**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation**

**Response to consultee and commentator comments on the draft remit and draft scope**

**Comment 1: the draft remit**

| Section | Consultees | Comments | Action |
|---|---|---|---|
| Appropriateness | Clinical Leaders of Thrombosis (CLOT) | Yes. | Comment noted. |
| | Atrial Fibrillation Association | Yes, we fully support this topic being referred to NICE for appraisal. | Comment noted. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |
| | Daiichi Sankyo | Yes, it is very appropriate for this topic to be referred to NICE for appraisal.<br>Warfarin is still the most commonly prescribed anticoagulant in the UK, and while it is an effective, suitable means of stroke prevention in patients with atrial fibrillation, it has a number of recognised limitations. This results in a significant proportion of patients at high risk of stroke that remain untreated.[1] A recent national stroke audit revealed that only 36% of patients with known AF are taking anticoagulants when they are admitted to hospital with a stroke.[2]<br>It is clear that this is still an area of unmet need.<br>1. Cowan C, Healicon R, Robson I, et al. Heart Published Online First: 24 February 2014. doi:10.1136/heartjnl-2012-303472<br>2. Sentinel Stroke National Audit Programme. Clinical Audit First Public Report. August 2013. Royal College of Physicians Clinical Effectiveness and Evaluation Unit on behalf of the Intercollegiate Stroke Working Party | Comment noted.<br>No action required. |

| Section | Consultees | Comments | Action |
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| | AntiCoagulation Europe (ACE) | We note that Edoxaban Tosylate does not yet have a current marketing authorisation for this indication in the Uk or Europe.<br>NICE Guideliness are in place for Apixaban, Rivaroxaban and Dabigatran (NOACS) and therefore it may be deemed appropriate for this technology to be considered to extend patient and clinical choice of anticoagulation options (when approval is in place) | Comment noted. Guidance will only be issued in accordance with the marketing authorisation. No action required. |
| | UK Clinical Pharmacy Association Haemostasis, Anticoagulation and Thrombosis Group (UKCPA HAT Group) | Yes. | Comment noted. |
| | Boehringer Ingelheim | It is appropriate to review this topic. | Comment noted. |
| | British Society of Haemostatis and Thrombosis | Yes. | Comment noted. |
| Wording | Clinical Leaders of Thrombosis (CLOT) | No issues. | Comment noted. |
| | Atrial Fibrillation Association | Yes, we believe it does. | Comment noted. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |

| Section | Consultees | Comments | Action |
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| | Daiichi Sankyo | The wording of the remit broadly reflect the issues of clinical and cost-effectiveness that should be considered. We suggest the following slightly amended wording: Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors. | Comment noted. At the scoping workshop, it was agreed that the remit should remain broad because the wording of the marketing authorisation is not yet known. Guidance will only be issued in accordance with the marketing authorisation. No action required. |
| | AntiCoagulation Europe (ACE) | No comment. | Comment noted. |
| | UKCPA HAT Group | No comment. | Comment noted. |
| | Boehringer Ingelheim | The wording appears to be appropriate. | Comment noted. |
| | British Society of Haemostatis and Thrombosis | Yes, but please see comments on 'Background Information'. | Comment noted. |

| Section | Consultees | Comments | Action |
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| Timing Issues | Clinical Leaders of Thrombosis (CLOT) | Not urgent as effective alternative treatments are already available. | Comment noted. This topic has been scheduled into the work programme with consideration of the need to provide timely guidance. No action required. |
| | Atrial Fibrillation Association | In October 2014, NICE will conduct a review proposal for technology appraisals 275, 256 and 249. It would seem cost effective if reference to this technoical appraisal could be included the October 2014 review, and if the review concluded that a multiple technology apprasial would be benefical, that the TA for Edoxaban tosylate, was carried out and completed in time to be included in the multiple technoical appraisal. | Comment noted. Attendees at the scoping workshop agreed that the single technology appraisal (STA) process was appropriate, in order to ensure timely guidance on edoxaban tosylate. No action required. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |

| Section | Consultees | Comments | Action |
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| | Daiichi Sankyo | Edoxaban tosylate addresses currently unmet clinical need in the area of stroke prevention in atrial fibrillation (as described above), and therefore guidance to the NHS on its use should not be delayed. | Comment noted. This topic has been scheduled into the work programme with consideration of the need to provide timely guidance. No action required. |
| | AntiCoagulation Europe (ACE) | The new AF Guidelines are currently in the review stage and are due to be published in June 2014.<br>If NICE considers this STA now, it is unlikely that this technology would have achieved marketing status in time of inclusion in the new AF guidelines? | It is too late for edoxaban to be included in the published NICE clinical guideline on management of atrial fibrillation. No action required. |
| | UKCPA HAT Group | Not urgent as not yet licensed and other agents already available | Comment noted. This topic has been scheduled into the work programme with consideration of the need to provide timely guidance. No action required. |

| Section | Consultees | Comments | Action |
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| | Boehringer Ingelheim | There are alternative NOACs already available to the NHS at this time. | Comment noted. This topic has been scheduled into the work programme with consideration of the need to provide timely guidance. No action required. |
| | British Society of Haemostatis and Thrombosis | Should be done through the normal mechanisms. Can see no reason for urgency as similar products already on the market | Comment noted. This topic has been scheduled into the work programme with consideration of the need to provide timely guidance. No action required. |
| Additional comments on the draft remit | | None. | |

**Comment 2: the draft scope**

| Section | Consultees | Comments | Action |
|---|---|---|---|
| Background information | Clinical Leaders of Thrombosis (CLOT) | Accurate and complete. | Comment noted. |
| | Atrial Fibrillation Association | In April 2012, NHS GRASP-AF tool reported prevalence of AF in England as 1.78%. The background information included in the draft scope paper has listed prevalence at 1.3%, this is based on much older (2006 and earlier) data and is now outdated. | Comment noted. The scope has been updated to state that the prevalence is approximately 2.0%, based on section 1.1 of NICE clinical guideline 180: http://www.nice.org.uk/guidance/cg180/resources/cg180-atrial-fibrillation-update-full-guideline3 |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |
| | Daiichi Sankyo | The background information should include reference to the fact that the majority of patients with atrial fibrillation are not receiving anticoagulation.[1,2] Indeed, studies have shown that the elderly[2,3] and those otherwise at high risk of stroke are especially undertreated[2,4] The main reason for underuse was physician choice (48%).[4]<br>1. Draft UK NSC consultation on screening for atrial fibrillation, 2013. Accessed: http://www.screening.nhs.uk/atrialfibrillation<br>2. Cowan C, Healicon R, Robson I, et al. Heart Published Online First: 24 February 2104. doi:10.1136/heartjnl-2012-303472<br>3. Friberg L et al, Circulation 2012; 125: 2298-2307<br>4. Kakkar AK, PLOS ONE, 2013: 8(5): 1-8 | Comment noted. The aim of the background section is to provide a brief overview of the condition and treatment pathway. No action required. |

| Section | Consultees | Comments | Action |
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| | Daiichi Sankyo | Additionally, the scope is incomplete in its description of current treatments. As highlighted above and in the recent UK National Screening Committee consultation on screening for Atrial Fibrillation[1], many eligible patients do not receive anticoagulation treatment. Of those that do, the majority receive warfarin; among those receiving warfarin, many are poorly controlled. That warfarin is still a mainstay of care of the UK, along with the resultant unmet clinical need, should be mentioned in the scope. | Comment noted. The aim of the background section is to provide a brief overview of the condition and treatment pathway. Consultees at the workshop noted that warfarin was the mainstay of treatment for this condition. No action required. |
| | AntiCoagulation Europe (ACE) | Agree. | Comment noted. |
| | UKCPA HAT Group | No comment. | Comment noted. |
| | Boehringer Ingelheim | This is accurate. | Comment noted. |
| | British Society of Haemostatis and Thrombosis | Heart rate is not always 'rapid' in Atrial fibrillation. Slow forms also occur. | Comment noted. The relevant section of the scope has been amended. |
| The technology/ intervention | Clinical Leaders of Thrombosis (CLOT) | Yes. | Comment noted. |
| | Atrial Fibrillation Association | We believe it is. | Comment noted. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |

| Section | Consultees | Comments | Action |
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| | Daiichi Sankyo | [redacted] is the brand name intended by Daiichi Sankyo for its active ingredient edoxaban, and has been filed for market authorisation in Europe.<br>The mechanism of action and mode of administration are correct. It is important to add, however, that it is administered once-a-day without the need for routine clinical monitoring, and can be taken with or without food.<br>While it is correct to state that edoxaban does not currently have marketing authorisation, we would like to clarify that the pivotal trial for this indication is complete[1], and the regulatory dossier was submitted to the EMA in [redacted].<br>Giugliano RP et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369(22): 2093-104 | Comment noted. The aim of the technology section is to provide a brief overview of edoxaban tosylate. No action required. |
| | AntiCoagulation Europe (ACE) | Agree. | Comment noted. |
| | UKCPA HAT Group | No comment. | Comment noted. |
| | Boehringer Ingelheim | This is accurate. | Comment noted. |
| | British Society of Haemostatis and Thrombosis | Yes | Comment noted. |

| Section | Consultees | Comments | Action |
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| Population | Clinical Leaders of Thrombosis (CLOT) | It may be appropriate to consider the very elderly as a separate group. | Comment noted. At the scoping workshop, attendees advised that it is difficult to define the 'very elderly' and there may be little evidence on the effectiveness of edoxaban tosylate in this subgroup. Attendees also noted that factors other than age (such as fitness) can also guide the choice of treatment. Attendees agreed it was not necessary to consider a subgroup defined by age. No action required. |
| | Atrial Fibrillation Association | We believe the population listed is comprehensive of all the AF at risk groups who may benefit from this therapy. | Comment noted. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |
| | Daiichi Sankyo | The population is appropriately defined. Comments with regard to subgroups are listed below in "Other considerations." | Comment noted. |
| | AntiCoagulation Europe (ACE) | Agree. | Comment noted. |
| | UKCPA HAT Group | Sub group analysis if available should look at different CHADS2 scores and different TTRs on warfarin | Comment noted. The draft scope included subgroups defined by level of stroke/thromboembolic risk and time in therapeutic range on warfarin. No action required. |

| Section | Consultees | Comments | Action |
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| | Boehringer Ingelheim | This is accurate. | Comment noted. |
| | British Society of Haemostatis and Thrombosis | It may be helpful to invite comments from cardiologists in respect of patients with Paroxysmal atrial fibrillation. | Comment noted. Several professional cardiovascular organisations were invited to comment on the draft scope. |
| Comparators | Clinical Leaders of Thrombosis (CLOT) | Warfarin remains the primary comparator at present in most areas and sould therfore be included. | Comment noted. |
| | Atrial Fibrillation Association | All are appropriate. | Comment noted. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |
| | Daiichi Sankyo | We agree that the listed comparators are appropriate.<br>With regard to warfarin, is it redundant to specify “in people for whom warfarin is suitable”? Would each of the other comparators not be considered only for those in whom the respective treatments are suitable? | Comment noted. The scope has been amended. |
| | AntiCoagulation Europe (ACE) | Agree. | Comment noted. |

| Section | Consultees | Comments | Action |
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| | UKCPA HAT Group | All appropriate but consider comparing with dual antiplatelets | Comment noted. Attendees at the scoping workshop agreed that dual antiplatelet therapy is not standard care within the NHS. Also, NICE clinical guideline 180 on the management of atrial fibrillation does not recommend dual antiplatelet therapy. No action required. |
| | Boehringer Ingelheim | These are appropriate. | Comment noted. |
| | British Society of Haemostatis and Thrombosis | Yes, these are the standard treatments, but there is not enough information at present to allow description of any one of them as 'best' | Comment noted. |
| Outcomes | Clinical Leaders of Thrombosis (CLOT) | Yes. | Comment noted. |
| | Atrial Fibrillation Association | Yes, we believe they will. | Comment noted. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |

| Section | Consultees | Comments | Action |
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| | Daiichi Sankyo | We suggest the following with regard to the outcomes considered:<br>CV mortality is included;<br>Net clinical outcome is included;<br>Individual adverse events (such as bleeds defined by site and severity) are considered separately from one another.<br>Additionally, we would like to note that a number of the outcomes mentioned are components of a composite endpoint in the pivotal edoxaban trial; the trial was therefore not powered to detect differences between treatments with regard to the individual elements of the composite. | Comment noted. Attendees at the scoping workshop agreed that the proposed additional outcome measures are already covered by the broad list of outcomes in the draft scope. Attendees agreed that the list of outcome measures should not be changed, in order to ensure consistency with previous appraisals (such as TA 275 Apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation). No action required. |
| | AntiCoagulation Europe (ACE) | Agree. | Comment noted. |
| | UKCPA HAT Group | Discontinuation due to side effects should be considered and need to ensure haemorrhagic stroke included | Comment noted. Attendees at the scoping workshop agreed that these measures are already covered by the broad list of outcomes in the draft scope. Attendees agreed that the list of outcome measures should not be changed. No action required. |

| Section | Consultees | Comments | Action |
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| | Boehringer Ingelheim | We belive that 'stroke' is a composite endpopint and should be split between ischaemic and haemorrhagic stroke. | Comment noted. Attendees at the scoping workshop agreed that these measures are already covered by the broad list of outcomes in the draft scope. The broad list of outcomes in the scope does not preclude the manufacturer or other consultees providing evidence on a subset of these (for example ischaemic compared with non-ischaemic stroke) or additional outcomes such as composite outcomes. Attendees agreed that the list of outcome measures should not be changed. No action required. |
| | British Society of Haemostatis and Thrombosis | Yes | Comment noted. |
| Economic analysis | Clinical Leaders of Thrombosis (CLOT) | No comments. | Comment noted. |
| | Atrial Fibrillation Association | The economic aspects seem comprehensive and appropriate. | Comment noted. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |
| | Daiichi Sankyo | No comment. | Comment noted. |

| Section | Consultees | Comments | Action |
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| | AntiCoagulation Europe (ACE) | No comment. | Comment noted. |
| | UKCPA HAT Group | No comment. | Comment noted. |
| | Boehringer Ingelheim | N/A | Comment noted. |
| | British Society of Haemostatis and Thrombosis | No comments. | Comment noted. |
| Equality and Diversity | Clinical Leaders of Thrombosis (CLOT) | No issues. | Comment noted. |
| | Atrial Fibrillation Association | We believe the remit encompasses of all groups who may benefit from this technology. | Comment noted. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |
| | Daiichi Sankyo | No comment. | Comment noted. |
| | AntiCoagulation Europe (ACE) | No comment. | Comment noted. |
| | UKCPA HAT Group | No comment. | Comment noted. |
| | Boehringer Ingelheim | N/A | Comment noted. |
| | British Society of Haemostatis and Thrombosis | Not in any manner I can readily think of. | Comment noted. |

| Section | Consultees | Comments | Action |
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| Innovation | Clinical Leaders of Thrombosis (CLOT) | The reduction in the need for monitoring can be seen as an improvement. | Comment noted. The manufacturer is invited to provide evidence on the innovative nature of the technology in its submission. |
| | Atrial Fibrillation Association | We believe the technology is innovative and has the potential to make a significant improvement to the safety, management and outcomes of non-valvular AF patients assessed at increased risk of suffering an AF-related stroke. We acknoeldge that since 2012, NICE has given guidance to three new anticoagulation therapies for non-valvular AF, however uptake by NHS services has been far lower than expected or hoped. Increasing innovative safe, efficent and effective options to prevent AF-related strokes, which can also greatly improve patient experience and quality of life is vital if lives are to be saved and the cost of AF-related strokes, to be reduced. | Comment noted. The manufacturer is invited to provide evidence on the innovative nature of the technology in its submission |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |

| Section | Consultees | Comments | Action |
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| | Daiichi Sankyo | The technology is an improvement compared to the current treatment received by the majority of patients (warfarin), and the pivotal trial provides data on dose adjustment that mimics real-life clinical practice.[1] Not only was the edoxaban dose adjusted at randomisation, but was also adjusted during the study for the following risk factors associated with increased edoxaban exposure: . moderate renal impairment (CrC 30-50ml/min); a body weight of 60 kg or less; and/or the concomitant use of verapamil, quinidine or dronedarone (potent P-glycoprotein inhibitors).<br><br>Edoxaban is the first of the NOACs to have **both** a once-daily dosing regimen **and** demonstrated significant CV mortality benefit compared to warfarin in this indication. Additionally, edoxaban will have the same dose for both of its intended indications.<br><br>1. Giugliano RP et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369(22): 2093-104 | Comment noted. |
| | AntiCoagulation Europe (ACE) | Potential additional anticoauglant treatment option for AF sufferers to complement exisitng VKA warfarin and other NOACS.<br>Could extend choice for clinicians and patients (if approved) | Comment noted. |
| | UKCPA HAT Group | No comment. | Comment noted. |
| | Boehringer Ingelheim | N/A | Comment noted. |
| | British Society of Haemostatis and Thrombosis | No comment. | Comment noted. |
| Other considerations | Clinical Leaders of Thrombosis (CLOT) | We would like to take into account the lack of an effective antidote to edoxaban at present. | Comment noted. |

| Section | Consultees | Comments | Action |
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| | Atrial Fibrillation Association | None. | Comment noted. |
| | Bristol-Myers Squibb and Pfizer | None. | Comment noted. |
| | Daiichi Sankyo | The proposed subgroups are appropriate.<br>With regard to the consideration of a subgroup defined by thromboembolic risk, can you please confirm which scoring system will be used? | Comment noted. Attendees at the scoping workshop agreed that it was not necessary to define the scoring system used to determine thromboembolic risk. Attendees noted that the choice of scoring system is likely to be based on that used in pivotal clinical trials. No action required. |
| | Daiichi Sankyo | In addition to the proposed subgroups, people who have not been previously treated with warfarin should be considered. | Comment noted. In the absence of a prior hypothesis about treatment being more effective or cost effective in this group of patients, NICE decided it was not necessary to specify this subgroup in the final scope. No action required. |
| | AntiCoagulation Europe (ACE) | No comment. | Comment noted. |
| | UKCPA HAT Group | No comment. | Comment noted. |

| Section | Consultees | Comments | Action |
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| | Boehringer Ingelheim | N/A | Comment noted. |
| | British Society of Haemostatis and Thrombosis | None, but suggest the following addition:<br>• level of stroke/thromboembolic risk (as determined by CHA2DS2VASC score) | Comment noted. Attendees at the scoping workshop agreed that it was not necessary to define the scoring system used to determine thromboembolic risk. Attendees noted that the choice of scoring system is likely to be based on that used in pivotal clinical trials. No action required. |

| Section | Consultees | Comments | Action |
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| Questions for consultation | Bristol-Myers Squibb and Pfizer | We would support a proposal to conduct a multiple technology appraisal (MTA) to update the guidance for apixaban, rivaroxaban and dabigatran etexilate. We believe it would be most logical for this to include edoxaban tosylate, and that the disadvantage of a delay to guidance would be outweighed by the benefit of MTA guidance for all four NOACs. | Comment noted. Consultees agreed that there were several reasons for conducting an STA for edoxaban: to ensure timely guidance, to potentially extend the choice of medication available to clinicians and patients, and to ensure fairness for all manufacturers of novel oral anticoagulants. Attendees noted it was not certain that the upcoming review proposal would recommend a review of the current guidance. For these reasons, attendees at the scoping workshop agreed that the STA process is appropriate for edoxaban tosylate. No action required. |
| | Daiichi Sankyo | Warfarin is the most widely used VKA, and therefore should be included as a comparator. Other VKAs are not sufficiently different from warfarin that they should be considered separately.<br><br>Subgroups are addressed above in “Other considerations”. | Comment noted. Attendees at the scoping workshop agreed it was not necessary to include other vitamin K antagonists as a comparator. Other vitamin K antagonists were not included in the draft scope, so no action is required. |

| Section | Consultees | Comments | Action |
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| | Daiichi Sankyo | To prevent the delay of guidance to the NHS on the use of edoxaban, it should be appraised through its Single Technology Appraisal process. It may be preferable to delay any future MTA so that the output of any STA guidance on edoxaban can be included (so as to ensure that the MTA is not immediately out of date at the time of publication). | Comment noted. Attendees at the scoping workshop agreed that the STA process is appropriate for edoxaban tosylate. No action required. |
| Additional comments on the draft scope. | Daiichi Sankyo | It remains unclear whether a future appraisal of edoxaban (if referred by the Department of Health) will be subject to Value-Based Assessment. Can you please clarify – based on the regulatory information we have provided – when we would receive the invitation to submit, and if that submission is likely to be subject to VBA? We appreciate that you cannot give a definite answer at this point, but any indicative timings you are able to provide will help us greatly in our planning. | Comment noted. The public consultation on value-based assessment has now closed and the NICE Board is considering the responses. NICE does not anticipate a change to the process of technology appraisal before the invitation to participate in the appraisal of edoxaban is sent out. No action required. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

Amdipharm Mercury (AMCo), Department of Health, Healthcare Improvement Scotland, Royal College of Nursing

**NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE**

**Single Technology Appraisal**

# Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation [ID624]

## Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

| **Version of matrix of consultees and commentators reviewed:**<br>Provisional matrix of consultees and commentators sent for consultation | | | | | |
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| **Summary of comments, action taken, and justification of action:** | | | | | |
| | Proposal: | Proposal made by: | | Action taken:<br>Removed/Added/Not included/Noted | Justification: |
| 1. | Pumping Marvellous | Pumping Marvellous | | Added | This organisation's interests are related to the appraisal topic and as per our inclusion criteria. Pumping Marvellous has been added to the matrix of consultees and commentators under "patient group" |

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| 2. | British Lung Foundation | NICE Secretariat | | Removed | This organisation does not have an interest related to this appraisal topic. British Lung Foundation has been removed from the matrix of consultees and commentators under 'professional groups'. |
| 3. | Research Institute for the Care of Older People | NICE Secretariat | | Removed | This organisation's interests are not related to the appraisal topic. Research Institute for the Care of Older People has not been removed from the matrix of consultees and commentators under "research groups" |
| 4. | Health Research Authority | Health Research Authority | | Removed | This organisation no longer wishes to be included in TA matrices. Health Research Authority has been removed from the matrix under 'relevant research groups' |

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| 5. | Mylan UK | NICE Secretariat | | Removed | This organisation's interests are not related to the appraisal topic and they do not manufacture warfarin. Mylan UK has been removed from the matrix of consultees and commentators under "comparator company" |