PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Is self-monitoring an effective option for people receiving long-term vitamin K antagonist therapy? A systematic review and economic evaluation.
AUTHORS	Sharma, Pawana; Scotland, Graham; Cruickshank, Moira; Tassie, Emma; Fraser, Cynthia; Burton, Christopher; Croal, Bernard; Ramsay, Craig; Brazzelli, Miriam

VERSION 1 - REVIEW

REVIEWER	Sue Jowett University of Birmingham, UK
REVIEW RETURNED	25-Feb-2015

GENERAL COMMENTS	Overall this is a clear and well written paper and moves forward the evidence on the clinical and cost-effectiveness of self-monitoring. The study methods used appear to be appropriate. I have a few comments to make which may require some further clarification or discussion in the paper, and I will concentrate mainly on the economic analysis. 1) Due to the nature of the paper, the economic modelling methods are presented more briefly than one would expect in a full paper on the economic model, and if I were to use a Philips modelling checklist, then there are many questions I would not be able to answer without going to the main NICE guidance report which is a little frustrating for a reader. The key information that does not appear to be available to the reader, even in an appendix, are the model inputs with regards to costs, utilities and clinical information. If all the systematic review results are to be made available, than the model inputs should be there as well. 2) The cost year does not appear to be stated. 3) It is stated that trials including children are included in the analysis, but very little is mentioned thereafter apart from descriptive data on ages of patients. Were the results for trials including children broadly in line with the overall result? Can we assume that self-management is cost-effective in this patient group as well? 4) From experience, the one area where trials do appear different in terms of clinical impact of self-management is due to the quality of usual care. The UK trial I was involved in, there was very good usual care, therefore the results only showed that self-management was as good as usual care. Therefore this result might differ from country to country, and it is no surprise that the base case result differs from

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	other UK evaluations. I think the discussion needs to consider this further – although the overall result points to cost-effectiveness of PSM, funders in the UK may be less convinced in paying for a machine per patient if usual care is doing a good job anyway. 5) What was the rationale behind the higher standard secondary care costs in the model compared to previous work? How much greater –it's difficult to tell without a table of inputs to refer to. 6) Although this scope of this study is not to consider new anticoagulants on the market (e.g. dabigatran), a mention in the discussion would be worthwhile. 7) In the assumptions, it states that 66.45% of standard care monitoring is in primary care, and this data is from a manufacturer's submission. Is this based on hard data? I would be wary of the estimate from a manufacturer of a new anticoagulant which could replace warfarin, as a higher cost of monitoring (and primary care monitoring is more expensive) will be favourable to any ICER they are calculating for their product.

REVIEWER	Brouwer, Jan 1. Nationale Thrombosis Center, Ede, the Netherlands 2. Sionsberg Hospital, Dokkum, The Netherlands
REVIEW RETURNED	05-Mar-2015

GENERAL COMMENTS	Very nice review with clear cut purpose and tailored for the practice. I include some suggestions for minor revision. Dear author, Very nice report that exactly focuses on self-management/ monitoring against standard care. This work includes the largest number of RCT's as suggested and known to me. The limitations were clear given. Hereby some minor suggestions. Page 4 Please describe the new anticoagulants in relation to the vitamin K antagonists and some differences. And why you think this work was necessary. I further would make a more in depth description of the presumed gained QALY's. Page 6 Please give a clear definition of the diagnosis of the major events (major bleeding and thromboembolic events). Was a description in the previous studies enough or did all studies have well defined criteria? What was seen as a major bleeding? According to which criteria (ISTH/ ASH?) Page 10 What was the relation of the deceased patients with the major events? If so, they should be accounted to the major events. This remains unclear.

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VERSION 1 – AUTHOR RESPONSE

Peer Reviewer 1
Please leave your comments for the authors below Overall this is a clear and well written paper and moves forward the evidence on the clinical and cost-effectiveness of self-monitoring. The study methods used appear to be appropriate.

I have a few comments to make which may require some further clarification or discussion in the paper, and I will concentrate mainly on the economic analysis.

1/ Due to the nature of the paper, the economic modelling methods are presented more briefly than one would expect in a full paper on the economic model, and if I were to use a Philips modelling checklist, then there are many questions I would not be able to answer without going to the main NICE guidance report which is a little frustrating for a reader. The key information that does not appear to be available to the reader, even in an appendix, are the model inputs with regards to costs, utilities and clinical information. If all the systematic review results are to be made available, than the model inputs should be there as well.

A methodological appendix (Appendix 2), detailing the key modelling inputs and assumptions, has now been provided as supplementary material, and cited in the main text of the manuscript.

2/ The cost year does not appear to be stated.

All costs are expressed in 2012/2013 Stirling. This has been clarified in the main text of the manuscript.

3/It is stated that trials including children are included in the analysis, but very little is mentioned thereafter apart from descriptive data on ages of patients. Were the results for trials including children broadly in line with the overall result? Can we assume that self-management is cost-effective in this patient group as well?

We accept that there was limited trial data available for this group, and it was not a formal subgroup analysis in the cost-effectiveness model. With the assumption that the overall effect of self-management would also apply to children (with appropriate support from a carer where necessary), self-management would also appear cost-effective in this group.

4/From experience, the one area where trials do appear different in terms of clinical impact of self-management is due to the quality of usual care. The UK trial I was involved in, there was very good usual care, therefore the results only showed that self-management was as good as usual care. Therefore this result might differ from country to country, and it is no surprise that the base case result differs from other UK evaluations. I think the discussion needs to consider this further – although the overall result points to cost-effectiveness of PSM, funders in the UK may be less convinced in paying for a machine per patient if usual care is doing a good job anyway.

A paragraph has been added to the discussion section highlighting this potential issue.

5/What was the rationale behind the higher standard secondary care costs in the model compared to previous work? How much greater –it's difficult to tell without a table of inputs to refer to.

The standard secondary care monitoring costs, per visit, come from national reference costs. The specific estimate for anticoagulation services, at an average cost of £23 per visit, was applied. 33% of these costs were assumed to be fixed and so not influenced by number of patient visits. Thus, an estimated cost per visit of £15 per patient visit was applied for secondary care monitoring. This is

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consistent with the values applied for secondary care warfarin monitoring for in the appraisals for the NOACs (full details and justification for the assumption are now included in the methodological appendix). Sensitivity analysis was used in our main report to assess the impact of applying the unit costs reported by Jowett et al., 2006, inflated to 2012/13 prices. The conclusions were robust to these changes.

6/Although this scope of this study is not to consider new anticoagulants on the market (e.g. dabigatran), a mention in the discussion would be worthwhile.

We did not consider NOACs as they were outwith the scope of our assessment. We are, therefore, limited in what we can say about them. A paragraph has been added to the background section: "Recently, new oral anticoagulants (NOACs), which do not require dose adjustment, such as dabigatran etexilate, rivaroxaban or apixaban have been proposed as a possible alternative to warfarin for the treatment of atrial fibrillation.10,11 However, NOACs are currently unsuitable for people with artificial heart valves, people with liver or renal dysfunctions and those who are taking concurrent medication, which may react with this class of anticoagulants. For these people warfarin remains the long term treatment of choice."

Another paragraph has also been added to the Discussion section: "Whilst new non-vitamin K antagonist oral anticoagulants were beyond the scope of this assessment, they offer an alternative option for many people with atrial fibrillation who are currently on warfarin. However, they are not suitable for all people who need anticoagulation therapy. Furthermore, due to the potential risk of bleeding, it is unlikely that people receiving warfarin who have stable INR may switch to the new oral anticoagulants. Therefore, there are still many people who receive warfarin rather than the new oral anticoagulants for whom self-monitoring is still of clinical relevance."

7/In the assumptions, it states that 66.45% of standard care monitoring is in primary care, and this data is from a manufacturer's submission. Is this based on hard data? I would be wary of the estimate from a manufacturer of a new anticoagulant which could replace warfarin, as a higher cost of monitoring (and primary care monitoring is more expensive) will be favourable to any ICER they are calculating for their product.

This proportional split was taken from NICE TA256. We recognise that there are potential limitations with the reliability of this figure, but is was informed by a survey of providers in England and Wales carried out in 2011 (Bayer 2011). Based on this, the manufacturer of Rivaroxaban estimated that 66.45% and 33.55% of warfarin monitoring appointments were managed in a primary and secondary care setting, respectively. These figures were therefore applied in the base case analysis in our model. Sensitivity analysis also assessed the cost-effectiveness of self-monitoring versus primary and secondary care standard monitoring separately. Conclusions were robust to these secondary analyses.

Bayer plc., pH associates. Data on File. Survey of anticoagulation services in the UK. 2011.

Peer Reviewer 2

Very nice report that exactly focuses on self-management/monitoring against standard care. This work includes the largest number of RCT's as suggested and known to me. The limitations were clear given. Hereby some minor suggestions.

Page 4

Please describe the new anticoagulants in relation to the vitamin K antagonists and some differences. And why you think this work was necessary. I further would make a more in depth description of the presumed gained QALY's.

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A paragraph referring to the new anticoagulants has been added to both the background and discussion sections of the manuscript (see also our response to peer reviewer 1 on this issue).

Page 6
Please give a clear definition of the diagnosis of the major events (major bleeding and thromboembolic events). Was a description in the previous studies enough or did all studies have well defined criteria? What was seen as a major bleeding? According to which criteria (ISTH/ ASH?)

With regard to 'major bleeding' and 'major thromboembolic events' we accepted the definitions used by individual trial investigators. Definitions varied between trials and not all trials referred to well defined criteria. In general, the included trials simply defined major events (bleeding or thromboembolic) as events/complications requiring hospital admission or medical assessment. Fatal bleeding or thromboembolic events were counted as deaths. It worth noting that deaths associated with anticoagulation therapy were reported in five trials. In total six deaths related to anticoagulation therapy occurred among participants receiving usual monitoring care (1 valve thrombosis, 2 myocardial infarctions, 1 retroperitoneal haemorrhage, 1 cerebral haemorrhage, and 1 gastrointestinal bleeding) and seven deaths occurred among participants who self-managed their therapy (1 valve thrombosis, 1 pulmonary embolism, 1 massive ischemic stroke, 2 myocardial infarctions, 1 cerebral haemorrhage, and 1 gastrointestinal bleeding). This has now been clarified in the results section of the manuscript.

Page 10
What was the relation of the deceased patients with the major events? If so, they should be accounted to the major events. This remains unclear.

Please see our response above.

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