care

The per-patient number of additional angiographies after the initial angiography (0.035, 0.037 for bivalirudin and heparin with GPI strategies, respectively, over the initial period) was assessed from the HORIZONS-AMI trial data. In order to avoid double-counting of angiography costs, only additional angiographies not leading directly to a repeat PCI were included (as the initial angiography preceded the intervention and was hence the same in both arms).

Numbers of initial PCIs, CABGs and episodes of conservative treatment were based on the distribution of initial treatments seen in HORIZONS-AMI. It was assumed that all (initial and repeat) PCIs would be performed immediately after angiography.

Unit costs for intervention procedures and associated treatment were based on NHS Reference Costs (HRGs, Table 41 within the MS).

The cost of the initial PPCI (and CABG) was divided into two components, to include hospital stay costs based on the HORIZONS-AMI trial. The assumed unit cost of the procedure only is £1,733.34 (Table 45, NHS 2009 HRG EA32Z), based on a non-ward cost published in a study of the effects of changing clinical practice on costs and outcomes of PCI (Denvir *et al*). According to clinical advice provided for the ERG, a treatment policy of PPCI may have a higher cost than other PCI treatment strategies, as a continuous, or 24-hour, service is required. The full HRG EA32Z amount (£3,151.52) was assumed for additional PCIs required for repeat revascularisation procedures. The corresponding values for CABG are £3,114.54 (Table 45, NHS 2009 HRG EA16Z) and £8,372.41. The non-ward cost proportion was based on Scottish 2008-09 specialty costs (Information and Statistics Scotland, 2009). This particular choice of parameter source was not justified in the MS.

For the base case analyses, the mean post-intervention length of initial hospital stay for patients on the heparin with GPI strategy within the HORIZONS-AMI trial was considered inappropriate for the UK setting, as this reflected a relatively low radial artery access (RAA) rate (see footnote 7, Table 42 within the MS). Instead, a mean length of stay of 4.4 days was assumed based on the National Infarct Angioplasty Project (NIAP, Goodacre *et al*.,[29]). This was partitioned into two periods, reflecting mean ward and ICU/CCU initial length-of-stay (2.45:1.95 days), on the basis of HORIZONS-AMI trial data. The observed relative reduction in initial length-of-stay for the bivalirudin strategy from the HORIZONS-AMI trial was applied to obtain the corresponding time for bivalirudin patients (2.5:1.7 days). The assumed (per day) unit cost for ICU/CCU is £813.54 (Table 45, NHS 2009 adult critical care cost (ICU) codes XC01Z-XC07Z and the CCU code CC7). The corresponding ward cost is £273.89 (Table 45, NHS 2004 cost – specific codes not provided).

The derivation of the per day ICU/CCU cost was subject of a request for additional information by the ERG from the manufacturer (see response to clarification letter, question B23). The response indicated that the estimate is an unweighted mean of the ICU codes (£1,168.48) and the CCU code (£458.60), i.e., (£1,168.48 + £458.60)/2. The manufacturer stated that using an unweighted mean is justified given that the relative proportions of ICU days and CCU days are unknown. However, a more robust estimate might be obtained by using the numbers of episodes to weight the average (£1,164), however this weighting may differ by the specific indication.

The non-ward cost (£8,872.67) of treating a stroke during the initial hospitalisation was estimated by the cost of stroke estimated from a UK model of thrombolysis vs. PPCI treatment in MI patients (Bravo Vergel *et al*.[30,31]). Ward costs were assumed to amount to 80% of the NHS 2009 HRG AA22Z cost, which is approximately £1,739. The choice of 80% was the subject of a request for additional information by the ERG from the manufacturer (see response to clarification letter, question B22). The manufacturer stated that "for stroke, typically, there [are] a number of imaging procedures but only few invasive procedures. In consequence, most of the costs accrued are ward costs."

For bleeding episodes occurring during the initial hospitalisation period, hospital length of stay was accounted for as part of the costs of the initial procedure. Additional examination and procedure costs of major bleeds during initial hospitalisation (£1,300 per event, excluding ward costs), were estimated as a percentage of the procedure cost of a repeat PCI, to avoid double-counting of the ward costs. This is based on an assumption and should be approached with caution.

5.2.8.3 Anticoagulant medication

Anticoagulant medication during the initial procedure consisted of the interventions of interest in the submission, namely bivalirudin, with or without glycoprotein inhibitor (GPI) treatment, and heparin with GPI treatment. The GPIs included in the model were abciximab, eptifibatide and tirofiban.

Bivalirudin and GPI usage was based on that of the HORIZONS-AMI trial. At the patient level, total numbers of vials were rounded up to account for wastage, and the mean number of vials used (Table 42 within the MS: bivalirudin, 1.23 vials; abciximab, 2.8 vials; eptifibatide, 1.64x 20mg injection and 2.51x75mg infusion vials) was applied in the economic model. This is appropriate as in usual clinical practice partially used vials would be discarded. Tirofiban was not used in the HORIZONS-AMI trial but is used in routine clinical practice in the UK. Hence, the proportions of patients who receive specific GPIs were based on observed usage reported within the BCIS 2009 audit (MS page 12: abciximab, 73.0%; eptifibatide, 8.1%; tirofiban 18.9%). The MS assumes that mean resource use per patient receiving tirofiban would require a single 12.5 mg vial.

Unit costs for bivalirudin (£310 per 250mg vial) and GPIs were drawn from the British National Formulary (BNF) costs for 2009-2010, sourced via MIMS (Table 43 within the MS).

- abciximab: £250.24/10mg vial
- eptifibatide: £42.79/20mg injection vial or £13.61/75mg infusion vial

- tirofiban: £160.72/12.5mg vial

Table 8 presents the expected drug costs applied within the model.

Table 8: Per patient expected drug costs included in the model

Drug treatment costs	Bivalirudin	GPI+Heparin
Bivalirudin	£369.48	£0.00
Abciximab	£42.62	£534.45
Eptifibatide (20mg)	£0.02	£6.21
Eptifibatide (75mg)	£0.03	£2.35
Tirofiban	£0.01	£28.95
Heparin	£0.00	£0.00
Total	**£412.17**	**£571.97**

The cost of heparin treatment was considered insignificant and was omitted from the model. The MS noted, and the ERG agrees, that this exclusion yields a result more favourable to the heparin with GPI strategy.

5.2.8.4 Management of clinical and treatment related adverse events

Following discharge from the initial hospitalisation, subsequent events and procedures were modelled using the heparin with GPI arm risk of any repeat revascularisation procedure, and the corresponding relative risk in the bivalirudin arm of the HORIZONS-AMI trial. Proportions of repeat intervention procedures, and of subsequent events, were estimated directly from HORIZONS-AMI data.

In general, differentiated strategies for treating any events after the index intervention are not accounted for within the model, that is, the use of bivalirudin during PPCI does not influence subsequent treatment decisions within the model. The argument used in the submission, and reiterated in the responses to a few of the ERGs requests for information (see response to clarification letter, questions B1(iv), B11, B21), is that "the treatment, available options and associated resource utilisation for post-intervention clinical events may be considered similar and relatively independent of the technology used in the index intervention". Whilst this argument may be valid, it is likely to result in underestimating the absolute cost estimates in each treatment group, however incrementally the impact of this is expected to be minimal.

For repeat procedures during the initial hospitalisation, PCI and CABG procedure costs (excluding ward costs to avoid double-counting) were estimated as discussed in Section 5.1.4.2 For repeat procedures after initial hospitalisation, but within the initial period, the full HRG costs were applied. A maximum of one repeat revascularisation procedure was assumed per patient, however in reality a small number of patients could undergo more than one repeat procedures. The use of medications, including anticoagulation treatment, during repeat

revascularisation procedures was not modelled directly, but assumed to be part of an overall treatment event for the revascularisation procedure, as discussed below.

The occurrence of bleeding episodes, ischaemic stroke and repeat MI were assessed according to the same principles whereby hospitalisation was subdivided into those resources including procedures only or both procedures and additional hospital admission.

The treatment of Q-wave MIs were distinguished from that for non-Q-wave MIs, with separate treatment costs were modelled for each type (Table 45 within the MS). The unit costs were: Q-wave AMI, £1,745,92, NHS 2009 HRG EB10Z; non- Q-wave AMI, £1,745,92 x 0.31 = £541.24 (non-Q-wave MIs after the initial hospitalisation were assumed to cost 31% of a Q-wave MI, based on a published direct cost comparison (Hlatky *et al*[32]). Clinical advice (Dr J Reckless) notes that this work is probably outdated. The overall cost of a major bleeding event after initial hospitalisation discharge was assumed to be £2,363.64, based on a proportion of about 0.75 of repeat PCI costs, derived from a US-based economic evaluation of the REPLACE-2 trial (Cohen *et al*[33]). Differences in bleeding costs between the treatment groups within the model reflect differences in the probability of the event occurring during the index hospitalisation and the probability of access site/non access site bleeds.

The model does not allow the possibility of a major bleeding event after the initial period. As noted above, such an omission is likely to result in underestimated costs in both treatment groups. The cost of blood products used for transfusion were not included in the base case analysis but were included used in the sensitivity analyses (see Section 5.1.6).

The occurrence of stent thrombosis events was not modelled separately. Following a request for clarification, the manufacturer stated that the representation of stent thrombosis events in terms of their clinical and economic impact is captured in the model by their manifestation as repeat MIs, repeat revascularisations and deaths. This is plausible provided stent thrombosis cannot occur independently of the above-listed events.

The full cost of treating an ischaemic stroke event (£10,611.21) was based on the study by Bravo Vergel *et al*.[30,31] However, the long-term costs of managing stroke, which can be considerable, were omitted from the economic analysis, hence the model estimate is likely to underestimate the total lifetime cost of care for stroke patient. As this relates to a small number of cases, and is lower in the bivalirudin group, this exclusion will favour the heparin with GPI group.

Radial artery access (RAA) is considered an advantage for PCI, compared to femoral artery access, as the incidence of non-CABG bleeding events is substantially reduced. As the

proportion of RAA procedures was relatively low in the HORIZONS-AMI trial (5.9%), the MS model assumes a value from the BCIS 2009 audit (42.5%; submission main report, page 12).

5.2.8.5 Long-term follow-up costs

Cardiovascular-related outpatient treatment and drug costs incurred during the initial period were modelled by an annual cost summary (£900 per patient per annum in the MS report, £899.77 in the model). This is justified within the MS on the basis of a lack of suitable alternative data (see Table 44 and Section 6.5.6, manufacturer's submission).

In general, the ERG believes that the approach to modelling resource use and associated costs is adequate for the decision problem under consideration. As noted above, there are certain instances whereby certain cost components have been ignored for practical reasons but, in general, this should not affect the results to any great extent.

5.2.9 Cost effectiveness results

Results from the base case model and various sensitivity analyses were presented in the form of mean total costs and quality-adjusted life years (QALYs) for both treatment strategies, and mean incremental costs and QALYs. Incremental cost-effectiveness ratios were presented for sensitivity analyses where bivalirudin was not dominant. Central estimates of incremental costs and outcomes presented within the submission were based on point estimates of parameter values rather than results of the PSA.

Modelled and assumed survival and QALY outcomes are presented in Tables 46, 47, and 48 of the MS. Total costs and disaggregated costs are presented in Tables 49 and 50 of the MS, respectively. Additional work undertaken by the ERG (see, for example, section 5.3, Table 9 below for details), to replicate the results for the base-case scenario (1 year) yielded very similar results.

In the base case analysis (and in the 3-year-based model), the bivalirudin strategy dominated the heparin with GPI strategy. Table 51 of the MS presents the main deterministic results, which are summarised in Table 9. 95% confidence intervals (CI) for the incremental costs and QALYs were provided in response to a request by the ERG.

Also, the empirical 95% confidence interval for incremental costs and QALYs for the bivalirudin strategy (compared to the heparin with GPI strategy) both include 0, and coincide with the 95% confidence ellipse for the cost-effectiveness plane scatter-plot (Figure 17 of the MS), which includes noticeable areas outside the South-East quadrant. Consequently, there is a small likelihood that bivalirudin does not dominate.

Table 9: Base-case model results

Strategy	Total costs (£)	Incremental costs (£)	Total QALYs	Incremental QALYs
Means, deterministic analyses				
Heparin with GPI	13,110	-	6.166	-
Bivalirudin	12,843	-267	6.256	0.089
Incremental means, PSA				
		-259		0.086
95% CI - percentiles		-515, 15		-0.005, 0.159

In view of these observations, and as a result of concerns outlined in Section 5.2.2, a thorough investigation of the model and associated results suggests that these results are likely to be plausible (please also refer to "Additional work undertaken by the ERG"). The corresponding ICERs were not calculated as the bivalirudin strategy is dominant compared to the heparin with GPI strategy.

5.2.10 Sensitivity analyses

Sensitivity analyses (see Section 5.2.10 below) included analyses using deterministic, univariate and scenario-based analysis, and PSA. PSA was presented both for the base case 1-year HORIZONS-AMI analysis and for the 3-year re-analysis. Probabilistic results were presented using cost-effectiveness planes and associated cost-effectiveness acceptability curves (CEACs).

Uncertainty in model input selection was assessed by replacing selected parameters with other plausible alternative values. In general, 95% CIs for survival and clinical event parameters from the HORIZONS-AMI trial were used to determine probability distributions for sensitivity analysis.

Appropriateness of probabilistic sensitivity analysis

Details of the parameters varied in the sensitivity analyses and the corresponding probability distributions were presented and discussed in the MS (see Tables 38, 40, 42, 44 and 45). Many of the entries in these tables were values estimated from HORIZONS-AMI data either at 1-year or 3-years of follow-up. Not all parameters in the model were subjected to sensitivity analyses. The MS includes some discussion of justifications for holding certain parameters constant within the PSA. However, the fact remains that in most instances these

are uncertain quantities rather than known values. It is likely that the inclusion of this additional uncertainty would not favour either treatment group but would increase the uncertainty surrounding the mean results.

The following tables (Table 10, 11), summarised from Tables 38, 40, 42, 44 and 45), detail the various fixed parameter values used in the economic modelling.

Table 10: Fixed parameter values in base-case and scenario-based sensitivity analyses

Variable	Value	Source	MS Table
Age at model entry (years)[1]	60.9	HORIZONS-AMI 1-year data (mean age of study population). Implemented in model via cohort characteristics.	38
Proportion male[1]	0.766	HORIZONS-AMI 1-year data. Implemented in model via cohort characteristics.	38
heparin+GPI - non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds if RAA use is 42.5%	0.733	HORIZONS-AMI 1-year data	38
alternative: 3 years follow-up	0.638	HORIZONS-AMI 3-year data	38
alternative: as in HORIZONS-AMI	0.612	HORIZONS-AMI 1-year data	38
alternative: 3 years follow-up and as in HORIZONS-AMI	0.754	HORIZONS-AMI 3-year data	38
bivalirudin – non-CABG HORIZONS-AMI major bleed, proportion of non-access site bleeds if RAA use is 42.5%	0.779	HORIZONS-AMI 1-year data	38
alternative: 3 years follow-up	0.786	HORIZONS-AMI 3-year data	38
alternative: as in HORIZONS-AMI	0.670	HORIZONS-AMI 1-year data	38
alternative: 3 years follow-up and as in HORIZONS-AMI	0.678	HORIZONS-AMI 3-year data	38
Non-CABG HORIZONS-AMI minor bleed, proportion of non-access site bleeds in both strategies	0.000	Assumed for simplicity, due to marginal impact on health economic results	38
Repeat MIs, proportion of Q-wave MIs in heparin with GPI strategy	0.474	HORIZONS-AMI 1-year data	38
alternative: 3 years follow-up	0.466	HORIZONS-AMI 3-year data	38
Repeat MIs, proportion of Q-wave MIs in bivalirudin strategy	0.613	HORIZONS-AMI 1-year data	38
alternative: 3 years follow-up	0.899	HORIZONS-AMI 3-year data	38
Any repeat revascularisation, proportion of PCI use (versus CABG use) in heparin with GPI strategy	0.839	HORIZONS-AMI 1-year data	38
alternative: 3 years follow-up	0.867	HORIZONS-AMI 3-year data	38
Any repeat revascularisation, proportion of PCI use (versus CABG use) in bivalirudin strategy	0.885	HORIZONS-AMI 1-year data	38
alternative: 3 years follow-up	0.885	HORIZONS-AMI 3-year data	38
Non-CABG HORIZONS-AMI minor bleed, proportion of non-access site bleeds in both strategies	0.000	Assumed for simplicity, due to marginal impact on health economic results	38
Average survival time of patients who died in 1-year period in heparin with GPI strategy (days)	59	HORIZONS-AMI 1-year data	38
alternative: 3 years follow-up	307	HORIZONS-AMI 3-year data	38
Average survival time of patients	83	HORIZONS-AMI 1-year data	38

who died in 1-year period in bivalirudin strategy (days)			
alternative: 3 years follow-up	343	HORIZONS-AMI 3-year data	38
Abciximab use in those with GPI use, probability	0.730	BCIS 2009 data	42
Eptifibatide use in those with GPI use, probability	0.081	BCIS 2009 data	42
Tirofiban use in those with GPI use, probability	0.189	BCIS 2009 data	42
Any GPI use, probability	0.953	HORIZONS-AMI 1-year data	42
Tirofiban 12.5 mg vials in those with tirofiban use	1	Assumption, see above	42
Bivalirudin use, probability	0.969	HORIZONS-AMI 1-year data	42
Any GPI use, probability	0.076	HORIZONS-AMI 1-year data	42
Probability of initial angiography[1]	1	Assumption	42
Probability of initial PCI	0.929	HORIZONS-AMI 1-year data	42
Probability of initial CABG	0.017	HORIZONS-AMI 1-year data	42
heparin+GPI - additional angiographies until the end of year 1	0.035	HORIZONS-AMI 1-year data	42
alternative: 3 years follow-up	0.071	HORIZONS-AMI 1-year data	42
bivalirudin - additional angiographies until the end of year 1	0.037	HORIZONS-AMI 1-year and 2-year data	42
alternative: 3 years follow-up	0.079	HORIZONS-AMI 1-year and 2-year data	42
heparin+GPI – mean total days of initial hospitalisation	4.40	Goodacre *et al*. Used to derive ward and ICU/CCU length-of-stay.	42
bivalirudin – days of initial hospitalisation if RAA use is 42.5% (mean)	4.20	Estimated from Goodacre *et al*. and HORIZONS-AMI 1-year data, see text. Used to derive ward and ICU/CCU length-of-stay.	42
Angiomax® (bivalirudin) 250mg vial cost[1,2]	310.00	www.mims.co.uk (accessed 29 Nov 2010)	43
heparin[1,2]	0.00	Assumption, due to marginal impact on economic analysis	43
ReoPro® (abciximab) 10 mg vial cost[1,2]	250.24	www.mims.co.uk	43
Integrilin® (eptifibatide) 20 mg vial (injection) cost[1,2] 75 mg vial (infusion) cost[1,2]	 42.79 13.61	www.mims.co.uk	43
Aggrastat® (tirofiban)12.5 mg vial[1,2]	160.72	www.mims.co.uk	43
			43

[1] remained unchanged throughout analyses
[2] treatment unit costs (therefore the use of fixed values is appropriate)

Table 11: Alternative values used in scenario-based sensitivity analyses

Variable	Value	Source	MS Table
Red blood cell units (PRBC or whole blood or other), mean number per patient with bleed	1.284	HORIZONS-AMI 1-year data	42
Platelets units (PRBC or whole blood or other), mean number per patient with bleed	0.172	NIAP HORIZONS-AMI 1-year data	42
Fresh frozen plasma units, mean number per patient with bleed	0.142	HORIZONS-AMI 1-year data, see text	42
Days of initial hospitalisation if RAA use as seen in HORIZONS-AMI (mean)	4.14	(Goodacre *et al*) and HORIZONS-AMI 1-year data, see text. Not directly used in the modelling	42
Cost - Red blood cells (1 bag)	139.72	National Blood Services (2009); standard red cells	45
Cost - Platelets (1 bag)	232.29	National Blood Services (2009); platelets (1.0 ATD)	45
Cost - Fresh frozen plasma (1 bag)	36.33	National Blood Services (2009); clinical FFP (250/300 mls UK sourced)	45

Justification for keeping each of the parameters listed in Tables 10 and 11 (above) fixed was sought from the manufacturer (see response to clarification question B4). The response provided various explanations, of which the most common reason for the clinical variables (Table 38 in the MS) was a lack of impact of the variable on the model results, combined with feasibility considerations. For the resource-use variables (mainly Table 42), the main reason given was that the fixed variables are set by standard practice. The responses are reasonable in the context of the decision problem under consideration.

Sampling from the joint distribution of the univariate distributions produced the multivariate PSA results, as discussed in Section 5.2.9. Irrespective of this issue, the true decision uncertainty is underestimated within the MS model.

Choice of uncertain distributions

Probability distribution types used for model parameter sensitivity analyses are included in the following table (Table 12).

Table 12: Probability distributions used in the sensitivity analyses

Parameter description group	Probability distribution
clinical event or procedure	beta
relative risk (clinical event/ procedure)	log-normal
initial procedure costs	triangular
mean life-expectancy	triangular
HRQoL utility decrements	triangular
mean drug vial usage	gamma
long-term treatment and outpatient costs	uniform

The use of triangular distributions is generally questionable, as the implication is that the probability density function changes in a restrictive manner about a specific value. Further, it is unclear why uniform distributions were used for costs, as this assumes that all values within the distribution are equally likely.

Three requests were made in the clarification letter to the manufacturer for additional information about the choice of probability distributions for model inputs the (questions B6, B7, B18). One question (B7) addressed the general issue of use of triangular and uniform distributions, requesting justification for each choice. The essence of the response centred on two arguments: for uniform distributions, the use of large margins (±50%), covers the range of possible values and little information (on the shape of the distribution) was available. However, there is also an implicit assumption that the distribution is likely to be symmetric about mean value. This distribution is used with cost data, and it is questionable whether this assumption is likely to hold in this context. On the other hand, from the general approach used to implement the model, which does not differentiate costs between strategies after the initial intervention, it is likely that this approach will produce cost estimates which do not favour either strategy.

The manufacturer argued that using triangular distributions is appropriate when the distribution is unknown but is known to have a mode as the probability density function changes more slowly than for other distributions. However, this distributional form is applied to life expectancy, disutilities and HRG costs, and it is likely that more information on the shape of such distributions is available than has been applied here. It is worth noting however that a more appropriate characterisation of uncertainty surrounding these parameters would be highly unlikely to influence the conclusions of the economic analysis.

A second question (B6) addressed the decision to use independent beta distributions, rather than a multinomial distributions (i.e. a Dirichlet) to characterise uncertainty surrounding the baseline event probabilities within the decision tree portion of the model. The response referred to: (a) the fact that any absolute risk can be correctly modelled probabilistically using a beta distribution; (b) the special status of the 'no additional complication' path, which is used as a catch-all path in the tree; and, effectively, (c) the practicalities of simulating a sum of independent beta random variables so that the sum is a valid probability. While the response does not address the question directly, in practice there will probably be little effect on the results of the PSA.

The last question (B18), requested information concerning handling uncertainty surrounding the length of hospital stay. The manufacturer's response indicated that gamma distributions with parameters which produce the 95% confidence limits from Table 42 are used for the heparin with GPI strategy. It appears the corresponding quantities for the bivalirudin arm are obtained by weighting the heparin with bivalirudin parameters by ratios reflecting the relative usage of normal ward (2.5/2.45) and ICU/CCU (1.7/1.95) discussed in Section 5.2.8.2, and using log-normal distributions to model the distribution which produces the 95% confidence interval for the resulting parameters. This approach appears reasonable under the circumstances, although the true variability may be somewhat underestimated, a possibility which is acknowledged in the response.

Deterministic sensitivity analyses

The selection of parameters subjected to deterministic sensitivity analyses is discussed in Section 6.6.2 of the MS. These relate to:

- adverse event risk and repeat procedure rates;
- anticoagulant use, percent in the bivalirudin strategy, type of GPI and average number of tirofiban vials used;
- variables impacting aspects of treating major bleeding episodes (RAA rates, non-ward costs, long-term HRQoL impact;
- length of initial hospital stay;
- discount rates.

A small number of combined scenarios were also tested.

The alternative values chosen for deterministic sensitivity analyses (see Tables 52, 53 in MS for summaries) were chosen as follows. For the heparin with GPI strategy event risks and revascularisation procedure rates, the risks of stroke (from 1% to 0,5%, to bring it closer to BCIS Audit 2009, PPCI value (0.2%)), repeat revascularisation (from 8.6% to 4.3% (at 1 year) to reflect BCIS Audit 2009 ratio to that of HORIZONS-AMI of 0.5), and mortality (at 1 year from 4.8% to 8.7%, the value from the NIAP) were changed. The MS notes the potential for inconsistency due to the use of different sources to populate these parameters.

GPI usage in the bivalirudin arm was replaced from 7.6%, the per-protocol rate for the HORIZONS-AMI trial to values of 13.3% for any GPI usage and of 7.2%, reported by Stone *et al*. The type of GPI assumed (the base case used 73% abciximab, 8.1% eptifibatide and 18.9% tirofiban, as per BCIS Audit 2009) was set to 100% (NIAP value) for abciximab; 100% eptifibatide, for which GPI costs are lowest; and, simultaneously, 52.9% abciximab and 47.% eptifibatide, from the HORIZONS–AMI trial. The number of vials of tirofiban was increased from 1 to 1.5.

Aspects of treating major bleeding episodes that were varied included: setting non-ward costs to include only the cost blood transfusion (original values: £77 for bivalirudin and £114 for heparin with GPI, Table 49 in MS). The alternative value is not clearly identified in the MS but the value used in the model coincides with the cost of a bag of 'red blood cells', £139.72 (see Table 45 in the MS). Also varied were the RAA rate (from 42.5% (BCIS Audit 2009) to 5.9% (HORIZONS-AMI trial) and 100% (limiting value), and long-term utility decrement (from none to 0.05).

Length of initial hospital stay was varied for the heparin with GPI strategy (from 4.4 to 7.2 days, the HORIZONS-AMI mean). A separate analysis assumed there was no difference between the two strategies (from 4.2 days for the bivalirudin strategy to 4.4).

Discount rates of 0% and 6% were also tested. Finally, a combined scenario of 100% eptifibatide and 100% RAA rate was also tested.

The results of the various deterministic sensitivity analyses are presented in Tables 52, 53 of the MS, without much additional comment elsewhere in the submission. In general, the resulting the bivalirudin strategy was dominant in almost all of the scenarios tested. The exceptions were:

- the exclusive use of eptifibatide as the GPI (ICER = £1,764),

- the combination of 100% eptifibatide use, 100% RAA, and no differential length between strategies for initial hospital stay (ICER = £4,106)

- a longer length of ward stay (increase of 0.33 days) for the initial hospitalisation (ICER = £415)

In general, the scenario-based results indicate the bivalirudin strategy is likely to remain cost-effective under the majority of scenarios. Given the structure of the model, it is unlikely that any plausible alternative scenarios would produce a contradictory result.

As noted in Section 4, the majority of patients within HORIZONS-AMI underwent femoral arterial access (n=3383) rather than radial arterial access (n=214). The manufacturer presented a sensitivity analysis which attempted to examine the impact of this factor on the cost-effectiveness of bivalirudin. Within this analysis, only the cost side of the model was adjusted. However, Figure 12 presents a subgroup analysis which suggests a non-significant worsening of other cause mortality for the bivalirudin radial access subgroup (relative risk=1.44, 95% CI 0.33 to 6.27). However, this subgroup analysis reflects a total of 7 events across both arms and should therefore be treated with considerable caution. A re-analysis based on this subgroup is unlikely to be meaningful.

5.2.11 Model validation

The measures taken to validate the economic model are detailed in Section 6.8 of the main report. In summary, the manufacturer states that the following activities were undertaken:

- all model elements and formulae were double-checked

- sample QALY results and cost results were hand-checked

- the functioning of discounting mechanism and relative-risk assumptions about treatment effect were checked by sample output

In addition, the manufacturer performed a comparison of their re-analysis of patient-level data against estimates published within Mehran *et al*.[7] The manufacturer provided a summary of deviations between these analyses; the ERG confirm that observed differences were negligible and would be highly unlikely to influence the model results.

Structural uncertainty was not investigated by the manufacturer (Section 6.6.1 of the MS). The impact of assumptions about model structure have been discussed in detail above (see Section 5.2.2). In summary, while the ERG has some concerns about the way in which the model has been implemented, these are unlikely to have a significant impact upon the conclusions of the economic analysis.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

The ERG undertook a number of additional analyses to ensure that the manufacturer's model was robust. In particular this additional work included:

- Checking consistency of all model parameter values between the model and the submission report
- Double-programming of the manufacturer's model within Excel to understand and verify the TreeAge model
- Further sensitivity analysis concerning the long-term Markov model

The findings of this additional work is detailed in the sections below.

6.1 Checking consistency of all model parameter values

The ERG identified the following issues:

(1) **Cost of PPCI.** The MS model includes a parameter which inflates the cost of PPCI by a factor of 1.168. The source of this parameter value is unclear from the MS, but does not influence the model results.

(2) **Costs of treating access site/non-access site minor bleeds.** There is a slight discrepancy between the MS report and the model in terms of the cost of a minor bleed (£80.60 in MS model, £79.26 in MS report)

(3) Costs of long-term cardiovascular treatment costs. The cost of long-term drug and outpatient appointments was marginally different between **th**e MS report and model (£899.77 in MS model, £900.00 in MS report). This discrepancy has only a minimal impact upon the model results

(4) MS model parameters not detailed in MS report. The following model parameters were not detailed in the submission:

a. The probability of stroke occurring during the index hospitalisation in each treatment group
b. The distribution of bleeds between access site/non-access site and during index/post-index hospitalisation
c. The distribution of repeat revascularisation procedures between PCI/CABG during index/post-index hospitalisation
d. The distribution of subsequent MI events between Q-wave/non-Q-wave during index/post-index hospitalisation

6.2 Double-programming of the manufacturer's model in Excel

Based upon the point estimates of parameters detailed in the manufacturer's model, the Excel model produced very similar estimates of costs and health outcomes for the two treatment groups, as shown in Tables 13 and 14.

Table 13: Comparison of deterministic results from the manufacturer and the ERG

	ERG model			Manufacturer model		
	Bivalirudin	Hep+GPI	Inc.	Bivalirudin	Hep+GPI	Inc.
Life years gained						
1-yr model LYGs (undiscounted)	0.974	0.960	**0.014**	0.974	0.960	**0.014**
Post-1-yr model LYGs	10.543	10.392	**0.151**	10.545	10.394	**0.152**
Sum LYGs	11.517	11.353	**0.165**	11.518	11.354	**0.165**
QALYs gained						
1-yr model QALYs (undisc)	0.6651	0.6557	**0.009**	0.665	0.656	**0.009**
Post-1-yr model QALYs (disc)	5.5904	5.5103	**0.080**	5.591	5.511	**0.080**
Sum QALYs	6.256	6.166	**0.089**	6.256	6.166	**0.089**

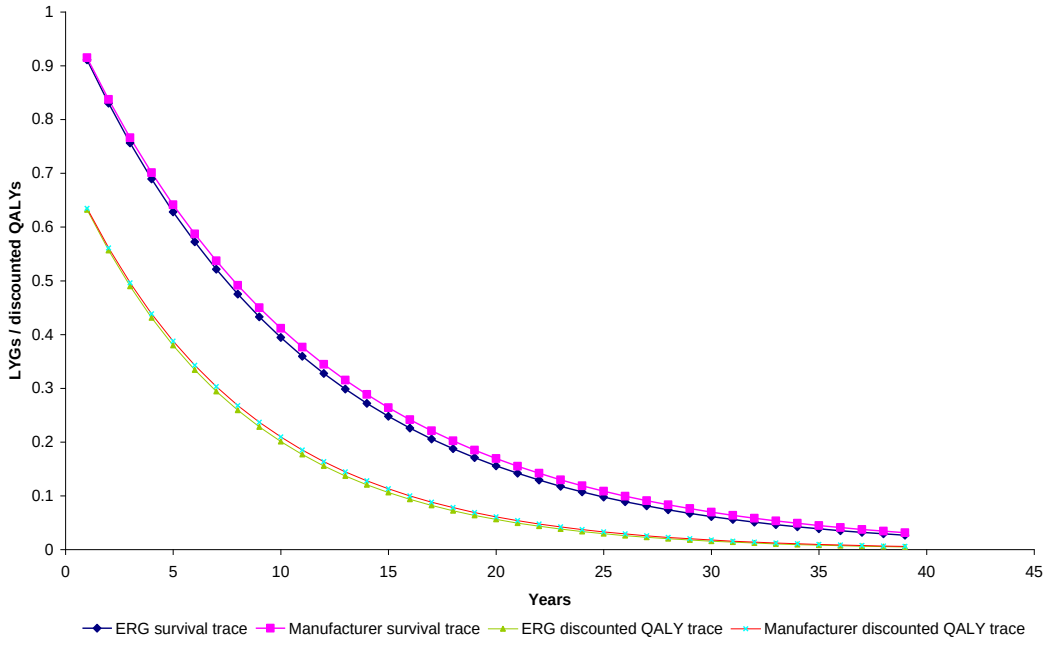
Table 14: Comparison of cost estimates produced by the manufacturer and the ERG

	ERG model			Manufacturer model		
	Bivalirudin	Hep+GPI	Inc.	Bivalirudin	Hep+GPI	Inc.
1-year model	£5,806	£6,174	**-£367**	5,837	6,204	**-£367**
Long-term model	£7,006	£6,905	**£100**	7,006	6,906	**£100**
Total cost	£12,812	£13,079	**-£267**	12,843	13,110	**-£267**

Table 13 shows that the results produced by the manufacturer and those re-generated by the ERG are very similar. During this double-programming exercise, a small error was identified within the Markov component of the manufacturer's model: whilst the model specifies a mean survival of 11.26 years and defines the transition probability as 1/survival, the actual

Markov trace produced by the manufacturer's model implies a survival duration of 11.77 years (shown in Figure 2).

Figure 2: Markov trace for long-term LYGs and QALYs



This does not appear to be intentional as the submission states that 11.26 years was intended. Given the complexity of the model programming approach, the source of this error within the model was unclear. The impact of this error upon the model results is however negligible (incremental cost = £270, incremental QALY = 0.087).

There is a further issue associated with the Markov component of the model. Given that the (intended) mean survival for patients surviving the initial period of the model was 11.26, and that the Markov model only has two states (alive and dead) the Markov component should clearly approximate a survival duration of 11.26 years. However, it doesn't. Instead, the manufacturer's model truncates the long-term time horizon after 39 1-year cycles (when surviving patients are 99.9 years of age). At this point, 2.7% of 1-year survivors are still alive but their subsequent survival and QALY contributions are ignored – the mean survival for this group is instead 10.91.

6.3 Sensitivity analysis to examine impact of long-term model

Given the limitations in the evidence used to simulate longer-term outcomes for patients following reperfusion, and the simplistic structure of the Markov component, this element of

the model should be considered highly uncertain. Table 15 demonstrates the impact of the time horizon upon the costs and outcomes of the two treatment groups.

Table 15: Impact of time horizon on incremental costs and QALYs gained

Markov duration	Bivalirudin		Heparin + GPI		Incremental cost	Incremental QALYs gained
	Cost	QALYs	Cost	QALYs		
0	£5836.92	0.67	£6204.49	0.66	**-367**	0.01
5	£9,085.91	3.26	£9,406.95	3.21	-£321.05	0.05
10	£10,840.59	4.66	£11,136.51	4.59	-£295.92	0.07
15	£11,788.24	5.41	£12,070.59	5.34	-£282.35	0.08
20	£12,300.04	5.82	£12,575.05	5.74	-£275.02	0.08
25	£12,576.45	6.04	£12,847.50	5.96	-£271.06	0.09
30	£12,725.72	6.16	£12,994.64	6.07	-£268.92	0.09
35	£12,806.34	6.23	£13,074.11	6.14	-£267.77	0.09
39 (base case)	**£12,843.18**	**6.26**	**£13,110.42**	**6.17**	**-£267.24**	**0.09**

Table 15 shows that according to the manufacturer's model, bivalirudin is consistently expected to dominate heparin+GPI irrespective of the model time horizon. However, it is noteworthy that the long-term Markov component inflates the short-term QALY benefit by a factor of around 9 (see first and last rows of Table 15). Despite these issues, the structure of the model and the use of a Markov component means that provided bivalirudin has a better survival rate and lower cost at 1-year, it will always dominate heparin with GPI over longer time horizons, even if the analysis had been restricted to the HORIZONS-AMI trial follow-up duration alone currently reported in peer-reviewed publications.

6.4 Conclusions following additional work undertaken by the ERG

The manufacturer's model suggests that a bivalirudin-based intervention is expected to dominate heparin plus GPI. Bivalirudin remained dominant across the majority of sensitivity analyses; in cases whereby it was more effective and more expensive than heparin plus GPI, the ICER for bivalirudin remained below £5,000 per QALY gained. A complete rebuild of the model did not identify any significant errors that have a marked impact upon the ICER. Despite the excessively complicated implementation of the model, the ERG believe that the economic analysis presented by the manufacturer is robust. The long-term costs and outcomes for both treatment strategies represents an area of considerable uncertainty and has a considerable impact upon the incremental QALY gain, however the conclusions of the economic analysis hold even when long-term costs and outcomes are excluded from the model.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The searches undertaken by the manufacturer did cover the basic terms necessary to find some of the evidence. There were large inconsistencies in the search strategies between databases resulting in potentially useful evidence being excluded, and a number of key databases were overlooked along with sources of grey literature.

The MS[1] contains one RCT only and does not appear to have missed any relevant RCTs. The MS[1] thoroughly and accurately described the included RCT. The RCT was consistent with the decision problem in terms of population and intervention. The comparator reflected common UK practice. The outcomes reported were relevant and appropriate. The RCT had some differences from standard UK practice, in terms of pre-procedural heparin administration, which was common in the RCT but rare in UK practice, and access site, which was predominantly femoral in the RCT but with radial access becoming increasingly common in UK practice. It is unclear how the RCT results would be reflected in practice given the lack of pre-procedural heparin in standard UK practice. Access site bleeding is less common with radial than femoral arterial access, and so the benefit in reduced bleeding from bivalirudin is likely to be lower in practice than in the RCT.

From RCT results, treatment with bivalirudin was associated with a significant reduction in cardiac mortality and major bleeding compared with the comparator at 30-days and one-year follow-up. Stent thrombosis up to 24 hours following PCI was more common with bivalirudin than heparin with GPI, however there was no significant treatment effect for stent thrombosis from one to 30 days, or at one-year follow-up. The increased stent thrombosis up to 24 hours was not accompanied by any increase in mortality. There were no significant treatment group differences in non-haemorrhagic stroke, myocardial infarction, or need for revascularisation at one year follow-up.

7.2 Summary of cost effectiveness issues

The manufacturer's model suggests that a bivalirudin-based intervention is expected to dominate heparin plus GPI. Bivalirudin remained dominant across the majority of sensitivity analyses; in cases whereby it was more effective and more expensive than heparin plus GPI, the ICER for bivalirudin remained below £5,000 per QALY gained. A complete rebuild of the model did not identify any significant errors that have a marked impact upon the ICER. Despite the excessively complicated implementation of the model, the ERG believe that the economic analysis produced from this is robust.

The work by the ERG has identified the following issues of note.

The literature search for relevant economic analyses has been reported in an inconsistent way but the conclusions are largely consistent with available evidence.

While the conceptual model is relatively simple, the manufacturer submitted a model which has been difficult to understand and validate due to its unnecessary complexity. The calculations required to estimate some of the model inputs have been made difficult by the fact that the source data, largely from the HORIZONS-AMI trial, cannot be disaggregated into the components required for the model. Many of these calculations require intermediate estimates which are based on ratios of two estimates from different sources. These estimates remain fixed in the model and are thus not subject to sensitivity analyses.

A number of values used in the model input do not match the values presented in MS. The effect of these discrepancies on the economic analyses results is however considered minor.

However, these issues are not considered to have any major impact on the overall robustness of the results of the economic analyses and the conclusions that can be drawn from them.

8 APPENDICES

Table 16: Economic evaluation: Critical Appraisal Checklist (based on Drummond *et al*,[34])

Item	Addressed	Comments
Was a well-defined question posed in an answerable form?	yes	
Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?	yes	The model submitted is based on two treatment arms, as per the HORIZON trial, for bivalirudin (with or without GPI therapy), and heparin with GPI therapy.
Was there evidence that the programme's effectiveness had been established?	yes	Results from relevant trials indicate the bivalirudin, which can often be taken without GPI, reduces the risk of major adverse events associated with PPCI procedures.
Is the study type reasonable?	yes	A cost-utility study, in which benefits are measured in QALYs, is appropriate as the effects of myocardial infarct and associated treatment are often long-term and impact on a patient's health status.
Were all the important and relevant outcomes and costs for each alternative identified?	yes	
Were outcomes and costs measured accurately in appropriate units (e.g. hours of nursing time, number of physician visits, years-of-life gained) prior to evaluation?	yes - mostly	Post-intervention events, costs and changes in QoL are included in the analysis. These seem to be appropriately chosen, The possibility of multiple post-intervention events of the same type was excluded, which has implications for estimated costs of treating events.
Is the perspective employed appropriate?	yes	NHS perspective used for costs and resource use; QALYs using appropriate utility discounts were used.
Were outcomes and costs adjusted for different times at which they occurred (discounting)?	yes	3.5% p.a. discounting with half-cycle correction was used
Has a lifetime horizon been used for analysis (or justified, in the case of a shorter horizon)?	yes	The long-term results are modelled to a 40 years time horizon.
Was an incremental analysis of the outcomes and costs of alternatives performed?	yes	Model produces: Total costs and QALYs estimated for each strategy, resulting in:

		mean incremental costs and QALYs, ICERs on a cost-effectiveness plane, and corresponding CEACs
Was a sensitivity analysis performed?	yes	Deterministic, univariate and multivariate PSA
Were the conclusions of the evaluation consistent with the evidence presented?	yes	

9 REFERENCES

1. The Medicines Company Submission to NICE: Single Technology Appraisal (STA) Bivalirudin (Angiox®) for the treatment of ST-segment elevation myocardial infarction Manufacturer's submission. 1-2-2011;

2. NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE Bivalirudin for the treatment of ST-segment elevation myocardial infarction: Final Scope. 2011;

3. Myocardial Ischaemia National Audit Project (MINAP) How the NHS cares for patients with heart attack. 2010;

4. British Cardiovascular Intervention Society Submission to NICE: Single Technology Appraisal (STA) Bivalirudin (Angiox®) for the treatment of ST-segment elevation myocardial infarction British Cardiovascular Intervention Society Professional Statement. 1-2-2011;

5. European Medicines Agency and Committee for Medicinal Products for Human Use European Public Assessment Report (EPAR) for bivalirudin (Angiox), last updated 12/02/2010. *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000562/human_med_000647.jsp&mid=WC0b01ac058001d125&murl=menus/medicines/medicines.jsp&jsenabled=true* 12-2-2010;

6. British Medical Association and the Royal Pharmaceutical Society British National Formulary 61. *http://bnf.org/bnf/* 1-3-0011;

7. Mehran, Roxana, Lansky, Alexandra J., Witzenbichler, Bernhard, Guagliumi, Giulio, Peruga, Jan Z., Brodie, Bruce R., Dudek, Dariusz, Kornowski, Ran, Hartmann, Franz, Gersh, Bernard J., Pocock, Stuart J., Wong, S Chiu, Nikolsky, Eugenia, Gambone, Louise, Vandertie, Lynn, Parise, Helen, Dangas, George D., and Stone, Gregg W. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *The Lancet* 3-10-2009; **374** 1149-1159.

8. Stone, Gregg W., Witzenbichler, Bernhard, Guagliumi, Giulio, Peruga, Jan Z., Brodie, Bruce R., Dudek, Dariusz, Kornowski, Ran, Hartmann, Franz, Gersh, Bernard J., Pocock, Stuart J., Dangas, George, Wong, S. Chiu, Kirtane, Ajay J., Parise, Helen, and Mehran, Roxana Bivalirudin during Primary PCI in Acute Myocardial Infarction. *New England Journal of Medicine* 22-5-2008; **358** 2218-2230.

9. Parodi, G., Antoniucci, D., Nikolsky, E., Witzenbichler, B., Guagliumi, G., and Peruga, J. Z. Impact of bivalirudin therapy in high-risk patients with acute myocardial infarction: 1-year results from the HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) trial. *JACC Cardiovasc Interv* 2010; **3** 796-802.

10. Tsujita, K, Nikolsky, E., Lansky, A. J., Dangas, G., Fahy, M., Brodie, B. R., and et al Impact of anemia on clinical outcomes of patients with ST-segment elevation myocardial infarction in relation to gender and adjunctive antithrombotic therapy (from the HORIZONS-AMI trial). *Am J Cardiol* 2010; **105** 1385-1394.

11. Mehran, R and et al Impact of baseline renal function on the safety and effectiveness of bivalirudin in patients with acute myocardial infarction undergoing primary angioplasty: The HORIZONS AMI trial. From the proceedings of the 57th annual scientific Session of American College of Cardiology (ACC). *ACC* 2008;

12. Wohrle, J, Desaga, M, Metzger, C, Huber, K, Suryapranta, H, Guetta, V, and et al Impact of transfer for primary percutaneous coronary intervention on survival and clinical outcomes (from the HORIZONS-AMI Trial). *Am J Cardiol* 2010; **106** 1218-1224.

13. Dangas, G., Mehran, R, Guagliumi, G., Caixeta, A., Witzenbichler, B., Aoki, J., and Horizons-AMI Trial Investigators Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. *J Am Coll Cardiol* 2009; **54** 1428-1446.

14. Dauerman, Harold L., Frederick, Paul D., Miller, Dave, French, William J., and for the National Registry of Myocardial Infarction- Current incidence and clinical outcomes of bivalirudin administration among patients undergoing primary coronary intervention for stent thrombosis elevation acute myocardial infarction. *Coronary Artery Disease* 2007; **18**

15. Bonello, Laurent, de Labriolle, Axel, Roy, Probal, Steinberg, Daniel H., Pinto Slottow, Tina L., Xue, Zhenyi, Kaneshige, Kimberly, Torguson, Rebecca, Suddath, William O., Satler, Lowell F., Kent, Kenneth M., Pichard, Augusto D., and Waksman, Ron Head-to-head comparison of bivalirudin versus heparin without glycoprotein IIb/IIIa inhibitors in patients with acute myocardial infarction undergoing primary angioplasty. *Cardiovascular Revascularization Medicine* 2007; **10** 156-161.

16. Chu, W. W., Kuchulakanti, P., Wang, P., Torguson, R., Clavijo, L., and Pichard, A. D. Bivalirudin versus unfractionated heparin in patients undergoing percutaneous coronary intervention after acute myocardial infarction. *Cardiovasc.Revasc.Med* 2006; **7** 132-135.

17. GUSTO investigators An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. *New England Journal of Medicine* 2-9-1993; **329** 673-682.

18. TIMI study group Thrombolysis In Myocardial Infarction. 2011;

19. Centre for Reviews and Dissemination Systematic reviews: CRD's guidance for undertaking reviews in health care. 2009; **3rd edition**

20. Downs, S. H. and Black, N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998; **52** 377-384.

21. Olchanski, N., Slawsky, K. A., Plent, S., Kado, C., and Cyr, P. L. Economic impact of switching to bivalirudin for a primary percutaneous coronary intervention in a US hospital. *Hosp.Pract.(Minneap.)* 2010; **38** 138-146.

22. Schwenkglenks, M, Brazier, JE, Szucs, TD, and Foxx, KAA Cost-effectiveness of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor in the treatment of non-ST-segment elevation acute coronary syndromes. *Value in Health* 2011; **14** 24-33.

23. Stone, GW, Ware, JH, Bertrand, ME, Lincoff, AM, Moses, JW, Ohman, EM, and ACUITY Investigators Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. *JAMA* 2007; **298** 2497-2506.

24. Drummond, MF, Jefferson, TO, and BMJ Economic Evaluation Working Party Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996; **313** 275-275.

25. Palmer, S, Sculpher, M, Phillips, Z, Robinson, M, Ginnelly, L, Bakhai, A, Abrams, K, Cooper, N, Packham, C, Alfakih, K, Hall, A, and Gray, D Management of non-ST-elevation acute coronary syndromes: how cost-effective are glycoprotein IIb/IIIA antagonists in the UK National Health Service? *International Journal of Cardiology* 2005; **100** 229-240.

26. NICE Guide to the methods of technology appraisal. *NICE* 2011;

27. Lacey, EA and Walters, SJ Continuing inequality: gender and social class influences on self perceived health after a heart attack. *J Epidemiol Community Health* 2003; **57** 622-627.

28. Curtis, L. Unit costs of health and social care. 2010;

29. Goodacre, S and et al Evaluation of the National Infarct Angioplasty Project Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D (NCCSDO). *NIHR* 2008;

30. Vergel, Y, Palmer, S, Assburg, C, Fenwick, E, de Belder, M, Abrams, K, and et al Is primary angioplasty cost effective in the UK? Results of a comprehensive decision analysis. *Heart* 2007; **93** 1238-1243.

31. Vergel, Y and et al The cost-effectiveness of primary angioplasty compared to thrombolytic therapy for acute myocardial infarction in the UK NHS. *York: University of York.* 2007;

32. Hlatky, MA, Boothroyd, DB, Brooks, MM, Winston, C, Rosen, A, Rogers, WJ, and et al Clinical correlates of the initial and long-term cost of coronary bypass surgery and coronary angioplasty. *Am Heart J* 1999; **138** 376-383.

33. Cohen, D. J., Lincoff, A. M., Lavelle, T. A., Chen, H. L., Bakhai, A., Berezin, R. H., Jackman, D., Sarembock, I. J., and Topol, E. J. Economic evaluation of bivalirudin with provisional glycoprotein IIB/IIIA inhibition versus heparin with routine glycoprotein IIB/IIIA inhibition for percutaneous coronary intervention: results from the REPLACE-2 trial. *Journal of the American College of Cardiology* 2004; **44** 1792-1800.

34. Drummond, MF, Sculpher, M, Torrance, GW, and et al Methods for the economic evaluation of health care programmes. 2005; **3rd**