Single technology appraisal (STA): Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

Comments on the Appraisal Consultation Document (ACD) from Boehringer Ingelheim Ltd, submitted 30th January 2012

As a commentator on the above STA, Boehringer Ingelheim Ltd (BI) submits the following comments on eight matters arising from the ACD for consideration by the Appraisal Committee.

Text highlighted in blue is commercial in confidence.
Text highlighted in yellow is academic in confidence.

1. The inclusion/exclusion criteria for ROCKET-AF match neither the UK AF population, nor the licensed indication for rivaroxaban.

The Appraisal Committee recommends that the characteristics of the cohort included in the economic model should represent people with atrial fibrillation in the UK. However, the inclusion/exclusion criteria for ROCKET-AF mean that a clinical evidence base for rivaroxaban in this indication is available for only xxx of the UK AF population.

A recent study (unpublished manuscript, Appendix 1, abstract submitted as academic in confidence) based on [redacted] patients with AF identified from the UK General Practice Research Database (GPRD), found that of those at intermediate/high risk of stroke and eligible for anticoagulant treatment (CHA_2DS_2-VASc≥1; n=[redacted] [redacted]), the proportion who would have been eligible for inclusion into ROCKET-AF was [redacted] ([redacted]). Across all AF patients, only [redacted] met the inclusion criteria for ROCKET-AF.

The main differentiator between the UK AF population and the patients in ROCKET-AF is that only three patients with $CHADS_2 < 2$ were included in ROCKET-AF. (Patel *et al*. 2001). As the extremely limited clinical evidence for the use of rivaroxaban in these patients, clinical effectiveness (and therefore cost-effectiveness) cannot be robustly assessed.

In Summary:

- ***Only [redacted] of the UK AF population are estimated to meet the inclusion criteria of ROCKET AF.***
- ***Any recommendation for the use of rivaroxaban in patients with $CHADS_2$ <2 would be unsupported by clinical evidence.***

2. One of the clinical experts at the 1st Appraisal Committee Meeting was nominated by the manufacturer, in contravention to the principles set out in the NICE 'Guide to the methods of technology appraisals'. (NICE 2008) This led to a

potential bias at the meeting in favour of the manufacturer, and therefore this expert's comments should be removed from the account of the appraisal meeting.

The ACD states:
"*Professor John Potter, Professor of Ageing Stroke Medicine, nominated by Bayer HealthCare – clinical specialist*" (Appendix B, page 36, of the ACD)

However, the "Guide to the methods of technology appraisals" (NICE 2008) states:

"*4.5.1 Two groups of experts – clinical specialists and patient experts – are selected by the Committee Chair from nominations provided by (non-manufacturer) consultees and commentators. Clinical specialists and patient experts provide written evidence and attend the Committee meeting to help in the discussion of the technology being appraised*."

The inappropriate use of a clinical expert nominated by the manufacturer is a clear breach of this principal and calls into question the impartiality of the evidence given by the clinical expert at the Committee Meeting.

As a consequence, we believe the opinions and evidence submitted by this clinical expert should be removed from consideration in the formulation of the Final Appraisal Determination (FAD), and replaced with those of an independent clinical expert nominated by a professional body.

In Summary:

- ***Use of clinical expert evidence provided by an expert nominated by Bayer Healthcare leads to potential bias towards the manufacturer.***

3. A technical error in the economic model leads to a bias in favour of the manufacturer. This would invalidate the current results, so additional corrected results would be required for any recommendation.

Annual event rates are provided for the warfarin patients in Table 18 of the manufacturer's submission (Page 112 of the Evaluation Report), per 100 patient-years. These event rates are incorrectly converted by the manufacturer into quarterly probabilities (in line with the 3-month Markov cycle in the economic model) using the following formula and the example of the rate for ischaemic stroke:

Quarterly rate = 1- (1-annual rate)^(1/4) (page 187 of the Evaluation Report)
= 1 – (1 – 0.0142)^(1/4)
= 0.357%

The reference quoted for this calculation is Briggs *et al*. (2006). However, this reference has been incorrectly used. The correct conversion of a rate into a probability is:

P = 1 – exp (-rt)
= 1- exp (-0.0142 x 0.25)
= 0.354%.

This re-calculated value represents the probability of one event, per patient, per timestep, and is the correct value that should be used.

This error introduces a bias in favour of rivaroxaban since cost-effectiveness is driven by the absolute risk reduction between the new technology (i.e rivaroxaban) and the comparator (i.e. warfarin). Using the incorrect calculation submitted by the manufacturer leads to a larger absolute baseline risk, leading to an increased absolute risk reduction when the relative risks (for rivaroxaban) are applied.

Although this error, when considered in isolation in a single event and a single timestep, is relatively small, the error is proliferated across additional clinical outcomes, the whole modelled cohort and the entire duration of the model timeframe (i.e. patient's lifetime). Further to this, as the model is nonlinear, and risk of stroke is dependant on stroke history, the impact of this error is further amplified.

We were unable to assess the impact of this error on the modelled results as the version of the economic model provided to us could not be re-run. However, the bias would be expected to be in favour of rivaroxaban.

In Summary:

- ***Baseline risks for patients on warfarin are over-estimated, leading to a bias in favour of rivaroxaban.***
- ***This bias exists over multiple outcomes and is applicable across the whole modelled cohort and entire patient life-time.***
- ***The impact of the error is amplified as the model is non-linear.***
- ***The economic model should be corrected before any recommendation using results based on it can be made.***

4. Base-case ICERs derived from the PSA should be used in line with Section 5.9.3 of the "Guide to the methods of technology appraisals". This omission favours rivaroxaban.

The NICE "Guide to the methods of technology appraisals" (NICE 2008) states:

"*5.9.3. When models consist of non-linear combinations of parameters, probabilistic sensitivity analysis should be used to generate mean costs and QALYs. In such models, setting parameters to their mean values will not provide the correct estimates of mean costs and QALYs*."

The manufacturer's model for this appraisal is non-linear (i.e. the risk of additional acute clinical events is dependant on occurrence of previous acute clinical events, e.g. stroke rate is dependant on risk of stroke, which changes if a patient has had a previous stroke). Therefore, costs and outcomes should be calculated from the PSA results in accordance with the above guidance.

Evidence of a bias in favour of rivaroxaban by omission of the PSA results can be illustrated by comparing the ICERs calculated from the point estimates and the median ICER estimated from the PSA graphs (results section of the manufacturer's submission). Insufficient detail is provided by the manufacturer to estimate the size of this effect. However, from the information provided, this difference appears substantial (~£10,000 per QALY, see deterministic ICER and PSA median on Page 295 and 297 of the Evaluation Report).

In Summary:

- ***The NICE methods guide states that ICERs should be calculated from PSA results for non-linear models to avoid bias.***
- ***This does not appear to have been done by the manufacturer and there appears to be bias in favour of rivaroxaban as a result of this omission.***
- ***Results from the PSA should be given due consideration.***

5. Dabigatran etexilate is a relevant comparator and should not be disregarded from any further analyses related to this appraisal. This comparison was performed by both the manufacturer and the ERG, therefore it should be considered in order that NICE is able to provide clear guidance to prescribers on the use of rivaroxaban with respect to dabigatran.

In the final scope for rivaroxaban, dabigatran is listed as a relevant comparator within the PICO table. Dabigatran has since been recommended by the Appraisal Committee (FAD currently subject to appeal) reinforcing the validity of this comparison.

In addition, we note the comment from the ERG, that "*The ERG considers that a fully incremental analysis of rivaroxaban, dabigatran, warfarin, aspirin and no treatment (placebo) is both possible and desirable*" (ERG report p127) and that "*the incremental analyses revealed that the relevant comparison was between dabigatran and rivaroxaban*" (ERG report p16). We therefore consider it surprising that the Committee has reached the following conclusion: "*The Committee concluded that it would not consider further the clinical effectiveness of rivaroxaban compared with aspirin or dabigatran etexilate*" (ACD section 4.7).

Whilst it appears that the committee regards the indirect evidence as insufficiently robust to provide a recommendation on the use of rivaroxaban with respect to dabigatran, we agree with the ERG that such an analysis is both possible and desirable.

There are data available to support a comparison of rivaroxaban with dabigatran, as detailed in the manufacturer's submission, and in the ERG report. For example, the ERG states that:

'There is a general trend in favour of dabigatran etexilate for ischaemic stroke, major extracranial bleed, and intracranial bleed, and a statistically significant difference (at the 5% level) in favour of dabigatran etexilate for minor extracranial bleed. There is a trend in favour of rivaroxaban for systemic embolism and a significant difference (at the 5% level) favouring rivaroxaban in MI and discontinuation. However, the ERG also considers it important to note that in the trial informing the rivaroxaban MI data set, (ROCKET AF), significantly more people had a history of prior MI at baseline in the warfarin group compared with the rivaroxaban group ($p < 0.05$). The ERG thus considers that as previous MI is one of the risk factors for future MI, the benefit observed with rivaroxaban in reducing the risk of MI compared to dabigatran etexilate may be confounded and should be interpreted with caution' (ERG report p74).

Note that '*the ERG has conducted exploratory analysis into the effect of assuming equivalence between rivaroxaban and dabigatran in MI prevention*' (ERG report p 127).

The ERG's analyses showed that dabigatran is cost effective compared with rivaroxaban, in that it yields a higher number of QALYs than rivaroxaban, at an additional cost that yields an ICER which is well below the acceptable cost effectiveness threshold. The ERG report states that:

'The results of the comparison between rivaroxaban and dabigatran on point estimates from the ERG's NMA [Network Meta-Analysis] *indicate that dabigatran is the more effective treatment, with an ICER of £34,680 per QALY gained* [for dabigatran compared with rivaroxaban]*. Following incorporation of the ERG's recommended adjustments, the ICER decreases to £12,701, with the exploratory analysis assuming equivalence of MI prevention between treatments yielding an ICER of £3,578. However, the ERG notes that the model is highly sensitive to changes in the discontinuation rates used and advises that the ICER of £12,701 per QALY gained, be considered in the context of the associated uncertainty'* (ERG report, page 130, see also table 61).

Given that the ERG advises that an ICER of £12,701 per QALY gained *[for dabigatran compared with rivaroxaban]*, should be considered in the context of the associated uncertainty, it seems unsubstantiated that the Committee has concluded that the results from the network meta-analysis are unreliable and that no comparison can be made between dabigatran and rivaroxaban. This is despite the ERG stating that a fully incremental analysis of rivaroxaban, dabigatran, warfarin, aspirin and no treatment (placebo) is both possible and desirable.

The rationale for the Committee's opinion that '*the manufacturer's and ERG's network meta-analyses contained wide confidence intervals and therefore the resulting efficacy point estimates were subject to considerable uncertainty*', seems unsubstantiated, given the ERG's revised network meta-analysis. The ERG states: '*Overall, use of a network of randomised controlled trials restricted to those that directly inform the decision problem that is the focus of this STA results in a more consistent analysis that provides greater precision around the effect estimates than that provided in the MS.*' The confidence intervals calculated by the ERG are not unusually large. Further, running a model probabilistically using distributions to reflect the uncertainty around model parameters is a standard procedure within economic modelling and one which specifically aims to reduce parameter uncertainty. Therefore we would be interested to see the results of a PSA comparing dabigatran with rivaroxaban using the ERG's NMA.

Importantly we also note that in section 3.21 of the ACD, the ICER is reported as being £3,578 for rivaroxaban compared with dabigatran etexilate. This is incorrectly reported. It should read £3,578 for dabigatran etexilate compared with rivaroxaban (see above).

In Summary:

- ***Dabigatran etexilate is a relevant comparator***
- ***This view is supported by the Scope and the ERG***
- ***The ERG has already provided estimates for the cost-effectiveness of dabigatran vs rivaroxaban that should not be disregarded.***

6. Using an ITT population in the appraisal of rivaroxaban is more appropriate than the safety on treatment population, since that would ensure higher applicability to the treatment decision in real-life, consistency across appraisals and comparability across results.

For the primary efficacy endpoint of stroke or systemic embolism, in the safety on treatment (SOT) population from the ROCKET-AF trial, the hazard ratio (HR) for rivaroxaban compared with warfarin was 0.79 (95% = CI 0.65 to 0.95). (Patel *et al*. 2011) For the same endpoint for dabigatran in RE-LY using the SOT population, the HR for dabigatran 150mg compared with warfarin was [redacted] (Boehringer Ingelheim Ltd, 2009).

By comparison, for the primary efficacy endpoint of stroke or systemic embolism for the ITT population in ROCKET-AF, rivaroxaban was shown to be not significantly different from warfarin, where the HR was 0.88 (95%CI = 0.75 to 1.03). (Patel *et al*. 2011) For the same primary efficacy outcome in RE-LY for the ITT population, there was a significant difference between dabigatran 150mg compared with warfarin, with a HR of 0.65 (95% CI = 0.52 to 0.81). (Connolly *et al*. 2009, Connolly *et al*. 2010)

Clearly the results are significantly affected by the analysis set selected for use. The figures above show that using the safety on treatment analysis leads to more favourable results, compared with when the intention to treat population is used.

It is important to be clear that **the results from the ITT population from RE-LY were used in the appraisal of dabigatran, not the safety on treatment analysis set, as was incorrectly stated at the Appraisal Committee meeting**. It was also suggested that, in line with the NICE methods guide, similar assumptions should be applied consistantly across technology appraisals for similar indications, to ensure a fair and transparent approach. For avoidance of doubt, the economic analyses considered in the appraisal of dabigatran etexilate were solely based on the ITT analysis set from RE-LY.

The ERG also states "*that the ITT population would better reflect the treatment effectiveness results that would be seen in clinical practice*" (page 4 of the Evaluation Report). ITT is more appropriate for the treatment decision of a physician as he/she does not know what will happen during the treatment afterwards, e.g. discontinuations due to side effects. The SOT population is by definition a *post-randomisation* analysis, and since the results of this analysis are subject to bias, it cannot be concluded that patients who will be treated in real life will approximate to the SOT analysis, unlike an ITT population. Clearly any cohort of patients selected for treatment in routine practice would be a *de facto* ITT population. Therefore **the outcomes experienced by these patients are best approximated by the ITT population, not the SOT population.** This is of particular importance given the relatively high reported discontinuation rate for rivaroxaban patients in ROCKET-AF (35.44%, page 608 of the Evaluation Report).

It is also worth mentioning that in the STA for dabigatran etexilate, the economic model submitted by Boehringer Ingelheim not only used the clinical findings from the ITT population, thus giving a conservative estimate of the efficacy of the drug, but in addition included the discontinuation rates as observed in RE-LY (and modelled beyond the trial duration for up to 6 years). Both these actions yielded conservative estimates for the ICERs for dabigatran etexilate vs. warfarin.

One potential concern, that an ITT analysis may be overly optimistic in assessing non-inferiority in clinical studies, does not actually hold in the circumstance of this STA, as the safety on treatment population is used to claim *superiority* in the primary endpoint, and not to assess the non-inferiority.

"In superiority trials the full analysis set is used in the primary analysis (apart from exceptional circumstances) because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol analysis, since the non-compliers included in the full analysis set will generally diminish the estimated treatment effect. However, in an equivalence or non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully." (ICH Expert Working Group, 1998)

Further to this, Fleming and Emerson (2011) state:

"Even in noninferiority trials, per-randomization analyses should be conducted. These analyses avoid the bias that occurs with per protocol on-treatment analyses when patients discontinue their randomized treatment for reasons related to the treatment itself and the patients who do so have a different risk profile from those who don't. The importance of per-randomization analyses is very apparent in ROCKET-AF. The on treatment analysis was based on observations that were truncated at 2 days after discontinuation of randomized treatment — a time frame likely to miss events related to inadequate coagulation during the transition to alternative treatment."

In addition the idea that an ITT analysis may be overly optimistic (and not conservative) in assessing non-inferiority in clinical studies is based on situations where the PP estimate lays between unity and the non-inferiority margin, whereas the ITT estimate is within the same range, but more close to unity due to discontinuations, treatment cross-overs, etc. In this situation PP is regarded as the more conservative analysis for non-inferiority. But if, even in a non-inferiority trial, the estimate shows some (e.g. numerical) superiority in PP (i.e. estimate is not in the range between the non-inferiority-margin and unity), the ITT estimate which is usually closer to unity is the more conservative estimate. Therefore the statement that PP is more relevant and conservative in non-inferiority studies cannot be applied to all data situations.

In Summary:

- ***The ERG stated in their evaluation report that the trial population from RE-LY was similar to the ROCKET-AF SOT population (page 578 of the evaluation report), which may have led the Appraisal Committee to state at the appraisal meeting that the SOT population was used for the dabigatran STA. This is incorrect since the ITT population was used in that appraisal.***
- ***For consistency, the ITT population should also be used in this current STA, and the ERG states that this is the preferred analysis.***
- ***The SOT population does not best reflect routine clinical practice.***
- ***The most valid analysis consistent with other STAs, and the general principles of economic evaluation, would be based on the ITT population.***
- ***In any indirect comparison of rivaroxaban extreme care must be taken to compare results from corresponding analysis populations. A previously published network meta-analysis comparing dabigatran etexilate to other treatment options used ITT populations. (Roskell et al. 2010)***

7. The control group in ROCKET-AF does not reflect the UK population since their average time-in-therapeutic range is below that which would be expected in routine UK practice.

The validity and applicability of the comparative efficacy of rivaroxaban versus warfarin was correctly called into question by the Appraisal Committee (Page 19, Section 4.4 of the ACD) due to the low mean (55%) and median (57%) percentage time in therapeutic range (TTR) recorded for warfarin patients within the ROCKET-AF trial. (Patel *et al*. 2011) This was also noted by the FDA, who stated that in ROCKET-AF, warfarin was not used "skillfully" (Fleming & Emerson 2011) and hence the standard by which the experimental observations were evaluated was lower than those recorded in clinical practice.

The average TTR values from ROCKET-AF are considerably lower than analogous values observed in other contemporary clinical trials (see Table below). These values concur with a study by Dolan *et al*. (2008) who performed a systematic review and meta-analysis of previous clinical trials within the same indication with a target INR of 2.0-3.0, and found that the mean TTR was 61.3%.

Trial	Population	Mean TTR	Reference
RE-LY	ITT all warfarin patients	64%	Ezekowitz *et al*. 2010
	ITT warfarin-experienced	67%	
	ITT warfarin-naïve	62%	
ARISTOTLE	ITT	62%	Granger *et al*. 2011
SPORTIF III	ITT	66%	Hylek *et al*. 2008
SPORTIF V	ITT	68%	Hylek *et al*. 2008
ACTIVE-W	ITT	64%	Connolly *et al*. 2006
ROCKET-AF	SOT	55%	Patel *et al*. 2011

In addition, the mean TTR in UK clinical practice appears to be better than the values observed in ROCKET-AF. A study by Gallagher *et al*. (2011), based on the GPRD which included 27,458 patients treated with warfarin with at least three INR measurements, found that the mean TTR was **63%**.

Lower TTRs are associated with poorer clinical outcomes such as increased risk of stroke or bleeding events (Hylek *et al*. 2006, Fuster *et al*. 2006, Morgan *et al*. 2009). This view is further supported by a study by Jones *et al*. (2005) which found that:

"*...a 10% increase in time out of (therapeutic) range was associated with an increased risk of mortality (odds ratio (OR) 1.29, p<0.001) and of an ischaemic stroke (OR 1.10, p=0.006) and other thromboembolic events (OR 1.12, p<0.001)*".

The Committee has requested that sub-group analyses of patients with improved centre TTR should be conducted in an attempt to model the UK population. However, it should be noted that:

1. This analysis should be done in the ITT population (see 6 above) based on the published standard Connolly method (used in ACTIVE-W and RE-LY), since, as the FDA has pointed out, differences in quartile %TTR ranges between the unpublished Bayer method and Connolly method exist:
   - Bayer-Quartiles: I: <=50.6%; II: 50.7-58.5%; III: 58.6-65.7%; IV: >65.7%
   - FDA-Connolly method Quartiles: I: <46.8%; II: 46.8-55.9%; III: 55.9-63.9%; IV: >63.9%
2. In RELY the post-hoc cTTR quartile analysis (ITT) was based on the following quartile ranges: I: <57.1%; II: 57.1-65.5%; III: 65.5-72.6%; IV: >72.6% (Wallentin *et al*. 2010)
3. In RE-LY there was a preplanned cTTR analysis (ITT) for centers above 60% and 65%.

Because ROCKET-AF has limited data from centres where warfarin therapy was skillfully applied (e.g. with a cTTR above 72%, i.e. the lower border of the upper quartile in RE-LY), the confidence in any conclusion drawn from such an analysis would be low.

In Summary:

- ***The mean TTR from ROCKET-AF is unusually low and not reflective of UK clinical practice***
- ***In RE-LY, the upper quartile for cTTR was 72.6%; ROCKET-AF has too few data from centres where warfarin was skillfully applied to make any meaningful comparison with rivaroxaban.***

8. There are two further errors in the model of significance:

- **increased utilities for patients with *additional* clinical events**
- **three-month event-free period following an event (identified by the ERG)**

There appears to be the potential for an increase in utility in the model following a clinical event. This occurs when a patient has a stroke (and experiences the associated decrease in utility) and then subsequently has an AMI. The utility value for the AMI is higher than for the stroke, so the patient's overall utility improves. This is counter intuitive and not reflective of the likely patient experience. It is unclear whether this bias would be in favour of rivaroxaban.

The ERG identifies an event-free period following a clinical event, which is considered a low priority as the bias is toward the less effective treatment. However, for comparisons with dabigatran, the bias would likely be in favour of rivaroxaban.

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Appendix 1: