NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Technology appraisals

Patient access scheme submission template

Romiplostim for the treatment of chronic idiopathic (immune) thrombocytopenic purpura

October 2009

THIS DOCUMENT SHOULD BE READ IN CONJUNCTION WITH OUR RESPONSE TO THE APPRAISAL CONSULTATION DOCUMENT SUBMITTED TO THE INSTITUTE ON 26TH NOVEMBER 2009.

Note: Confidential information is redacted

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Clinical Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Clinical Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Romiplostim (Nplate®) for chronic immune (idiopathic) thrombocytopenic purpura (ITP)

3.2 Please outline the rationale for developing the patient access scheme.

Our rationale for developing the patient access scheme is to financially compensate the NHS for any potential wastage resulting from the temporary non-availability of the 100mcg vial. Our original evidence submission and our response to the Appraisal Consultation Document (ACD) assumed the availability of both the 250mcg and the 100mcg vials. [redacted]

However, the 250mcg vial of romiplostim is the only vial size that is currently available and licensed for use in the UK. The 100mcg vial is expected to be commercially available and licensed for use by [redacted]. The ACD states that the Appraisal Committee *"was persuaded that the availability of a smaller vial size would increase the flexibility of dosing, reduce wastage and consequently improve the overall cost effectiveness of romiplostim."* We have demonstrated in our response to the ACD (see pages 13-18 of our ACD response) that the availability of the 100mcg vial would indeed increase the flexibility of dosing, reduce wastage and consequently demonstrate that romiplostim is a cost effective treatment. We have therefore developed the patient access scheme to financially compensate the NHS for potential wastage resulting from the temporary non-availability of the 100mcg vial.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The scheme is a financially based scheme. Our proposal is to offer a [redacted] rebate on the list price of the 250mcg vial in order to financially compensate the NHS for potential wastage resulting from the temporary non-availability of the 100mcg vial. [redacted]

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

This patient access scheme applies to the whole population for which romiplostim is licensed. The license indication for romiplostim is in a group of chronic ITP patients and not for all chronic ITP patients; specifically it is licensed as a second-line treatment in non-splenectomised patients where surgery is contraindicated and as a second-line treatment in splenectomised patients who are refractory to other treatments.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme we are proposing is a financially based scheme which equates to a [redacted] rebate on the list price of the 250mcg vial (in order to financially compensate the NHS for potential wastage resulting from the temporary non-availability of the 100mcg vial). [redacted]

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

This patient access scheme applies to the whole population for which romiplostim is licensed.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

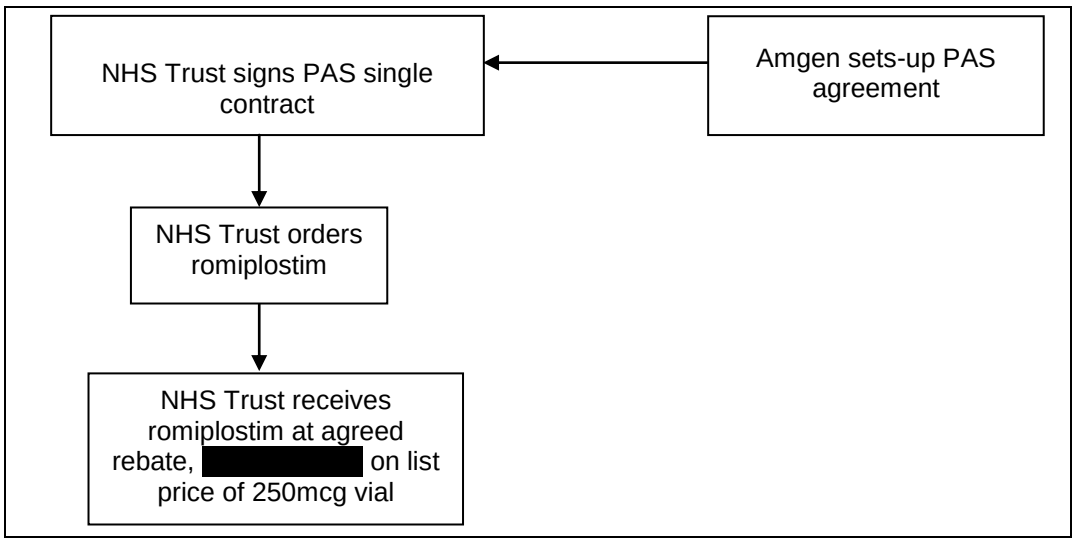
The scheme is a financially based scheme. Our proposal is to offer a [redacted] rebate [redacted] on the list price of the 250mcg vial in order to financially compensate the NHS for potential wastage resulting from the temporary non-availability of the 100mcg vial. [redacted]

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

[redacted]

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

There is no wholesaler involved in distributing romiplostim to the Trusts and distribution is direct (from manufacturer) to pharmacy. We will be responsible for administering the [redacted] rebate [redacted] and distributing stock to the Trusts. The onus is upon us, the manufacturer, to implement the rebate [redacted]



3.10 Please provide details of the duration of the scheme.

The purpose of the scheme is to financially compensate the NHS for potential wastage resulting from the temporary non-availability of the 100mcg vial and we anticipate the 100mcg vial to be commercially available and licensed for use by [redacted]. However, as required by PPRS agreement the scheme will remain in place [redacted] at least until the proposed review date of any resulting NICE guidance. [redacted]

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

The patient access scheme does not require any additional forms, registration or other administrative process to claim the rebate. The scheme requires a single contract to be set-up between the manufacturer and the individual NHS Trust.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The patient access scheme applies to the entire licensed population. The population presented in our main submission as well as our response to the ACD is the whole population for which romiplostim is licensed (consequently, the scheme applies to the whole population for which romiplostim is licensed).

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

The technology appraisal is still in process. We submitted our evidence submission to NICE on 16 October 2008 and in October 2009, NICE issued their ACD. Our original submission as well as our response to the NICE ACD assumed the availability of both the 250mcg and the 100mcg vial, [redacted]
The 250mcg vial of romiplostim is the only vial size that is currently available and licensed for use in the UK. [redacted]

In our ACD response, we updated the economic model to reflect the assumptions considered by the Appraisal Committee to be key drivers as well as our approach to all these key drivers, one being dosing. Consequently, we have demonstrated in our response to the ACD that the availability of the 100mcg vial would increase the

flexibility of dosing, reduce wastage and render romiplostim a cost effective treatment.

We have developed the patient access scheme to financially compensate the NHS for potential wastage resulting from the temporary non-availability of the 100mcg vial (following our response to the ACD issued in October 2009, we informed NICE and the Department of Health of our intention to submit a patient access scheme). Using the economic model presented in our ACD response, we are able to demonstrate that in the current scenario where the 100mcg vial is not available and with the introduction of the patient access scheme in the form of a [redacted] rebate on the 250mcg vial, romiplostim is a cost effective option.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The current model assumes the availability of both the 100mcg and 250mcg vials. However, the 250mcg vial of romiplostim is the only vial size that is currently available and licensed for use in the UK. The patient access scheme of a [redacted] straight rebate on the price of the 250mcg vial was therefore developed to financially compensate the NHS for potential wastage resulting from the temporary non-availability of the 100mcg vial.

In the ACD issued for romiplostim in October 2009 it was stated that, *"The Committee was persuaded that the availability of a smaller vial size would increase the flexibility of dosing, reduce wastage and consequently improve the overall cost effectiveness of romiplostim."* We have indeed demonstrated in our response to the ACD (submitted in November 2009) that the availability of the 100mcg vial would increase the flexibility of dosing, reduce wastage and consequently prove that romiplostim is a cost effective treatment. In our ACD response (see pages 13-18 of our ACD response), we assumed the availability of both the 100mcg and 250mcg vial and presented a revised base case using a more appropriate and clinically relevant calculation of the average dose where the average number of whole vials required for the average patient on romiplostim treatment is 0.99 - 1.04 250mcg vials (realistic versus conservative approach) per non-splenectomised patient and 1.35 - 1.49 250mcg vials (realistic versus conservative approach) per splenectomised patient when expressed in terms of 250mcg vials). In this analysis, we demonstrated that romiplostim remains a cost effective option with ICERs of £21,306-£25,951 in the non-splenectomised group and £13,951-£31,060 in the

splenectomised group (see Table 3.6 on page 23 of our ACD response).

As the 250mcg vial of romiplostim is the only vial size that is currently available and licensed for use in the UK, we have offered a rebate to compensate the NHS for the potential wastage due to the non-availability of the 100mcg vial. Using the methodology as described in our ACD response to calculate average dose (see Table 3.3 on page 14), we first performed an analysis of average dose (the average number of whole vials required for the average patient) assuming the non-availability of the 100mcg vial. We then calculated the average potential dose wastage without the 100mcg vial across the splenectomised and non-splenectomised groups to be [redacted]. The potential additional wastage and the resulting compensatory rebate of [redacted] are detailed in Table 1.

Table 1: Calculation of patient access scheme rebate level necessary to compensate for the non-availability of the 100mcg vial*

	Non-Splenectomised	**Splenectomised**
Average Dose as per ACD response (realistic versus conservative approach) assuming the availability of the 100mcg vial		
• Average number of whole vials per patient with (both 250mcg & 100mcg vials available)	0.99 - 1.04 250mcg vials	1.35 - 1.49 250mcg vials
Average Dose calculated using the same methodology in our ACD response (realistic versus conservative approach) assuming the non-availability of the 100mcg vial		
• Average number of whole vials per patient (only 250mcg vial available)	[redacted]	[redacted]
Potential wastage (%) assuming the non-availability of the 100mcg vial		
• Wastage (%) with no 100mcg vial (realistic approach) • Wastage (%) with no 100mcg vial (conservative approach)	([redacted]-0.99)/[redacted] = [redacted] ([redacted]-1.04)/[redacted] = [redacted]	([redacted]-1.35)/[redacted]= [redacted] ([redacted]-1.49)/[redacted] =[redacted]
Average rebate to compensate for potential wastage assuming the non-availability of the 100mcg vial		
• Average Rebate (realistic approach) • Average Rebate (conservative approach)	[redacted]	

***The average number of whole vials is Table 1 is expressed solely in terms of the number of 250mcg vials required as romiplostim is constantly priced per mcg across vial sizes (e.g. 1.50 100mcg vials can be converted into number of 250mcg vials by multiplying it by (100/250), which yields 0.60 250mcg vials).**

In the current scenario without the 100mcg vial and with a [redacted] rebate, we demonstrate that romiplostim is a cost effective option with ICERs of £24,795 - £28,278 in the non-splenectomy group and £4,615 - £16,530 in the splenectomy group (see sections 4.7 to 4.13 below).

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data does not change in the presence or absence of the patient access scheme as this scheme is a financially based scheme designed to compensate the NHS for potential wastage resulting from the temporary non-availability of the 100mcg vial.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

There will be no costs associated with the implementation and operation of the proposed patient access scheme as this scheme is one involving a straight rebate of [redacted].

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

There will be no additional treatment related costs incurred by implementing the patient access scheme as this scheme is a financially-based scheme involving a straight rebate of [redacted]

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

In our ACD response, we updated the economic model to reflect the assumptions considered by the Appraisal Committee to be key drivers of the economics as well as our approach to all these key drivers, one being dosing. We also assumed the availability of the 100mcg vial. Consequently, we have demonstrated in our response to the ACD that the availability of the 100mcg vial would increase the flexibility of dosing, reduce wastage and render romiplostim a cost effective treatment.

Given that the 250mcg vial of romiplostim is the only vial size that is currently available and licensed for use in the UK, following our response to the ACD issued in October 2009, we informed NICE and the Department of Health of our intention to submit a patient access scheme to financially compensate the NHS for potential wastage resulting from the temporary non-availability of the 100mcg vial. Using the economic model presented in our ACD response, we are able to demonstrate that in the scenario without the 100mcg vial and with the patient access scheme of [redacted] rebate on the 250mcg vial, romiplostim remains a cost effective option. For ease of reference, we first present in Table 2 the results as detailed in our ACD response (which assumed the availability of the 100mcg vial and therefore did not incorporate a patient access scheme). Table 3 presents the results without the patient access

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

scheme and the non-availability of the 100mcg vial. Table 4 presents the **revised base case**, i.e. results assuming non-availability of the 100mcg vial and with the patient access scheme of [redacted] rebate. [redacted]

Table 2: Cost effectiveness results as presented in our ACD Response (Table 3.6 on page 23) assuming availability of 100mcg vial

	Non-Splenectomy		Splenectomy	
	Romiplostim	**Active Comparator**	**Romiplostim**	**Active Comparator**
Realistic Approach (as described in our ACD response)				
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed and associated costs (£)	£19,257	£28,172	£15,471	£21,599
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	N/A	£32,277	N/A	£14,339
LYG	22.91	20.10	23.88	21.96
LYG difference	N/A	2.81	N/A	1.92
QALYs	11.93	10.41	12.38	11.35
QALY difference	N/A	1.51	N/A	1.03
ICER (£)	N/A	**£21,306**	N/A	**£13,951**
Conservative Approach (as described in our ACD response)				
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed and associated costs (£)	£19,257	£28,172	£15,471	£21,599
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	N/A	£39,313	N/A	£31,921
LYG	22.91	20.10	23.88	21.96
LYG difference	N/A	2.81	N/A	1.92
QALYs	11.93	10.41	12.38	11.35
QALY difference	N/A	1.51	N/A	1.03
ICER (£)	N/A	**£25,951**	N/A	**£31,060**

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost effectiveness ratio.

Table 3: Cost effectiveness results assuming non-availability of 100mcg vial and without the patient access scheme [redacted] rebate on 250mcg vial

	Non-Splenectomy		Splenectomy	
	Romiplostim	**Active Comparator**	**Romiplostim**	**Active Comparator**
Realistic Approach (as described in our ACD response)				
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed and associated costs (£)	£19,257	£28,172	£15,471	£21,599
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	N/A	£86,115	N/A	£58,614
LYG	22.91	20.10	23.88	21.96
LYG difference	N/A	2.81	N/A	1.92
QALYs	11.93	10.41	12.38	11.35
QALY difference	N/A	1.51	N/A	1.03
ICER (£)	N/A	**£56,846**	N/A	**£57,032**
Conservative Approach (as described in our ACD response)				
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed and associated costs (£)	£19,257	£28,172	£15,471	£21,599
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	N/A	£93,151	N/A	£74,940
LYG	22.91	20.10	23.88	21.96
LYG difference	N/A	2.81	N/A	1.92
QALYs	11.93	10.41	12.38	11.35
QALY difference	N/A	1.51	N/A	1.03
ICER (£)	N/A	**£61,490**	N/A	**£72,918**

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost effectiveness ratio.

Table 4: Cost effectiveness results assuming non-availability of 100mcg vial and with the patient access scheme [redacted] rebate on 250mcg vial *(Revised Base Case following ACD Response and PAS)*

	Non-Splenectomy		Splenectomy	
	Romiplostim	**Active Comparator**	**Romiplostim**	**Active Comparator**
Realistic Approach (as described in our ACD response)				
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed and associated costs (£)	£19,257	£28,172	£15,471	£21,599
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	N/A	£37,561	N/A	£4,743
LYG	22.91	20.10	23.88	21.96
LYG difference	N/A	2.81	N/A	1.92
QALYs	11.93	10.41	12.38	11.35
QALY difference	N/A	1.51	N/A	1.03
ICER (£)	N/A	**£24,795**	N/A	**£4,615**
Conservative Approach (as described in our ACD response)				
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed and associated costs (£)	£19,257	£28,172	£15,471	£21,599
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	N/A	£42,838	N/A	£16,988
LYG	22.91	20.10	23.88	21.96
LYG difference	N/A	2.81	N/A	1.92
QALYs	11.93	10.41	12.38	11.35
QALY difference	N/A	1.51	N/A	1.03
ICER (£)	N/A	**£28,278**	N/A	**£16,530**

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost effectiveness ratio.

Table 5: Cost effectiveness results assuming [redacted]

(Scenario Analysis)

	Non-Splenectomy		Splenectomy	
	Romiplostim	**Active Comparator**	**Romiplostim**	**Active Comparator**
Realistic Approach (as described in our ACD response)				
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed and associated costs (£)	£19,257	£28,172	£15,471	£21,599
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	N/A	£17,942	N/A	-£6,509
LYG	22.91	20.10	23.88	21.96
LYG difference	N/A	2.81	N/A	1.92
QALYs	11.93	10.41	12.38	11.35
QALY difference	N/A	1.51	N/A	1.03
ICER (£)	N/A	**£11,844**	N/A	**Dominant**
Conservative Approach (as described in our ACD response)				
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed and associated costs (£)	£19,257	£28,172	£15,471	£21,599
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	N/A	£23,711	N/A	£6,427
LYG	22.91	20.10	23.88	21.96
LYG difference	N/A	2.81	N/A	1.92
QALYs	11.93	10.41	12.38	11.35
QALY difference	N/A	1.51	N/A	1.03
ICER (£)	N/A	**£15,652**	N/A	**£6,253**

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 6: Incremental results assuming non-availability of 100mcg vial and without the patient access scheme [redacted] rebate on 250mcg vial

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Non-Splenectomy (Realistic approach)							
Active Comparator (see ACD response)	[redacted]	20.10	10.41	£86,115	2.81	1.51	**£56,846**
Romiplostim	[redacted]	22.91	11.93				
Non-Splenectomy (Conservative approach)							
Active Comparator (see ACD response)	[redacted]	20.10	10.41	£93,151	2.81	1.51	**£61,490**
Romiplostim	[redacted]	22.91	11.93				
Splenectomy (Realistic approach)							
Active Comparator (see ACD response)	[redacted]	21.96	11.35	£58,614	1.92	1.03	**£57,032**
Romiplostim	[redacted]	23.88	12.38				
Splenectomy (Conservative approach)							
Active Comparator (see ACD response)	[redacted]	21.96	11.35	£74,940	1.92	1.03	**£72,918**
Romiplostim	[redacted]	23.88	12.38				

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost effectiveness ratio.

Table 7: Incremental results assuming non-availability of 100mcg vial and with the patient access scheme of [redacted] rebate on 250mcg vial *(Revised Base Case following ACD Response and PAS)*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Non-Splenectomy (Realistic approach)							
Active Comparator (see ACD response)	[redacted]	20.10	10.41	£37,561	2.81	1.51	**£24,795**
Romiplostim	[redacted]	22.91	11.93				
Non-Splenectomy (Conservative approach)							
Active Comparator (see ACD response)	[redacted]	20.10	10.41	£42,838	2.81	1.51	**£28,278**
Romiplostim	[redacted]	22.91	11.93				
Splenectomy (Realistic approach)							
Active Comparator (see ACD response)	[redacted]	21.96	11.35	£4,743	1.92	1.03	**£4,615**
Romiplostim	[redacted]	23.88	12.38				
Splenectomy (Conservative approach)							
Active Comparator (see ACD response)	[redacted]	21.96	11.35	£16,988	1.92	1.03	**£16,530**
Romiplostim	[redacted]	23.88	12.38				

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost effectiveness ratio.

Table 8: Incremental results assuming [redacted] (Scenario Analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Non-Splenectomy (Realistic approach)							
Active Comparator (see ACD response)	[redacted]	20.10	10.41	£17,942	2.81	1.51	**£11,844**
Romiplostim	[redacted]	22.91	11.93				
Non-Splenectomy (Conservative approach)							
Active Comparator (see ACD response)	[redacted]	20.10	10.41	£23,711	2.81	1.51	**£15,652**
Romiplostim	[redacted]	22.91	11.93				
Splenectomy (Realistic approach)							
Active Comparator (see ACD response)	[redacted]	21.96	11.35	-£6,509	1.92	1.03	**Dominant**
Romiplostim	[redacted]	23.88	12.38				
Splenectomy (Conservative approach)							
Active Comparator (see ACD response)	[redacted]	21.96	11.35	£6,427	1.92	1.03	**£6,253**
Romiplostim	[redacted]	23.88	12.38				

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

The deterministic sensitivity analyses presented here are as described in our ACD response for this technology appraisal. We addressed the following key points raised in the ACD (please refer to the ACD response, pages 10-23, for a detailed discussion on the sensitivity analysis).

We have presented further sensitivity analysis to demonstrate how the ICERs change when factors beyond that described in our ACD response are varied

(such as treatment pathway mix, response rates and response time of comparators). These are detailed in Appendix 1.

1. Appropriate comparator pathway
   We acknowledge and agree with the Appraisal Committee that the appropriate comparator pathway could involve starting with an active treatment rather than 'watch and rescue'. However, we consider that this was implemented inconsistently in the sensitivity analysis presented in the ACD. Specifically, the proportion of patients starting with the active treatment (rituximab) in the comparator arm (100%) is not consistent with the proportion of patients who subsequently go onto receive this treatment in the romiplostim arm (59%). We have performed this analysis in the ACD response (see pages 10-12 of our ACD response) by consistently setting the proportion of patients who receive rituximab in the comparator arm equal to the proportion of patients who receive rituximab further down the treatment pathway in the romiplostim arm, with the proportion set consistently, but perhaps unrealistically, at 100% in both arms. This consistent analysis results in a smaller increase in the ICERs compared to the inconsistent analysis presented in the ACD.

2. Costs of bone marrow tests and blood film assessment
   We agree with the sensitivity analysis presented in the ACD which included the cost of bone marrow tests and blood film assessment in the cost of treating with romiplostim. In clinical studies, 3.69% (10/271) of subjects were reported to have bone marrow reticulin. We conservatively assume (see pages 19-21 of our ACD response) that 10% of patients require a bone marrow biopsy in the model. Blood film assessments are recommended prior to starting romiplostim and may be required if a patient loses response to romiplostim. Therefore, we assume that two blood film assessments are required. Based on the assumption that 10% of patients are likely to require one-off bone marrow tests and that a total of two blood film assessments are required during their course of treatment, we demonstrate that the ICERs increase marginally and not by the extent presented in the ACD.

3. Use of EQ-5D data from RCT
   We agree in principle on the use of EQ-5D data from our RCTs. However, the EQ-5D data from the trials were based on 125 patients pooled across placebo and romiplostim arms under the conservative assumption that there is no treatment effect on utility. In this instance, we believe that the time trade-off utility values based on a sample size of 359 people (almost three times larger than our trial) would significantly add to the strength of the utility data. Therefore, we postulate that it would be inappropriate to ignore these data in an area where such data is scarce. A pragmatic approach would be to pool the two sources of utility data in order to obtain more robust estimates of utility scores in ITP based on a larger sample as well as to minimize any bias resulting from pooling across arms of the RCTs. We have presented in our ACD response (see pages 21-22 of our ACD response) revised ICERs from pooling the two sources of utility data.

4. Number of vials used per person

The sensitivity analysis presented in the ACD which increased the number of vials used per patient had a large effect on the ICERs, especially for the splenectomised group. We understand the concerns raised by the Appraisal Committee with regards to potential wastage and vial sharing and have presented in our ACD response (see pages 13-18 of our ACD response) clear and detailed information on our dosing calculations and demonstrate that within the dosing limits stated in the Summary of Product Characteristics (SPC), and with the availability of a 100mcg vial, the average number of whole vials required per average patient (allowing for wastage and no vial sharing) yields cost effective ICERs.

In addition, we demonstrate in this document (as described in our responses to questions 4.3 and 4.7) that in the current scenario without the 100mcg vial and with a [redacted] rebate, romiplostim is a cost effective option with ICERs of £24,795 - £28,278 in the non-splenectomy group and £4,615 - £16,530 in the splenectomy group.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

A summary of the PSA results for the various scenarios with and without the rebate of [redacted] is presented in Table 9. The detailed scatter plots and cost effectiveness acceptability curves (CEACs) for the revised base case (without 100mcg vial and [redacted] rebate) are shown in Figures 1a-1h. The detailed scatter plots and CEACs for all other scenarios presented in Table 9 are shown in Appendix 1.

Table 9: Probabilistic sensitivity analysis summary results

	Probability of being cost effective at threshold	
	£20,000 (conservative versus realistic approach)	**£30,000 (conservative versus realistic approach)**
ACD Response Base Case, (Table 3.6 Page 23) - with 100mcg & 250mcg vials		
Non-splenectomy	13% - 34%	47% - 67%
Splenectomy	62% - 96%	81% - 97%
Scenario without 100mcg vial and without [redacted] rebate		
Non-splenectomy	0% - 0%	0% - 1%
Splenectomy	0% - 0%	0% - 2%
REVISED BASE CASE - without 100mcg vial and with [redacted] rebate		
Non-splenectomy	12% - 33%	47% - 66%
Splenectomy	63% - 95%	82% - 98%
[redacted]		
Non-splenectomy	62% - 74%	83% - 87%
Splenectomy	85% - 98%	92% - 99%

Figure 1a: Revised base case – Assuming non-availability of 100mcg vial and with the patient access scheme of [redacted] rebate on 250mcg vial for non-splenectomised group (realistic approach)

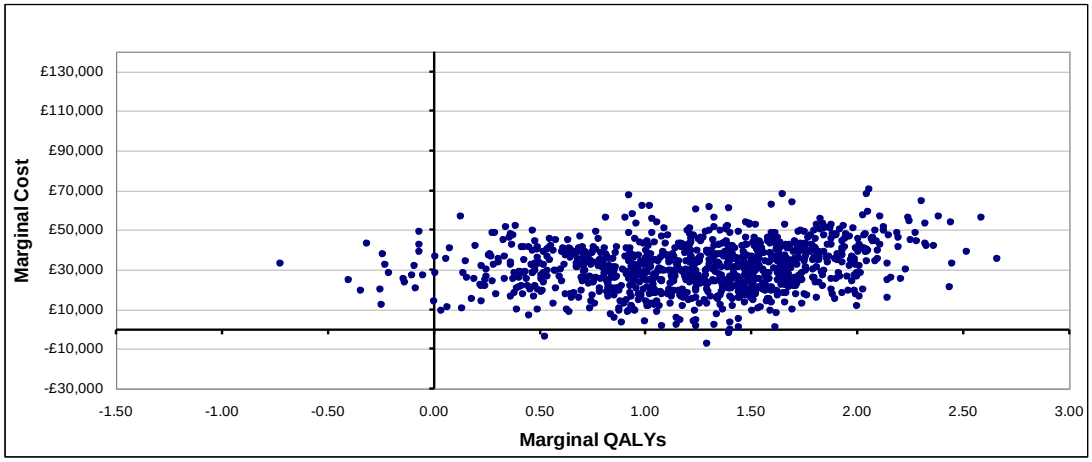


Figure 1b: Revised base case – assuming non-availability of 100mcg vial and with the patient access scheme of [redacted] rebate on 250mcg vial for non-splenectomised group (realistic approach)

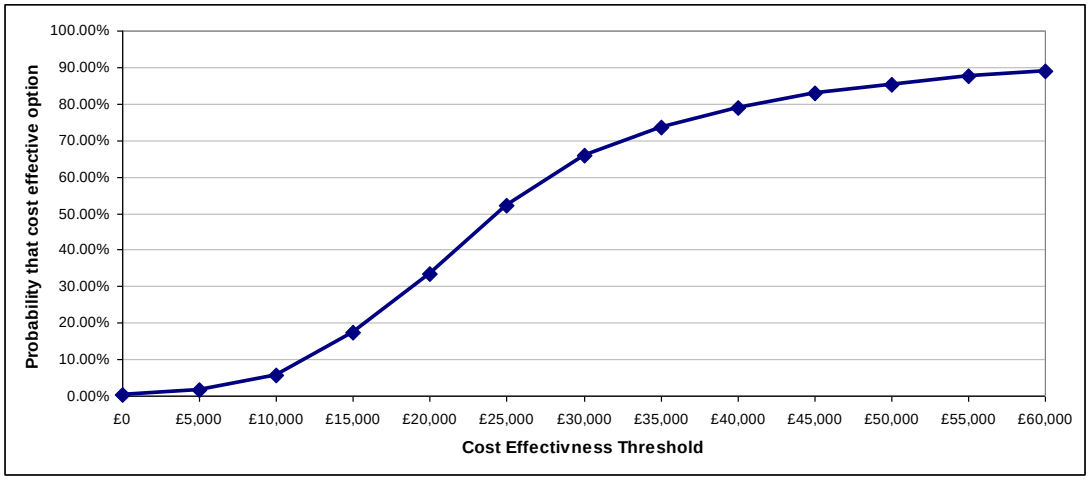


Figure 1c: Revised base case – Assuming non-availability of 100mcg vial and with the patient access scheme of [redacted] rebate on 250mcg vial for non-splenectomised group (conservative approach)

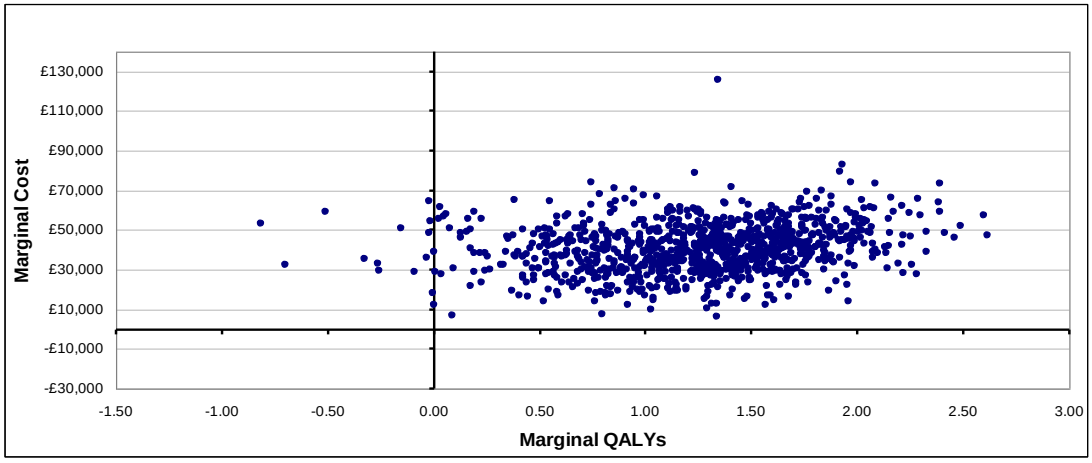
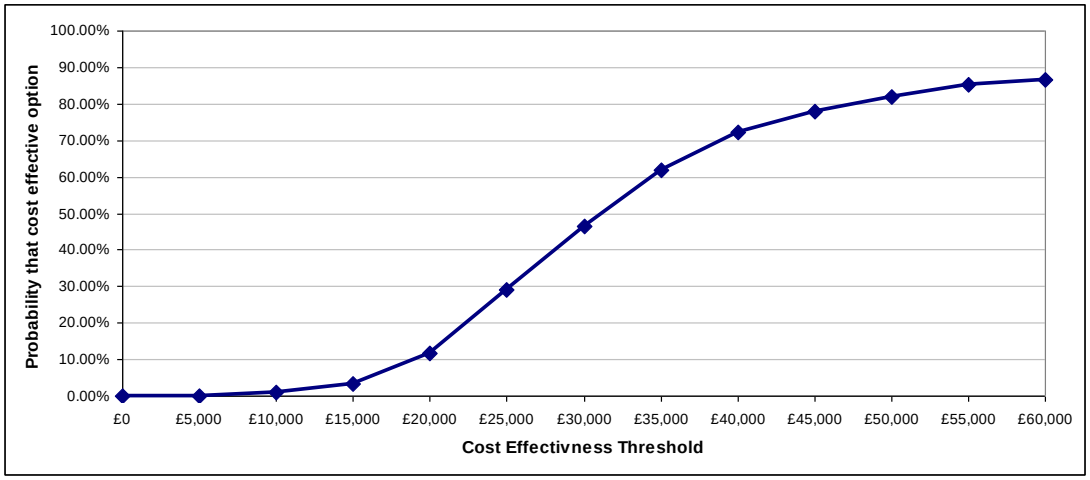


Figure 1d: Revised base case – Assuming non-availability of 100mcg vial and with the patient access scheme of [redacted] rebate on 250mcg vial for non-splenectomised group (conservative approach)



- **Figure 1e: Revised base case – Assuming non-availability of 100mcg vial and with the patient access scheme of [redacted] rebate on 250mcg vial for splenectomised group (realistic approach)**

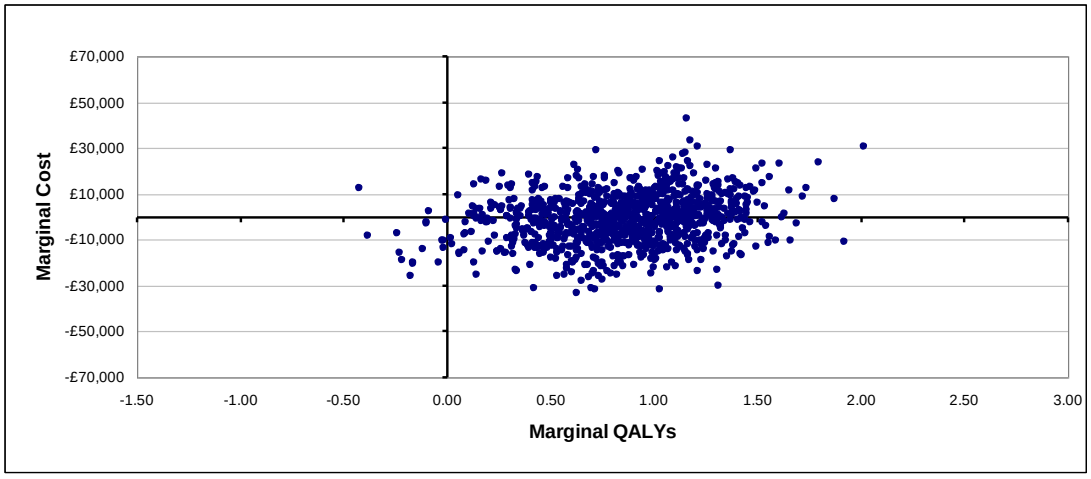


Figure 1f: Revised base case – Assuming non-availability of 100mcg vial and with the patient access scheme of [redacted] rebate on 250mcg vial for splenectomised group (realistic approach)

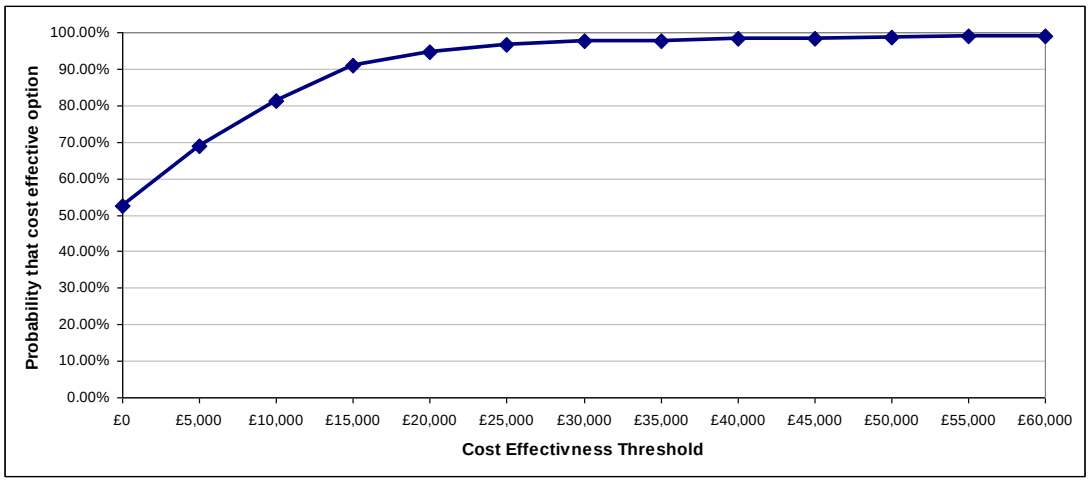


Figure 1g: Revised base case – Assuming non-availability of 100mcg vial and with the patient access scheme of [redacted] rebate on 250mcg vial for splenectomised group (conservative approach)

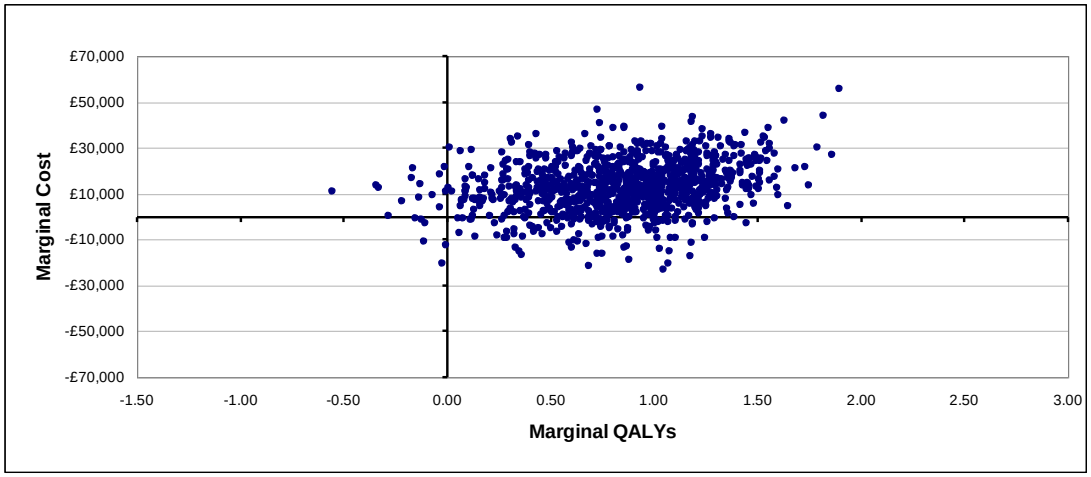
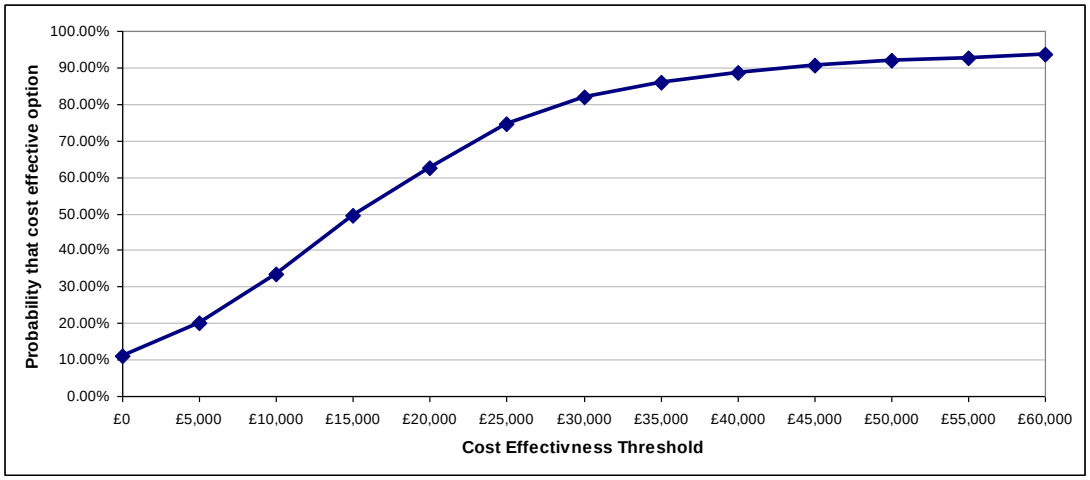


Figure 1h: Revised base case – Assuming non-availability of 100mcg vial and with the patient access scheme of [redacted] rebate on 250mcg vial for splenectomised group (conservative approach)



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

The key scenario analysis relates to the different assumptions with respect to dosing, i.e. conservative versus realistic approach as explained in our response to the ACD (see pages 16-18 of our ACD response). Table 10 below summarises the changes in the ICER over the different dosing assumptions in light of the patient access scheme.

Table 10: Scenario Analysis (Realistic Versus Conservative Approach)

	Non-Splenectomised **Realistic approach vs. Conservative approach**	**Splenectomised** **Realistic approach vs. Conservative approach**
ICERs as in ACD response Table 3.6, Page 23 (*assume 100mcg & 250mcg vials are available)*	£21,306 - £25,951	£13,951 - £31,060
Revised base case *(assume no 100mcg vial and with [redacted] discount)*	£24,795 - £28,278	£4,615 - £16,530
Scenario Analysis [redacted]	£11,844 - £15,652	Dominant - £6,253

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

The patient access scheme we have proposed is a financially based scheme [redacted]

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is

shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 11: Results showing impact of patient access scheme on ICERs

	ICER* for Romiplostim versus:			
	Active Comparator (see ACD response)			
	ACD Response (with 100mcg & without [redacted] rebate)	**Without PAS (without 100mcg & without [redacted] rebate)**	**With PAS – Revised Base Case (without 100mcg & with [redacted] rebate)**	**[redacted]**
Non-Splenectomy	£21,306 - £25,951	£56,846 - £61,490	**£24,795 - £28,278**	£11,844 - £15,652
Splenectomy	£13,951 - £31,060	£57,032 - £72,918	**£4,615 - £16,530**	Dominant - £6,253

***ICERs are given as a range between realistic and conservative approaches as explained in our ACD response (see pages 16-18 of our ACD response).**
PAS: patient access scheme.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

APPENDIX 1: QUESTION 4.9 – ADDITIONAL SENSITIVITY ANALYSIS (SA) TO THAT PRESENTED IN OUR ACD RESPONSE

We have presented the following additional sensitivity analyses (to that described in our ACD response) to understand the robustness of the ICERs:

- SA1: Treatment of chronic ITP is individualized and there is no fixed treatment pathway. This analysis looks at changing the treatment pathway mix, particularly by increasing the usage of comparator treatments by 25% (in favour of treatment pathway without romiplostim).

- SA2: Time on treatment determines time with platelet response and consequently risk of bleeds. This analysis looks at increasing the response time for comparators by 50% (in favour of treatment pathway without romiplostim as this means longer time on treatment, more bleeds averted and avoidance/delay of rescue medications for the comparators).

- SA3: The ACD states that the uncertainty surrounding the relative efficacy of romiplostim over active comparators is large. It was not possible to perform an indirect comparison as there were no RCTs for the comparators (and it was not possible to extract hazard ratios). Although the true uncertainty of the relative efficacy estimates is unknown and there is a range of plausible estimates for relative efficacy, we believe that romiplostim remains cost effective across this range. To demonstrate this, we use Rituximab as an example and assume the best case response rates for Rituximab of 75% (Zaja 2008a[3]) instead of 57.7% assumed in the base case (in favour of treatment pathway without romiplostim).

- SA4: We explained in our ACD response that the time trade-off (TTO) utility values are likely to significantly add to the strength of utility data in an area where data is scarce. The description of the vignettes in the TTO study is highly relevant is it was based on ITP disease questionnaires and health states defined in the economic model. We acknowledge that vignettes can exaggerate differences between health states and have therefore performed this analysis scaling back (i.e. decreasing the utility values) the relative results of the TTO study where there are no trial-based utility values, to reflect relative differences observed in the trial where there are trial-based EQ-5D data values (likely to bias against romiplostim).

- SA5: It is possible that a proportion of the HRG costs for bleeds could be accounted for in the rescue medication costs. We have therefore performed this analysis setting the costs of bleeds to £0. This is unrealistically and highly conservative as setting HRG costs to £0 includes setting all costs such as hospitalization, bed time, nurse costs to £0 and not just costs specific to rescue medications.

[3] Zaja F, Battista ML, Pirrotta MT et al. Lower dose rituximab is active in adults patients with idiopathic thrombocytopenic purpura. Haematologica 2008; 93(6):930-933.

Table: Additional Sensitivity Analyses

	ICER for Romiplostim versus:			
	Active Comparator (see ACD response)			
	ACD Response (with 100mcg & without [redacted] rebate)	**Without PAS (without 100mcg & without [redacted] rebate)**	**With PAS – Revised Base Case (without 100mcg & with [redacted] rebate)**	**[redacted]**
BASE CASE				
Non-Splen	£21,306-£25,951	£56,846-£61,490	**£24,795-£28,278**	£11,844-£15,652
Splen	£13,951-£31,060	£57,032-£72,918	**£4,615-£16,530**	Dominant-£6,253
SA1: Increasing usage of comparator treatments by 25%				
Non-Splen	£23,636-£28,453	£60,500-£65,317	**£27,254-£30,867**	£13,820-£17,771
Splen	£18,313-£36,012	£62,882-£79,317	**£8,654-£20,980**	Dominant-£10,349
SA 2: Increasing response time for comparators by 50%				
Non-Splen	£24,840-£29,706	£62,079-£66,946	**£28,495-£32,145**	£14,925-£18,915
Splen	£20,606-£38,606	£65,931-£82,644	**£10,784-£23,319**	Dominant-£12,507
SA 2: Assuming best case response rates for Rituximab of 75% (Zaja 2008a) instead of 57.7% assumed in the base case				
Non-Splen	£22,128-£26,826	£57,824-£62,513	**£25,468-£28,985**	£12,394-£16,239
Splen	£15,327-£32,607	£58,497-£74,536	**£5,576-£17,605**	Dominant-£7,230
SA 4: Scaling back utility values in TTO study (see Table A1 for scaled back utility values).				
Non-Splen	£21,968-£26,757	£58,612-£63,400	**£25,565-£29,196**	£12,212-£16,138
Splen	£14,380-£32,015	£58,786-£75,160	**£4,757-£17,038**	Dominant-£6,445
SA 5: Setting cost of bleeds to £0				
Non-Splen	£27,191-£31,835	£62,731-£67,375	**£30,679-£34,162**	£17,728 - £21,537
Splen	£19,913-£37,021	£62,993-£78,880	**£10,577-£22,491**	Dominant-£12,215

***ICERs are given as a range between realistic and conservative approaches as explained in our ACD response; SA: Sensitivity Analysis.**

Table A1: EQ-5D Utility Values from RCT & Survey (Page 22 of ACD response)

State	EQ5D RCT Utilities	UK Survey Utilities	Scaled Values (Survey Utility *X* Scaling Parameter*)
Platelet > 50,000 and no bleed	0.794	0.863	0.794
Platelet > 50,000 and OP bleed	NA*	0.734	0.670
Platelet < 50,000 and no bleed	0.762	0.841	0.762
Platelet < 50,000 and OP bleed	NA*	0.732	0.668
Platelet < 50,000 and IH bleed	NA*	0.038	0.035
Platelet < 50,000 and GI bleed	NA*	0.54	0.493
Platelet < 50,000 and other bleed	NA*	0.54	0.493

*Scaling parameter - Average difference between RCT & Survey Utilities = [1- ((0.863-0.794)/0.863) + (0.841-0.762)/0.841)/2)] **= 1- 0.0869 = 0.9131**

OP – Outpatient; IH – Intracranial Haemorrhage; GI – Gastrointestinal; *Insufficient data to calculate these values and so assumed to be the same as the UK survey utilities

APPENDIX 2: QUESTION 4.10 – DETAILED SCATTER PLOTS AND CEACS FOR ALL SCENARIOS

Figure 2a: ACD Response base case – Assuming availability of both 100mcg and 250mcg vials for non-splenectomised group (realistic approach)

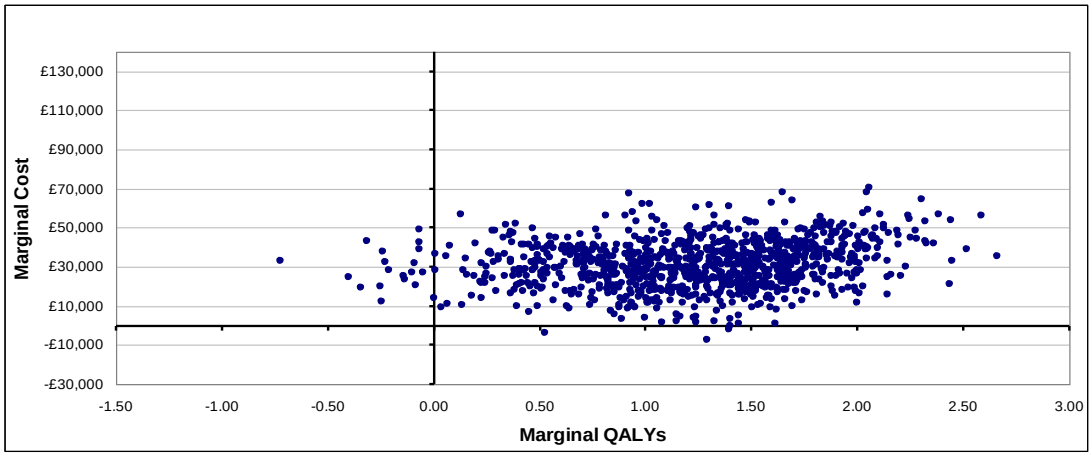


Figure 2b: ACD Response base case – Assuming availability of both 100mcg vial and 250mcg vials for non-splenectomised group (realistic approach)

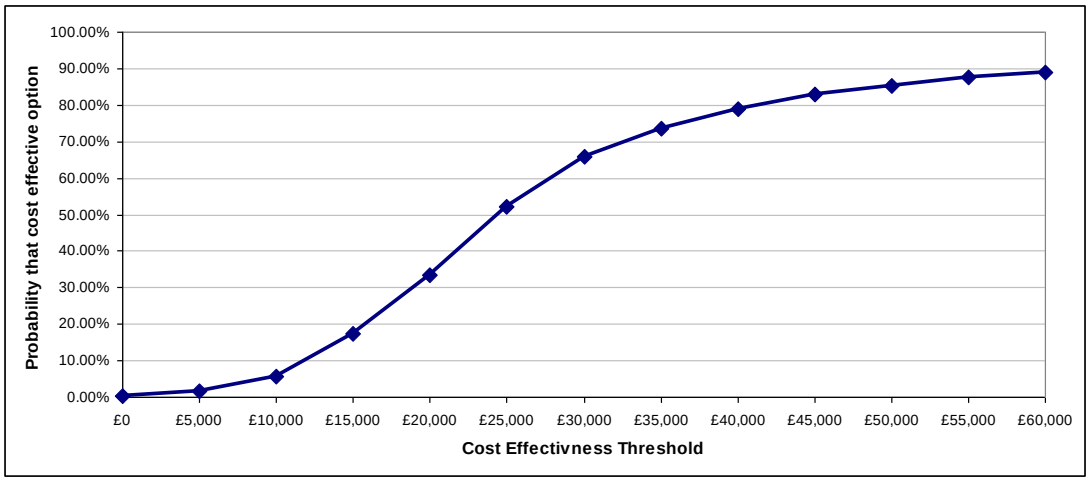


Figure 2c: ACD Response base case – Assuming availability of both 100mcg vial and 250mcg vials for non-splenectomised group (conservative approach)

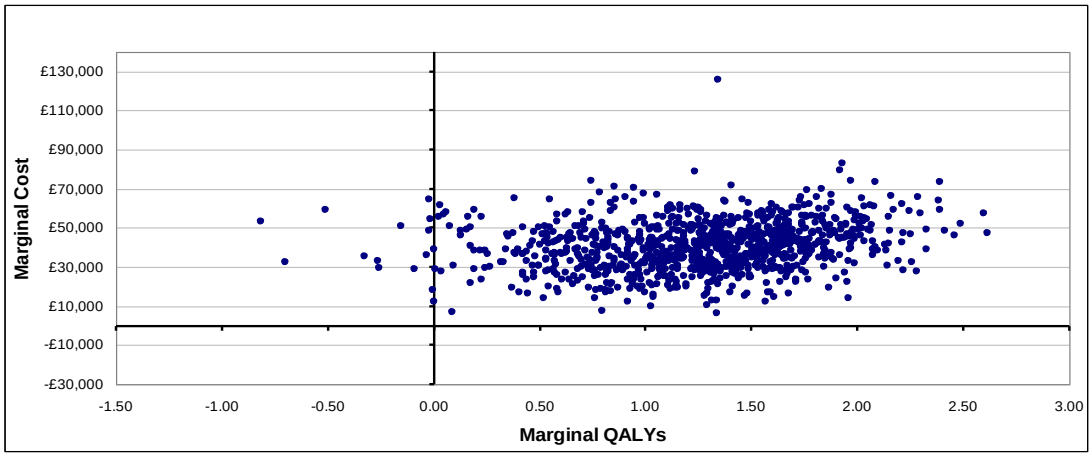


Figure 2d: ACD Response base case – Assuming availability of both 100mcg vial and 250mcg vials for non-splenectomised group (conservative approach)

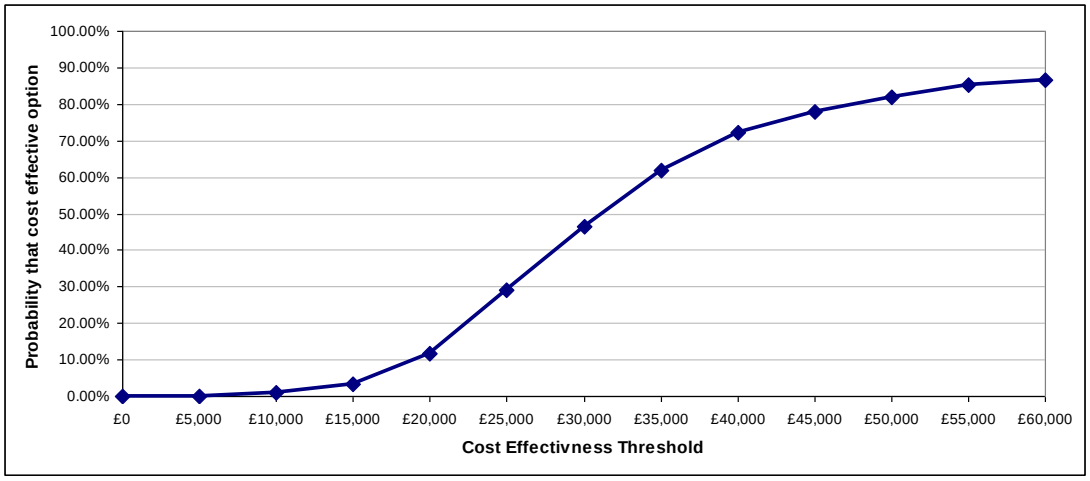


Figure 2e: ACD Response base case – Assuming availability of both 100mcg vial and 250mcg vials for splenectomised group (realistic approach)

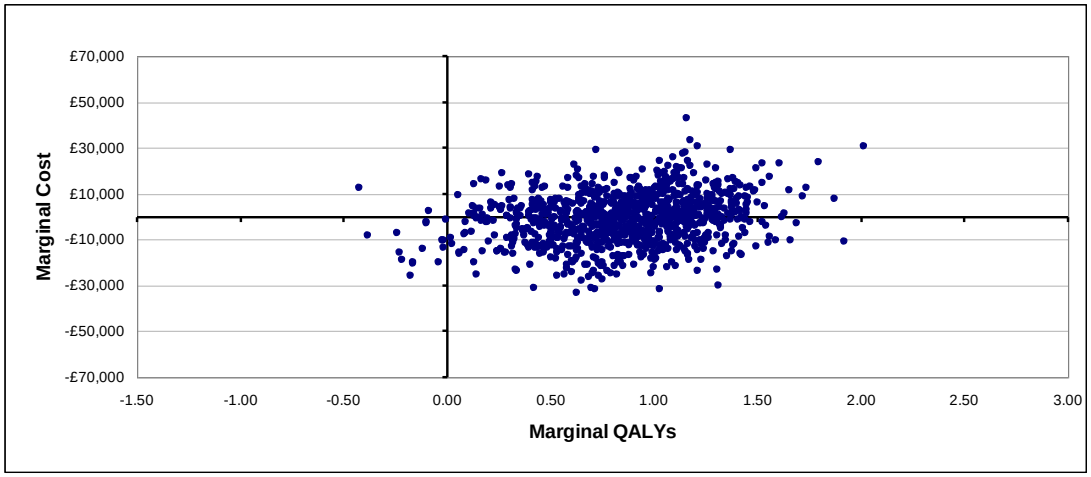


Figure 2f: ACD Response base case – Assuming availability of both 100mcg vial and 250mcg vials for splenectomised group (realistic approach)

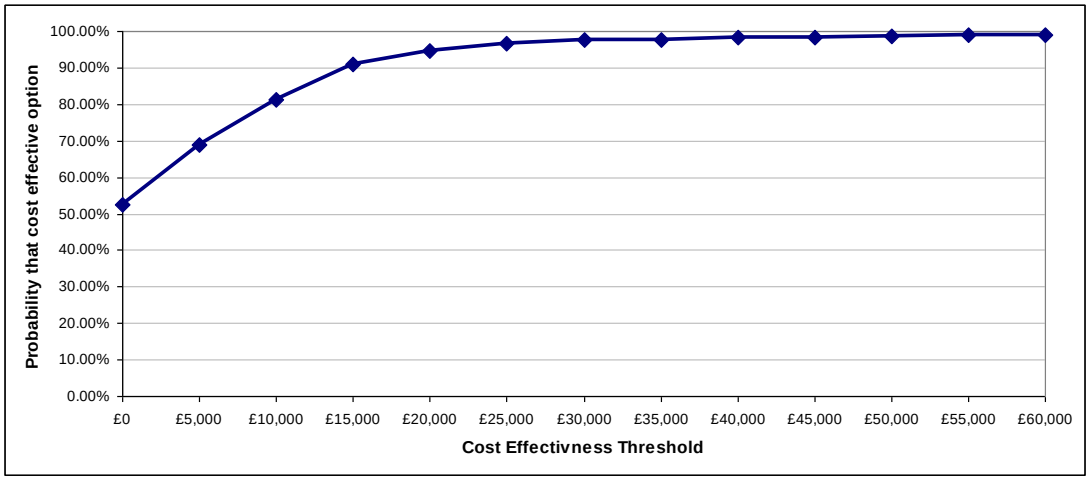


Figure 2g: ACD Response base case – Assuming availability of both 100mcg vial and 250mcg vials for splenectomised group (conservative approach)

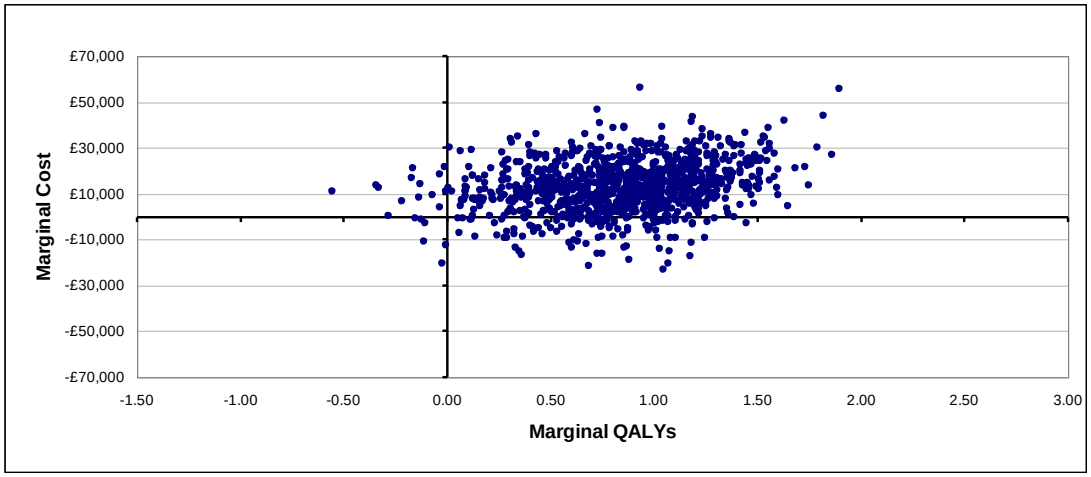


Figure 2h: ACD Response base case – Assuming availability of both 100mcg vial and 250mcg vials for splenectomised group (realistic approach)

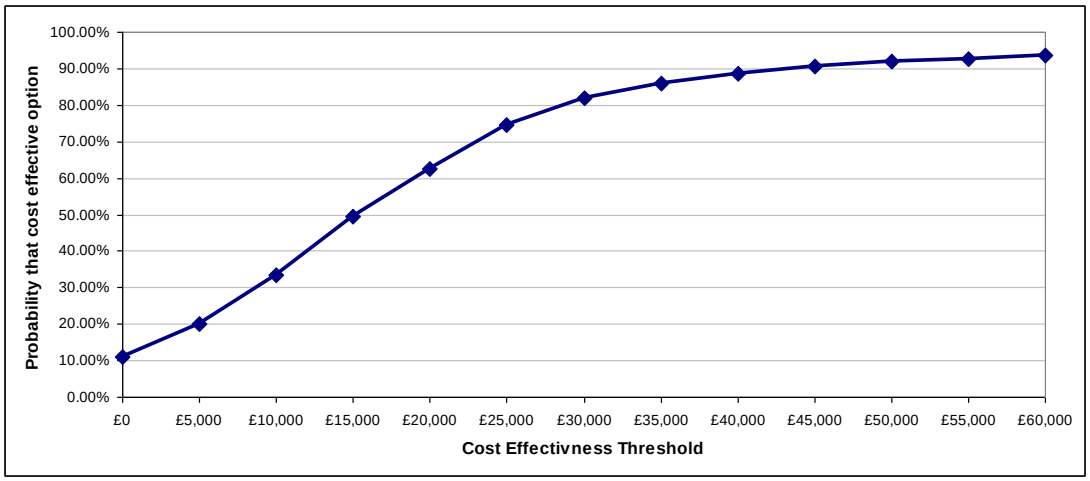


Figure 3a: Scenario Analysis – Assuming non-availability of 100mcg vial and without patient access scheme of [redacted] rebate on 250mcg vial for non-splenectomised group (realistic approach)

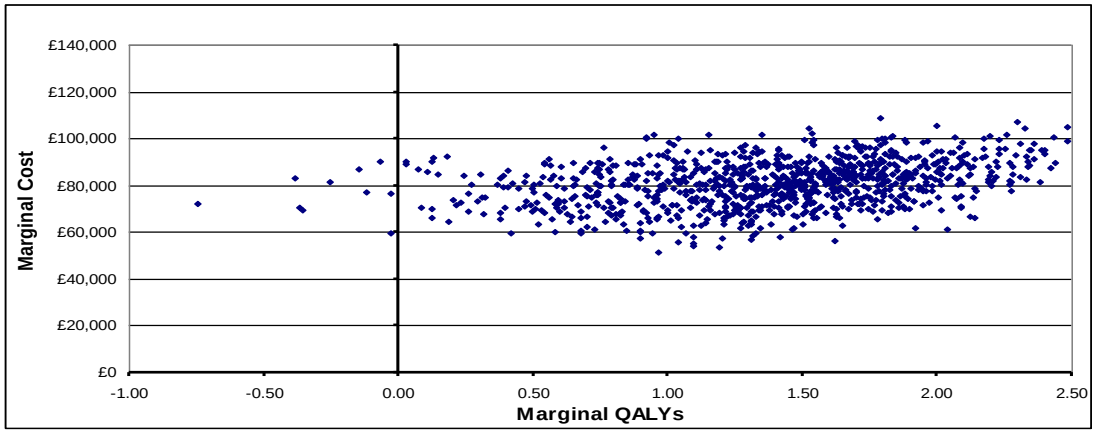


Figure 3b: Scenario Analysis – Assuming non-availability of 100mcg vial and without patient access scheme of [redacted] rebate on 250mcg vial for non-splenectomised group (realistic approach)

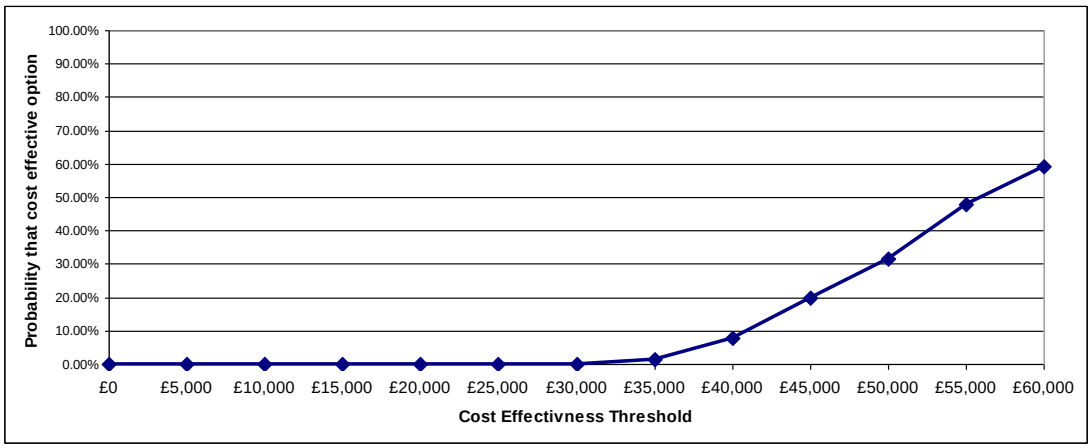


Figure 3c: Scenario Analysis – Assuming non-availability of 100mcg vial and without patient access scheme of [redacted] rebate on 250mcg vial for non-splenectomised group (conservative approach)

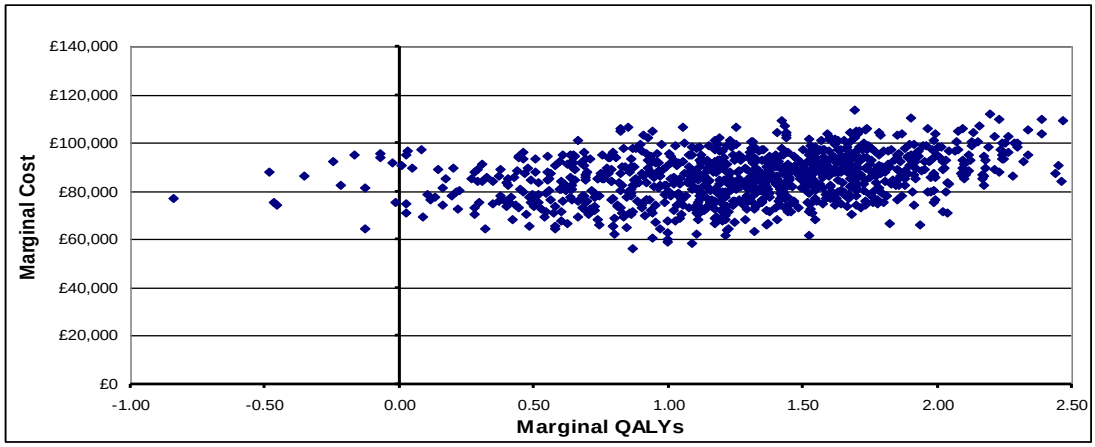


Figure 3d: Scenario Analysis – Assuming non-availability of 100mcg vial and without patient access scheme of [redacted] rebate on 250mcg vial for non-splenectomised group (conservative approach)

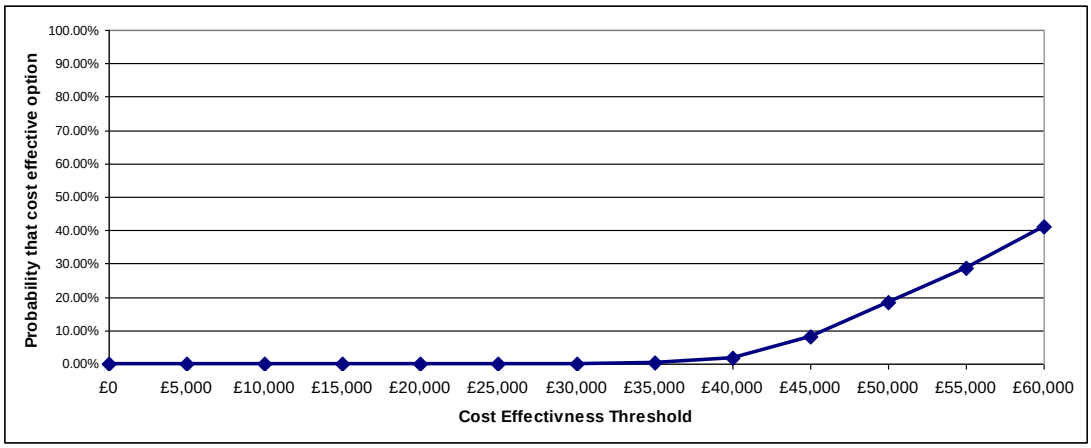


Figure 3e: Scenario Analysis – Assuming non-availability of 100mcg vial and without patient access scheme of [redacted] rebate on 250mcg vial for splenectomised group (realistic approach)

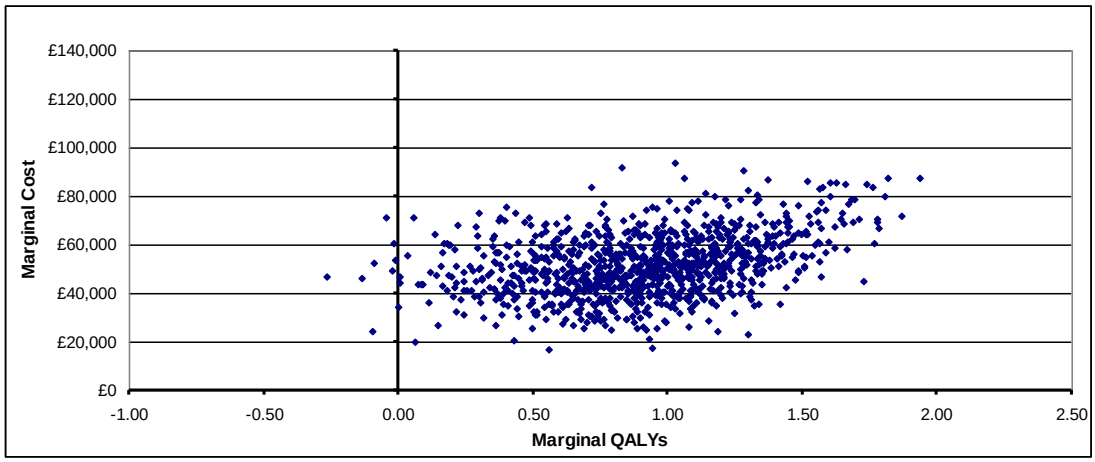


Figure 3f: Scenario Analysis – Assuming non-availability of 100mcg vial and without patient access scheme of [redacted] rebate on 250mcg vial for splenectomised group (realistic approach)

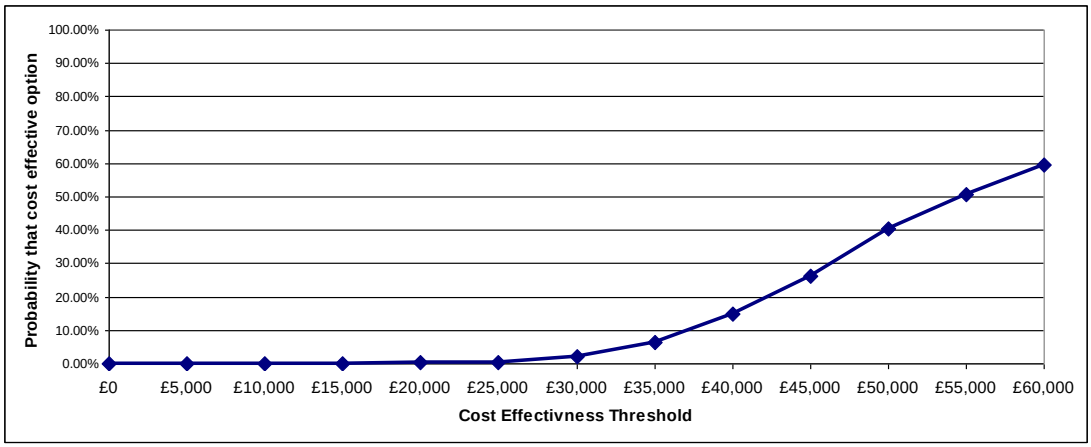


Figure 3g: Scenario Analysis – Assuming non-availability of 100mcg vial and without patient access scheme of [redacted] rebate on 250mcg vial for splenectomised group (conservative approach)

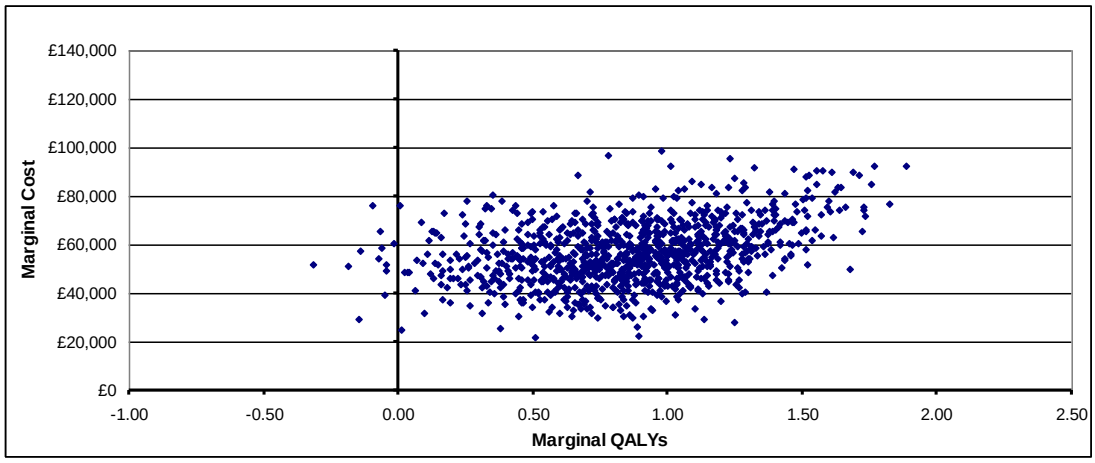


Figure 3h: Scenario Analysis – Assuming non-availability of 100mcg vial and without patient access scheme of [redacted] rebate on 250mcg vial for splenectomised group (conservative approach)

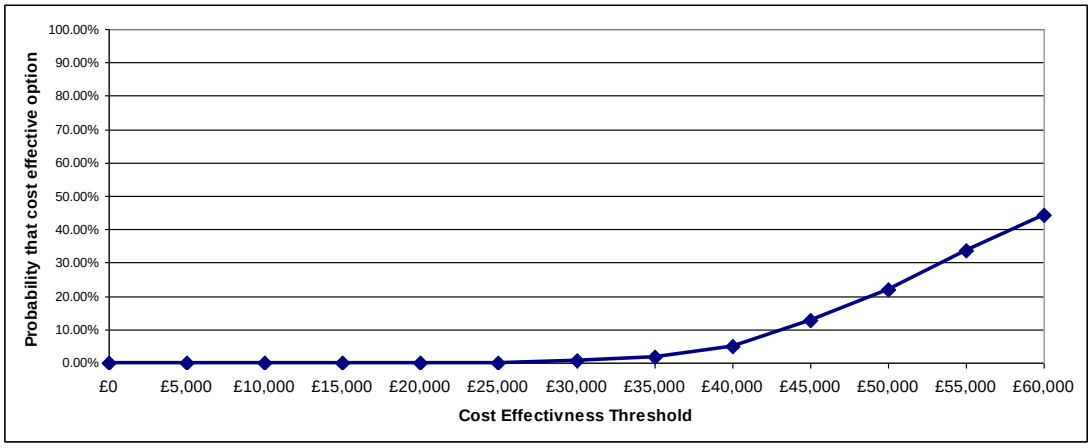


Figure 4a: Scenario Analysis – [redacted] (realistic approach)

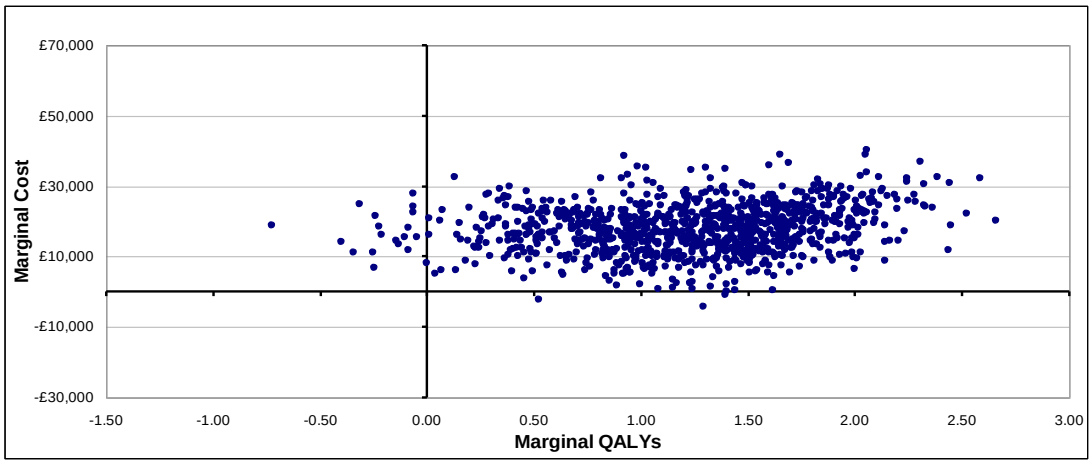


Figure 4b: Scenario Analysis - [redacted] (realistic approach)

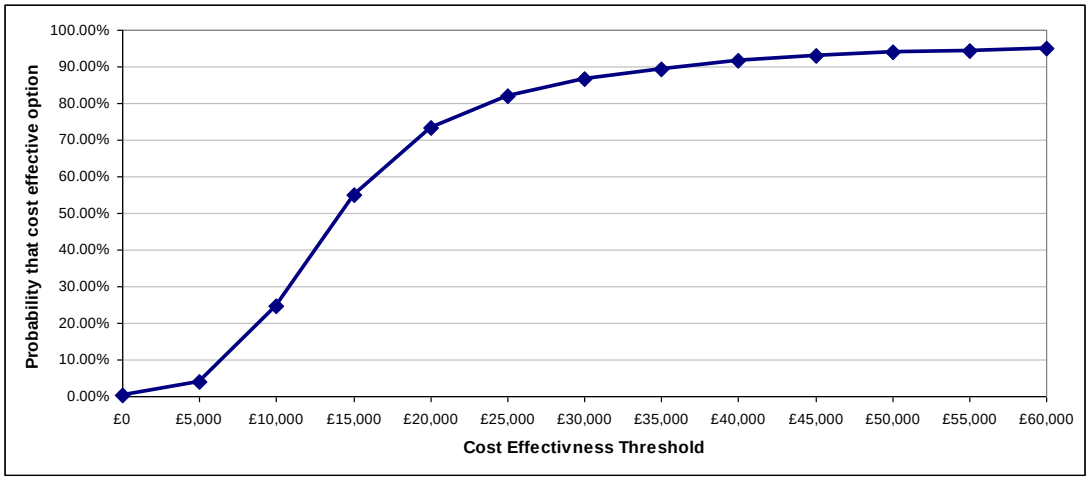


Figure 4c: Scenario Analysis - [redacted] (conservative approach)

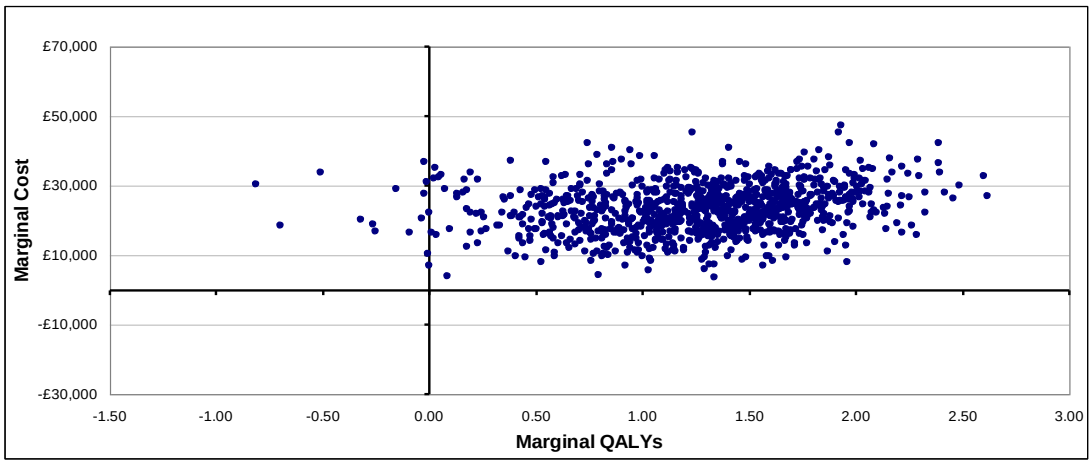


Figure 4d: Scenario Analysis - [redacted] (conservative approach)

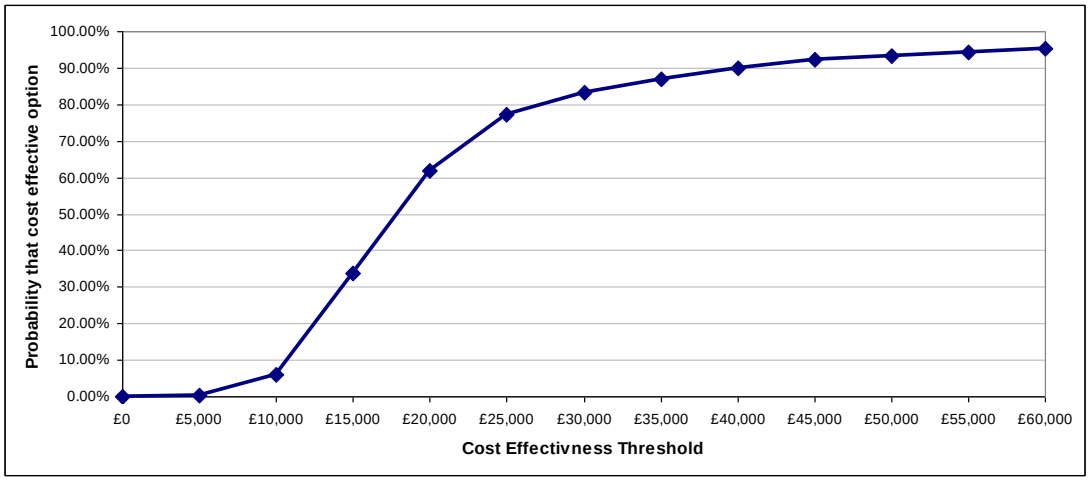


Figure 4e: Scenario Analysis - [redacted] (realistic approach)

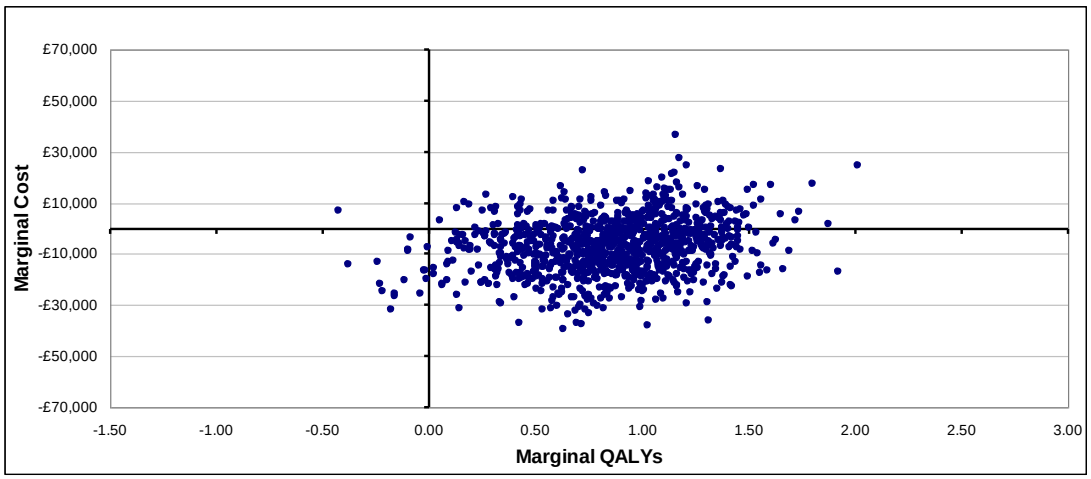


Figure 4f: Scenario Analysis - [redacted] (realistic approach)

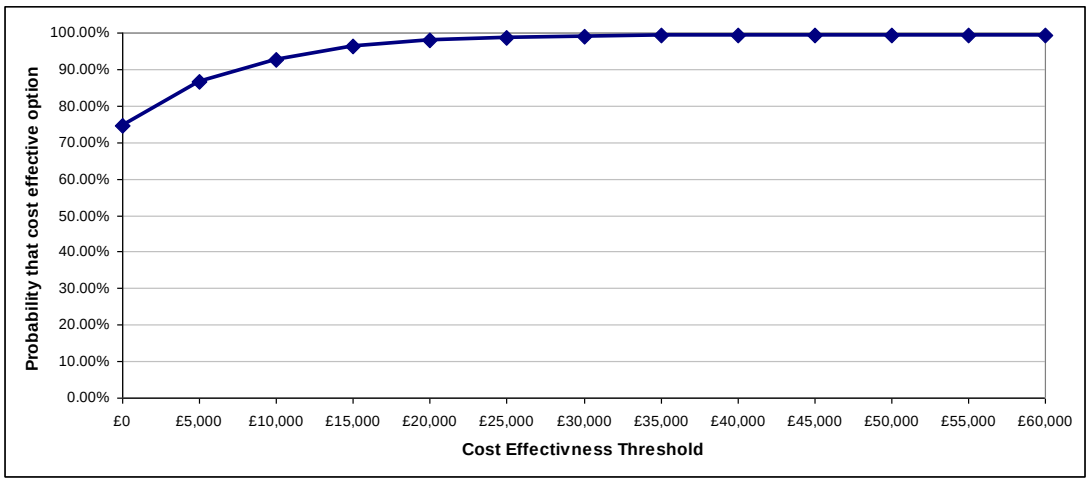


Figure 4g: Scenario Analysis - [redacted] (conservative approach)

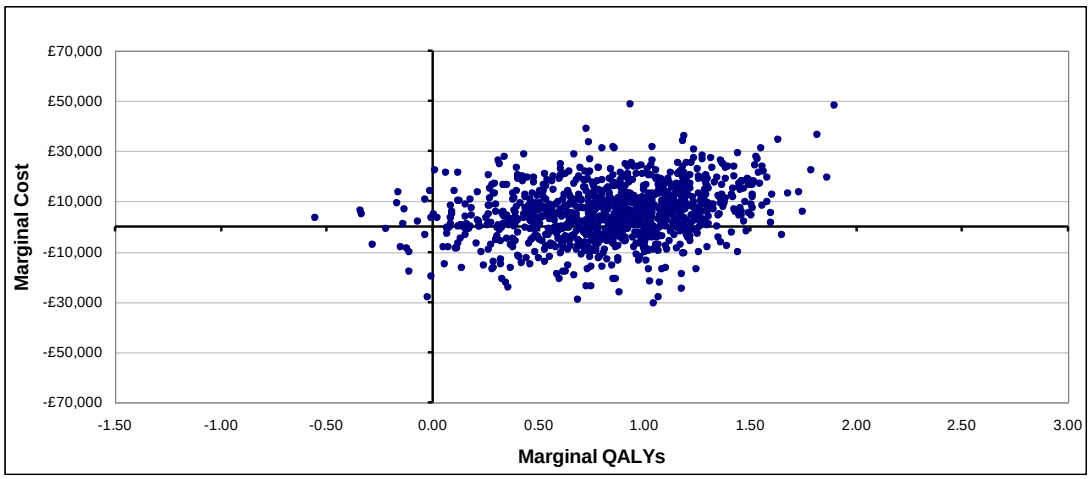


Figure 4h: Scenario Analysis - [redacted] (conservative approach)