NICE National Institute for Health and Care Excellence

Self-monitoring coagulometers (CoaguChek XS system, INRatio2 PT/INR monitor and ProTime Microcoagulation system) for self-testing or self-managing coagulation status in people with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy is intended

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Bradford District CCG	1.	1.1		Whilst the views of stakeholders wrt to NOACs varies widely, it is a fact that they have an important place in the pathway of care So some mention perhaps needs to be given Will self monitoring have any role in NOAC care (I suspect the "official" view will be no, but unofficially there may be some pressure "to check to be sure". This might be factored in even if qualitatively. Would be good to see the reference for the 1.4% estimate. I have seen much higher estimates.	**Please note that according to the NICE final scope, this assessment was limited to people receiving long-term vitamin K antagonist (VKA) therapy (not people receiving NOACs).** **1.4 % estimate was based on the Anticoagulation Commissioning Guide published in 2007 (http://www.nice.org.uk/usingguidance/commissioningguides/anticoagulationtherapyservice/anticoagulationtherapyservice). This reference is provided in section 2.1.**

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	2.		1.4	Personally I think a stronger place should be given to absolute risk changes here in addition to the RRR This allows commissioners to get more of a ready reckoner on real world value than point estimates of ICER (and the further more complex analysis etc)	**No response required.**
	3.	12	1.4	The estimates of cost effectiveness might be more clearly put The casual reader has got to work really hard to understand this. Given that most stakeholders will only ever read the exec summary, and most wont really understand the economics, I feel it could be made clearer.	**Whilst we appreciate that the cost-effectiveness findings can be difficult to follow for individuals who are not familiar with economic evaluation concepts, please note that the results have been presented and summarised according to the requested structure for reporting cost-effectiveness results of DARs. Efforts could be made to simplify the language in the final published report.**

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	4.	12	1.4	An 80% chance of being CE at threshold of £20k is a useful finding However, commissioner might well say that what they really need to know is the absolute cost of implementing such a strategy and which patient groups it is most suitable for – given the evidence base. And perhaps differential economics within this.	**No response required.**
	5.	13		Generalisability This is important finging on the uncertainty of the generalisability of the findings of the analysis I think it has an important bearing on how the real world value of this technology will play out Commissioner might readily make a case that there is only sufficiently robust evidence (given the seeming wide uncertainties about the clinical	**Please note that the scope of the current assessment was limited to people with atrial fibrillation and heart valves requiring long-term vitamin K antagonist therapy.** **The issues around conditions and technology have been addressed in section 1.4 (under the sub-title 'Discussion') and discussed in more details in Chapter 5, section 5.2.**

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				evidence, and especially the results of the economic model – ICER ranges) that there is only a case for highly selective introduction in those whom were studied in the key trials. Needs a little more clarity on whether we are talking ALL conditions where INR monitoring is in play or just AF, just DVT….does the effectivness and the cost effectivness of the technology vary. I would assume mostly this is a technology where the economics will work out for highly selected groups of lifelong anticoagulated patients? If so that needs to be clear. The revised AF guideline might clarify this, but I am not sure it will do so with sufficient detail.	**The cost-effectiveness modelling was carried out for cohorts with atrial fibrillation and mechanical heart valve. The analysis by indication showed the cost-effectiveness estimates to be similar in both groups. The impact of age (as a risk factor for thromboembolic and haemorrhagic events) on cost-effectiveness was also assessed, as was the baseline risk of thromboembolic events for people receiving standard care (estimated by levels of INR control). Applying constant relative risks (for adverse clinical events), the results suggest that self-monitoring becomes less cost-effective in patients that achieve high levels of INR control in standard care (and consequently face a low risk**

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					of adverse events). The results of these subgroup analyses are presented in Chapter 4 (Table 28).
	6.	13		Conclusions The sentence re “unlikely to be cost effective if no reduction in thromboembolic strokes” etc is absolutely key. The eventual definitive recommendation should be clear about which groups would be most likely to benefit stroke wise, this will be key to implementation.	**No response required (see above).**
	7.			General comment Reading through it overall our impression is that the assessement doesn’t say much and doesn’t add substansively to a rapidly evolving market	**No response required.**

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				This is especially the case where pathways are changing rapidly (DVT and PE) and new products are entering clinical practice (NOACs)… The impact of NOACs is difficult to predict, it is possible there will be a move to using this technology to check coagulation whilst patient is taking a NOAC – obviously this would destroy the economic case for NOACs, which is already very fragile in some indications. It will be interesting to see how the committee deliberations uses this evidence to develop a clear recommendation for clinicians and commissioners about the place of this technology. There is a danger that by the time the eventual recommendation is out and influencing clinical	

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				practice it will be out of date. Whilst the devices remain outside of prescription and whilst there is not national tariff for anticoagulation it seems quite difficult to see how these machines will become widely used.	
AntiCoagulation Europe(ACE) Charity	8.	-	General	AntiCoagulation Europe(ACE) provides information, education and support to individuals on anticoagulation therapy such as warfarin for conditions including Atrial Fibrillation, mechanical heart valves and thrombotic disorders which all increase the risk of blood clots that could lead to serious conditions such as stroke. We actively campaign for patient choice and empowerment when making decisions surrounding the management of anticoagulant treatment such as VKA warfarin treatment and access to self-testing and monitoring by using devices designed for this purpose. Our objectives include:	**It was beyond the scope of this assessment to model people who suffered from any thrombotic conditions other than those with atrial fibrillation and heart valve disease receiving long-term term vitamin K antagonist therapy.** **The clinical-effectiveness of self-monitoring in mixed population was assessed as a subgroup analysis which reflects the population who are suffering from any thrombotic**

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				Ensuring INR self-monitoring technology is available and accessible and on prescription through the NHS for eligible patients requiring long term warfarin treatment for any condition • Increase awareness and benefits of INR self-monitoring • To ensure that all those taking long term warfarin for any condition are able to partake in an informed discussion with their managing clinician about the option of self -monitoring. In our opinion, the current diagnostic assessment focusses on people with AF and heart valves patients but should also include individuals who suffer **from any**	**conditions requiring long term anticoagulant therapy. Please see section 3.2 (clinical effectiveness results).**

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				thrombotic condition which will require long anticoagulation therapy to reduce their heightened risk of blood clots. NICE clinical guidelines CG 144(2012) (1.4) states that patients should not routinely be offered self-management or self - monitoring options to patients who have had DVT or PE and are being treated with a VKA(warfarin) ACE is concerned that these patients may be denied access to self -monitoring whereas AF and Heart Valve patients may become eligible and therefore this is inequitable in terms of patient choice	
	9.	2	Cost effectiveness	We were unable to review the de nova economic model to assess the cost –effectiveness of INR Self - monitoring as it was developed in TreeAge	**No response required.**

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				Pro software which requires purchasing a licence for use. The cost is prohibitive to the Charity and therefore we are disadvantaged in not having had access to the model for the purpose of commenting on its finding other than to the references made in the report	
	10.	66	Summary of clinical effectiveness results	Substantial benefits in reduced thromboembolic events demonstrated with patients who are self-monitoring and time in therapeutic range slightly increased from that in standard care. Evidence has shown that participants younger than 55 years old who self- monitored had a striking reduction in thromboembolic events. Men with mechanical heart valves who self -monitored also had a significant reduction in haemorrhagic events *Henegan C et al. Self-monitoring of anticoagulation: systematic review and*	**No response required.**

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				meta-analysis of individual patient data. Lancet 2012 Anecdotal evidence provided by ACE members indicates that people who self - manage achieve increased TTR due to a greater understanding of warfarin management. They take ownership of their condition, are supported by their doctors and can be assisted by family or carers to support this process. Self - management should be encouraged with patients being given adequate, appropriate and timely training with adequate controls in place to meet clinical and quality guidelines on efficacy and patient safety. Patient choice - - 77 -93% expressed preference for self –monitoring over standard care. In ACE's	

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				experience, once a warfarin patient has explored the option of self-testing/management with their Doctor and then decides to pursue this option; it's unlikely that they will return to INR testing in a primary or secondary care setting. Challenges arise when people who wish to self – test/manage are refused or denied due to local prescribing guidelines that prevent the patients gaining access to the strips or, are self testing and then not supported when changing doctors or going into another CCG area With an aging population and potential AF screening programmes being considered, more of the population will be diagnosed with the condition and require anticoagulants to keep them save. Warfarin is an established treatment and can be monitored effectively, however, it can be	

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				affected by diet and other medications. The benefits are that dose adjusting can be undertaken to correct INR levels. Individuals who wish to protect themselves from risk of stroke or bleeds can check their INR whilst working, travelling and carry on with day to day activities with minimal disruption with the reassurance of using a bespoke device which is quality assured and meets CE standards. Family and carers can support the individual and the benefits of a finger prick test done at home at a convenient time negates disruption and added costs caused by travelling to clinics for INR testing. With a rising retirement age, many people will need to work longer and therefore, the impact of balancing work responsibilities with attending clinics to maintain therapy can be burdensome. By contrast, we have families where children are	

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				benefitting from using a monitor and therefore managing their condition and treatment in a effective and positive manner	
	11.	70	Cost effective ness	If evidence demonstrates that self –management significantly lowers risk of thromboembolic events; this then reduces overall costs to the NHS in managing patients in secondary and primary care either as an inpatient or outpatient requiring clinical input, diagnosis and INR control. Currently, approx. 47% of patients who are diagnosed with AF receive anticoagulation therapy. This means than over 50% are at an increased risk of clotting which could lead to a stroke. AF related stroke is likely to have greater health and cost implications for the individual, their family and carers. For some people, warfarin can be difficult to manage with some individuals struggling to stay in TTR which can increase risk of a clot or bleed. AF patients could benefit from	**It is acknowledged that the wider impact of stroke on costs to patients and their families were not factored in to the model. Further, consistent with other models of new anticoagulation drugs, the impact of stroke on carers health related quality of life was not considered.**

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				access to self -monitoring to reduce their risk and whilst we note that the interpretation demonstrates that this is not considered cost effective in the initial stages; we would suggest that the financial reduction in clinical time across any anticoagulation clinic setting would start to reduce with resources being utilised in other areas of need in the NHS	
	12.	134	Clinical effectiveness	York study – notable outcomes, confirming evidence that self - management significantly reduces thromboembolic events and halved risk in people with heart valves. Time in therapeutic range(TTR) higher in self managers. Patient choice – 80% participants choosing to continue after the trials – indicating positive outcomes of managing their conditions confidently and competently	**No response required.**

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	13.	135	Cost effectiveness	ACE notes the findings that self –management is deemed to be cost effective whilst self – testing is not. As the cost effectiveness case is so strongly influenced by up - front costs such as education and training; we would suggest that the costs of providing these to meet the NHS standards be met by the equipment provider which should impact of the cost effectiveness case in turn.	**Please note that it is more the cost associated with the increased frequency of testing, coupled with a less favourable effect of self-testing on thromboembolic events, that undermines its cost-effectiveness in the base case analysis.**
National Clinical Guideline Centre, RCP	14.	General	Overall	We are grateful for the opportunity to comment on this report. We consider this a very reasonable report and we agree with the conclusion that self-monitoring/management is unlikely to be cost-effective from an NHS perspective.	**No response required.**
	15.	General	Overall	The group wished to raise the additional issue, that there may be additional patient and societal costs involved when patients need to take time off work to attend anticoagulant clinics. While we realise that this is not part of standard economic	**Point acknowledged.**

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				analysis, it may be worth acknowledging the potential importance of this factor and that there may be other economic benefits of home monitoring in some patient groups.	
Royal College of Nursing	16.			No comments.	
Roche Diagnostics	17.	1-2	1	This report highlights the substantial evidence supporting the clinical effectiveness of self-monitoring, in particular self-management, with CoaguChek XS compared to standard care. This is supported by a robust evidence base of 22 RCTs using the CoaguChek device. Compared to standard care self-monitoring is highly cost-effective with the conservative cost estimates used in this analysis.	**No response required.**
	18.	1 3	1.1 1.4	We would like to highlight the substantial amount of evidence assessing self-monitoring versus usual care, not the limited amount as stated in the	**Please note that last line of section 1.1 is part of the background section and does not include the results of**

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				last line of section 1.1. Of the 26 RCTs identified in the review the vast majority were based on the different CoaguChek systems, indicating substantial evidence for the clinical effectiveness for the intervention. This evidence is largely based on the different versions of the CoaguChek system giving the system a very robust evidence base. However, there appears to be very limited evidence on the clinical effectiveness of the INRatio device, as shown in 1.4.	**the clinical effectiveness review. In the Results section as well as in the Discussion section we have highlighted that the majority of the trials were based on the CoaguChek system.**
	19.	3	1.4	The statement 'There was greater reduction in thromboembolic events and all-cause mortality through self-management but not through self-testing is supported and in general self-management seems to be the overall preferred approach to give patients most control over their condition. However, we would like to point out that the evidence on self-testing is dominated by one large US trial (Matchar 2010) and that self-	**No response required.**

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				testing may have a role for patients that are (not yet) confident enough to self-manage.	
	20.	3	1.4	The statement 'Improvements in quality of life in the self-monitoring group were only observed in non-UK based studies' is questioned over its importance since many clinical studies across NICE appraisals will be of global context. Recognised improvements in quality of life are key whether UK or otherwise.	**Point accepted. The sentence will be amended as follows to include overall results about quality of life:** ***'Improvements in quality of life in the self-monitoring group were observed in 6 of the 9 trials that reported quality of life outcomes. Two UK-based trials reporting quality of life data did not show significant difference between self-monitoring and standard care'.***
	21.	4	1.4	Cost-effectiveness: The analysis clearly showed that self-monitoring is cost-effective compared to standard care. Self-monitoring with CoaguChek and INRatio2 seem to result in very similar overall	**No response required.**

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				health and social care costs, however this is largely based on clinical trials using CoaguChek only.	
	22.	4	1.4	Cost-effectiveness: the higher monitoring costs of self-testing compared to usual care assumed delivery of this service model within the existing services. However, self-monitoring may be supported by different service models.	**No response required.**
	23.	4	1.4	In the 2nd paragraph of Cost effectiveness section there is a typo on CoaguChek	**Point accepted, this will be corrected accordingly.**
	24.	5/6	1.4	Discussion & Generalisability of findings: We agree with the authors that given the rarity of thromboembolic and haemorrhagic events, meta-analysis of similar trials provides a more powerful means of estimating the true effect of self-monitoring on these clinical outcomes (4.1, p. 76). Due to the low statistical heterogeneity this approach resulted in a robust estimate of the significant reduction in thromboembolic events for	**No response required.**

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				patients self-monitoring compared to standard care. Sub-group analyses by clinical indication, type of control care, type of monitoring or country will naturally result in fewer data being available and increased statistical uncertainty or insufficient power to estimate effects. We also like to point out that there is no established standard care model in the NHS and services will also see a mix of patients by indications. The pooled results from the meta-analysis may therefore be representative for the 'average patient' suitable for self-monitoring in the NHS.	
	25.	5	1.4	'While the CoaguChek device appears to have the most robust evidence…' this seems understated: the presented analysis clearly demonstrates that CoaguChek has a robust evidence base in terms of demonstrated clinical effectiveness and the review did not identify any evidence on clinical effectiveness of INRatio2 exclusively.	**Point accepted.The sentence will be amended as follows:** ***'While the CoaguChek device has the most robust evidence, ProTime and, particularly, INRatio do not.'***

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	26.	5	1.4	The technical evaluations of the CoaguChek XS device demonstrate that it is superior to the previous version (CoaguChek S) in terms of accuracy and precision. Please also note typo of CoaguChek within this paragraph.	**Section 3.2 ('Performance of point-of-care devices') indicates that Coaguchek XS has shown to be more accurate and precise than version S.** **The typo of CoaguChek will be amended.**
	27.	7	2.1	'Impact of health problem… section' states that there is limited evidence on the effectiveness compared to other ways of delivering services. This statement is questioned based upon the 26 RCTs discussed in this review.	**Please note that this was written as a part of the background section and does not include the results of the clinical effectiveness review.**
	28.	7	2.1	Due to the evidence available it is suggested that the first sentence of paragraph two, within 'Impact of health problem…' is changed to 'The use of point of care coagulometers for self-monitoring avoid unnecessary….	**Point accepted, this will be corrected accordingly.**
	29.	9	2.2	Last sentence within Summary of CoaguChek system suggests CoaguChek XS plus is suitable	**Point accepted. The sentence will be amended as follows:**

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				for home testing. This is incorrect as the CoaguChek XS is the home testing device and the CoaguChek XS Plus for healthcare professional use only.	***'The CoaguChek XS Plus model is aimed primarily at healthcare professionals and possesses additional features to the XS system including increased storage and connectivity for data management.'***
	30.	19	3.2	Within Table 1 the inclusion of CoaguChek XS Plus is questionable within the scope of this evaluation as CoaguChek XS Plus is not suitable for patient self-monitoring.	**Point accepted. Data on CoaguChek XS Plus will be omitted from Table 1.**
	31.	95	4.2	Within Table 19 the CoaguChek Plus should read CoaguChek XS Plus, although as per above, comment 14, this should be removed.	**Point accepted – the typo will be amended. Please note that the use of CoaguChek XS Plus was included as a shared equipment cost for patients being monitored under standard primary care.**
	32.	95	4.2	We like to highlight that the annual variable costs of standard care for INR monitoring in primary	**Expert opinion was sought on the average number of visits required for**

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				and secondary care in this analysis (£156 per year) are significantly lower than the costs (£248 per year) assumed in the recent NICE appraisals (TA 249, TA256 and TA 275)of newer anticoagulants. This results in a conservative estimate of the cost-effectiveness of self-monitoring compared to standard care.	**patients being monitored in standard care, and whilst this is highly variable across individual patients, an average of 10-12 was a consistent response. This was also consistent with the mean number of monitoring visits for patients in the control arm of the largest UK based trial of self-management (SMART). However, we acknowledge that less stable patients may require a greater number of monitoring visits per year.**
	33.	98	4.2	Within Costs of self-monitoring, the assumption that testing frequency has no relative effects on outcomes is questioned, in that clinical data has shown greater time in range through more frequent monitoring (Heneghan, Lancet 2006), which is known to reduce adverse events (Wan et al Anticoagulation control and prediction of adverse events in patients with atrial fibrillation –	**To clarify, we have assumed that the increased testing frequency delivers significant clinical benefits in the base case analysis (assumed to be mediated through improved time in therapeutic range). However, we also considered scenarios of equal testing frequency with standard monitoring**

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				A systematic review – Circulation Cardiovascular Quality and Outcomes, 2008.	**and self-monitoring, and under this scenario we assumed do difference in effects between the alternatives; i.e. no increase in testing frequency, no difference in effects.**
	34.	98	4.2	Within Equipment, clarification is sought over the meaning of 'proportional price' provided by INRatio 2.	**This is a typo, it should read "promotional" price.**
	35.	99	4.2	The cost estimate for the training in secondary care (and the review visit costs) may be conservative by assuming £85 pounds per hour contact or £21.25 per 15 minutes compared to the variable costs of £15.33 assumed for a standard INR monitoring visit.	**The lower cost of £15.33 was previously estimated by the ERG for NICE TA249, based on the assumption that 33% of the average cost of secondary care monitoring (per patient visit) is fixed, and so not likely to change substantially with varying degrees of monitoring throughput. Therefore, £15.33 was applied to secondary care monitoring visits in the model (this does not relate to an explicit duration of staff time).**

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					However, training patients to self-manage was considered a more explicit use of staff time that could divert activity away from other beneficial activity. A nationally available cost per hour of direct patient contact was therefore applied to ensure this opportunity cost was fully captured.
	36.	101	4.2	Assuming 36 calls for INR control when self-testing in table 21 is over estimated. If patients only phoned when INR readings were outside the therapeutic range for dose-adjustment the average number of calls could be significantly less.	**Advice was sought on the extent to which self-monitoring people phone in test results. It was advised that this varies considerably between individuals, with some people phoning in every test result (pure self-testing), others self-managing and phoning only if there is a problem, and others somewhere in between the previous two scenarios. Without having data on the distribution of**

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					people along this continuum, the two extremes were modelled (in equal proportions) to assess the overall cost-effectiveness of self-monitoring as a whole.
	37.	99	4.2	Within consumables and Bi-annual routine assessments, the rationale for EQA is recognised as a means to provide reassurance on the performance of the device and procedure of the user, therefore minimising any risk of result reliability, by comparing the device results with another device enrolled in an established EQA scheme. This comparison should be performed using the same technology so that results are more easily compared. An established EQA scheme is available for all CoaguChek devices through NEQAS / WEQAS; however it is unclear if such a scheme exists for INRatio and ProTime.	**No response required.**

Self-monitoring coagulometers (CoaguChek XS system, INRatio2 PT/INR monitor and ProTime Microcoagulation system) for self-testing or self-managing coagulation status in people with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy is intended

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	38.	105	4.2	Major stroke costs in table 22: The assumptions made seem to underestimate the opportunity costs to the NHS based on the reduced number of excess bed days used in the base case. Using the figure in the sensitivity scenario no. 9 in table 29 seems more appropriate.	**The excess bed day costs published by the department of health are an estimate of the cost per day spent in hospital above a defined upper trim-point for each HRG. This also reflects the way that the national tariff is calculated to pay trusts for long-stay patients. The standard HRG tariff is applied for the episode, and only those days spent in hospital above the trim-point are paid on a per day basis using the excess bed day tariff.** **Therefore this approach was used when using the NHS reference costs to estimate the acute cost of a long-stay stroke patient.** **We recognise that this might be a conservative estimate of the true**

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					opportunity cost to trusts. For this reason, we have also assessed the impact of using the higher estimate based on the application of excess bed day costs for every additional day spent in hospital above the mean length of stay for the relevant HRGs. This further improves the cost-effectiveness of monitoring strategies that reduce thromboembolic events.
	39.	135	5.1	The statement 'A brief overview of diagnostics performance of the various CoaguChek systems demonstrated that across several studies INR results were more accurate in adults and children when comparing CoaguChek XS with other CoaguChek models', is supported.	**No response required.**
Lifeblood: The Thrombosis Charity	40.			We found the document dense and difficult to read. We were not clear that self monitoring with self dosing had been compared with self	**No response required.**

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				monitoring and someone else dosing.	
Joint submission from Royal College of Pathologists and the British Committee for Standards in Haemotology	41.	10	2.4 CARE PATHWAYS	NICE guidance on AF (2006) is out of date and several new technologies have been approved in this field. Some of these are more effective than warfarin. SIGN guidelines 2013 recommend warfarin or one of the alternatives as anticoagulation option.	**Please note that according to the NICE final scope, this assessment focused on long-term vitamin K antagonist (VKA) therapy and not on new oral anticoagulants (NOACs) or novel target specific oral anticoagulants (TSOAs).** **The SIGN guidelines 2013 considers novel antithrombotics (such as dabigatran etexilate, rivaroxaban or apixaban) as an alternative to warfarin only for the treatment of AF (but not for the treatment of heart valve diseases). Moreover, the guideline points out the relative lack of experience of the long-term use of these novel anticoagulants compared**

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					with a VKA.
	42.	11	2.4 CARE PATHWAYS	There is no one 'standard' model of anticoagulation care. The paragraph itself mentions of various models identified by NICE in the commissioning guidance. The statement '…….as an alternative to standard UK anticoagulation care' is therefore contradictory and confusing. Self monitoring is one of the monitoring options amongst several others. This is important to identify and understand. PSM is being compared with a 'standard' service where there is no specified 'standard'. Most studies compare self monitoring with the traditional service which could take any form and has wide variability in quality of anticoagulation control. There is wide clinical, operational and financial heterogeneity amongst the various models of 'standard' anticoagulation service. This varies between different countries and data from	**While we recognise that 'standard monitoring practice' varies considerably between clinics/hospitals within the UK as well as between different countries, for the purpose of this assessment we have defined 'standard monitoring/care' as the INR monitoring managed by a range of health professionals in primary and secondary care (as for NICE final scope). This has been clearly stated in section 2.3 'Comparators' and again in section 3.1 'Comparators'.** **Please note that in order to take into consideration the variation between services in terms of anticoagulation**

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				international studies is not comparable.	**control practice and in order to explain heterogeneity between included trials, we have conducted subgroup analyses according to the type of service provision (primary versus secondary care).** **For the economic modelling, we costed primary and secondary care monitoring using unit costs consistent with those used in the evaluation of the NOAC drugs.**
	43.	11	2.5	'…….compared with standard monitoring practice'. As the standard monitoring practice is not a defined or a single entity, 'traditional monitoring practices' would be preferable.	**See our response above. No change required.**
	44.	28	Standard anticoagulant manage	Confirms the variation in service of what is deemed as 'standard'. The comparator is not a single entity but a wide variety of services which are based in primary/secondary care instead of	**See our response above.**

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			ment	being managed by patient.	
	45.	36	Thrombo embolic events	Line 18: Thrombolytic should read thromboembolic.	**The typo will be amended.**
	46.	3, 49	1.4 results	The practice of patient self-testing and self-management are not standardised. There is widespread heterogeneity in the quality of this service. This is reflected in the wide TTR for PSM and PST in the studies reviewed (52-80%). This may explain some confusing results where PSM (but not PST) is shown to be associated with reduced thrombo-embolic complications. This is difficult to explain except by patient selection bias, heterogeneity of studies, lack of standards for PSM, PST and the 'standard' service.	**It is worth noting that the majority of included studies assessed self-management and only a few trials assessed self-testing. The self-testing results were dominated by the largest published trial so far, the THINRS, which enrolled 2,922 people and had a highly specialised routine care and the longest follow up period. It is probable that the high quality of standard care in this trial does not mirror traditional monitoring practice. The lack of a significant difference in the number of thromboembolic events between self-testing and routine care could be explained by the rigorous**

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					criteria used to ensure standard care in the THINRS. This has been acknowledged in section 5.2 page 138 ('Uncertainties from the assessment – Clinical effectiveness').
	47.			The differences in thromboembolic events and quality of INR control were not significant in UK based studies.	**No response required.**
	48.	137	5.2	The clinical variation in PSM, PST vs standard care and the highly selected population studied doesn't allow comparisons to be made easily. Inferences based on this data should not be extrapolated to wider population without a much larger prospective study.	**No response required.**

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	49.			The advent of new oral anticoagulants for use in Atrial fibrillation should be taken into account when making recommendations for warfarin monitoring. The new oral anticoagulants do not require INR monitoring and NICE has done cost benefit analysis for these technologies comparing with 'standard' practices. There have been no cost benefit analysis of PSM and PST.	**Please note that according to the NICE final scope, this assessment focused on long-term vitamin K antagonist therapy and not on new oral anticoagulants (NOACs) or novel target specific oral anticoagulants (TSOAs).** **To our knowledge NOACs cannot be considered universally applicable anticoagulants, as, to date, their effects in patients with mechanical heart valves has yet to be established and such patients need to be treated with warfarin.**