THE UNIVERSITY OF LIVERPOOL

SLEEPS (Safety profiLe, Efficacy and Equivalence in Paediatric Intensive care Sedation)Trial

Health Economics Analysis Plan

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1 HEALTH ECONOMICS ANALYSIS PLAN: SLEEPS TRIAL

1.1 Primary objective and summary of economic evaluation methods

The economic evaluation will assess the cost effectiveness of two intravenous sedative agents (clonidine versus midazolam) that are administered in the treatment of critically ill children using clinical data from the SLEEPS trial. An economic evaluation has been integrated into the design of the trial. The primary outcome of the SLEEPS trial is adequate sedation; a child is adequately sedated if s/he spends "at least 80% of total time sedated within COMFORT range of 17 to 26". This measure of effectiveness will be calculated by the medical statistics team and made available to the health economists working on the trial.

Clinical research forms (CRFs) used by the clinical team have been designed to capture the duration and intensity of care provided to each child, based on standard criteria for level of care, as well as any complications experienced. Details of the resources associated with salient clinical events will therefore be recorded. For each of the two treatment groups, adequate sedation levels will be compared and the measure of benefit used in the economic evaluation will be additional case of adequate sedation observed. Given the methodological limitations surrounding preference-based outcomes measurement in young children, outcomes will not be expressed in terms of preference-based metrics, such as the quality-adjusted life year (QALY).

The economic evaluation will be performed from an NHS hospital services perspective using NHS direct costs only; non-NHS costs will not be considered.

In the primary analysis, costs and benefits will be identified, measured and valued for each trial participant from the date and time of randomisation to 14 days post treatment cessation. An incremental cost-effectiveness analysis (CEA) will be conducted in order to calculate the incremental cost per additional case of adequate sedation observed. A range of sensitivity and a scenario analysis will be performed alongside the primary analysis.

2 USING DATA FROM THE SLEEPS TRIALTO INFORM ECONOMICANALYSES

2.1 Data collection, calculation and analyses

All data received by the health economists working on the economic evaluation will be reviewed carefully on receipt following data entry and cleaning by the central trial administrative team. Specifically, all unique patient identifiers and completion dates will be checked and verified. The health economists involved in the study anticipate having access to the unblinded health economics data whilst the trial is in progress; this is to ensure that data are being collected as specified in the SLEEPS protocol and related CRFs and that any data entry errors/procedures can be corrected/amended as early as possible.

Where appropriate, efforts will be made to identify and/or impute missing data. Missing NHS resource use data are often straightforward to locate. Extracts of hospital contact records are available from all trial sites, and these will be cross-checked against SLEEPS trial records to ensure that any conflicts or omissions are detected and corrected. Multiple imputation methods may be used to impute missing data and avoid biases associated with complete case analysis (Briggs 2003); however, missing data is not anticipated to represent a major problem as all data for use in the economic evaluation will be routinely collected by hospital staff using the CRFs.

2.1.1 Collection and validation of resource use data

Resource use data will be collected via the CRFs that are used by the clinical team to collect clinical effectiveness data during the trial; these forms will be the key source of significant health service resource input data whilst the trial participants attend hospital. There are ten individual CRFs per trial participant that will be used for data collection during the trial. The health economists involved in the study were consulted during the pilot and design stages of the CRFs.

The study CRFs will capture all resource use related to the child's hospital inpatient stay, including diagnosis and treatment as well as transfers between wards and hospitals. Specifically, individualised resource use will be estimated for the resources associated with each child's intervention, length of stay in paediatric intensive care unit (PICU), length of stay in high dependence unit (HDU), length of stay in general ward, duration of mechanical ventilation during the hospital admission, surgical procedures performed during the hospital

admission, tests or investigations performed during the hospital admission, and resources associated with treatment of serious adverse events (SAEs). Duration of resource use for significant resource items during the hospital admission will also be recorded.

2.1.2 Unit costs

Unit costs for resources used by children who participate in the study will be obtained from a variety of primary and secondary sources, with the majority being obtained from secondary sources. All unit costs employed will follow recent guidelines on costing health and social care services as part of an economic evaluation (Drummond 2005, NICE 2013). Where necessary, secondary information will be obtained from ad hoc studies reported in the literature. Unit costs of hospital and community health care costs will be largely derived from national sources and will take account of the cost of the health professionals' qualifications (Curtis 2012). Some costs will be valued using the NHS Reference Costs (2011-12), a catalogue of costs compiled by the Department of Health in England (Department of Health 2012). Drug costs will be obtained from the British National Formulary (BNF 2012) and MIMS (2013). All costs will be expressed in pound sterling and valued at 2011-2012 prices. None of the costs will be inflated or deflated for use in the economic evaluation. For the primary analysis, unit costs will be combined with resource volumes to obtain a net cost per trial participant covering all categories of hospital costs. All unit costs employed will follow recent guidelines on costing health care services as part of economic evaluation. The calculation of these costs will be underpinned by the concept of opportunity cost.

2.1.3 Statistical analyses and calculation of cost-effectiveness ratios

Independent-sample t-tests will be used to test for differences in resource use, costs, and number of cases of adequate sedation observed between treatment groups. All statistical tests will be two-tailed. If appropriate, multiple regression analysis will be used to estimate the differences in total cost between clonidine and midazolam groups and to adjust for potential confounders, including the covariates incorporated into the main clinical analyses. In the primary analysis, the incremental cost-effectiveness analysis ratio (ICER) of interest will be the incremental cost per additional case of adequate sedation observed. The results of the economic evaluation will be restricted to the patients for whom the primary outcome in the SLEEPS trial is available.

For the economic evaluation, differences in mean costs and effects between the groups will be calculated. The ICER will be calculated as the difference in costs (ΔC) divided by the difference in number of cases of adequate sedation. The economic evaluation will estimate the cost per additional case of adequate sedation observed, and the primary analysis will follow trial participants from randomisation to 14 days post treatment cessation as this will ensure that any differences in costs or healthcare resource use that result from the intervention will be captured. Discounting of future costs or benefits will not be applied as the time horizon is less than 12 months.

Estimates of the probability of clonidine being less costly, more effective, dominant or dominated relative to standard care at different ceiling ratios will be calculated. Non-parametric bootstrap estimation will be used to derive 95% confidence intervals for mean cost differences between the trial groups and to calculate 95% confidence intervals for ICERs. The planned economic evaluation will conform to nationally agreed design and reporting guidelines and will incorporate detailed resource use and clinical effectiveness data from all subjects recruited into the trial. The proposed analytical strategy will follow the recent requirements stipulated by decision-making bodies.

Uncertainty around the conclusions about whether or not treatment is cost effective will be represented in the form of cost-effectiveness acceptability curves (CEAC). This will show the probability of the addition of treatment being cost-effective at a range of maximum values (termed ceiling ratios, Rc) that decision-makers may be willing to pay for an additional case of adequate sedation. The CEACs and the probability of treatment being cost-effective will be calculated based on the proportion of simulations with positive net benefits at a range of ceiling ratios.

2.1.4 Sensitivity and scenario analyses

A series of simple and probabilistic sensitivity analyses will be undertaken to explore the implications of uncertainty on the estimated ICER and to consider the broader issue of the generalisability of the study results. One-way sensitivity analysis will include the following parameter variations: higher per diem PICU/HDU ward cost; lower per diem PICU/HDU ward costs; use of fractions of time in estimation of total length of stay and estimation of costs from randomisation to 14 days post-ventilation cessation. A scenario analysis will also be conducted and will be undertaken from a wider NHS perspective – additional GP visit, accident and emergency and hospital re-admissions costs will be included.

A final exhaustive list of the sensitivity analyses investigated will be made available (including *post hoc*[1] analyses) and the results of all analyses conducted will be included in the final report.

References

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Briggs A, Clark T, Wolstenholme J, Clarke P. Missing... presumed at random: cost-analysis of incomplete data. Health Econ 2003;12(5):377-92.

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[1] Post hoc analyses comprised widening and narrowing the definition of adequate sedation from '80% of total time sedated within a COMFORT score range of 17 to 26' to 75% and 85% respectively.