Reviewer's report

**Title:** Financial Impact of adopting Implantable Loop Recorder Diagnostic for unexplained syncope compared with Conventional Diagnostic Pathway in Portugal

**Version:** 3  
**Date:** 18 November 2013

**Reviewer:** Sarah Davis

**Reviewer's report:**

Major Compulsory Revisions:

Second paragraph after the 'Model' heading: I would strongly question the rationale for using two different studies to estimate the diagnosis rates in the ILR and standard care arms, especially given the availability of a randomised comparison between ILR and standard care (Farwell 2004). How can you be certain that the populations are equivalent between the two studies? How can you be certain that the follow-up methods and classification of events was equivalent. I would prefer to see the data from Farwell 2004 being used in the basecase analysis, with a sensitivity analysis conducted to explore the potential impact of improved ILR technology on diagnosis rates which could be based on the PICTURE study.

You claim, in paragraph 2 after the 'Model' heading, that there is little data on the probability of recurrent syncope. However the Farwell 2006 paper (Farwell et al, European Heart Journal 2006. 27:351-357 doi:10.1093/eurheartj/ehi602) reporting longer-term follow-up from the EaSyAS study (Farwell 2004) does in fact provide survival curves for time to first syncopal recurrence and time to second syncopal recurrence. This is based on a randomised comparison of ILR against conventional testing. Why was this data not used to populate your model?

Paragraph 1 of the methods section suggests that patients are assumed to be successfully treated following diagnosis. The implication appears to be that no further syncopal episodes occur. Please clarify whether that is the assumption made in the model. It is not clear to me that everyone who has an ILR guided diagnosis will have no further syncopal episodes. A Reveal guided diagnosis in the PICTURE study is described here as being a successful capture of an ECG during an event. Can all patients having this outcome be assumed to receive treatment which prevents all future syncopal occurrences?

In the results section, you describe the hospital 'cost offsets' from preventing syncopal recurrences which would otherwise result in admission. You also say that the break-even point is the end of the ILR device's battery life, however, you don't quantify explicitly the cost of providing the ILR strategy i.e the device cost and the cost of device implantation and removal and any follow-up appointments.
When you 'dynamically calculate' the diagnostic yield on a year by year basis, by multiplying the probability of a syncopal event by the probability of diagnosis in those experiencing a syncopal event, you are assuming that each event has an independent probability of resulting in diagnosis. However, if someone is having syncopal episodes of a nature that cannot be reliably diagnosed by the ILR, it is likely that the ILR will consistently fail to diagnose the cause each time rather than having a fixed probability of being successful each time.

Exploration of uncertainties in the model appears to be limited to the presentation of a probabilistic sensitivity analysis and consideration of several differences sources for resource use following syncopal recurrence. This is contrary to the last statement made under the 'Model' heading where it is stated, "several sensitivity analyses were conducted to investigate how the conclusion is changed based on various assumptions on syncope episode recurrence and performance of the ILR." I would like to see scenario analyses presented exploring all of the key model assumptions and structural uncertainties as the probabilistic sensitivity analysis only explores parameter uncertainty for those data sources used in the model and doesn't address any uncertainties regarding model structure, assumptions or choice of data sources.

In the first sentence under the 'Costs' heading you describe how five sources are used to estimate the cost of 'syncope episode admission'. However, in the second paragraph under 'Model' you discuss the rate of syncopal 'episodes' without discussing how episodes relate to admissions. What proportion of syncopal episodes result in admission? Are you assuming all those occurring in the model result in admission? If so, how is this assumption justified?

Please clarify exactly how the costs associated with admissions and injuries are estimated. Clarify what you mean by, "in 29.1% of trauma/injury cases 4.7% are severe." Was the rate of severe injuries zero in the other 60.9% of trauma/injury cases? Or do you mean to say that 29.1% of syncopal events were associated with trauma, of which 4.7% were severe trauma.

Table 2 is also confusing. How does the data in the column labelled 'Occurrence of minor/major trauma' relate to the DRG codes. Is DRG code 767 being assumed to occur 8.44% of the time? Is code 468 being assumed to occur 43.76% of the time? If not, why are they being presented in the same rows within this Table. How has the figure of 1,686.05 Euros in the right hand column been arrived at? It is also not clear how the proportions discussed under the heading 'Costs' relate to the 8.44% and 43.76% figures presented in Table 2, although they appear to be coming from the same source papers.

Please justify why there are no transitions to the death state in patients who have received a diagnosis (unless this is simply a case of the arrow being missed from Figure 1).

Minor Essential Revisions:
You say 'out of all available options...we chose 0.81 syncope events per year
based on Farwell 2004' and you claim that using the rate from Farwell is conservative. What were the other data sources you considered and how did their rates compare?

Farwell 2004 had a particularly old population (mean age over 70 in both arms). Have you considered the potential impact of the age difference between your population (starting age of 61) and the Farwell 2004 population.

Please clarify the diagnosis rates applied each year as the wording is a little ambiguous. Are the rates given per event, per annum or cumulative probabilities?

The description of the Markov states is a little confusing. There appears to be just one state for patients with 'unexplained or recurrent syncope' which is labelled as 'US' in Figure 1 and described as 'recurrent syncope' on line 6 after the 'Model' heading. However, it is then stated that patients with 'unexplained or recurrent syncope' face a probability of experiencing a recurrent syncope event. So is there one state for people with a history of unexplained syncope but no recurrent syncope for that cycle and then another state for those with a history of unexplained syncope and recurrent syncope that cycle? If so, then this should be made clear by the addition of a recurrent syncope state to Figure 1.

The Markov diagram in Figure 1 suggests no transitions to the death state after diagnosis? Is that the case or does the diagram need to be revised to show transitions from the diagnosed state to the death state? If so, please provide details on the rate of death after diagnosis.

Figure 1 has transition probabilities from unexplained syncope to death with different subscripts for the ILR and standard care diagnostic strategies. Does the death rate vary according to diagnostic the strategy? If not, I would consider removing the subscripts to show that the rates are the same.

Table 1: There is a big difference between Edvardsson and the other studies in Table 1 in the rate of electrophysiology testing and coronary angiography. Is this due to significant differences in the definition of the unexplained syncope population between these studies?

The distributions used to populate the probabilistic sensitivity analyses should be tabulated. This could be done in a supplementary appendix if this isn't considered important enough for the main article.

Discretionary Revisions:

There could be more details regarding the study population. In particular, how was 'unexplained syncope' defined. Is it syncope that remains unexplained after a clinical history, physical examination and 12-lead ECG, or is it syncope that is unexplained after four weeks of external event recorder monitoring, an electrophysiological test and a tilt-test? The diagnostic yield is likely to be dependent on how many investigations have been done to exclude particular diagnoses. In the abstract the indication is described as 'early referral for ILR',
and the conclusions section discusses 'use of ILR early in the assessment,' but it isn't clear what constitutes 'early' and whether the populations in the studies used to inform the model are consistent with this definition of 'early' ILR use.

Is the cycle length one year? How is that justified? The cycle length should be low enough that the chance of having two syncopal events within one cycle is minimised.

Study population, paragraph 2: I'm concerned that the incidence of particular DRG codes being reported does not give a reliable estimate of the rate of admissions for syncope, particularly as syncope itself may not be recorded as the primary reason for admission when other injuries or significant comorbidities are present. This data is being used to estimate the size of the patient cohort but a single patient could be admitted twice in one year, leading to the cohort size being overestimated. What alternative data sources could be used to estimate the incidence of syncope and why were these rejected in favour of the source used?

Your estimate of the cohort size suggests that you are restricting your cohort to those with a hospital admission for syncope, but this isn't clear from your description of the study population in the statements given in the first paragraph after the heading 'Study population'.

7 to 9 lines before the 'Study population' heading you say, "Brignole 2012 (23), after a long-term follow-up of ISSUE-2, projected almost the entire cohort to be diagnosed at the end of 4 years". It would be better to cite the 80% figure given by Brignole et al in their article, rather than saying 'almost the entire cohort'. As Brignole et al are actually citing the results from another study by Furukawa et al, it would be better to cite the source study and not Brignole et al's reporting of this study, which doesn't give any details regarding the study's methods. (T. Furukawa, R. Maggi, C. Bertolone, D. Fontana, M. Brignole Additional diagnostic value of very prolonged observation by implantable loop recorder in patients with unexplained syncope. J Cardiovasc Electrophysiol, 23 (2012), pp. 67–71)

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests