Appendix E2 Quality and applicability checklists for economic evaluations

Abbreviations: IER, implantable event recorder; VAS, visual analogue scale; TTO, time trade-off; QALY, quality adjusted life-year; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; RCT, randomised controlled trial; GDG, guideline development group

| **Study identification**<br>***MSAC 2003*** | | |
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| **Section 1: Applicability (relevance to specific guideline review question(s) and the NICE reference case)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 1.1 Is the study population appropriate for the guideline? | Yes | Patients with recurrent unexplained syncope after secondary testing |
| 1.2 Are the interventions appropriate for the guideline? | Yes | IER versus no further testing |
| 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context? | Partly | Australia Medicare (Government funded health-care) |
| 1.4 Are costs measured from the NHS and personal social services (PSS) perspective? | No | Australian Medicare perspective with societal costs considered if separately if significant |
| 1.5 Are all direct health effects on individuals included? | Yes | |
| 1.6 Are both costs and health effects discounted at an annual rate of 3.5%? | No | 5% |
| 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)? | Yes | |
| 1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers? | Yes | Patient reported EuroQol EQ-VAS |
| 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the | No | Non preference based EuroQol EQ-VAS used not the EQ-5D index score which is based on general public TTO valuation of EQ-5D states |

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| general public? | | |
| **1.10 Overall judgement: Partially applicable**<br>Costs are not applicable to UK but otherwise the approach is similar to reference case. QALYs not based on preference based measure. | | |
| Other comments: Could be adapted to UK perspective. | | |
| **Section 2: Study limitations (the level of methodological quality)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 2.1 Does the model structure adequately reflect the nature of the health condition under evaluation? | Yes | Diagnostic and post-diagnostic outcomes included. But design of decision tree has been restricted due to data available. Authors state that an alternative structure would be preferable in which the probability of no recurrence (spontaneous remission) is considered separately from the probability that a diagnosis is made during a recurrent episode. |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Partly | 3 year horizon is likely to capture diagnostic outcomes but may underestimate benefits of treatment. Extension to 5 years considered in sensitivity analysis. |
| 2.3 Are all important and relevant health outcomes included? | Yes | Outcome is successful treatment following diagnosis and this is linked to a health state with no further syncopal episodes, whereas non diagnosed and unsuccessfully treated patients are assumed to have further episodes. |
| 2.4 Are the estimates of baseline health outcomes from the best available source? | Yes | Diagnostic effectiveness data for IER was best available at time of study. Assumed no further diagnosis in comparator arm. |
| 2.5 Are the estimates of relative treatment effects from the best available source? | No | It is not clear where estimates of probability of successful treatment following diagnosis were taken from. |
| 2.6 Are all important and relevant costs included? | No | Weren't able to quantify resource use associated with further diagnostic investigations following recurrence. |
| 2.7 Are the estimates of resource use from the best available source? | Partly | Published estimates used to determine rate of recurrence causing injury requiring treatment. These were acceptable to MSAC reviewer |
| 2.8 Are the unit costs of resources from the best available source? | No | Best source for study perspective but not UK NHS estimates |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |

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| 2.11 Is there no potential conflict of interest? | Yes | Model adapted from manufacturer submission by independent reviewer |
| **2.12 Overall assessment: Potentially serious limitations**<br>It is not clear what evidence has been used to estimate the proportion of patients successfully treated and the model is sensitive to this outcome | | |
| Other comments: | | |

| **Study identification**<br>**Simpson 1999 and Krahn 1999** | | |
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| **Section 1: Applicability (relevance to specific guideline review question(s) and the NICE reference case)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 1.1 Is the study population appropriate for the guideline? | Unclear | Unclear how unexplained syncope has been defined. Does not state what is done to investigate the syncope before it is classified as unexplained. |
| 1.2 Are the interventions appropriate for the guideline? | Partly | Comparisons made are relevant to decisions regarding optimal sequencing of diagnostic tests |
| 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context? | Partly | Canadian (Simpson 1999) and US healthcare (Krahn 1999) systems |
| 1.4 Are costs measured from the NHS and personal social services (PSS) perspective? | No | Simpson 1999 states third-party payer perspective. Krahn 1999 states societal perspective but considering direct healthcare costs only. Neither is UK NHS and PSS |
| 1.5 Are all direct health effects on individuals included? | No | Outcomes following diagnosis, such as treatment and reduced recurrences, not considered |
| 1.6 Are both costs and health effects discounted at an annual rate of 3.5%? | NA | Future costs and benefits not considered |
| 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)? | No | Diagnosis is only health outcome considered |
| 1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers? | NA | |
| 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public? | NA | |

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| **1.10 Overall judgement: Partially applicable**<br>Costs not applicable but could be adapted to UK setting. Benefits not measured using QALYs. | | |
| Other comments: Estimates of cost-effectiveness are not sufficiently applicable to NICE's reference case criteria but study demonstrates principle that cost-effectiveness is dependent on ordering of diagnostic tests. | | |
| **Section 2: Study limitations (the level of methodological quality)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 2.1 Does the model structure adequately reflect the nature of the health condition under evaluation? | No | Patient outcomes following diagnosis have not been considered |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Unclear | Time horizon is not clearly stated but it is implied that it covers the diagnostic period only and does not capture patient outcomes following diagnosis. |
| 2.3 Are all important and relevant health outcomes included? | No | Post diagnostic outcomes resulting from treatment are not captured. |
| 2.4 Are the estimates of baseline health outcomes from the best available source? | Unclear | Published estimates of diagnostic yield are used but it is not clear if these have been systematically identified or whether they have been reviewed to determine their appropriateness. Definition of diagnosis is not given for each test |
| 2.5 Are the estimates of relative treatment effects from the best available source? | NA | Treatment effects not included. |
| 2.6 Are all important and relevant costs included? | No | Treatment costs following diagnosis not included |
| 2.7 Are the estimates of resource use from the best available source? | NA | Resource use is restricted to diagnostic testing which is defined by the diagnostic strategies |
| 2.8 Are the unit costs of resources from the best available source? | No | Okay for stated perspective but not appropriate for UK NHS perspective |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Krahn: Yes<br>Simpson: No | Krahn presents the incremental cost per additional diagnosis associated with the addition of IER to the end of each diagnostic strategy. However, the ICERs given do not follow from the data presented |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | Sensitivity analyses are used to estimate high end and low end estimate based on the uncertainty in diagnostic costs (Krahn and Simpson) and diagnostic yield (Krahn not Simpson) |
| 2.11 Is there no potential conflict of interest? | Unclear | One author is employee of company with commercial interest in implantable event recorders. |

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| **2.12 Overall assessment: Potentially serious limitations**<br>Due to lack of information regarding the cohorts from which the estimates of diagnostic yield have been derived and whether the tests are being used in similar populations within the model |
| Other comments: |

| **Study identification**<br>***Farwell 2004 and 2006***<br>As this is a trial based economic evaluation, the methodological quality of the study for the **clinical outcomes** has been assessed within the clinical review using the appropriate criteria for an RCT | | |
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| **Section 1: Applicability (relevance to specific guideline review question(s) and the NICE reference case)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 1.1 Is the study population appropriate for the guideline? | Yes | Considered to be representative of the population with unexplained syncope after secondary tests |
| 1.2 Are the interventions appropriate for the guideline? | Yes | Although patients in both groups had access to Holter and external event recorder monitoring after randomisation and the GDG felt these would not be appropriate investigations in patients with infrequent TLoC episodes |
| 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context? | Yes | UK secondary care setting |
| 1.4 Are costs measured from the NHS and personal social services (PSS) perspective? | Yes | |
| 1.5 Are all direct health effects on individuals included? | Yes | |
| 1.6 Are both costs and health effects discounted at an annual rate of 3.5%? | No | Study < 2 years follow-up |
| 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)? | No | Reports outcomes of diagnosis and first and second recurrences and quality of life measures, but QALYs not calculated |
| 1.8 Are changes in health-related quality of life | Yes | |

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| (HRQoL) reported directly from patients and/or carers? | | |
| 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public? | No | Includes quality of life measures (SF-12 and VAS), but these do not provide preference based utility scores |
| **1.10 Overall judgement: Partially applicable**<br>Costs and clinical outcomes reported separately. Benefits not measured using QALYs | | |
| Other comments: | | |
| **Section 2: Study limitations (the level of methodological quality)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 2.1 Does the model structure adequately reflect the nature of the health condition under evaluation? | NA | Trial based evaluation |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Partly | Follow-up may not be sufficient to demonstrate benefits of lower recurrence rates after diagnosis. Significant difference in second recurrence for Farwell 2006 but not Farwell 2004 suggesting that impact of treatment on recurrence is dependent on time-frame. |
| 2.3 Are all important and relevant health outcomes included? | Yes | |
| 2.4 Are the estimates of baseline health outcomes from the best available source? | Partly | Clinical outcomes derived from single RCT |
| 2.5 Are the estimates of relative treatment effects from the best available source? | Partly | Clinical outcomes derived from single RCT |
| 2.6 Are all important and relevant costs included? | No | Costs of treating diagnosed cause of TLoC not included |
| 2.7 Are the estimates of resource use from the best available source? | Partly | Clinical outcomes derived from single RCT |
| 2.8 Are the unit costs of resources from the best available source? | Partly | Local estimates of UK NHS costs rather than national reference cost |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | No | Costs and outcomes reported separately. IER cost not included so cannot calculate incremental cost. |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity | No | |

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| analysis? | | |
| 2.11 Is there no potential conflict of interest? | No | Authors have received funding from IER manufacturer |
| **2.12 Overall assessment: Potentially serious limitations**<br>Reasonable methodological quality as a source of comparative data on resource use and NHS costs during follow-up, and does report recurrences and HRQoL. However, paper doesn't combine cost and clinical outcomes to estimate cost-effectiveness. Cost of IER implantation not included so cost per additional diagnosis could not be calculated by reviewer. | | |
| Other comments: | | |

| **Study identification**<br>***Krahn 2003***<br>As this is a trial based economic evaluation, the methodological quality of the study for the **clinical outcomes** has been assessed within the clinical review using the appropriate criteria for an RCT (Krahn 2001 reports the RCT and Krahn 2003 reports the economic outcomes). | | |
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| **Section 1: Applicability (relevance to specific guideline review question(s) and the NICE reference case)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 1.1 Is the study population appropriate for the guideline? | Yes | Considered to be representative of the population with unexplained syncope after secondary tests |
| 1.2 Are the interventions appropriate for the guideline? | Yes | |
| 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context? | Partly | Canadian government funded health care system |
| 1.4 Are costs measured from the NHS and personal social services (PSS) perspective? | No | Societal perspective stated but only direct medical costs included<br>Not UK NHS and PSS |
| 1.5 Are all direct health effects on individuals included? | Partly | Quality of life is not reported. Recurrences after testing only reported for patients who received a diagnosis (Krahn 2001) |
| 1.6 Are both costs and health effects discounted | NA | Based on 1 year follow-up |

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| at an annual rate of 3.5%? | | |
| 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)? | No | |
| 1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers? | NA | |
| 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public? | NA | |
| **1.10 Overall judgement: Partially applicable**<br>Costs are not UK NHS and benefits have not been estimated using QALYs | | |
| Other comments: | | |
| **Section 2: Study limitations (the level of methodological quality)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 2.1 Does the model structure adequately reflect the nature of the health condition under evaluation? | NA | Trial based evaluation |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | No | Follow-up not likely to be long enough to capture all relevant post testing outcomes such as reductions in recurrences following diagnosis |
| 2.3 Are all important and relevant health outcomes included? | Partly | Recurrence free during post diagnosis follow-up reported but quality of life not reported |
| 2.4 Are the estimates of baseline health outcomes from the best available source? | Partly | Clinical outcomes derived from RCT but sample size was small and cross-over was greater in one arm |
| 2.5 Are the estimates of relative treatment effects from the best available source? | Partly | Clinical outcomes derived from RCT but sample size was small and cross-over was greater in one arm |
| 2.6 Are all important and relevant costs included? | No | Treatment costs not included. Cost savings of preventing future recurrences not included. |
| 2.7 Are the estimates of resource use from the best available source? | Partly | Clinical outcomes derived from RCT but sample size was small and cross-over was greater in one arm |
| 2.8 Are the unit costs of resources from the best available source? | No | Okay for stated perspective but not appropriate for UK NHS perspective |

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| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | No | |
| 2.11 Is there no potential conflict of interest? | No | There is a potential conflict. IER devices provided by manufacturer |
| **2.12 Overall assessment: Potentially serious limitations**<br>Does not capture impact of post-diagnostic treatment on HRQoL | | |
| Other comments: | | |

| **Study identification**<br>***Rockx 2005***<br>As this is a trial based economic evaluation, the methodological quality of the study for the **clinical outcomes** has been assessed within the clinical review using the appropriate criteria for an RCT | | |
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| **Section 1: Applicability (relevance to specific guideline review question(s) and the NICE reference case)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 1.1 Is the study population appropriate for the guideline? | Yes | Considered to be representative of the population with unexplained syncope after secondary tests |
| 1.2 Are the interventions appropriate for the guideline? | Yes | It is likely that 48 hr Holter monitoring would be used in patients with very frequent (e.g daily) events whilst external event recorders would be used in patients with less frequent events so these may not be realistic comparators in the same population. |
| 1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context? | Partly | Canadian government funded health care system |
| 1.4 Are costs measured from the NHS and personal social services (PSS) perspective? | No | Third party payer perspective. Not UK NHS and PSS |
| 1.5 Are all direct health effects on individuals included? | No | Outcomes after diagnosis such as quality of life or recurrences are not reported |
| 1.6 Are both costs and health effects discounted at an annual rate of 3.5%? | NA | Follow-up was <1 year |

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| 1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)? | No | |
| 1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers? | NA | |
| 1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public? | NA | |
| **1.10 Overall judgement: Partially applicable**<br>Costs are not UK NHS and benefits have not been estimated using QALYs | | |
| Other comments: | | |
| **Section 2: Study limitations (the level of methodological quality)** | **Yes/ Partly/ No /Unclear /NA** | **Comments** |
| 2.1 Does the model structure adequately reflect the nature of the health condition under evaluation? | NA | Trial based evaluation |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | No | Not sufficient to capture benefits of reduced recurrences from treating diagnosed cause of TLoC |
| 2.3 Are all important and relevant health outcomes included? | No | Quality of life not measured. Recurrence rate after treatment not measured. |
| 2.4 Are the estimates of baseline health outcomes from the best available source? | Partly | Clinical outcomes derived from single RCT and cross-over was greater in one arm |
| 2.5 Are the estimates of relative treatment effects from the best available source? | Partly | Clinical outcomes derived from single RCT and cross-over was greater in one arm |
| 2.6 Are all important and relevant costs included? | No | Treatment costs not included. Cost savings of preventing future recurrences not included. |
| 2.7 Are the estimates of resource use from the best available source? | Partly | Clinical outcomes derived from single RCT and cross-over was greater in one arm |
| 2.8 Are the unit costs of resources from the best available source? | No | Okay for stated perspective but not appropriate for UK NHS perspective |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |

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| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | No | |
| 2.11 Is there no potential conflict of interest? | Yes | No potential conflict identified |
| **2.12 Overall assessment: Potentially serious limitations**<br>Does not capture impact of post-diagnostic treatment on recurrences and HRQoL | | |
| Other comments: | | |