Author’s response to reviews

Title: Cost-utility of enoxaparin compared with unfractionated heparin in unstable coronary artery disease

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PDF covering letter
**Table of Reviewers' Comments and Actions**

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<td>1</td>
<td>DB</td>
<td>1. Are the results robust enough to be conclusive for various types of health care systems, not only because of differences in revascularisation practice but also differences in health care politics, variation in reimbursement and so on?</td>
<td>Additional comments added to 'Policy implications' section</td>
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<td>2</td>
<td>DB</td>
<td>2. What are the limitations and weaknesses of taking data from many different studies, results from some, quality of life from others, and some of the costs from still others? Could this influence the outcome and thereby the conclusions?</td>
<td>Re-worded second two paragraphs in 'Limitations of the study' to cover this.</td>
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<td>3</td>
<td>DB</td>
<td>This study has analysed one of the low molecular weight heparins and there are certainly no data for comparison. It would be of some interest to mention this in the discussion as competing companies often argue on basis of differences in ?prices?.</td>
<td>Changes made to 'Policy implications' section</td>
</tr>
<tr>
<td>4</td>
<td>FS</td>
<td>1. The presentation of the study appears unbalanced, with very limited information in the text, particularly on methods and sources of data, and a large appendix. It is important that the authors include brief but informative details in the main text about the literature search methods, the characteristics of the trials that provide evidence of effectiveness, the population and methods used in the study from which quality of life information is drawn, the sources and calculation methods for cost data.</td>
<td>See comments</td>
</tr>
<tr>
<td>5</td>
<td>FS</td>
<td>2. The authors correctly emphasise the risks involved in generalising results of economic studies undertaken in different countries or settings. However, they do not seem to be equally cautious in applying the results of the existing clinical trials in their cost-effectiveness calculations. The authors do mention that sub-group analysis at the country level would not be feasible, but fail to provide a qualitative discussion of the possible implications of differences between countries and settings, particularly with regard to the generalisability of effectiveness data.</td>
<td>Comments added to 'Limitations of the study' section, also see actions in point 1.</td>
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<td>6</td>
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<td>3. Some concerns arise with regard to the assessment of the costs of the alternative strategies. Costing methods are illustrated in the appendix (although not mentioned in the text). These indicate that multiple sources have been used, ranging from commercial organisations to individual hospital Trusts, from Royal Colleges to published studies. The authors may have been looking for accurate sources for each cost item, but the resulting overall picture might be misleading. It would have made more sense to gather all the cost information from a single source, addressing the potential variability through a comparison of different settings and/or a sensitivity analysis. It is difficult to estimate what the impact of the costing methods used may be. On one hand, the analysis shows that under a wide range of assumptions, enoxaparin has a favourable economic impact. On the other hand, the analysis shows small differences between the alternative therapies, which could be overturned by estimation errors that may appear small if observed in isolation.</td>
<td>Amendment to 'Resource use and costs' and 'Limitations of the study' sections.</td>
</tr>
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<td>7</td>
<td></td>
<td>4. The authors do not explicitly mention a key assumption underlying their cost analysis, i.e. the assumption leading to the inclusion in the analysis of nursing time and of shares of capital equipment related to the administration of unfractionated heparin, computed at their full cost. This involves a judgement on the opportunity cost of such components. The inclusion of nursing time and equipment costs reduces the overall cost difference between the two strategies. The consequences of this should be explained to the reader.</td>
<td>Amendment to 'Policy implication' section</td>
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<td>8</td>
<td></td>
<td>5. The three scenarios described on page 9 are redundant and confusing. If the perspective chosen for the analysis is that of the NHS, transfer payments (VAT, NI, superannuation) should be included and should form part of the base case analysis. Incidentally, I could not find an illustration of scenario 2 in the results table. The meaning of scenario no. 3 is most unclear. It should be clearly explained to the reader why treatment costs for cardiac events should be first excluded and then included in two separate scenarios, if there is a strong reason for doing so.</td>
<td>Amendments to 'Model ad sensitivity analyses' section and Table 4.</td>
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**Point 9**  
**FS**  
6. Two of the tables (1 and 5) are at the same time too large and not wholly informative. The authors should make an effort to select the most relevant information in the two tables but they should also make sure that the following information is included. In table 1, information on the outcomes assumed in previous economic evaluations should be added. Table 5 should include an indication of what the extremas of the sensitivity analysis refer to, without requiring the reader to look up table 4 or other information in the paper at the same time.

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**Point 10**  
**FS**  
7. It may be important to discuss briefly the organisational implications of switching to enoxaparin for the patients examined, while unfractionated heparin may still be used for other patients. Another point for discussion is the possible existence of alternatives to the two drugs considered, which may change the terms of the cost-effectiveness comparison.

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**Point 11**  
**FS**  
Minor comments:  
1. Page 5, line 3: “unstable stable angina”  
2. Page 5, lines 3 and 6: “non-Q-wave” is hyphenated in different ways

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**Point 12**  
**FS**  
3. Page 5, last line of 2nd paragraph: what form of heterogeneity do the authors refer to? How is this related to the fact that studies use different pharmacological varieties?

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**Point 13**  
**FS**  
4. Page 6, 5th line from bottom of page: “if” should be “is”  
5. Page 7, 1st line of 4th paragraph: rephrase from “although…”; this should read “The following limitations were detected in one study:…”

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**Point 14**  
**FS**  
6. Page 9, 1st and 2nd lines: this sentence is unclear and should be reworded

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**Point 15**  
**FS**  
7. Page 21, table 4: it should be made clear that values in the table represent differences between the two strategies

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**Point 16**  
**JPB**  
1) This paper reports a cost-utility analysis of enoxaparin as a treatment of unstable coronary disease compared to unfractionated heparin (UFH). The reason for choosing enoxaparin among the low molecular weight heparins is unclear. If enoxaparin is really better in terms of cost-utility than UFH, what about the others?

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**Point 17**  
**JPB**  
2) As with all similar cost-utility (and cost-effectiveness) studies, the authors had to make numerous assumptions the validity of which is difficult, if not impossible, to assess. They performed a rather extensive sensitivity analysis, which, actually attenuates this limitation. However, it does not clear it out entirely.
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<td>18</td>
<td>JPB 3) The values introduced in the model for the cost parameters have been drawn from the UK environment, making the results to apply essentially to UK health care setting, and of limited value for other settings.</td>
<td>-</td>
<td>As above (point 18)</td>
</tr>
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<td>19</td>
<td>JPB 4) The referee was unable to check the relevance and validity of these values. Since the results are extremely depend on them, one should trust the authors for their careful proper selection.</td>
<td>-</td>
<td>As above (point 18)</td>
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<td>20</td>
<td>JPB 5) The explanation the authors gave for not using the meta-analysis results is not convincing. In any case, it looks more appropriate to rely on properly pooled data, which have a better external validity, rather than on individual, selected, trial results. For missing outcomes, the authors could have contacted the investigators and done the meta-analysis themselves.</td>
<td>-</td>
<td>As mentioned in the Methods / Effectiveness section, the meta-analysis only reported the death rates outcome separately and so these results could not be used in the cost-utility model. We accept that the way round this would be to contact the authors, however, this was beyond the time and budget of the project.</td>
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<td>21</td>
<td>JPB 6) As any report in pharmacoeconomics, the paper is difficult to read for a physician with limited background and skills in the field.</td>
<td>-</td>
<td>We hope that the changes made following the reviewers’ helpful comments will have clarified and improved this for all readers including clinicians.</td>
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<td>22</td>
<td>JPB 7) In total, I doubt this paper will be informative enough to clinicians or any health care givers in countries other than UK, with different patients, divers concomitant treatments.</td>
<td>-</td>
<td>This is a common problem of economic evaluations and currently one that is being debated among health economists. However, we hope that the level of detail (particularly in the additional file), a major advantage of BMC publications, will allow readers to adapt the model to their local circumstances.</td>
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Additional acknowledgement to referees for their helpful comments.