Health Economics Analysis Plan for ASPIRED

Multi-centre open label randomised controlled trial of immediate enhanced ambulatory ECG monitoring versus standard monitoring in acute unexplained syncope patients: The ASPIRED study.

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1.0	20/12/2022	Initial Creation

Overview

The health economic analysis will estimate the incremental costs and quality adjusted life years (QALYs) of immediate, enhanced (14-day) ambulatory ECG monitoring compared to standard care monitoring in acute unexplained syncope patients. The health economic analysis will be conducted in two parts. First, a within-trial cost effectiveness analysis (i.e. comparing the observed costs and QALYs of the intervention and control groups during the trial period) will be performed, and second, an analysis of the long-term cost effectiveness will be conducted by developing a *de novo* decision analytic model. For the within-trial analysis, along with the incremental cost per QALY gained, we will also estimate the incremental cost per syncope episode avoided.

Within trial cost-effectiveness analysis

Methodology

In the within trial cost-effectiveness analysis, the incremental cost per QALY gained by using immediate, enhanced (14-day) ambulatory ECG monitoring compared to standard care monitoring in acute unexplained syncope patients will be estimated by calculating the QALYs and health service costs within the trial period. First, we will conduct disaggregated analysis for the two trial arms which will include summary EQ5D values (mean, SD) at baseline and each follow up point, and items of resource use (mean number per patient and/or proportion) at each time point. QALYs within the trial will be estimated using the area under the curve technique, and costs within the trial period will be estimated by applying national unit costs to the resource use. Within trial incremental cost per QALY will be estimated by comparing the incremental costs and incremental QALYs between enhanced (14-day) ambulatory ECG monitoring and standard care monitoring. We will also estimate the incremental cost per syncope episode avoided.

Quality of Life and Quality adjusted life years (QALYs)

EQ-5D-5L questionnaire responses at baseline and 12, 24 months will be used to estimate the patients' quality of life (i.e., utility) at each time point. In line with the NICE recommendations, utility scores will be estimated by mapping the 5L descriptive system data onto the 3L value set using the mapping algorithm developed by the Decision Support Unit (Hernández Alava et al. 2017) using the 'EEPRU dataset' (Hernández Alava et al. 2020). If the baseline mean utility values are imbalanced between treatment arms, the utilities will be adjusted using regression techniques, as recommended by Manca et al (2005).

Dealing with missing data

We define responders as any patient who has completed the EQ5D questionnaire for at least one of the follow-up time points, in order to maximise the number of responders. In addition, clinically, there

is likely to be a big difference between cases with no follow up data and those with one or two time points missing.

The primary analysis will include all patients who have any follow up data, and we would use multiple imputation techniques for estimating the missed utilities for patients with missing data at the follow up points. This will allow us to include all cases with at least some follow up data i.e., only those with no utility values at any follow-up point would be excluded from the primary analysis.

We will also perform scenario analyses using interpolation for dealing with missing data. For cases with interim time point(s) missing (i.e., 12 months), we use will use linear interpolation of value at previous time point (i.e., utility at baseline) and the next time point (i.e., 24 months). For cases with last time point missing (i.e., 24 months), we use will use value at previous time point (i.e., utility at 12 months).

We will also estimate the baseline utilities for patients without missing follow up data and patients with missing follow up data (i.e. those who did not respond to any questionnaires) to identify if there are any systematic differences in utility values between the two groups (i.e. responders and non-responders to questionnaires). If the non-responder cases have markedly different baseline values to the responders, then we would undertake a secondary analysis in which we carry forward the baseline value for non-responders.

Estimating within trial QALYs

The curve of utility over different time points will be constructed for each patient using the approach mentioned above and the QALYs for each arm will be estimated by calculating the area under the curve for health utility over the two-year period. The patients who died during the trial will be included with zero utility from the date of death. The average QALYs of all the patients will be used to estimate the overall within trial QALYs as we assume that EQ5D captures any disutility including syncope.

Syncope episodes

The data from the trial would provide us with the number of syncope episodes (both self-reported, and those identified in medical records) at one and two years, for both immediate, enhanced (14-day) ambulatory ECG monitoring and standard care monitoring. The base case analysis will use self-reported syncope at one year in acute unexplained syncope patients. Sensitivity analyses will be performed using self-reported syncope episodes at two years, and syncope episodes identified from medical records at both one and two years.

Resource Use and Costs

All health care consumption and costs within the trial period will be estimated from a health care perspective. Resource use data determined from electronic case report forms (eCRF) will be combined

with national unit costs to estimate the overall costs. Only syncope related resource and costs will be included, this will include the need for investigations, GP visits, ED attendances, outpatient visits, hospitalisation (including ICU/CCU/HDU), additional investigations/imaging, and drug therapy. The differences in the rates of related surgeries/procedures will captured from the CRF and included as well.

The costs of investigations (i.e. 24-hour tape (Holter), 48-hour tape, 72-hour tape, 5-day tape, 7-day patch monitor, 14-day patch monitor or Implantable Loop Recorder) will be estimated by multiplying the number of tests with their unit costs sourced from NHS reference costs, respectively.

The GP visits from patient reported data from monthly text/email questionnaires will be used to estimate the costs of GP visits. Total number of GP visits over the two year period will be estimated and multiplied by the unit costs of GP visit (sourced from PSSRU unit costs).

The costs of syncope will be estimated based on whether the patient was admitted or not. If the patient was not admitted, the costs of syncope will be from NHS reference costs (HRG Code: 180) which relates to the ED (or outpatient visits) attendances with syncope. Similarly, the costs associated with elective hospital attendances will be estimated by multiplying the average number of visits in each arm with the unit costs sourced from NHS Reference Costs (Code: OPROC) which relate to outpatient visits.

If the patient was admitted, the length of stay will be used to estimate the costs by using a daily cost spent dependent on the location i.e. general ward hospital or CCU/HDU/ICU.

The costs of the investigations (Diagnostic Electrophysiology Study, Echocardiogram, CT Coronary Angiogram, Diagnostic coronary angiogram, Tilt Table test, Cardiac MRI or Exercise Tolerance Test) will be captured from the eCRF and combined with national unit costs to estimate the costs of investigations.

The costs of anti-arrhythmia drugs will be estimated by combining the usage (based on the respective dose and frequency) and the unit costs estimated from British National Formulary (BNF) and electronic market information tool (eMIT).

The costs of surgeries or procedures (Ablation, Cardiac valve surgery, Coronary artery bypass graft, Therapeutic coronary angiogram +/- coronary artery stent, Elective cardioversion, Permanent pacemaker placement and Permanent defibrillator placement) will be estimated by multiplying the proportions of patients receiving these treatments with the corresponding national average costs from the NHS reference costs.

Dealing with missing data

In terms of the missing cost data, it is anticipated that the CRF cost data will be close to 100% complete. As such, we do not expect to have any missing data.

Estimating within trial costs

The overall resource use for each patient will be multiplied with the unit costs (i.e. national average costs) to provide the estimated cost for each patient in the trial. The average cost of all the patients will then be used to estimate the overall within trial costs in each arm.

Estimating within-trial cost-effectiveness

The QALYs and costs for each arm of the trial (i.e. for each strategy) during the follow-up will be used to estimate the incremental cost effectiveness ratio (ICER) of immediate, enhanced (14-day) ambulatory ECG monitoring compared to standard care monitoring in acute unexplained syncope patients. Confidence intervals for the within trial ICER will be estimated to capture the sampling uncertainty.

As well as cost per QALY, we will also estimate the incremental cost per syncope episode avoided in the within-trial analysis. We will estimate the number of syncope episodes from the trial data, and combine with the cost per patient to estimate the incremental cost per syncope episode avoided. Confidence intervals will also be estimated to capture the sampling uncertainty.

Long-term cost-effectiveness modelling

Methodology

Long-term cost-effectiveness will be estimated by developing a simple *de novo* decision analytic model. The within-trial costs and QALYs from the trial will be combined with the costs/QALYs beyond the trial period (for the survivors) estimated from the model to understand the long-term cost-effectiveness.

It is assumed that any benefits of the use of immediate, enhanced (14-day) ambulatory ECG monitoring compared to standard care monitoring, if demonstrated, are expected to be captured within the trial period. Any benefits relating to identifying the patients with and without arrhythmia should be reflected in the proportion of patients alive, and their quality of life, at the end of trial period.

At the end of the trial period, the patients alive in each arm are assumed to have similar life expectancy as the general population. The mean utilities in each arm at the end of the trial period will be extrapolated over the whole lifetime to estimate the lifetime QALYs.

Estimating life expectancy

Based on the data from NICE guidelines and published literature, the life expectancy will be estimated using the general population mortality rates. Age and gender adjusted general population mortality,

based on national life tables for United Kingdom, will be to estimate the mean (undiscounted) life years for patients without intervention.

Estimating long-term QALYs

Long-term quality adjusted life years will be estimated by extrapolating the utilities at the end of the trial period over the whole lifetime with the proportions of patients alive over time in the respective health states.

The utilities at the end of the trial period will be extrapolated for the whole lifetime by using age adjustments in line with the NICE methods consultation document that states "If baseline utility values are extrapolated over long time horizons, they should be adjusted to reflect decreases in health-related quality of life seen in the general population and to make sure that they do not exceed general population values at a given age". As such, the utility values at the end of the trial period will be adjusted for age using the formula from Ara 2010, which states that $Utility$ = 0.9508566 + 0.0212126 $* Male$ - 0.0002587 $* age$ - 0.0000332 $* age$^2.

These utilities will be combined with the proportion of patients alive in each model cycle over the lifetime and the NICE recommended discount rate of 3.5% per annum will be used to estimate the discounted long-term QALYs.

Estimating long-term costs

Long-term costs will be estimated by multiplying the annual costs of the general population by the proportions of patients alive over time in the respective health states. Analyses will be conducted assuming zero annual costs, and also using annual costs for patients for general population extracted from the relevant published literature as there is debate around the inclusion of future unrelated medical costs in modelling (Kearns 2020). These annual costs will be combined with the with the proportion of patients alive in each model cycle over the lifetime and the NICE recommended discount rate of 3.5% per annum will be used to estimate the discounted long-term costs.

Estimating long-term cost-effectiveness

The lifetime QALYs and costs each arm of the trial (i.e., for each strategy) will be used to estimate the incremental cost effectiveness ratio (ICER) of the use of immediate, enhanced (14-day) ambulatory ECG monitoring compared to standard care monitoring. Parameter uncertainty will be included in probabilistic sensitivity analysis based on Monte Carlo simulation. Cost effectiveness acceptability curves (CEACs) will be plotted to identify the probability of the immediate, enhanced (14-day) ambulatory ECG monitoring being cost effective compared to standard care for a range of threshold values for an additional QALY. One-way sensitivity analyses will explore the potential impact of key model parameters upon lifetime costs and QALYs.

Finally, we plan a sensitivity analysis if there is a difference in survival between arms at 2 years and there is a clinical rationale for the difference. We will explore whether the results are sensitive to the assumption that survivors have normal life expectancy by using life expectancy estimates from a population with a relevant comorbidity (such as cardiac conduction abnormalities) instead of normal life expectancy.

References

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