NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Anticoagulation Europe (ACE)	• Are there any equality related issues that need special consideration and are not covered in the appraisal consultation document? Under the NICE Guidelines CG 36, it is recommended that AF patients be offered aspirin or warfarin (VKA) dependent on the level of risk. Patients who commence warfarin treatment will need to be regularly monitored to ensure they stay in therapeutic range to avoid clots and bleeding episodes and make adjustments to diet for this purpose. Further adjustments to lifestyle will need to be considered – such as travel and factoring in regular venous or pin prick blood tests which may involve visiting a hospital, anticoagulation clinic setting or their GP Anticoagulant clinic. Whilst AF is a condition that predominately is seen in a senior population, younger people do present with AF and therefore, the impact of having to undergo regular monitoring which involves managing work arrangements can lead to anxiety and concerns from the employer and employee. With the age of retirement increasing, individuals diagnosed with AF could be working longer and therefore their continued therapy management could impact on their working life. Constant venous sampling can traumatise the veins and cause pain. Pinprick sampling whilst less invasive, can cause discomfort and bruising to the digits. Many AF patients cannot tolerate warfarin for a number of clinical reasons and those with AF who receive no medication are at a fivefold increased risk of stroke. Stroke accounts for around 53,000 deaths each year in the UK and an estimated 150,000 have a stroke in the UK each year. Stoke can cause a range of disabilities with the NHS having to mange costly treatment and on going support to the patient. The key conclusions as summarised in the ACD have acknowledged the issues surrounding warfarin usage and, under ‘Equalities, considerations and social value judgements’ section 4.2 ‘ the Committee ‘recognised the potential benefits of Dabigatran for people with AF’	Comments noted. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee’s considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.40 and 4.16 – 4.19). The manufacturer’s additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.

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	By not considering Dabigatran as an alternative treatment to patients and in particular, those who cannot tolerate warfarin and therefore are left unprotected from the heightened risk of stroke could be deemed to be 'unfair' to those patients. Patients need to reduce the anxiety of the fear of having a stroke when diagnosed with AF and knowing that there is a therapy to give that protection will bring re-assurance and confidence to patients. In terms of equality, Dabigatran will offer an alternative oral anticoagulant for those patients for which warfarin is currently unviable. It will enable patients to manage their chronic condition with a treatment that has increased efficacy in reducing stroke. Defining equality as 'a state of being equal' puts this into perspective – depriving patients of an alternative therapy that can give protection is 'discriminating' against those who are unfortunate in that they can't stabilise on warfarin or it's deemed unsuitable by the clinicians. Reducing risk of stroke in 'all' AF sufferers should be paramount in current healthcare provision in the UK.	
Arrhythmia Alliance	Executive summary of points: A-A calls upon NICE to consider the wider cost model of '**the patient health outcomes relative to the total costs**.' AFA believes that the draft negative appraisal has not considered the costs incurred by this failure to treat and protect due to the fear of complications in the management of warfarin. A-A suggests that if stroke reduction is not successfully managed, then existing treatment therapy cannot be considered cost effective. A-A asks that that the Committee consider a QAL model for this group of patients who would have far longer years of QAL and for whom a validated risk stratification schema has been endorsed by leading international and national professional bodies (CHA_2DS_2VASc). A-A asks the Committee to consider AF patients with either poor control on warfarin	Comments noted. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.40 and 4.16 – 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.

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	(<60%) in therapeutic range, making warfarin useless in reducing the risk of stroke, or a non-bleeding contraindication to warfarin. A-A calls upon the Committee to include representation from Primary Care and Commissioners. A-A calls upon the Committee to issue guidance on Dabigatran with consideration to the points A-A has highlighted in its response to the Appraisal Consultation document. Have all the relevant evidence been taken into account? Audits from stroke admissions of people in AF show that 8% of those presenting with stroke have warfarin within therapeutic range and only 27% were receiving warfarin in any form. NICE figures highlight 166,000 high risk AF patients should be on warfarin, but evidence shows that only one third of warfarin treated patients are within therapeutic range. So current models are not successful at reducing risk or stroke and thus cannot be considered cost- effective. Atrial Fibrillation (AF) is the highest single risk factor for stroke. AF is known to be responsible for 45% of all embolic strokes, resulting in more than 12,500 strokes per year in England and Wales. AF-related strokes are usually more severe, leading to greater rates of death and disability. The current leading oral anticoagulant can lead to a stroke risk reduction of 50%-70%. However, the existing therapy (warfarin) is simply not achieving its potential. This is due to a reluctance to prescribe warfarin, due to the complexity of its management and fear of associated risks. Therefore warfarin's level of effectiveness is not achieved for the majority of AF patients at risk of stroke. Evidence[i] shows that only 18% of patients are adequately treated: The medical cost of a single stroke in first year is £9,500 - £14,000. Hospital admission costs following a stroke are £103 million and post-discharge care £45 million. These costs do not include continuing costs after the first year, nor do they include costs associated with long term disability or the human-social cost, which is incalculable. A-A suggests that failure to adequately reduce stroke risk, which is well documented and results in thousands of preventable ischemic strokes	

Consultee	Comment	Response
	attributable to AF, should be factored into the QAL. Although A-A is aware that this is qualitative data from a relatively small number of AF patients, a recent survey amongst highlighted that 54% of the AF patients asked, (who are still in employment) reported that warfarin had a very high impact on their job and employment. A-A strongly believes that denial of a new, safe and more effective treatment for this group of AF patients would discriminate against their opportunity to access work, maintain employment and succeed in promotion, regardless of ability, due to INR testing requirements Oral anticoagulants are largely prescribed by and managed by Primary Care physicians, however in reviewing Dabigatran, this group of specialists was not represented. Neither were Commissioners who, without guidance issued by NICE, will face considerable pressure	
Arrhythmia Alliance	**Are the summaries of clinical cost effectiveness reasonable interpretation of the evidence?** AFA is mindful that budgetary pressures within the NHS are ever-present and inevitable, and as a result, financial pressure demands sound reasoning and compelling arguments before new therapies can be recommended. To this end, part of 'efficiency' is cost. However, as recommended in the QIPP, Right Care programme, 'Commissioning for Value': '*value must also be measured by outputs, not inputs. Hence it is patient health results that matter.'* The RE-LY trials showed a reduction in relative risk when compared with warfarin of 10% in the 110mg dose arm, and 35% in the 150mg dose. While the ERG had been tasked to consider QAL for AF patients 75yrs+, NICE guidance also indicates anticoagulation for some at: '*age 65 years or over with one of the following: diabetes mellitus, coronary artery disease, or hypertension'*. A-A believes that the cost effectiveness comparison for these patients should be without anticoagulation or aspirin.	Comments noted. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.40 and 4.16 – 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.

Consultee	Comment	Response
	An NHS priority is to reduce the number of strokes suffered. The current guidance acts against this, despite trial evidence (RE-LY) and expert witness statements, given prior and at the Appraisal meeting. A-A believes that this will result in: - Continued rise in the event of strokes due to AF - Conflicts between patients and clinicians - No local guidelines, leading to inequality of services and care and cost inefficiencies - Promotion of unwarranted inequalities in stroke risk reduction	
Arrhythmia Alliance	**Are the provisional recommendations sound and a suitable basis for guidance to NHS?** To deny recommendation of Dabigatran would be to allow risk to continue. A national audit in England has demonstrated that the quoted prevalence of AF is below that originally thought (1.2% against 1.7%). Despite NICE Guidance 2006, and update of QOF, the level of intervention for patients with AF and at risk of stroke is largely unchanged. A-A believes this is primarily due to resistance to warfarin. A-A calls for the Appraisal Committee to reconsider the draft decision to be mindful to deny guidance, in light of this evidence. A-A does not believe that the provisional recommendations are sound or of a suitable basis for guidance to the NHS. A-A does not believe that the current recommendations are sound and act as a suitable basis for guidance to the NHS.	The Final Appraisal Determination recommends dabigatran as an option for the prevention of stroke and systemic embolism in people with atrial fibrillation. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.40 and 4.16 – 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.
Arrhythmia Alliance	**Groups who need particular consideration to ensure avoidance of unlawful consideration?**	Comment noted. The manufacturer's response to the Committee's request for inclusion of a patient cohort that better reflected people with atrial

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	A-A asks the committee to be mindful to the fact that the average age of UK AF patients is not 77 years, as indicated by the ERG models, but indeed far younger. The models presented by the ERG do not represent current clinical practice. Denial of guidance to Dabigatran would be discriminatory towards those AF patients who are poorly controlled/ are difficult to control on warfarin.	fibrillation in the UK and the Committee's discussion of the manufacturer's revised analysis is summarised in sections 3.37 and 4.17 of the Final Appraisal Determination.
Atrial Fibrillation Assocation	AFA is mindful that budgetary pressures within the NHS are ever-present and inevitable, and as a result, cost effectiveness has to be a reasonable expectation before new therapies can be recommended. However when comparing treatments it is important not to just consider cost but also effectiveness and this should take into account the wide gap between clinical trial data and real clinical practice. While this difference has been recognised for some time it is probably best summarised but the QIPP, Right Care programme, 'Commissioning for Value': **'value must also be measured by outputs, not inputs. Hence it is patient health results that matter,'** The AFA has amassed and documented the experiences of a vast number of patients and health care workers that have been shared with us. These accounts are a true representation of the "health results" of patients suffering from AF in the UK today. In light of this amassed patient feedback and respected published data we have formulated the following summary of point on behalf of patients suffering from AF: 1) **AF is the greatest risk factor for stroke and results in more severe strokes** **2) Patients with AF are not prescribed appropriate stroke prevention in the vast majority of cases** **3) The main reasons for this are patient and physician resistance to using warfarin.** **4) For those patients on warfarin large numbers of patients are difficult to control and spend >60% outside the target therapeutic range – rendering warfarin of no benefit.** **5) The NHS should use warfarin as the first choice therapy but must**	Comments noted.

Consultee	Comment	Response
	accept that many will have expensive strokes if an alternative is not available for those patients unable to maintain INR **6) The committee does not have representation from all relevant professionals** We present arguments for these points in more detail as follows.	
Atrial Fibrillation Association	1) AF is the greatest risk factor for stroke Atrial Fibrillation is known to be responsible for 45% of all embolic strokes, resulting in more than 12,500 strokes per year in England and Wales. AF strokes are usually more severe and cause more death and disability. The medical cost of a stroke in first year is £9,500 - £14,000 per stroke. Embolic strokes are likely to be represented at the high end of this range. Hospital stay costs following a stroke are £103 million and post-discharge care, £45 million. These costs do not include continuing costs after first year, nor do they include costs associated with long term disability or the human cost, which is incalculable. The well-documented and persistent failure of warfarin adequately to reduce stroke risk results in thousands of preventable ischemic strokes attributable to AF. The AFA suggests that these preventable strokes should be factored into the QAL.	Comment noted.
Atrial Fibrillation Association	2) Patients are not prescribed appropriate stroke prevention In clinical trials warfarin has been associated with a stroke risk reduction in AF patients of 50%-70%. However, this potential is not being realised in routine clinical practice, leaving thousands at risk of preventable strokes. Warfarin is under-prescribed for many reasons including the complexity of dosing and patient management as well as fear of the associated bleeding risks. Consequently, almost half the AF patients for whom warfarin is indicated are not on warfarin and remain at extremely high risk of severe, debilitating and expensive strokes.	Comment noted. The Committee's discussion of current practice is summarised in section 4.2 of the Final Appraisal Determination.
Atrial Fibrillation Association	3) The main reason for lack of stroke prevention is patient and physician resistance	Comment noted. The Committee's discussion of the limitations of warfarin is summarised in section 4.2

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	to using warfarin Management of warfarin is complex and time-consuming for primary care physicians who currently gain equal financial reward for prescribing aspirin to tackle stroke prevention in AF patients. There is therefore great incentive against prescribing warfarin. It is also recognised that those at greatest risk, the elderly, are less likely to be given warfarin because of perceived fear of complications. However although the ERG had been tasked to consider QAL for AF patients 75+, there are large numbers of younger patients who according NICE guidance should also be prescribed anticoagulants including 'those with a history of stroke and those aged 65 years or over with one of the following: diabetes, coronary artery disease, or hypertension.' The AFA has collected survey evidence from this age. Of those still in employment, 54% reported that warfarin had a very high impact on their job and employment. This will be increasingly relevant as the age of the population and retirement ages increase.	of the Final Appraisal Determination.
Atrial Fibrillation Association	4) For those patients on warfarin large numbers of patients are difficult to control and spend >60% outside the target therapeutic range – rendering warfarin of no benefit. As few as 18% of AF patients are adequately treated to prevent stroke. Estimates vary but only 60-70% of AF patients are thought to be diagnosed in the UK. Of those, 97% are considered at moderate or high risk, and hence in need of anticoagulation therapy according to the most recent international expert consensus guidelines. Of patients indicated, NICE's own review of the literature in 2006 concluded that only 54% actually receive warfarin. Published evidence on the amount of time patients spend in therapeutic range indicate that of warfarinised AF patients, only 56% are within range at any one time. As simple combination of these numbers suggests that at any one time, warfarin is effectively and safely reducing stroke risk in only 18-21% of AF patients.	Comment noted. The Committee's discussion relating to the difficulty of INR control is summarised in section 4.2 of the Final Appraisal Determination.
Atrial Fibrillation	5) The NHS should use warfarin as the first choice therapy but must accept that	The Committee considered the additional

Consultee	Comment	Response
Association	many will have expensive strokes if an alternative is not available AFA strongly believes that comparison of dabigatran with well-controlled warfarin is ignoring the cost of stroke those patients in whom warfarin is ineffective or impossible to use. A fair comparison is therefore to aspirin or to nothing. Therefore denial of a new, safe and more effective treatment for these AF patients is not based on a fair appraisal. We would propose that dabigatran should be recommended for the following patients if they are at moderate or high risk of stroke according to the $CHADS_2VASc_2$ system: a) those in whom warfarin is poorly controlled (<70% time in therapeutic range) or in whom complications result from poor control (bleed/TIA/stroke) b) those for whom warfarin INR monitoring will limit their opportunity to access work, maintain employment and access promotion	information provided by the manufacturer. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.40 and 4.16 – 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.
Atrial Fibrillation Association	6) The committee does not have representation from all relevant professionals The oral anti-coagulants are largely prescribed by and managed by primary care physicians, however in reviewing dabigatran, this group of physicians was not represented. Neither were commissioners who, without guidance issued by NICE, will face considerable pressure. The AFA calls upon the committee to include representation from Primary Care and Commissioners.	Comment noted. An NHS commissioning expert, selected by NHS Salford was present at the second Appraisal Committee meeting.
Atrial Fibrillation Association	**Conclusions**: AFA does not believe that the current recommendations are sound or that they represent as a suitable basis for guidance to the NHS. An NHS priority is to reduce the number of strokes. The current recommendations act against this priority, despite trial evidence (RE-LY) and expert witness statements, given before and at the appraisal meeting. AFA believes that this will result in:	Comment noted. The Final Appraisal Determination recommends dabigatran as an option for the prevention of stroke and systemic embolism in people with atrial fibrillation within its licensed indication.

Consultee	Comment	Response
	- Continued rise in the event of strokes due to AF - Conflicts between patients and clinicians - No local guidelines, leading to inequality of services and care and cost inefficiencies - Promotion of unwarranted inequalities in stroke risk reduction AFA calls upon the Committee to issue guidance on dabigatran with consideration to the points AFA has highlighted in its response to the appraisal consultation document.	
Boehringer Inhelheim	Please consider this document as Boehringer Ingelheim's formal response to the Appraisal Consultation Document (ACD) resulting from the 1st Appraisal Committee meeting for the Single Technology Appraisal (STA) of dabigatran etexilate for the prevention of stroke in atrial fibrillation. This response is split into three sections. Firstly, we list the instances in the ACD that we believe to be either typographical error, factually inaccurate or potentially misleading to the reader. These comments are generally limited to Sections 2 and 3 of the ACD since Section 4 is a reflection of the Committee's deliberations, and therefore cannot by definition be factually inaccurate. We would be extremely grateful if these comments could be given serious consideration during the formulation of the Final Appraisal Determination (FAD). Secondly, we provide further clarification and detail regarding the sequence dosing regimen. The purpose of this section is to state for the record the process, as seen from our perspective, that led to the confusion surrounding this issue at the 1st Committee Meeting. Thirdly, we include for completeness our previously submitted response to the request for further information as laid out in the ACD. Therefore this document in its totality can be regarded as our full response to the ACD. We welcome the opportunity to submit this response and look forward to the ensuing discussions at the next Committee meeting on September 20th.	The FAD has been amended to correct any typographical errors. The Committee considered the additional information provided by Boehringer Ingelheim. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.38 and 4.16 – 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.
Boehringer	We note that the main reason for the preliminary decision of "minded not to	Comment noted. The Appraisal Consultation

Consultee	Comment	Response
Ingelheim	recommend" is uncertainty surrounding the sequential dosing regimen of dabigatran etexilate (DBG) as per the approved EU label. We would like to take the opportunity to fully clarify how and why this regimen was presented in our original submission, and how the uncertainty surrounding this issue subsequently persisted up to and during the 1st Committee Meeting. We made our original submission on October 5th 2010. As this date was well in advance of our expected date for the receipt of positive CHMP opinion from the EMA, it was necessary to present the economic evaluation according to the most likely product label that would be received in the UK. Based on discussions with the EMA prior to our submission to NICE, it was clear that an EU label mirroring that issued in Canada on October 28th 2010 was the most likely scenario. In Canada, DBG 150mg bid is licensed for use in all eligible patients up to the age of 80 years. DBG 110mg bid is licensed for use in all eligible patients aged 80 years and over. Therefore, under the final scope, it was necessary for us to assess the cost-effectiveness of DBG used according to this posology in accordance with the expected label. Therefore we decided to present BOTH the sequential dosing regimen, and the regimens as studied in the RE-LY trial to provide not only the cost-effectiveness according to the expected label with its underlying clinical rationale, but also to provide cost-effectiveness information in patient cohorts as randomised in the RE-LY trial. It was never intended that these regimens should be compared with one another. As stated in our original submission: "*Interventions 1 [150mg b.i.d in all patients] and 2 [110mg b.i.d in all patients] follow the original design of the RE-LY trial and will provide cost-effectiveness estimates for each DBG dose in a general, eligible AF population. However, given the clear dose-response demonstrated in Sections 3 and 4, it is clear that one or other of the*	Document and the Final Appraisal Determination state that the Committee concluded that the sequence of dabigatran 150 mg twice daily followed by dabigatran 110 mg twice daily once people reach 80 years would be the only regimen appropriate for the assessment of the cost effectiveness of dabigatran relative to warfarin in the whole eligible UK population. The draft guidance decision related to uncertainty around the assumptions used in the economic model, in particular, relating to the patient cohorts, the inclusion of dyspepsia management costs, disability and mortality risks after stroke by treatment, disutility associated with dabigatran, INR monitoring costs and the cost effectiveness in people with differing levels of INR control.

Consultee	Comment	Response
	doses may be more appropriate in patients of differing risk profiles. Therefore intervention 3 [sequence] targets each dose within a specific patient population as per the current proposed SPC, thereby increasing the overall capacity to benefit." (Section 6.2.1, page 151 of our original submission) We attempted twice more to reinforce this principle with the ERG. Firstly, in the ERG's clarification letter (sent 28th October 2010) we were asked to provide: *"…the results of the cost-effectiveness analysis using simultaneous comparisons between dabigatran (150mg and 110mg) and all comparators…*" (Question B5, page 384 of the full ACD information package) Our response (dated 11th November 2010) stated: "*It is … not reflective of the expected posology according to the draft SPC currently under EMA review and already approved in Canada… These comparisons can not and should not be made in the sequence model as the clinical data used is specific to dose and age*." (Response to Question B5, page 397 of the full ACD information package) Nevertheless, on receiving their full report (9th February 2011) it was clear that the ERG had continued to incorrectly compare all alternatives with one another across all patients and had concluded that 150mg bid (extendedly) dominated 110mg bid. We were asked only to check for factual inaccuracies in the ERG report, of which we firmly believed this was such an instance. Therefore, in our response (dated 16th February 2011) we reinforced this principle for the second time: "*The final scope states that DBG is to be appraised within its licensed indication. Throughout the report the ERG's own analyses repeatedly compare DBG 110mg bid directly with DBG 150mg bid. It is inappropriate to continually make this comparison without providing the context that the proposed licensed indication for DBG is for the two doses to be used in different patient groups*." (Issue 8, page 631-2 of the full	

Consultee	Comment	Response
	ACD information package) The ERG did respond to this issue, but unfortunately we were not immediately privy to their response and our first sight of it was on receiving the full ACD documentation on August 10th 2011, only after the 1st Committee meeting. In their response the ERG stated: "*The manufacturer has not presented a factual inaccuracy. The ERG has undertaken a full incremental analysis by comparing all available treatments for each sub-group. The manufacturer's proposed licensed indication is not a treatment option in the RE-LY trial but a post-hoc subgroup analysis and has not been recommended by the FDA. However, it was included to determine whether it was a cost-effective option.*" (Response to issue 8, page 631-2 of the full ACD information package) This is extremely disappointing because the resulting confusion at the 1st Committee meeting could have been easily avoided. The cost-effectiveness presentation given at the meeting continued with the ERG's flawed comparison. However, the Committee quickly accepted Boehringer Ingelheim's explanation that the sequence regimen model was the only one appropriate for decision making in light of the approved label, and that it cannot be compared with the single dose regimen model. This conflict led to the ERG making an impromptu, manual calculation during the meeting itself that should not have been performed as it was methodologically erroneous. NICE have since agreed that this calculation was invalid. Had we had sight of the above response prior to the 1st Committee meeting we would surely have made strong representations to ensure that the correct analyses were prepared by the ERG for the meeting. It is difficult to understand why the ERG consistently chose to disregard our clear and continual provision of the most likely product label. The ERG was wrong to state that this issue was not a factual inaccuracy. The final scope states that cost-	

Consultee	Comment	Response
	effectiveness is to be examined within the product's licensed indication and we have always provided the most accurate information regarding our likely licensed indication to the best of our knowledge. We assume that the Committee would concur that the most up-to-date information on the likely licensed indication during ongoing regulatory review could only come from the manufacturer. Further, given the fact that this was already the approved indication in Canada, and that we had made explicit reference to this in our commentary on November 11th 2010, we remain puzzled by the ERG's obvious reticence to accept the likelihood of this label. We also do not understand the relevance of any recommendation or otherwise by the FDA to this appraisal. Finally, although the EPAR was not available prior to the 1st Committee Meeting, we informed NICE on 15th April 2011 that CHMP positive opinion had been received and provided the draft SPC on 19th April 2011, which confirmed the sequence dosing regimen. Clearly the ERG either did not have access to this information before the 1st Committee Meeting, or it was not accounted for. In light of these complicated circumstances we are grateful to the Committee for choosing the pragmatic option of "minded not to recommend". We welcome the opportunity to provide further clarification and information directly to the Committee and look forward to a productive discussion at the 2nd Committee Meeting.	
Department of Health	The Department of Health has no substantive comments to make regarding this consultation.	No action required.
Heart Rhythm UK	**Issue 1 Failure to address the population problem of poor uptake of anti-coagulation amongst high risk patients** **Description of problem:** The guideline needs to take greater account of the current major community health problem of inadequate management of AF. There has been poor implementation of the NICE 2006 AF guideline on anti-	Comment noted. The Committee's discussion relating to the difficulty of INR control is summarised in section 4.2 of the Final Appraisal Determination. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's

Consultee	Comment	Response
	coagulation. This is illustrated by work carried out interrogating GP databases using the GRASP-AF tool. Uploaded information is available from some 868 practices totalling a population of over 6 million patients, some 108.000 with AF. Amongst high risk patients (CHADS > 1), 45.8% were not receiving an oral anti-coagulant. A contra-indication to anti-coagulation was recorded in only 35.5% of this untreated group. Barriers to warfarin appear to include the accessibility of frail and elderly patients to anti-coagulant monitoring, the ability of some patients to cope with variable warfarin dosing and the attitudes of both medical staff and patients to warfarin. Dabigatran presents a very real opportunity to overcome at least some of these barriers**.** **Description of proposed amendment** Consideration needs to be given to alternative comparators to warfarin. Amongst patients who for a wide variety of reasons cannot take warfarin, a more appropriate comparator would be aspirin. There should therefore be a reappraisal of the cost efficacy of dabigatran therapy in comparison with aspirin for patients amongst whom warfarin therapy is inapplicable. This could be achieved by combining the results of the RELY and BAFTA studies. **Result of amended model or expected impact on the result (if applicable)** We do not think that this amendment can be fitted into the current model. An alternative illustration is provided. This was prepared for the West Yorkshire Cardiovascular Network by York Health Economics Consortium. This analysis was based on combining results from RELY and BAFTA and hence was based on a number of assumptions. It was limited to patients over the age of 75. The base case incremental cost per QALY was £4820 for dabigatran 150mg and £10,050 for dabigatran 110mg, both in comparison with aspirin. In population terms, extrapolating from the GRASP data, there are over 250,000 patients nationally with AF and known risk factors at high risk of stroke who are currently not treated with an oral anti-coagulant. If these patients were treated with any anti-coagulant, it would offer the potential to reduce stroke rates in the UK by	considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.38 and 4.16 – 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website

Consultee	Comment	Response
	some 4800 strokes each year. Dabigatran and the other new anti-coagulants offer the possibility for a major new initiative in stroke prevention in providing therapy for patients who currently cannot access warfarin services.	
	Issue 2 Additional consideration of the benefits of dabigatran in relation to time in therapeutic range on warfarin **Description of problem** The current ACD does not adequately explore the importance of time in therapeutic range. This issue is of such magnitude that it is likely to dwarf other issues, such as the cost of anti-coagulation monitoring with warfarin, which have been highlighted. The current ACD also fails to consider to what extent the population in RELY is comparable with the UK population in quality of anti-coagulant control. Amongst countries which contributed patients to the RELY study, the UK was fifth best for quality of anti-coagulant control The mean TTR for UK centres was 72% compared with a median of 65% for the study as a whole. **Description of proposed amendment** We would recommend that the model is rerun, based on the quartiles of time in therapeutic range with warfarin in the RELY study, presented by Wallentin et al. More information is required on the distribution of time in therapeutic range amongst UK patients. We believe that some information may be available from the manufacturers of anti-coagulant management guidance software which would help inform the significance of this proposal in terms of the number of patients eligible for warfarin therapy based on poor time in therapeutic range. The York Health Economics Consortium model carried out for the West Yorkshire Cardiac and Stroke Network gave the following results. **Cost per QALY for dabigatran compared with warfarin** **150mg** **110mg** **Base case** £12640 £31315 **TTR < 56.9** £2800 £8720	Comment noted. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.38 and 4.16 – 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.

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	TTR 56.9-65.4 £5165 £19450 **TTR 65.4-72.4** £29354 £18990 **TTR > 72.4** Warfarin more cost effective. It seems probable therefore that considering different TTR ranges will have a very major effect on the conclusions of the ACD as to cost efficacy in different patient groups and we would encourage the appraisal to pursue this issue further	
	Issue 3 Insufficient attention to disadvantaged patient groups **Description of problem** Many patients cannot take warfarin for reasons other than simple bleeding risk. This can be for a variety of reasons including, poor mobility and frailty limiting access to anti-coagulant monitoring services and impaired mental capacity causing difficulties in variable drug dosing. It is unethical to deny these patients a potentially highly cost effective treatment **Description of proposed amendment** As already discussed, aspirin may be a more appropriate comparator for some of these patient groups. Alternatively, the model should consider that it is unlikely that there is a single, unique cost of anti-coagulant control with warfarin. For example, the costs are likely to be substantially higher in a patient who requires domiciliary visits for blood sampling or who requires direct supervision of variable warfarin dosing. **Result of amended model or expected impact on the result (if applicable)** The model therefore needs to be amended to ensure that the full costs of anti-coagulant control in disadvantaged groups are considered. The results are likely to reduce the incremental cost of dabigatran in comparison with warfarin amongst disadvantaged patients	The Final Appraisal Determination recommends dabigatran within its licensed indication as an option for the prevention of stroke and systemic embolism in people with atrial fibrillation. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option (see section 4.19 of the Final Appraisal Determination).

Consultee	Comment	Response
NHS Salford	On behalf of NHS Salford I would like to submit our comments on the above appraisal consultation document for which NHS Salford is a consultee. ***Comments from Sarah Cannon Public Health Manager*** ▪ From the evidence presented we are in agreement with the Committees view not to recommend dabigatran etexilate for the prevention of stroke and systemic embolism and would view this as suitable guidance for the NHS. ▪ The ACD highlights areas of uncertainty regarding cost effectiveness and we would agree with the Committees request for further analysis. In particular the agreement of the suitable time horizon for this patient group, number of monitoring appointments and the investigation of cost effectiveness for those who have poorly controlled INR versus those with stable INR. Greater Manchester cardiac network have recommended this definition of poorly controlled as Indicators for instability of anticoagulation include: ➢ Low time in therapeutic range (TTR) once stabilised on warfarin (usually 5 months.) The INR % of time in the therapeutic range of 2-3 should be 60% or greater. (TTR should be measured for individual patients using the Rosendaal Method) ➢ Clinic visit frequency greater than 50% above the clinic schedule of visits for patients who stay consistently within the target INR after stabilisation. ➢ Increases in visits that are predictable e.g. due to co-prescription of antibiotics, inter current illness, vomiting providingthese are infrequent should be excluded from this calculation. ➢ Initial stabilisation cannot be achieved within three months ➢ INR >5 more than 5 times per year ▪ We would also be interested in the quantification of the impact of an increased gastrointestinal bleed on NHS resources compared to lower incidence of haemorrhagic stroke and intracranial haemorrhage. Equally consideration of the	Comments noted. The NICE guide to the methods of technology appraisal states that a lifetime time horizon for clinical and cost effectiveness is appropriate for chronic diseases where costs and outcomes occur over a patient's lifetime The Committee considered the additional information provided by the manufacturer. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. e. The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19). The manufacturer's additional submission and revised analyses submitted in response to the

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	higher discontinuation rates considering the advantages outlined of less inconvenience for patients. It is also not clear what the affect of dabigatran would be for NHS anticoagulation services in terms of overall societal costs.	Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.
NHS Salford	**Medicines management team comments** NHS Salford agrees with many of the statements noted in the CSAS review as detailed below ▪ Warfarin is the most cost effective treatment in patients with atrial fibrillation with INR control within the recommended range. In this group, the ICER for dabigatran vs warfarin is £60,895 per QALY. We feel further review should be on those patients with poor INR control where dabigatran might offer a cost effective treatment. This is where GM cardiac network have positioned this drug (see attached algorithms) ▪ The manufacturer of dabigatran has assumed higher attendances for monitoring warfarin than is usual in clinical practice. They estimate 20 visits per year per patient for INR monitoring where clinical practice suggests that 5-12 visits is more realistic. This makes warfarin appear more expensive and consequently makes dabigatran appear relatively cost effective. ▪ Also, PCTs might currently be in block contracts for anticoagulation services which are not able to respond quickly to changes in demand for attendances that dabigatran patients would produce. The savings in clinic attendances may not materialize in practice and if it does so it will not be immediate. ▪ Time in therapeutic range should be considered in sensitivity analysis of clinical and cost effectiveness. In the RE-LY study, mean TTR for warfarin in the UK was 72% . The RE-LY study did not demonstrate superiority of dabigatran over warfarin above a median TTR of 67%. ▪ Time horizon should be included in further assessments of cost effectiveness. The	Comments noted. The Committee considered additional information provided by the manufacturer. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website. The Committee was aware that comments received during the consultation largely agreed that INR monitoring costs are likely to be higher than the ERG's lower estimate of £115.14 and possibly higher than £414.90 in some cases. The Committee

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	time horizon influenced the ICER greatly with a 2-year time horizon resulting in ICERs of £75,891per QALY in people under 80yrs old and £23,403 per QALY in people over 80 yrs old for the dabigatran sequential regimen vs warfarin ▪ No information is provided regarding dabigatran as a second line treatment in patients who are inadequately treated with warfarin. This is a potential treatment option that was not modelled in the manufacturer's submission but it should be considered in case it is a cost effective treatment in this specific patient group. This is where GM cardiac network has positioned this drug (see attached algorithym) ▪ Safety. There is an increased risk of gastrointestinal bleed with dabigatran 150mg and there is no specific antidote in the event of haemorrhage or overdose. The RE-LY study was conducted over a 2 year period and further safety data over a longer time period should be requested. Recent restrictions to the drugs license in Japan need examined (we have not yet received the data surrounding this from the company despite asking for it). ▪ Patient Acceptability: Discontinuation rates in the RE-LY study were higher amongst patients treated with dabigatran than with warfarin. This is not clearly explained. Warfarin, unlike dabigatran, is associated with a number of inconveniences such as food and drug interactions, regular monitoring and dose adjustments which can cause disruption and inconvenience. However a quantification of this impact was not presented in the ACD and factored into the cost effectiveness model. Proper quantification of this could affect the relative cost effectiveness of dabigatran compared to warfarin. ▪ There were limitations to the quality of the research: Patients were treated in the RELY study who would not have been eligible for treatment in the UK, using the current NICE guidelines. This affects the generalisability of the RELY study to UK	accepted the manufacturer's approach (of using £241.54 per annum), acknowledging that although INR costs may vary widely, this assumption was reasonable. See section 4.16 of the Final Appraisal Determination. The NICE guide to the methods of technology appraisal states that a lifetime time horizon for clinical and cost effectiveness is appropriate for chronic diseases where costs and outcomes occur over a patient's lifetime The Committee considered the issue of increased risk of gastrointestinal bleeding with dabigatran 150 mg twice daily. The Committee's discussion is summarised in section 4.7 of the Final Appraisal Determination. More detailed information on the drug-drug and drug-food interactions of warfarin are presented in the manufacturer's submission. The Committee considered the higher discontinuation rates in the dabigatran arm of the trial, and assumed that this was most likely to relate to intolerance, although without direct patient level data this could not be established with certainty. Further modelling captured any increased costs related to treatment of dyspepsia. The Committee concluded that the population included in the trial was appropriate and broadly

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	clinical practice. ▪ We feel the issue of patient choice needs to be clarified and that just because patients want dabigatran (who have stable INRs on warfarin) this is not enough reason to switch therapy. ▪ A clear positioning statement that this is a second line treatment in those who cannot be managed on current accepted UK treatment (warfarin) would allow PCTs to use this new drug in patients that will benefit from it and in an affordable way to the NHS.	relevant to UK clinical practice. See section 4.3 of the Final Appraisal Determination. The Committee concluded that the decision about whether to start treatment with dabigatran in people with atrial fibrillation should be made after an informed discussion between the responsible clinician and the person about the safety risks and benefits of dabigatran compared with warfarin. It also concluded that, for people currently receiving warfarin, the potential risks and benefits of switching to dabigatran should be considered in light of their level of INR control. See section 4.20 of the Final Appraisal Determination.
NHS Salford	**Comments received from the Greater Manchester Cardiac Network** ▪ We agree with the comments in the CSAS document in that the focus on the further review, specifically looking at cost effectiveness should be on the group of patients with poor INR control on warfarin and who also have a CHADSVASC score of 3+ ▪ Warfarin should remain the 1st line treatment and in accordance with the attached algorithms and guidance which have been developed with clinicians across Greater Manchester ▪ An economic model has been developed in Greater Manchester, which is currently being validated by Manchester University which will support PCTs in planning their services by gaining a better understanding of the impact of the introduction of *any* new anticoagulation therapies for the treatment of patients with AF. The model aims to use local population data combined with the attached treatment algorithm to identify potential eligible patients for the new treatments and compare this with alternative scenarios. The data to populate the model will be obtained by running the GRASP-AF tool	Comments noted. The Committee considered the additional information provided by the manufacturer. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19). The manufacturer's additional submission and

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	▪ We believe that the drug should only be prescribed in primary care and then only after communication is received from the anti-coagulation clinic/GPwSIs or locally agreed 'gatekeeper' has confirmed all reasonable attempts to maintain stable INRs of 2-3 have been exhausted or that patients have been stopped due to contra-indications or adverse drug reactions ▪ The number of attendances for monitoring warfarin is largely irrelevant in cost effectiveness terms for those commissioners who have block contracts ▪ Further work is needed to define what is classed as 'poor control' as estimated visits per year per patient may not be a good enough marker ▪ As Rivaroxaban is hot on the heels of Dabigatran should NICE consider a multi-technology appraisal not two single appraisals	revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website
Royal College of Nursing	i) **Has the relevant evidence has been taken into account?** The evidence considered seems comprehensive. ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with this condition. The preliminary views on resource impact and implications should be in line with established standard clinical practice. iii) **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add.	Comments noted

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	The RCN would welcome guidance to the NHS on the use of this health technology. iv) **Are there any equality related issues that need special consideration that are not covered in the ACD?** We are not aware of any specific issue at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	
Royal College of Physicians	We note that the committee has requested further information from the manufacturer before a decision is made to recommend (or not recommend) the use of dabigatran etexilate for the prevention of stroke and systemic embolisation in people with atrial fibrillation. This information will include a cost effectiveness analysis comparing dabigatran with warfarin using different effectiveness data, different scenarios for reflecting the cost of warfarin monitoring, and assumptions suggested by the ERG. **1. Has all of the relevant evidence been taken into account?Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We believe that the ACD presents a reasonable interpretation of the evidence for the use of dabigatran etexilate as stroke prevention therapy, versus the currently available treatment, which is warfarin. **2. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The provisional recommendation by the committee is suitable. Our experts would like to make the following points regarding requests made by the committee for further analysis and information:	Comment noted. Comment noted. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19).

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	i) European marketing authorisation has apparently restricted the use of dabigatran as a long-term anticoagulant to a dose schedule based on age, so that the higher dose of 150mg bd will only be available to patients aged <80 years and the lower dose of 110mg bd will be used in all patients aged ≥80 years. The committee has requested a re-analysis of the cost effectiveness of dabigatran versus warfarin based on this sequential regimen using relative risks from the whole cohort, rather than those based on a post-hoc subgroup analysis of treatment effects at age <80 years and ≥80 years. However, a pre-specified subgroup analysis of patients aged <75 years and ≥75 years did reveal significant treatment by age interactions at different doses of dabigatran, and these effects would be lost if data from the whole cohort are used. The relative risks based on analyses of the pre-specified age groups should be reasonable approximations of expected outcomes in the groups aged <80 and ≥80 years, and could be used instead.	The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.
	ii) The committee noted that a key uncertainty was the generalisability of the results from RE-LY to people with AF in the NHS. The committee asked for a resubmission of the cost-effectiveness analysis using a patient cohort representing people with AF in the UK (Gallagher et al 2008). The UK cohort, which was taken from the GP research database from 2000 onwards, included all patients with AF aged above 40 years. The UK cohort therefore included patients aged <65 years, and also included a significantly higher proportion of patients with lower CHADS2 scores compared to the RE-LY cohort; 43.2% of the UK cohort had a score of <2 versus 31.9% of the RE-LY cohort. Therefore the RE-LY cohort is probably more representative of the patient population who are eligible for thromboprophylaxis with anticoagulation based on current NICE guidelines.	The Committee concluded that the population included in the trial was appropriate and broadly relevant to UK clinical practice. See section 4.3 of the Final Appraisal Determination.
	iii) The committee asked that the cost-effectiveness model is run using a per-patient cost of £115.14 for anticoagulant monitoring. This cost of £115.14 is likely to be an underestimate - as it is not clear that it takes into account the costs of monitoring warfarin in patients who are unable to attend anticoagulation clinics and require district nurse visits for blood testing or supervision of warfarin administration.	The Committee was aware that comments received during the consultation largely agreed that INR monitoring costs are likely to be higher than the ERG's lower estimate of £115.14 and possibly higher than £414.90 in some cases. The Committee accepted the manufacturer's approach (of using £241.54 per annum), acknowledging that although INR costs may vary widely, this assumption was reasonable. See section 4.16 of the Final Appraisal Determination.
	iv) The committee asked that the cost-effectiveness model is run assuming that disability and mortality risks after stroke are treatment-independent. However, there is evidence that the severity of ischaemic stroke is reduced in patients taking warfarin compared to those taking aspirin, and reduced in patients on warfarin with therapeutic INRs versus those with subtherapeutic INRs.(Hylek et al, New England Journal of Medicine 2003) As dabigatran users are more likely to be adequately anticoagulated	The Committee was aware, having heard from the clinical specialists, that the manufacturer's assumption that a stroke would be less severe after

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	compared to warfarin users, given the relative lack of drug and food interactions associated with dabigatran use, it is expected that fewer ischaemic strokes occurring in dabigatran-users will be fatal or disabling compared to ischaemic strokes occurring on warfarin. Therefore a cost-effectiveness model which disregards this effect will be biased in favour of warfarin.	treatment with dabigatran than warfarin was plausible and that there is evidence that both the incidence and the severity of stroke may vary according to the treatment received. See section 4.13 of Final Appraisal Determination.
	3. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? We have not identified any aspects of the recommendations that unlawfully discriminate against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief.	Comment noted.
	4. Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document? The present situation in which there is reduced access to anticoagulation monitoring and treatment among patients with limited mobility or age-related illnesses such as early dementia has not been taken into account in the present cost-effectiveness analysis. A high proportion of patients who would benefit from anticoagulation are elderly, relatively immobile, socially isolated and/or suffering from cognitive difficulties. Such patients, who are otherwise eligible for anticoagulation, are often never offered treatment (Gallagher et al, Journal of Thrombosis and Haemostasis, 2008) or decline treatment, because warfarin is perceived as being too inconvenient or too unsafe to use if there are doubts about the patient's compliance and cooperation with treatment monitoring. Cognitive impairment in particular is recognised as an independent risk factor for bleeding complications on warfarin therapy, (Diug et al, Stroke 2011). With adequate support and supervision from services such as district nursing, there is no reason why patients with early dementia cannot take warfarin safely. The limiting factor is access to such support services. Dabigatran is more likely to be acceptable to patients and clinicians when patients have difficulties travelling to anticoagulation clinics to comply with monitoring or have cognitive impairment and struggle with dose changes, as this drug does not require	Comments noted. The problems associated with warfarin are discussed in section 4.2 of the Final Appraisal Determination.

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	blood test monitoring, and dosing is fixed which means that the drug can be safely added to dosette boxes and taken alongside the patient's other medications. This in turn is likely to increase the uptake of anticoagulation in patients at risk of thromboembolic events across the community, and produce savings through the prevention of a greater number of thromboembolic events. Such savings are not reflected in the current version of the Markov model used to evaluate the cost effectiveness of dabigatran versus warfarin. In this model, the assumption is that all patients start treatment when offered either warfarin or dabigatran. Although some allowance is made for switching from one medication to another or stopping treatment if adverse effects occur, the model does not allow for the possibility that fewer patients may decide to start anticoagulation when offered warfarin compared to dabigatran. Data on the likely difference in uptake between the two medications are probably lacking, but plausible differences in uptake could be factored into the model as part of a sensitivity analysis.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
None submitted		

Comments received from commentators

Commentator	Comment	Response
Bayer	***Question: Has all of the relevant evidence been taken into account?*** **Anticoagulant monitoring cost – ACD 1.2, 3.16, 3.28, 3.30, 3.34, 4.11, 4.15** To estimate the cost of anticoagulant monitoring, the manufacturer derived the value used in the base-case modelling from the NICE costing report that accompanied NICE clinical guideline 36 for atrial fibrillation. The cost of INR monitoring was then inflated to 2010 prices (£414.90). Such costing tools are produced by NICE to allow individual NHS organisations and local health economies to assess the impact	Comments noted. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.40 and 4.16 – 4.19). The manufacturer's additional submission and

Commentator	Comment	Response
	guidance will have on local budgets. Therefore, this seems to be a reasonable source for the costs. The ERG stated that it was likely that the average cost of monitoring had been overestimated in the model, which may bias the results in favour of dabigatran due to the inclusion of fixed costs of monitoring. In their view, fixed costs will only be offset if warfarin is no longer used in the UK and should not therefore be included. The alternative costs used by the ERG were £279.45, £241.54 and £115.14 instead of £414.90 assumed by the manufacturer. **Bayer has a number of comments regarding the issue of the cost of anticoagulant monitoring:** 1. We do not agree that the cost of anticoagulant monitoring has been overestimated in the manufacturer's model. 2. It would seem that a costing report produced by NICE is a reasonable reference source for the cost of anticoagulant monitoring in the UK. If it is not considered appropriate, then it could be questioned what purpose it currently serves. 3. We do not agree with the ERG that fixed costs of anticoagulation should be excluded. The monitoring costs proposed by the ERG of £279.36 and £241.54 are therefore not appropriate: • According to the Drummond checklist [Drummond et al. Methods for the Economic Evaluation of Health Care Programmes. 3rd Edition. 2005] *"……Were all the important and relevant costs and consequences for each alternative identified? Were the capital costs, as well as operating costs, included?"* • NHS reference costs are a recommended source according to the methods guide [5.5.4 Guide to the methods of technology appraisal 2008]. According to the NHS Reference Costs 2010/2011 Collection Guidance, 2010, "*when undertaking costing of outpatient attendances at procedure level……All relevant overheads should be included; this covers clinic/location/ treatment function overheads in addition to an element of NHS provider wide overheads."* Further, *"the fundamental principle is that reference costs*	revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.

Commentator	Comment	Response
	should be produced using full absorption costing. This means that each reported unit cost will include the direct, indirect and overhead costs associated with providing that treatment / care". Reference Costs data is used for a variety of purposes - including to calculate the PbR tariff. As Reference Costs and Tariff costs are recommended as a source of costs for appraisals [5.5.4 Guide to the methods of technology appraisal 2008] this suggests that costs which include fixed elements are appropriate. • Under the resource impact section of the methods guide [5.13. 7 Guide to the methods of technology appraisal 2008*] "If implementation of the technology could have substantial resource implications for other services, the effects on the submitted cost-effectiveness evidence for the technology should be explored."* Again, this supports the use of the overall cost of the service displaced. • *"If introduction of the technology requires additional infrastructure to be put in place, consideration should be given to including such costs in the analysis"* [5.5.7 Guide to the methods of technology appraisal 2008]. If such costs are considered worthy of inclusion when additional infrastructure is needed, then the impact of disinvesting in the infrastructure of anticoagulation clinics over time should be modelled. This therefore mandates the inclusion of the fixed costs. • We strongly believe that fixed costs should be included in estimates of resource use. However, even if this is not accepted to be the case in the short-term, the ERG's approach of removing all of the fixed costs from the estimate does not seem realistic; fewer patients attending clinics will invariably lead to rationalisation and consolidation of services over time, which will indeed therefore release such fixed costs. Furthermore, without the introduction of the new oral anticoagulants, increasing demand for these services in the future associated with the ageing population may lead to further pressure on existing services or the need to invest in additional clinics. 4. The use of the 2005 Birmingham SMART trial by the ERG which reported an average annual cost of anticoagulation control of £98.47 (inflated to 2009/10; £115.14), seems contradictory to their comment that the manufacturer could have used more current published costs. This study was a randomised controlled trial and therefore could be argued is not representative of routine clinical practice. Patients in the trial had taken warfarin for at least 6 months, with a target INR of 2.5-3.5. Not all of the patients had AF and the mean age of those recruited was 65. GPs were	

Commentator	Comment	Response
	asked to remove patients from computer lists they believed should be excluded from the trial on clinical or social grounds. All of these factors reduce the applicability to the appraisal in question. 5. Bayer agrees with the clinical advisers to the ERG that there is high variability of monitoring costs in practice - variability will be driven by the local arrangements for anticoagulant monitoring. In addition, Bayer agrees that people with well-controlled INR will have lower costs than people with uncontrolled INR. **Dyspepsia associated with dabigatran etexilate treatment – ACD 1.2, 3.32, 3.34, 4.15** Bayer share the concern about whether appropriate costs have been applied with respect to discontinuations (and the implications in terms of stroke risk) due to dyspepsia and the symptomatic treatment of dyspepsia. If the patient does not discontinue due to this side effect of treatment, they are likely to receive symptomatic therapy for longer than the first three months of therapy. In addition, the manufacturer's submission uses an antacid as first line treatment for dyspepsia – if long term symptomatic treatment is required, the cost of introducing H_2-receptor antagonists or proton pump inhibitors should also be considered. **Long term costs and disutility associated with myocardial infarction – ACD 3.12, 3.26** Bayer agrees with the ERG that long term costs and disutility associated with myocardial infarction should be modelled. Since the Manufacturer's Submission, further data has been presented that reports acute coronary syndrome events associated with dabigatran and this is therefore an important point - acute coronary syndromes were observed in 13 patients (0.9%) on treatment with dabigatran and in 3 patients (0.2%) on warfarin (P=0.02). [Schulman, S et al. Dabigatran or warfarin for Extended Maintenance Therapy of Venous Thromboembolism, Abstract O-TH-033. Special Issue: Abstracts of the XXIII Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting, July 23-28 2011, ICC Kyoto, Japan Volume 9, Issue Supplement s2, p731, July 2011]. The RE-DEEM study has also been published since the submission and this also reports on	

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	cardiovascular ischaemic events.[Oldgren, J et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. European Heart Journal 2011. *doi: 10.1093/eurheartj/ehr113*] ***Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** No comment further to those made above. ***Question: Are the provisional recommendations sound and a suitable basis for guidance to the NHS?*** No comment further to those made above. ***Question: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?*** No comment ***Question: Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?*** No comment	
Bristol Myers Squibb and Pfizer	Bristol-Myers Squibb Pharmaceuticals Ltd. and Pfizer Ltd. welcome the opportunity to review and comment on the Appraisal Consultation Document (ACD) relating to the ongoing appraisal of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (AF). BMS/Pfizer believe that AF patients should have access to all efficacious medicines in the UK. However, we have some concerns about the basis of the Appraisal	Comments noted. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.40 and 4.16 –

Commentator	Comment	Response
	Committee's (AC) conclusions relating to the appraisal of dabigatran. In summary: • We believe that any recommendation for dabigatran should be specifically for patients suitable for warfarin, as there is no robust evidence in patients unsuitable for warfarin. Furthermore, the clinical data suggest that this recommendation should be further restricted to patients who are not at high risk of bleeding. • Robust warfarin monitoring costs are not available for this appraisal. Those previously developed by NICE should be used as a basis for decision-making, rather than the alternative estimates preferred by the ERG, which are less representative of UK clinical practice and more opaque in their methodology. It should be noted, however, that even the costs developed by NICE require further refinement as they may underestimate the monitoring costs in the UK. • Cost effectiveness analyses of medicines in AF should assume that the risk of disability and mortality post stroke are treatment dependent. They should also examine the impact of time in therapeutic international normalised ratio (INR) range (TTR) rather than INR ranges alone. We therefore ask the AC to take these comments into account in its reconsideration of its preliminary recommendation.. **Detailed Comments in ACD** Our detailed comments on the ACD and Evaluation Report are structured under the four questions posed by NICE in the consultation: 1. Has all of the relevant evidence been taken into account? 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? 3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? 4. Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? **1. Has all of the relevant evidence been taken into account?**	4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.

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	BMS/Pfizer consider that all relevant clinical evidence has been taken into account, and we are not aware of any additional cost effectiveness evidence that should be taken into account **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** BMS/Pfizer disagree with some of the summaries of clinical and cost effectiveness and believe they are not reasonable interpretations of the evidence. **Clinical evidence** Results of the RE-LY study indicate that dabigatran 150mg is superior to warfarin in preventing stroke and systemic embolism, however, we note the high rates of bleeding in patients taking the 150mg dose. Both doses of dabigatran were associated with a higher rate of gastrointestinal (GI) bleeds (dabigatran 150 mg: RR 1.50, 95% CI 1.19 to 1.89 p<0.001; dabigatran 110 mg: RR 1.10, 95% CI 0.86 to 1.41 p 0.43).[1] Consideration should therefore be given to NOT recommending dabigatran in patients who have a high risk of bleeding. Whilst the RE-LY study shows superiority for dabigatran 150mg compared with warfarin in preventing stroke and systemic embolism, we do not agree with the ERG's view that the open label design of this trial is free from bias. Patients who had previously failed with warfarin, and who were then subsequently randomised to the warfarin treatment arm, would be aware of the treatment they were receiving and would be more likely to discontinue from the study. Furthermore, whilst the adjudication of events in the study was blinded, there could still be a reporting bias because patients or clinicians might be more likely to report an event where they are aware of the treatment assigned. An illustration of the potential impact of open label vs double blind double dummy trials is given by comparing the SPORTIF III [2] and V trials [3]. SPORTIF III and V were trials with identical protocols but SPORTIF III uses a PROBE design whereas SPORTIF V was a double-blind RCT. The incidence of stroke events was found to be lower in the ximelagatran arm compared with the warfarin arm in the open label study, wheras in SPORTIF V the opposite result was observed. Apart from the countries involved, there were few differences between these trials, including TTR, which was similar (66% in SPORTIF III and 68% in SPORTIF V). Although it is	

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	impossible to establish the exact reason for this discrepancy in the results, the possibility that knowledge about novel therapy or warfarin treatment assignment on the part of those collecting outcome measurements could have contributed to the observed results cannot be excluded. Therefore a similar possibility exists and cannot be excluded with regard to the RE-LY study. Both of these potential effects may over-estimate the benefit of dabigatran in the trial. Clinical evidence should therefore ideally be derived using a double-blind, double dummy, randomised, controlled trial. Finally, the majority of patients within the RE-LY study were those who would be suitable for warfarin. This means that the efficacy and safety of dabigatran has not been studied in patients who are unsuitable for warfarin – which is likely to be a significant proportion of AF patients in the UK. Consideration should therefore be given to recommending dabigatran in warfarin suitable patients only, rather than all non-valvular AF patients, as per the licensed indication. **Cost effectiveness evidence – monitoring costs** According to the ERG, a key weakness in the manufacturer's model is the choice of anticoagulation monitoring cost. They believe the manufacturer's preferred cost is an over-estimate, so as a consequence have introduced a much lower monitoring cost into the appraisal compared with that preferred by the manufacturer. BMS/Pfizer believe that the manufacturer has systematically reviewed the cost literature and appropriately chosen the most generalisable cost to the UK population – which is that derived by NICE in the costing template for their AF clinical guideline [4]. This cost is partly based on NHS reference costs (which are routinely used in economic evaluations) and are more nationally representative compared with costs derived from local studies. However, this cost is still limited because the resource use in primary care is based on crude and unsubstantiated assumptions, and so in the longer term, more robust estimates will be required. The cost preferred by the ERG is derived from a cost effectiveness analysis undertaken by Connock et al. [5], which estimated the cost of warfarin monitoring to be £98.47 (£73.86 - £123.09) (2005 prices) using the SMART trial [6] and the economic methods of Jowett et al. [7]. As there is very limited information in these publications regarding the quantities of each type of resource use, it is unclear how	

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	robust and nationally representative these costs actually are. This study bases the resource use on what was observed in the SMART trial; however, this may not be representative of clinics nationally as clinical trials do not often represent routine clinical practice, and the study was undertaken at a specific geographical locality in the UK. On this basis the ERG's monitoring cost of £115 should not be relied upon for decision-making purposes. BMS/Pfizer also recommend that monitoring costs higher than those being used should be considered by the Committee. For example, the CG36 costs assume that 25% of monitoring will occur in secondary care and 75% in primary care, based on a 2006 survey conducted by the National Patient Safety Agency [8]. However, with the introduction of new oral anticoagulants in the UK, consideration should be given to a potential shift of use to centralised clinics concentrated within secondary care, in order to achieve economies of scale. This is very likely to occur if the use of warfarin reduces the need for the majority of monitoring to be carried out in primary care. As such, we recommend that alternative estimates be considered based on a higher percentage of monitoring being undertaken in secondary care. Increasing the ratio for secondary care monitoring from 25% to 75% significantly increases the CG36 cost (**from £382.9 to £504.9 at 2006 prices**), which implies that the current costs being considered by the AC are potential under-estimates. In addition, the ERG (see table 51 pp116 of ERG report) consider two scenarios: (1) the possibility of the variable costs of primary care being savings (ERG alternative 1) and (2) only the variable costs of primary and secondary care being savings (ERG alternative 2). However, the calculations made to deduct fixed secondary care costs from the NHS references are arbitrary and crude. Furthermore, BMS/Pfizer do not agree with the ERG's assumption that primary care fixed costs would not be saved as a result of the introduction of new oral anticoagulants not requiring routine monitoring. Indeed, we would expect a reduction in the number of clinics in primary care and at least some fixed cost savings to be made by the NHS. In addition, with a rescaling of clinics in secondary care, due to a reduction in the demand for monitoring, we would expect a reduction in fixed costs too. BMS/Pfizer therefore suggest that fixed costs are included in the savings attributed to new oral therapies. **Cost effectiveness evidence – modelling assumptions** In their economic model the manufacturer assumed that disability and mortality risks after stroke are treatment-dependent, an assumption that the ERG argue is not appropriate. BMS/Pfizer consider that these risks would be treatment independent	

Commentator	Comment	Response
	for chronic or long-term risk of disability and mortality, but not so for acute phases of stroke, where avoidance of severe stroke may impact on both disability and mortality in a treatment dependent manner. For example, the RE-LY [1] study shows that, compared with warfarin, dabigatran 150mg bd significantly reduced the incidence of disabling and fatal stroke (modified Rankin score 3 to 6) with a relative risk of 0.66 (95% CI 0.50, 0.88). Similarly, the AVERROES trial [9] shows that, compared with aspirin, apixaban results in a significantly lower incidence of disabling and fatal strokes (modified Rankin score 3 to 6) of 2.3% vs 1% respectively (0.43 HR (95% CI= 0.28, 0.65). BMS/Pfizer would request that the Committee consider our alternative assumption. Lastly, we note that the ERG have undertaken an analysis of the cost effectiveness of dabigatran based on those patients who were able to maintain their INR values within particular ranges. We believe this approach is not appropriate because INR is highly variable over time, meaning a significant proportion of patients would be excluded from this analysis if their INR varied across these ranges. Time in therapeutic INR range (TTR) is a more robust approach to capturing the cost effectiveness of dabigatran according to the extent of INR control. **3. The provisional recommendations are a sound and suitable basis for guidance to the NHS** BMS/Pfizer consider the provisional recommendations set out in the ACD are NOT a sound basis for guidance to the NHS. BMS/Pfizer advocate that AF patients should have access to all efficacious medicines and note that the RE-LY trial suggests that dabigatran 150mg is superior to warfarin in the prevention of stroke and systemic embolism. BMS/Pfizer would therefore request that any NICE recommendation for dabigatran be restricted to those patients for whom there is sufficient clinical evidence. Notwithstanding the bias inherent in an open-label trial design, the RE-LY study was undertaken in a predominately warfarin suitable patient population. However, there is an important and significant patient population with AF who are unsuitable for warfarin because of intolerance, poor response or personal preference (factors such as; impact on quality of life, work absence for monitoring, strict monitoring of diet, and other medications). No clinical trial has demonstrated the efficacy and safety of dabigatran in this warfarin unsuitable patient population and so dabigatran should not be recommended for all AF patients in the absence of such evidence.	Comment noted. Warfarin-unsuitable patients were not included in the trial. However, if warfarin is indicated, but the patient is unable to take it, for reasons of intolerance, personal preference or poor response, the Committee considered that dabigatran would be much more likely have the same therapeutic benefit as in warfarin-suitable patients, than a different benefit. The Committee concluded that there was no biologically plausible reason, or research evidence to justify excluding them from the recommendation.

Commentator	Comment	Response
	As mentioned above, BMS/Pfizer also note the higher rates of major and life-threatening bleeding with dabigatran 150mg and would therefore suggest that these patients are specifically excluded from any recommendation by NICE. In summary, any recommendation for dabigatran should be restricted to non-valvular AF patients who are **suitable** for warfarin and have a low risk of bleeding. **4.** Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? BMS/Pfizer do not consider there are any aspects of the recommendations that need particular consideration regarding unlawful discrimination against any group. **References** 1. Connolly SJ, et al., *Dabigatran versus warfarin in patients with atrial fibrillation.* N Engl J Med, 2009. **361**(12): p. 1139-51. 2. Olsson, S.B. and Executive Steering Committee of the SPORTIF III Investigators, *Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III):randomised controlled trial.* Lancet, 2003 **362**(9397): p. 1691-8. 3. Albers, G.W., et al., *Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial.* JAMA, 2005 **293**(6): p. 690-8. 4. NICE, *Atrial fibrillation: the management of atrial fibrillation. Costing report*. 2006, National Institute of Health and Clinical Excellence: London. 5. Connock, M., et al., *Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling.* Health Technology Assessment, 2007. **11**(38). 6. Fitzmaurice, D.A., et al., *Self management of oral anticoagulation: randomised trial.* BMJ 2005. **331**: p. 1057-62. 7. Jowett, S., et al., *Patient self-management of anticoagulation therapy: a trial-based cost effectiveness analysis.* Br J Haematol, 2006. **134**: p. 632-9. 8. National Patient Safety Agency, *Risk assessment of anti-coagulant therapy*. 2006, National Patient Safety Agency.	

Commentator	Comment	Response
	9. Connolly, S.J., et al., *Apixaban in Patients with Atrial Fibrillation.* N Engl J Med, 2011. **364**: p. 806-17.	
CSAS	On behalf of Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for Dabigatran etexilate for the prevention of stroke and systemic embolism in people with atrial fibrillation as an alternative to adjusted dose warfarin. We are in agreement with the recommendations in the ACD not to recommend dabigatran for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective as a replacement for warfarin. • **Warfarin is the most cost effective treatment in patients with atrial fibrillation with INR control within the recommended range.** In this group, the ICER for dabigatran vs warfarin is £60,895 per QALY. The Committee has requested 'further comment and consideration' of cost effectiveness in this subgroup. The focus of further review should be on those patients with poor INR control where dabigatran might offer a cost effective treatment. • **The manufacturer of dabigatran has assumed higher attendances for monitoring warfarin than is usual in clinical practice.** They estimate 20 visits per year per patient for INR monitoring where clinical practice suggests that 5-12 visits is more realistic. This makes warfarin appear more expensive and consequently makes dabigatran appear relatively cost effective**.** • **Time in therapeutic range should be considered in sensitivity analysis of clinical and cost effectiveness.** In the RE-LY study, mean TTR for warfarin in the UK was 72% . The RE-LY study did not demonstrate superiority of dabigatran over warfarin above a median TTR of 67%. • **Time horizon should be included in further assessments of cost effectiveness.** The time horizon influenced the ICER greatly with a 2-year time horizon resulting in ICERs of £75,891per QALY in people under 80yrs old and £23,403 per QALY in people over 80 yrs old for the dabigatran sequential regimen vs warfarin. • **No information is provided regarding dabigatran as a second line**	Comments noted. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's considerations of the additional evidence are summarised in the Final Appraisal Determination (sections 3.35 - 3.40 and 4.16 – 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.

Commentator	Comment	Response
	treatment in patients who are inadequately treated with warfarin. This is a potential treatment option that was not modelled in the manufacturer's submission but it should be considered in case it is a cost effective treatment in this specific patient group. • **Safety.** There is an increased risk of gastrointestinal bleed with dabigatran 150mg and there is no specific antidote in the event of haemorrhage or overdose. The RE-LY study was conducted over a 2 year period and further safety data over a longer time period should be requested. • **Patient Acceptability:** Discontinuation rates in the RE-LY study were higher amongst patients treated with dabigatran than with warfarin. This is not clearly explained. Warfarin, unlike dabigatran, is associated with a number of inconveniences such as food and drug interactions, regular monitoring and dose adjustments which can cause disruption and inconvenience. However a quantification of this impact was not presented in the ACD and factored into the cost effectiveness model. Proper quantification of this could affect the relative cost effectiveness of dabigatran compared to warfarin. • **There were limitations to the quality of the research: Patients were treated in the RELY study who would not have been eligible for treatment in the UK, using the current NICE guidelines. This affects the generalisability of the RELY study to UK clinical practice.**	

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	We would support all concerns raised within the NICE appraisal. NHS Dorset has a higher prevalence of Atrial Fibrillation due to our older population (almost double national rate), but also a much higher proportion of patients already well controlled on warfarin (3 x higher than in the model). Warfarin is the most cost effective treatment in patients with atrial fibrillation with INR control within the recommended range. The manufacturer of dabigatran has assumed higher attendances for monitoring warfarin than is usual in clinical practice. Given current local costs of warfarin treatment, switching patients to dabigatran would cost an additional Â£7-14 milllion per year depending on dose of dabigatran. Time in therapeutic range should be considered in sensitivity analysis of clinical and cost effectiveness.	Comment noted. The Committee considered the additional information provided by the manufacturer. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation, and selecting out a group not to receive it on the basis of an arbitrary level of time in therapeutic range had an insufficient evidence base. The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
	Section 3 (The manufacturer's submission)	Time horizon should be included in further assessments of cost effectiveness. The time horizon influenced the ICER greatly with a 2-year time horizon resulting in ICERs of Â£75,891per QALY in people under 80yrs old and Â£23,403 per QALY in people over 80 old for the dabigatran sequential regimen vs warfarin Â No information is provided regarding dabigatran as a second line treatment in patients who are inadequately treated with warfarin. This is a potential treatment option that was not modelled in the manufacturer's submission but it should be considered in case it is a cost effective treatment in this specific patient group.	The NICE guide to the methods of technology appraisal states that a lifetime time horizon for clinical and cost effectiveness is appropriate for chronic diseases where costs and outcomes occur over a patient's lifetime
	Section 4 (Consideration of the evidence)	We would support all of the concerns raised in the NICE appraisal. Safety - There is an increased risk of gastrointestinal bleed with dabigatran 150mg and there is no specific antidote in the event of haemorrhage or overdose. Â The RE-LY study was conducted over a 2 year period and further safety data over a longer time period should be requested. Patient Acceptability - Discontinuation rates in the RE-LY study were higher amongst patients treated with dabigatran than with warfarin. Â This is not clearly explained. Â Limitations to the quality of the research - Patients were treated in the RELY study who would not have been eligible for treatment in the UK, using the current NICE guidelines. This affects the generalisability of the RELY study to UK clinical practice.	The Committee considered the issue of increased risk of gastrointestinal bleeding with dabigatran 150 mg twice daily. The Committee's discussion is summarised in section 4.7 of the Final Appraisal Determination. Due to the adverse effects associated with dabigatran, Section 1.2 of the Final Appraisal Determination recommends that the decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran should be considered in light of their level of international normalised ratio (INR) control. The Committee concluded that the population included in the trial was appropriate and broadly relevant to UK clinical practice. See section 4.3 of the Final Appraisal Determination.

Role*	Section	Comment	Response
	Section 5 (Implementation)	Given current local costs of warfarin treatment, switching patients to dabigatran would cost an additional Â£7-14 milllion per year depending on dose of dabigatran.	The Committee concluded that for the whole population of people with atrial fibrillation who need anticoagulation for the prevention of stroke and systemic embolism, dabigatran is a cost-effective option. See section 4.19 of the Final Appraisal Determination. NICE makes recommendations based on cost-effectiveness rather than the overall budget impact of a technology.
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	We accept that NICE have undertaken an analysis based on what the manufacturer submitted. Our view is that NICE should ask BI to resubmit an analysis of clinical and cost effectiveness based on sub groups of the anticoagulated AF population split by time in therapeutic range. This data is available, and has been published (eg Wallentin et al, Lancet, 2010). It demonstrates the differential risk and benefit of dabigatran (compared to warfarin) by time in therapeutic range. Our interpretation of this evidence (though we note it was from a post hoc sub group analysis) is that in well controlled patients warfarin achieves better outcomes and is safer, in less well controlled patients dabigatran is superior. Cost effectiveness modelling should follow this. We therefore encourage NICE to ask the manufacturer to conduct analysis by TTR. As a minimum, TTR should be considered in sensitivity analysis of clinical and cost effectiveness. Â In the RE-LY study, mean TTR for warfarin in the UK was 72%. Â The RE-LY study did not demonstrate superiority of dabigatran over warfarin above a median TTR of 67%. In a well controlled population as in much of the UK, the results dont generalise well.	Comment noted. The Committee considered the additional information provided by the manufacturer. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website

Role*	Section	Comment	Response
	Section 3 (The manufacturer's submission)	It is important that the variable costs of anticoagulation patient cost is modelled. There IS substantive variation in costs to commissioners. There is also significant difference between the price that commissioners might pay and actual provider costs. BI has assumed higher attendances for monitoring warfarin than is usual in clinical practice. They estimate 20 visits per year per patient for INR monitoring where clinical practice suggests that 5-8 visits is more realistic in established patients. Data from the NHS Reference cost database for anticoagulation does not match the data quoted in the ACD, by an order of magnitude. Both of the above points need to be incorporated into the economic analysis, preferably as a core component of the base case. we do not agree with the values of the utilities used. There are sufficient NICE Assessment reports on stroke and MI to enable us to validate the values used but NICE has not provided any detail. Â NICE should push BI to provide this info, especially given higher discontinuation rates with dabigatran etexilate 150 mg. we are surprised the costs of events has not been disclosed. Again we have comparative data from other NICE assessments.	The Committee was aware that comments received during the consultation largely agreed that INR monitoring costs are likely to be higher than the ERG's lower estimate of £115.14 and possibly higher than £414.90 in some cases. The Committee accepted the manufacturer's approach (of using £241.54 per annum), acknowledging that although INR costs may vary widely, this assumption was reasonable. See section 4.16 of the Final Appraisal Determination.
	Section 4 (Consideration of the evidence)	In the absence of evidence of rationale, we agree that dyspepsia should be modelled through the entire model, as a common adverse effect and given higher patient withdrawals for RE-LY with dabigatran, it seems plausible that patients would maintain the a/e and potentially reduce dose to 110mg BD thus reducing health benefit or that a patient would discontinue treatment and revert back to treatment with warfarin assuming no contraindication. 4.1.2 – we would ask for review of evidence to support the hypothesis that a stroke would be less severe after treatment with dabigatran than warfarin. Â At present we are uncertain of the evidence underpinning this assumption in the manufacturers model and it seems possible that there are a number of factors (e.g dose, drug interactions, co-morbidities) which may influence this assumption.	The Committee heard from the clinical specialists that the manufacturer's assumption that a stroke would be less severe after treatment with dabigatran than warfarin was plausible and that there is evidence that both the incidence and the severity of stroke may vary according to the treatment received. The Committee also noted the ERG's views about disutility of dabigatran and the inclusion of dyspepsia management costs throughout treatment (see sections 3.30 and 3.31). The Committee agreed that including all of these assumptions would be a more conservative approach. See section 4.13 of the Final Appraisal determination.

Role*	Section	Comment	Response
	Section 5 (Implementation)	Our view is that by considering this indication in the way BI have submitted the data, NICE have reached a defensible conclusion ? in the whole cohort of patients with AF, using dabigatran over warfarin does not represent a rational (or affordable) use of NHS resources. We do think that NICE have not reached the right conclusion, however. We feel that dabigatran DOES have a place in the pathway of care. Our interpretation of the evidence available is that dabigatran is clinically significantly superior (and thus highly cost effective) in the cohort of patients whom despite efforts to attain good therapeutic control are unable to do so (measured by TTR less than 65%).	Comment noted. The Committee considered the additional information provided by the manufacturer. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website

Role*	Section	Comment	Response
	Section 6 (Proposed recommendations for further research)	obviously both the NICE CG on AF and commisisoning guidance is relevant here. Locally it would seem that disinvestment in anticoagulation services would be unlikely, therefore any direct costs for dabigatran would represent new investment. Â If significant number of patiuents are switched from warfarin to dabigatran it is likely to have an inflationary effect on the cost per patient as the clinics will have to cover the same fixed costs with less tariff income coming in. This should be factored into the impact model. There are significant numbers of patients with medium or high risk AF who are not receiveing anticoagulation currently. Our view is that Warfarin is and remains the drug of choice for this cohort. The evidence that dabigatran is superior to warfarin is not compelling – high NNT, not affordable, probably not cost effective. We would hope that NICE will reflect this in their eventual advice.	Comment noted. The Committee considered the additional information provided by the manufacturer. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website
	Section 7 (Related NICE guidance)	The composition of the Committee and experts seems rather GP light. This is important, both strategically and operationally given the emphasis on primary care led anticoagulation in AND in terms of GP taking on principal reposnsibility for commissioning.	Comment noted. An NHS commissioning expert, selected by NHS Salford was present at the second Appraisal Committee meeting.

Role*	Section	Comment	Response
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	Why would NICE need cost effectiveness data on the subgroup of people who are already well controlled on warfarin as warfarin is the most cost effective treatment. The focus should be on patients with poor INR control on warfarin.	Comment noted. The Committee considered the additional information provided by the manufacturer. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation, and selecting out a group not to receive it on the basis of an arbitrary level of time in therapeutic range had an insufficient evidence base. The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website
NHS Professional	**Section 2** (The technology)	The marketing authorisation is not consistant with NICE CG36. The population used in the trial did not represent people at risk of AF in the UK. In practice there is a danger that patients will not be stepped down when they reach the age of 80, therefore risk of bleeding may be higher than that considered.	The Committee concluded that the population included in the trial was appropriate and broadly relevant to UK clinical practice. See section 4.3 of the Final Appraisal Determination. NICE only makes recommendations within the context of the marketing authorisation.

Role*	Section	Comment	Response
	Section 3 (The manufacturer's submission)	Information on use of dabigatran as an option in patients who are not controlled with warfarin should be considered. 3.6 and 3.9 are not relevent to the licensed indication and TIAs in patients over 80 years old was not a primary outcome.	The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. See section 4.19 of the Final Appraisal Determination.
	Section 4 (Consideration of the evidence)	I would disagree with the statement that patients in the trial were broadly representative of patients treated on the NHS in the UK. Saftey over a number of years should be a prime consideration (2 years is not enough). Any clinical commissioning group would be extremely unwise to adapt a black triangle drug with limited safety data around a new service, and consequently decommission existing warfarin and INR monitoring clinics.	The Committee concluded that the population included in the trial was appropriate and broadly relevant to UK clinical practice. See section 4.3 of the Final Appraisal Determination. The Committee recognised the adverse effects associated with dabigatran and the limited safety data compared with warfarin. See Sections 4.6, 4.7 and 4.20 of the Final Appraisal Determination.

Role*	Section	Comment	Response
	Section 5 (Implementation)	I would advise that any such new drug for AF should be managed with caution and the primary drug/service should be the existing warfarin and monitoring clinics at least until long term safety data emerges. This is not simply a drug substitution for an existing drug but rather a service redesign - who would redesign a service around a new black triangle drug with limited safety data?.... There are other drugs also coming to the market for stroke prevention in AF (rivaroxiban and apixiban) - where will they fit in? Should data on these drugs also be considered?	The Committee concluded that the decision about whether to start treatment with dabigatran in people with atrial fibrillation should be made after an informed discussion between the responsible clinician and the person about the safety risks and benefits of dabigatran compared with warfarin. It also concluded that, for people currently receiving warfarin, the potential risks and benefits of switching to dabigatran should be considered in light of their level of INR control. See section 4.20 of the Final Appraisal Determination. Data on other treatments currently without a marketing authorisation in this indication cannot be considered as part of this single technology appraisal. NICE only issues guidance on technologies with a marketing authorisation.
	Section 4 (Consideration of the evidence)	Warfarin should still be the first line treatment but Dabigatran will be a cost-effective option if it is going to prevent a stroke in a high risk patient (as defined by CHADS2)where there is an absolute contraindication to Warfarin or if they are currently on Warfarin treatment and their TTR is less than 65%.	The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. See section 4.19 of the Final Appraisal Determination.

Role*	Section	Comment	Response
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	It is important that variable costs of anticoagulation are modelled as we agree there is variation in commissioning costs. The manufacturer looks to have assumed higher attendances for monitoring warfarin than is usual. An estimate of 5-8 visits appears realistic in established patients. It is important to the NHS to understand the health outcomes of dabigatran versus warfarin and clarify if it is cost effective across the entire eligible patient population , in the analysis we want to understand whether warfarin dominates dabigatran and remains the most clinically and cost effective intervention for patients who are already well controlled with warfarin. Â A definition of well controlled INR on warfarin would be required (i.e. time in therapeutic range as X%) In the absence of evidence of rationale, dyspepsia should be continued through the entire model, as a common a/e and given higher patient withdrawals for RE-LY with dabigatran, it seems plausible patients would maintain the a/e and potentially reduce to 110mg BD thus reducing health benefit or that a patient would discontinue treatment and revert back to treatment with warfarin assuming no contraindication.	The Committee was aware that comments received during the consultation largely agreed that INR monitoring costs are likely to be higher than the ERG's lower estimate of £115.14 and possibly higher than £414.90 in some cases. The Committee accepted the manufacturer's approach (of using £241.54 per annum), acknowledging that although INR costs may vary widely, this assumption was reasonable. See section 4.16 of the Final Appraisal Determination.
	Section 2 (The technology)	No specific comment	No action required.

Role*	Section	Comment	Response
	Section 3 (The manufacturer's submission)	Dabigatran is expected to be prescribed in primary care and it essential that GP views are represented on this technology. Â The sequential model presented by the manufacturer is reflective of the license of the two doses of dabigatran etexilate however there are concerns in terms of the practical application of this model in clinical practice and the necessity to identify individuals 80 years+ for dose reduction. Should these individuals not be identified, this potentially exposes individuals to more harm in terms of bleeding risk, which negates overall perceived benefit of treatment. The treatment sequence at present does not permit patients to revert back to warfarin as a 2nd line agent, which seems to represent a likely scenario given the evidence from RE-LY indicated higher withdrawal rates for dabigatran compared to warfarin. Â We would ask that this sequence is included in analysis. We also ask subgroup analysis of patients currently well controlled on warfarin at present, as warfarin we believe may remain the most cost effective treatment for this group of patients. Â Would need to define good control e.g. time in therapeutic range (TTR)	The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. See section 4.19 of the Final Appraisal Determination. NICE only issues guidance within the context of the marketing authorisation, which stipulates that the lower dabigatran dose is used once people reach age 80 years.

Role*	Section	Comment	Response
	Section 4 (Consideration of the evidence)	There are noted inconveniences with warfarin+monitoring, warfarin is a once daily therapy where, monitoring may provide support for concordance to treatment, one disadvantage of dabigatran is the necessity for twice daily dosing. Noted that the incidence of gastrointestinal bleeding was significantly higher for both doses of dabigatran dabigatran 150 mg BD was associated with a significantly higher incidence of major gastrointestinal bleeding and life threatening gastrointestinal bleeding. Â It is important to ensure that the health gain from lower incidence of stroke are balanced against the higher rate of GI bleeding with dabigatran. Locally disinvestment in anticoagulation services would be unlikely, therefore any direct costs for dabigatran represents new investment. Â There appears to be significant variation in the costs of anticoagulant monitoring, paid by commissioners. We ask for review of evidence that a stroke would be less severe after treatment with dabigatran than warfarin.At present, uncertain of the evidence of assumption in the manufacturers model and seems possible there are factors (e.g dose, drug interactions,co-morbidities) to influence this assumption	Comments noted. The Committee considered the issue of increased risk of gastrointestinal bleeding with dabigatran 150 mg twice daily. The Committee's discussion is summarised in section 4.7 of the Final Appraisal Determination. The Committees consideration of the effect on anticoagulation services is summarised in section 4.14 of the Final Appraisal Determination. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and 4.19).
	Section 5 (Implementation)	There are significant numbers of patients with medium or high risk AF who are not currently receiving anticoagulation. At present it appears that locally warfarin is and remains the gold standard treatment 1st choice and certainly is considered the agent which enables PCTs to ensure equitable affordable access and health gain for all eligible patients.	Comment noted.
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	Agree	No action required.

Role*	Section	Comment	Response
	Section 2 (The technology)	There are also increasing concerns over safety, with increased risk of GI bleed. There is no antidote to treatment with dabigatran to reverse its action if needed - this needs to be noted I think. Also more patients in RELY taking Dabigatran discontinued compared to warfarin - is this because of poorer tolerability?	Comments noted. The Committee considered the issue of increased risk of gastrointestinal bleeding with dabigatran 150 mg twice daily. The Committee's discussion is summarised in section 4.7 and 4.20 of the Final Appraisal Determination.
	Section 3 (The manufacturer's submission)	Trial population - concerns about this - those excluded and agree with ERG concerns that the definition of AF not same as that in NICE guideline. Also disagree with warfarin monitoring costs - in practice INR is not done as frequently in the majority of llong term patients as assumed, so this could affect the cost effectiveness analysis. Also, no monitoring is given for Dabigatran - on the contrary, with new drugs there is raised concerns and usually specialist initiation and possible follow up (so more costly than GP appointments) and GP appointments may need to be more frequent with a newer therapy, particularly where tolerability issues have been identified in the trials. Given its cost, the most likely treatment pathway would be to use this second line after warfarin - but we have no information from the manufacturer of its place in therapy at this stage. Time in therapeutic range needs consideration.	The Committee concluded that the population included in the trial was appropriate and broadly relevant to UK clinical practice. See section 4.3 of the Final Appraisal Determination. The Committee was aware that comments received during the consultation largely agreed that INR monitoring costs are likely to be higher than the ERG's lower estimate of £115.14 and possibly higher than £414.90 in some cases. The Committee accepted the manufacturer's approach (of using £241.54 per annum), acknowledging that although INR costs may vary widely, this assumption was reasonable. See section 4.16 of the Final Appraisal Determination. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. See section 4.19 of the Final Appraisal Determination.

Role*	Section	Comment	Response
	Section 4 (Consideration of the evidence)	Agree Agree also about warfarin monitoring costs - we would still have to run this service e.g for all the patients on warfarin who cannot tolerate dabigatran, so there would be no cost savings in de-commissioning a service.	Comment noted.
NHS professional	**Section 1** (Appraisal Committee's preliminary recommendations)	Warfarin is the most cost effective treatment in patients with atrial fibrillation with INR control within the recommended range. Â In this group, the ICER for dabigatran vs warfarin is Â£60,895 per QALY. Â The Committee has requested ?further comment and consideration' of cost effectiveness in this subgroup. Â The focus of further review should be on those patients with poor INR control where dabigatran might offer a cost effective treatment. The manufacturer of dabigatran has assumed higher attendances for monitoring warfarin than is usual in clinical practice. They estimate 20 visits per year per patient for INR monitoring where clinical practice suggests that 5-12 visits is more realistic. This makes warfarin appear more expensive and consequently makes dabigatran appear relatively cost effective Time in therapeutic range should be considered in sensitivity analysis of clinical and cost effectiveness. Â In the RE-LY study, mean TTR for warfarin in the UK was 72% . Â The RE-LY study did not demonstrate superiority of dabigatran over warfarin above a median TTR of 67%.	The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation, and selecting out a group not to receive it on the basis of an arbitrary level of time in therapeutic range had an insufficient evidence base. See section 4.19 of the Final Appraisal Determination.
	Section 2 (The technology)	The forthcoming review for National Screening Committee on screening for AF suggests: ?Among 12,000 UK patients with chronic AF only 57% of high-risk patients were receiving anticoagulant treatment, while 38% of low-risk patients were being prescribed anticoagulants	Comment noted.

Role*	Section	Comment	Response
	Section 3 (The manufacturer's submission)	Time horizon should be included in further assessments of cost effectiveness. The time horizon influenced the ICER greatly with a 2-year time horizon resulting in ICERs of Â£75,891per QALY in people under 80yrs old and Â£23,403 per QALY in people over 80 yrs old for the dabigatran sequential regimen vs warfarin Â No information is provided regarding dabigatran as a second line treatment in patients who are inadequately treated with warfarin. This is a potential treatment option that was not modelled in the manufacturer's submission but it should be considered in case it is a cost effective treatment in this specific patient group.	The Committee agreed with the ERG that the general approach taken by the manufacturer to estimate the lifetime cost effectiveness of dabigatran was appropriate. See section 4.9 of the Final Appraisal Determination. The NICE guide to the methods of technology appraisal states that a lifetime time horizon for clinical and cost effectiveness is appropriate for chronic diseases where costs and outcomes occur over a patient's lifetime.
	Section 4 (Consideration of the evidence)	Safety. Â There is an increased risk of gastrointestinal bleed with dabigatran 150mg and there is no specific antidote in the event of haemorrhage or overdose. Â The RE-LY study was conducted over a 2 year period and further safety data over a longer time period should be requested. Patient Acceptability: Discontinuation rates in the RE-LY study were higher amongst patients treated with dabigatran than with warfarin. Â This is not clearly explained. Â Warfarin, unlike dabigatran, is associated with a number of inconveniences such as food and drug interactions, regular monitoring and dose adjustments which can cause disruption and inconvenience. However a quantification of this impact was not presented in the ACD and factored into the cost effectiveness model. Proper quantification of this could affect the relative cost effectiveness of dabigatran compared to warfarin. There were limitations to the quality of the research: Patients were treated in the RELY study who would not have been eligible for treatment in the UK, using the current NICE guidelines. This affects the generalisability of the RELY study to UK clinical practice.	Comments noted. The Committee considered the issue of increased risk of gastrointestinal bleeding with dabigatran 150 mg twice daily and the limited safety data compared with warfarin. The Committee's discussion is summarised in sections 4.7 and 4.20 of the Final Appraisal Determination. The Committee concluded that the population included in the trial was appropriate and broadly relevant to UK clinical practice. See section 4.3 of the Final Appraisal Determination.

Role*	Section	Comment	Response
NHS professional	**Section 1** (Appraisal Committee's preliminary recommendations)	NHS Dudley supports the need for further data from the manufacturer. We support the indication not to support the use of dabigatran in all AF patients but would like to see more clarity over the use in patients intolerant to warfarin - including a definition of intolerance	Comment noted. Warfarin-unsuitable patients were not included in the trial. However, if warfarin is indicated, but the patient is unable to take it, for reasons of intolerance, personal preference or poor response, the Committee considered that dabigatran would be much more likely have the same therapeutic benefit as in warfarin-suitable patients, than a different benefit. The Committee concluded that there was no biologically plausible reason, or research evidence to justify excluding them from the recommendation.
	Section 2 (The technology)	an alternative to warfarin is welcomed however the opportunity cost of investing in a new technology must be weighed against the high cost-effectiveness of warfarin.	Comment noted.
	Section 3 (The manufacturer's submission)	NHS Dudley has a number of concerns and questions: 1. Warfarin is still the most cost-effective treatment for AF for patients within the recommended INR range. It would be helpful for the manufacturer to focus on those patients where INR control is poor. 2. Warfarin monitoring costs submitted by manufacturer are much higher than those experienced locally. 3. Analysis of impact of TTR essential. Patients may wish to take dabigatran due to perceived ease of use when compared to warfarin however if outcomes are better with warfarin for well controlled patients then they should be aware of this! 4. Safety concerns - the high reporting of ADRs and tolerabilty with dabigatran are of concern. 5. Compliance issue - When patients are being monitored for INR non-compliance can be picked up but as there is no monitoring patients discontinuing dabigatran may adversely affect the impact of any budget that a commissioning organisation decides to invest in dabigatran	The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. See section 4.19 of the Final Appraisal Determination. Comments noted. The Committee considered the issue of increased risk of gastrointestinal bleeding with dabigatran 150 mg twice daily. The Committee's discussion is summarised in section 4.7 and 4.20 of the Final Appraisal Determination.

Role*	Section	Comment	Response
	Section 5 (Implementation)	There is a considerable impact to the use of this drug both in budgetary and service terms. The managed introduction in order to target the drug at those patients most likely to benefit will be challenging not least because most patients intolerant to warfarin are not currently known by secondary care services but have been discharged back to primary care. Considerable resources will be required to identify suitable patients,ensure appropriate prescribing, education and clarity on the benefits of the drug especially in light of current media coverage.	Comments noted.
NHS Professional		I am a rural general practitioner and many patients on warfarin are elderly, infirm, many having blood testing at the surgery or at home. Given their age and general medical complexity an oral non-monitored non-adjustable and non-interacting, efficacious, above those incorporated in most urban practices. I have had at least 1 death and many hospital admissions directly related to warfarin usage. i could see no general practitioners on your advisary body but trust PHCT members have been represented and costing include ruralety health care activity.	Comment noted. An NHS commissioning expert, selected by NHS Salford was present at the second Appraisal Committee meeting.
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	Agree with recommendation - no clear evidence that dabigatran will confer additional benefits over warfarin. Concerns re: long-term safety and risk of toxicity in older patients	Comment noted.
	Section 2 (The technology)	what is definition of severe renal impairment?	Please refer to the summary of product characteristics (SPC) for dabigatran.

Role*	Section	Comment	Response
	Section 3 (The manufacturer's submission)	Patients with good INR control with warfarin are unlikely to benefit from dabigatran. Â Would resources be better used to improve INR control in patients on warfarin especially if ttr is less than 60-65%	The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. See section 4.19 of the Final Appraisal Determination.
NHS Professional		I am a Consultant in Public Health Medicine working on CVD prevention. Â I have been working with PCT commissioners on the provision of community based anticoagulation services and INR monitoring.	Comment noted.
	Section 1 (Appraisal Committee's preliminary recommendations)	The cost-effectiveness analysis should take into account a more realistic assumption on the cost of anti-coagulation monitoring. Â I do not know on what basis the manufacturer estimates the cost of INR monitoring to be Â£414. Â Based on current prices a community based provider carrying out about 2000 tests per year will not cover costs at Â£240 per patient. So including a variable of Â£115.14 for a revised analysis is unrealistic.	The Committee was aware that comments received during the consultation largely agreed that INR monitoring costs are likely to be higher than the ERG's lower estimate of £115.14 and possibly higher than £414.90 in some cases. The Committee accepted the manufacturer's approach (of using £241.54 per annum), acknowledging that although INR costs may vary widely, this assumption was reasonable. See section 4.16 of the Final Appraisal Determination.
NHS Professional	**Section 3** (The manufacturer's submission)	The manufacturers estimate of the cost of warfarin monitoring is high. Â A HTA published in 2007 gave the costs as Â£69 a year and a Keele Medicines Management team estimated the costs to be around Â£200 a year	The Committee was aware that comments received during the consultation largely agreed that INR monitoring costs are likely to be higher than the ERG's lower estimate of £115.14 and possibly higher than £414.90 in some cases. The Committee accepted the manufacturer's approach (of using £241.54 per annum), acknowledging that although INR costs may vary widely, this assumption was reasonable. See section 4.16 of the Final Appraisal Determination.

Role*	Section	Comment	Response
	Section 4 (Consideration of the evidence)	No information is providing regarding dabigatran as a second line option for patients who frequently present with an INR outside of the therapeutic range. It is these patients for whom this drug may be a cost-effective option No specific antidote is a serious consideration to the use of this drug	The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. See section 4.19 of the Final Appraisal Determination.
Patient		I am an example of an AF patient linked to tachy brady syndrome with multiple serious risk factors on long term triple therapy blood thinning (clopidogrel +aspirin + self injected low dose clexane)being clinically intolerant of warfarin, in my case because of embolism in big toe after 10 weeks on warfarin + aspirin resulting in hospitalisation on Flolan and then experiencing similar symptoms within 6 days of restarting warfarin. Cholesterol embolisation (purple toe) caused by warfarin cannot be ruled out. Three consultants (cardiologist, vascular surgeon and haemotology) advise that this treatment should be replaced by a new anticoagulant alternative to warfarin + an antiplatelet as soon as this can be prescribed. Quite apart from the potential costs from potential stroke and bleeding, the headline drug cost to the NHS of my current treatment far exceeds the cost of dabigatran as the cost of the clexane alone is over Â£6.50 daily and it is far less effective	The Final Appraisal Determination recommends dabigatran within its licensed indication as an option for the prevention of stroke and systemic embolism in people with atrial fibrillation.

Role*	Section	Comment	Response
	Section 1 (Appraisal Committee's preliminary recommendations)	The Committee, unlike NETAG or UKCPA or RPS in their very recent prescribing guidance, do not appear to have given sufficiently serious consideration to the most appropriate and effective provision for a minority of patients who are clinically unable to be prescribed warfarin. It is accepted that dabigatran is 35% more effective than warfarin in preventing strokes and systemic embolism from which it follows that dabigatran is even more effective than the current alternative treatments of aspirin, clopidogrel and aspirin or in my case clopidogrel, aspirin and daily self injected low dose clexane, the latter being required long term by three consultants (cardiologist, vascular surgeon and heamotology)because of the peculiar risks of my condition. I had the warfarin initially added to the aspirin after post operative DVTs. UKCPA, endorsed by RPS, state that aspirin, with or without clopidogrel, is not a suitable alternative to warfarin or NOACs in patients with AF.... as it offers far less protection against stroke. NETAG recommends the use of dabigatran for patients intolerant to warfarin. These patients have no choice and are to be denied Â effective licensed therapy.	The Final Appraisal Determination recommends dabigatran within its licensed indication as an option for the prevention of stroke and systemic embolism in people with atrial fibrillation. This definition would therefore include patients who are clinically unable to be prescribed warfarin.

Role*	Section	Comment	Response
	Section 4 (Consideration of the evidence)	The Committee appear to be willing to deny a great opportunity to provide effective treatment at last for those patients who can not be prescribed warfarin for clinical reasons. The cost to the NHS and patients and families and in some cases the wider economy from the now unnecessary additional strokes, embolisms and deaths in this category of patients will justifiably attract widespread clinical, moral and possibly even legal condemnation. The additional overall cost to the system of providing proper care for these patients is comparatively small compared to providing the new treatment for all patients most of whom have a reasonably effective alternative with the current therapy. Â I accept Â my case is unusual in that the cost to the NHS of my long term blood thinning triple therapy of clopidogrel, aspirin and low dose self injected clexane is nearly three times the projected cost of dabigatran, Â but there is something seriously wrong with the system if I am prevented from getting much more effective and safer therapy which would cost the NHS thousands of pounds less each year and for the long term.	The Final Appraisal Determination recommends dabigatran within its licensed indication as an option for the prevention of stroke and systemic embolism in people with atrial fibrillation.

Role*	Section	Comment	Response
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	I would concur with the Appraisal Committees recommendation of not to recommend the use of dabigatran in patients with AF. I am unconvinced of the cost-effectiveness of this treatment when its costs are more than three times the costs of warfarin + monitoring. It is important to remember that the RE-LY was a non-inferiority study and the results demonstrate that dabigatran is non-inferior New guidance to physicians in Japan has raised concerns about the need to monitor renal function "Physicians in Japan are recommended to perform renal-function tests before and during treatment, with doses to be reduced or treatment stopped upon signs of renal impairment or bleeding' As a significant portion of the costs of warfarin involves monitoring, if we are simply to replace INR monitoring with U&E measurements, the cost-effectiveness of this treatment [dabigatran] seems even further reduced	Comments noted. The Committee considered the additional information provided by the manufacturer. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. The additional evidence and the Committee's considerations of the additional evidence relating to cost effectiveness in people who are well controlled on warfarin are summarised in the Final Appraisal Determination (sections 3.38, 3.40, 4.18 and, 4.19). The manufacturer's additional submission and revised analyses submitted in response to the Appraisal Consultation Document , including all the details of the data described in this document and reviewed by the Committee, is available as part of the ACD evaluation report on the NICE website.

Role*	Section	Comment	Response
	Section 2 (The technology)	Although this novel technology has been promoted as being superior to warfarin, there is no evidence to suggest this is the case in the groups of patients who would typically require warfarin + monitoring. It would also seem the requirements to monitor for bleeding are implicit in treatment. Of some considerable importance is the fact that whilst warfarin bleeding can be reduced / stopped by Vit K administration, this approach will not work with dabigatran. This could have profound implications where there is significant bleeding.	Comment noted. The Committee accepted that the technology had been calculated to be cost effective for the whole population of patients with atrial fibrillation. It concluded that evidence for stratifying by INR control was insufficient to exclude the minority of people with very good control from the recommendation of dabigatran as a potential treatment option. See section 4.19 of the Final Appraisal Determination. The Committee considered the issue of increased risk of gastrointestinal bleeding with dabigatran 150 mg twice daily, and the limited safety data compared with warfarin. The Committee's discussion is summarised in section 4.7 and 4.20 of the Final Appraisal Determination.
NHS Professional	**Section 3** (The manufacturer's submission)	The use of anecdotal post - hoc sub group analysis is frought with potential dangers and may be likened to "data dredging". Any sub-group analysis needs to be pre-specified and justification for specifying such an analysis. I would agree with the Apraisal Committees change in the cost-effectiveness, the 110 mg BD is not associated with the same level of benefits.	Comment noted. The Committee concluded that the sequence of dabigatran 150 mg twice daily followed by dabigatran 110 mg twice daily once people reach 80 years would be the only regimen appropriate for the assessment of the cost effectiveness of dabigatran relative to warfarin in the whole eligible UK population.
	Section 4 (Consideration of the evidence)	I believe that the Committee has summerised the evidence wery well and I would agree with the conslusions	Comment noted.

Role*	Section	Comment	Response
	Section 5 (Implementation)	The costs of implementaion for significant numbers of patients would be considerable and place a considerably burden on local resources should the committee recommend use of dabigatran. Locally we could not afford to change significant numbers of patientv from warfarin to dabigatran and we would need to prioritise warfarin intolerant patients or those patients who were poorly controlled (INR) on warfarin. There are no new resources available to implement widespread use of dabigatran in significant numbers of patients at this time	Comment noted.
NHS Professional	**Section 7** (Related NICE guidance)	I would recommend a review 2 years after guidance is finalised	Comment noted.

References:

[i] Baruch L, Gage BF, Horrow J et al. Can patients at elevated risk of stroke treated with anticoagulants be further risk stratified? Stroke 2007;38: 2459–63

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3 McBride D, Bruggenjurgen B, Roll S et al. Anticoagulation treatment for the reduction of stroke in atrial fibrillation: a cohort study to examine the gap between guidelines and routine medical practice. J Thromb Thrombolysis 2007;24:65–72