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Methodological issues surrounding the use of baseline health-related quality of life data to inform trial-based economic evaluations of interventions within emergency and critical care settings: a systematic literature review

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Abstract

Background: Trial-based cost-utility analyses require health-related quality of life data that generate utility values in order to express health outcomes in terms of quality-adjusted life years (QALYs). Assessments of baseline health-related quality of life are problematic where trial participants are incapacitated or critically ill at the time of randomisation. This review aims to identify and critique methods for handling non-availability of baseline health-related quality of life data in trial-based cost-utility analyses within emergency and critical illness settings.

Methods: A systematic literature review was conducted, following PRISMA guidelines, to identify trial-based cost-utility analyses of interventions within emergency and critical care settings. Databases searched include the NIHR Journals Library (1991 to July 2016), Cochrane Library (all years); National Health Service (NHS) Economic Evaluation Database (all years) and Ovid Medline/Embase (without time restriction). Strategies employed to handle non-availability of baseline health-related quality of life data in final QALY estimations were identified and critiqued.

Results: A total of 4224 published reports were screened, 19 of which met the study inclusion criteria (mean trial size 1,670); 14 (74 %) from the UK, 4 (21%) from other European countries and 1 (5%) from India. Twelve studies (63%) were based in emergency departments and 7 (37%) in intensive care units. Only one study was able to elicit patient-reported health-related quality of life at baseline. To overcome the lack of baseline data when estimating QALYs, 8 (42%) studies assigned a fixed utility weight corresponding to either death, an unconscious health state or a country-specific norm to patients at baseline, 4 (21%) ignored baseline utilities, 3 (16%) applied values from another study, 1 (5%) generated utility values via retrospective recall and 1 (5%) elicited utilities from experts. A preliminary exploration of these methods shows that incremental QALY estimation is unlikely to be biased if balanced trial allocation is achieved and subsequent collection of health-related quality of life data occurs at the earliest possible opportunity following commencement of treatment followed by adequate number of follow-up assessments.

Conclusion: Trial-based cost-utility analyses within emergency and critical illness settings have applied different methods for QALY estimation, employing disparate assumptions about the health-related quality of life of patients at baseline. Where baseline measurement is not practical, measurement at the earliest opportunity following commencement of treatment should minimise bias in QALY estimation.

Key points for decision makers:

- employ appropriate randomisation strategy to ensure baseline comparability across treatment groups
- initial assessment of health-related quality of life of patients at the earliest time possible post randomisation and
- inclusion of a constant or imputed baseline value rather than ignoring it.

1. Introduction

Economic evaluations are increasingly being conducted alongside phase III and phase IV randomised controlled trials of various interventions such as surgical procedures, drug treatments, diagnostic tests and behavioural interventions [1]. In the United Kingdom (UK), government agencies such as the National Institute for Health and Care Excellence (NICE) for England and Wales, the All Wales Medicines Strategy Group (AWMSG) for Wales and the Scottish Medicines Consortium (SMC) for Scotland have established decision-making processes that draw heavily upon economic evidence collected within the context of randomised controlled trials, whilst its research funding bodies such as the National Institute for Health Research (NIHR) routinely request the inclusion of economic assessment methods within large-scale clinical trials [1],[2]. Similarly, economic evidence collected within the context of randomised trials is increasingly being used to inform the regulatory and reimbursement decisions of government agencies in other nations [3, 4]. Depending on the research question, trial-based economic evaluations can take the form of cost-consequence analyses, cost-effectiveness analyses or cost-utility analyses. Cost-utility analyses are particularly appealing to decision makers as they permit cost-effectiveness comparisons to be made using the quality-adjusted life year (QALY) metric for different health care interventions across disparate health conditions. It is unsurprising therefore that cost-utility analysis using the QALY outcome measure (which combines length of life and health-related quality of life in a single measure of health consequence) remains the preferred evaluative method in the technology appraisal guidance of many government agencies [1],[2].

To generate the QALYs needed to inform trial-based cost-utility analyses, data on survival and data on health-related quality of life measured at baseline and subsequent follow-up time points are required for trial participants. Randomised controlled trials conducted in emergency and critical care settings have used various multi-attribute utility instruments, including the EQ-5D [5], SF-6D [6] and Health Utilities Index-3 (HUI-3) [7], to reflect preferences for patient health states; these are normally converted into health utility values using established algorithms [8-10]. In critical care settings, the psychometric properties of the EQ-5D and the SF-12 (from which the SF-6D can be derived) were recently examined in two patient populations, namely patients diagnosed with acute respiratory distress syndrome [11] and survivors of out of hospital cardiac arrest [12]. The authors of both studies reported satisfactory performance of these instruments in the respective patient populations. However, asking patients to complete these measures around the time of recruitment (commonly taken as the baseline measurement) into randomised controlled trials conducted within emergency and critical care settings can be problematic; patients are commonly incapacitated and unable to provide a self-assessment of their health status at or around the time of randomisation [13],[14]. Problems also arise because the event of interest is often acute in nature rather than pre-planned; the unknown timing makes it difficult to collect baseline data from participants during the occurrence of the event and at the point of recruitment into the trial. Alternative strategies used to collect patient-reported outcome data in clinical trials more broadly, such as researcher-administered interviews (face-to-face or, in the context of longer term follow-up by telephone), can also be problematic to implement when patients are critically ill for the same reasons. Even where trial participants are conscious, the nature of some health conditions (for example cardiac arrest and serious traumatic injury) around the time of randomisation can often raise ethical objections to collecting patient-reported outcome data. Solutions adopted by previous trial-based economic evaluations within emergency and critical illness settings have included delaying the time at

which health-related quality of life is assessed until patients are well enough to complete questionnaires [15],[16], [17] , asking patients to retrospectively recall [18] their pre-randomisation health state and use of proxies such as patients' next of kin or health professionals [19]. The impact of this heterogeneity of method upon the findings of economic analyses is unclear.

An early systematic review of the critical care literature conducted in 2002 provided evidence of the difficulty of conducting within-trial cost-utility analyses involving critically ill or injured patient populations [20]. Of the 29 economic analyses identified in that review, none was a cost-utility analysis. This systematic review therefore aimed to identify and critique approaches to collection of health-related quality of life data and subsequent estimation of QALYs in the absence of directly and contemporaneously measured baseline values in trial-based cost-utility analyses of interventions within emergency and critical illness settings. To our knowledge this problem has not been addressed before and there is scope to develop recommendations for future best practice to inform health economics researchers in emergency or critical care. The paper is structured as follows: section 2 outlines the systematic review methods followed by presentation of the results in section 3. A critical appraisal of the methods identified in the review for dealing with lack of baseline health-related quality of life data when estimating QALYs is presented in section 4. The aim is to understand the implications of the assumptions underlying each method and the likely impact on cost-effectiveness results. The discussion and conclusions are presented in section 5.

2. Methods

The NIHR Journals Library (1991 to July 2016), Cochrane Library (all years); National Health Service (NHS) Economic Evaluation Database (all years) and Ovid Medline/Embase (without time restriction) were searched. Search item groupings included terms and derivatives for “intensive care”, “economic evaluation” and “randomised controlled trial”. Full details of the search strategy are provided in Appendix A in the supplementary online material.

Included studies were cost-utility analyses of interventions based in emergency or critical care settings, for example accident and emergency departments or intensive care units, which were conducted alongside randomised controlled trials. The randomisation (allocation to trial arm) had to be made whilst patients were in an emergency or critical care setting and consequently unable/incapacitated to provide self-assessment of their health status. Eligible studies had to have collected preference-based health-related quality of life data from trial participants themselves, by proxy (e.g. relatives, healthcare professionals) or from an external source (for example, another study or expert opinion) to support the subsequent economic analysis. Studies were excluded if they did not include a cost-utility analysis or if the condition was non-acute, e.g. management of influenza, where patients could normally give written consent. In addition, because of the way disability-adjusted life years (DALYs) are calculated (i.e. the disutility weights are calculated for specific disease conditions and not based on patient preferences [21]), within-trial cost-utility analyses that reported outcomes in terms of DALYs were excluded. Mental health care related studies were excluded because of the particular methodological challenges presented. Non-English studies and the grey literature were also excluded.

Literature searches and reviews were performed in two stages in accordance with PRISMA guidelines [22] and included studies published until July 2016. First, titles and abstracts were screened to identify and retrieve potentially relevant reports. Second, retrieved full reports were assessed for eligibility. Both stages were completed independently by two reviewers (MD, FA) checking against pre-specified inclusion and exclusion criteria, with disagreements resolved through consensus. For eligible studies, data were extracted on the clinical setting, clinical condition, study perspective, time horizon, sample size, participant demographics, preference-based health-related quality of life instrument(s), timing of data collection, source of (and where applicable accompanying assumptions around) baseline health-related quality of life data and methods used to estimate QALYs. The quality of included studies was assessed using the strategy reported by Kendrick et al [23] and included the quality of the randomisation process, blinding of outcome assessment and completeness of follow-up (see Appendix B in the supplementary online material for further details). The review was registered on the PROSPERO register of systematic reviews (registration number CRD42016046174).

Finally, the conduct and reporting of each trial-based economic evaluation was assessed against selected items on the CHEERS checklist [24] for reporting single study-based economic evaluations of interventions and expanded to include : i) study methods, including description of target population, clinical settings, perspective of the analysis, study time horizon and whether or not cost and effects were discounted and if so by what amount; ii) method of data collection (including the type of preference-based health-related quality of life instrument used and the follow-up time points at which data collection was conducted); iii) method used to calculate QALYs, including, where applicable, how the non-availability of baseline health-related quality of life data was handled when estimating QALYs; iv) characterisation of uncertainty; and v) a critical and thematic appraisal of the reported methods used to handle non-availability of baseline health-related quality of life data in subsequent QALY estimation. Characterisation of uncertainty was assessed by examining whether studies reported parameter estimates together with associated measures of uncertainty (e.g. standard errors, confidence intervals, etc.) and investigated the impact of known methodological assumptions on final estimates of cost-effectiveness. Simple descriptive statistics were used to summarise characteristics of included studies and the methods used to handle non-availability of baseline health-related quality of life data in the cost-utility analyses. Results are presented narratively in textual format, providing numbers and corresponding percentages in brackets where appropriate.

3. Results

3.1 Summary of RCTs included in the review

A total of 4224 published reports (e.g. published papers, book chapters, monographs, etc.) were screened (Figure 1), of which 4113 were excluded after initial review of titles and abstracts. Of the remaining 111 full reports retrieved, 92 (83%) were excluded: 35 reported no economic evaluation outcomes at all (i.e. did not report cost-effectiveness, cost-consequence or cost-utility outcomes), 16 reported economic evaluation outcomes that were not cost-utility based (i.e. were either cost-consequence or cost-effectiveness analyses in which the measures of health outcomes were not synthesised into preference-based metrics), 13 were conducted in non-emergency or critical care settings, 12 were duplicate reports, 15 were protocol papers and 1 study expressed the health outcomes

of the economic evaluation in DALY terms. A list of all 111 reports that reached the second stage of the review process is provided in Appendix C in the supplementary online material.

Table 1 summarises the baseline characteristics of the 19 trial-based cost-utility analyses included in the review, published between 2004 and 2016. The majority of studies, 14 (74 %), were conducted in the UK, 4 (21 %) in other European countries (namely Denmark, Norway, Germany and Netherlands/Switzerland) and 1 (5%) in India. The mean number of patients in the underpinning randomised controlled trials was 1760 (range 180 to 6182), mean age was 53 years (range of means: 0.51 to 78) and mean percentage of males was 57% (range: 30% to 76%). In terms of clinical setting, 12 (63%) studies were based in emergency departments and included conditions such as emergency resuscitation for out-of-hospital cardiac arrest or acute asthma in adults and children and 7 (37%) in intensive care units.

One study [27] did not report a time horizon for the economic evaluation. The mean time horizon for the within-trial component of the economic evaluations in the remaining 18 studies was 8 months (median 9 months and range 1 to 12 months). Some studies extrapolated outcomes beyond the trial follow-up period using decision analytic modelling methods [25, 26, 28] with up to 60 months [25] and lifetime [15, 16, 28, 29] extrapolations beyond the study follow-up periods. Most economic evaluations were conducted from the perspective of the UK National Health Service (NHS) (n=4) or the NHS/Personal Social services (n=9) in accordance with NICE guidance for appraising health technologies [30]. One further UK study adopted a societal as well as an NHS perspective [30]. Of the 5 non-UK studies [18] [25, 27, 31, 32] included in the review, 4 studies [18, 27, 31, 32] adopted a health services perspective, whilst one study adopted a third-payer perspective described as excluding costs to sectors other than the health sector and out-of-pocket expenses [25]. Most of the economic evaluations did not discount costs and effects in line with the relatively short time horizons of the within-trial analyses. Where studies had extrapolated cost and effects beyond the trial follow-up, discount rates of between 3.0% [25] and 3.5% [16, 28, 29, 33] per annum were applied to both costs and effects. In terms of study quality, all 19 (100%) studies reported using a randomisation process that was assessed as adequate according to the criteria described in Appendix B in the supplementary online material; 16 (84%) were un-blinded and 9 (47%) reported $\geq 80\%$ completion rates for the primary outcome at end of follow-up.

3.2 Measurement of health-related quality of life

The most widely used generic preference-based health-related quality of life instruments include the EuroQoL EQ-5D [5] and the SF-6D [6] but other generic preference-based instruments such as the Health Utilities Index Mark 3 (HUI-3) [7] and the 15D-instrument [34] are also available for use.

Table 2 presents a summary of the health-related quality of life data collection methods applied in the included studies and how non-availability of health-related quality of life data at baseline was handled in the QALY estimation. For the purpose of this review, we measured the baseline (or first) time point for describing health-related quality of life as reported by individual studies; conventionally in trial-based economic evaluations this is taken as the time of randomisation. Nine (47%) of the 19 studies used the EQ-5D to measure health-related quality of life of patients, 5 (26%) used the EQ-5D in combination with another instrument (primarily the SF-12/36 [26, 33, 35], HUI-3 [32] and the paediatric PedsQL [36]), 1 (5%) [18] used the 15D instrument [34] and another 1

(5%) used the HUI-3 [28]. The remaining 3 (17%) studies [29] [25, 27] did not report a primary health-related quality of life data collection process. Rather, the economic evaluations in these 3 studies were informed by utility data extracted from external sources. In the study by Harvey and colleagues [29], age- and gender-specific utility values for the UK adult population were combined with survival estimates from the trial in order to estimate QALYs in the cost-utility analysis. Specifically, Harvey and colleagues "estimated the quality-adjusted life expectancy for each survivor at hospital discharge based upon the Office of National Statistics age and sex-specific life expectancy tables and the EQ-5D age- and sex-specific quality of life weights". Gyrd-Hansen [25] and colleagues used 5 year QALY estimates for patients living with stroke obtained from the Oxford Stroke study [37] and stratified by stroke severity to inform the cost-utility analysis. Rosenthal et al [27] applied a QALY reduction of 0.37 per day for patients in an intensive care unit, which they obtained for from a secondary study [38]. In addition, "...an extra decrement of 0.2 QALYs was assumed for patients at age 65 years, and an annual decrement of 0.005 [39] each year over 65 was considered as well".

3.3 Methods used to handle non-availability of baseline health-related quality of life in QALY estimation

Only one [40] of the 16 studies that prospectively collected health-related quality of life data was able to do so at baseline (using date from 932 (86%) of the 1084 study participants). This study recruited patients with acute severe asthma from emergency departments. Patients had to be able to at least provide verbal consent and those with life threatening illness were excluded. EQ-5D data were collected at baseline by the recruiting physician. In the remaining 15 studies, the earliest time point recorded for data collection directly from study participants varied from 2 days post-randomisation [41] to 12 months post-randomisation . The reported reasons for not assessing health-related quality of life at randomisation mostly reflected the condition of trial participants at this time point, concerns around utility measurement in these clinical settings, or reluctance to prioritise health-related quality of life assessment in studies with substantial data collection burden.

The reported strategies used to handle the non-availability of health-related quality of life data at baseline in subsequent cost-utility analyses were available from 14 of the 15 studies that failed to collect baseline data and can be classified into four broad categories [note: the economic evaluation based on REAC-2 trial [32] data had not yet been published at the time of undertaking this review]:

- i) Eight (57%) studies assigned a fixed health utility value to all participants at baseline. This included assuming a zero value or a health state equivalent to death [33] [16] [17] or a utility value of -0.40 reflecting an unconscious health state for the EQ-5D-3L [13] [26] [35]. One study [42] obtained baseline utility from an external source (i.e. the Health Survey of England) stratified by age and sex and another study [43] assumed equivalent baseline utility values across trial arms without reporting the actual values used.
- ii) Four (29%) studies [41] [15] [31] [28] estimated QALYs using only the available data (i.e. from the first time point at which health-related quality of life was measured: 2 days post-randomisation in the study by Goodacre et al (2005) [41], 1 month post-randomisation in the study by Schuster et al (2015), 3 months post-randomisation in the study by Mouncey et al (2015) [15] and 1 year post-randomisation in the subset of CHiP trial participants with traumatic brain injury [28]. This

- effectively ignored the impact of interventions on participant's health-related quality of life prior to these time points on final QALY calculations.
- iii) One (7%) study [18] asked patients to retrospectively recall at 14 days post-randomisation their pre-randomisation health state.
 - iv) Finally, one other (7%) study [19] elicited external evidence on utility values associated with specific baseline health states using Delphi methods. The health status of participants measured at baseline was then translated/mapped onto EQ-5D-3L health states using evidence elicited from experts for incorporation in the final QALY calculations.

3.4 Assessment of uncertainty around assumptions used to incorporate baseline utility in final QALY estimation

Extensive sensitivity analyses were used by the included studies to investigate the impact that methodological assumptions (mostly around the inclusion of different cost variables reflecting alternative perspectives for the economic evaluation) had on incremental cost-utility estimates. However, only one [19] of the 15 studies that did not collect baseline health-related quality of life data directly from patients (excluding the yet to be published analysis based on the REAC-2 trial [32]) specifically assessed the impact of the method and assumptions used to estimate baseline utilities on the cost-effectiveness results (Table 2). In that particular study [19], varying the assumptions used to estimate baseline utilities had little impact on the final cost-effectiveness results.

4. Implications of methods for handling non-availability of baseline quality of life data

4.1 Ignoring or assuming a fixed baseline utility value

The selection of baseline health-related quality of life data in trial-based cost utility analyses is significant in two ways: first as an adjustment covariate within regression to estimate incremental costs and QALYs [44]; and second as the first point in an area-under-the-curve estimation of individual patient QALYs.

The importance of the method of baseline health-related quality of life measurement is driven by the success of the trial randomisation in achieving a balanced allocation of individuals (in terms of patient characteristics) between treatment arms. Baseline adjustment of health-related quality of life as a covariate within regression has become normal practice because of the need to manage the effect of baseline imbalances [44]. In the presence of baseline imbalances, different approaches to adjust for missing baseline health-related quality of life are likely to yield different answers. In this circumstance, exploring alternative baseline proxy covariates may provide the best approach although trial stratification variables may adequately achieve this. As a general point, when estimating cost-effectiveness ratios with incremental QALYs close to zero, findings are likely to appear (perhaps artificially) sensitive to assumptions about baseline adjustment, since the incremental cost-effectiveness ratio (ICER) denominator may switch sign according to the approach taken.

In terms of area-under-the-curve (AUC) calculations, in the presence of balanced allocation, incremental QALY estimation may be robustly estimated. If it is assumed there is a true and variable unobserved baseline health-related quality of life, then assuming a fixed value should not systematically bias the incremental QALY gain or cost-effectiveness estimation. This is shown algebraically in Appendix D in the supplementary online material. In fact in the presence of imbalances, imposing a fixed baseline in the presence of an adequate number of multiple

follow-up valuations may only introduce limited bias as only the first of a series of measurements contributing to the area-under-the-curve is affected. For example if QALY estimation is captured over a one year follow-up period and the first measurement is at 2 weeks then any baseline assumption will have a small effect on the overall incremental QALY gain. Ignoring the true baseline and starting from a delayed first measurement may introduce more significant bias since the area between the baseline and first measurement is lost. Conversely, this bias would be exacerbated in the absence of an adequate number of multiple follow-up valuations. Algebraically the degree of bias is proportional to the magnitude of the time interval between randomisation and the first data collection point and the magnitude of the QALY gain between the two time intervals (Appendix E in the supplementary online material). Similarly, Figure 2 shows an example of a trial with a 12 month follow-up period where we assume no long term differences between treatment groups and a difference of 0.1 at the earliest follow-up, time t . Assume time t is a trial design choice and can be varied. The error of taking the AUC from the earliest follow-up and not attempting a baseline estimate is minimal at 1 week and considerable at 6 months. If an analyst does include a baseline assessment, then it doesn't matter what baseline value is chosen between 0 and 1 (note utility values can take negative values in practice), AUC_1 is the same regardless. Having a baseline assessment is increasingly important the more delayed the first measurement. When there is imbalance at baseline, ignoring it and choosing a common baseline value will have a minimal effect for an early first measurement. Suppose the baseline imbalance in health utility was 0.1 (the same as the treatment effect at time t). Then the bias of missing the imbalance in the baseline model is similar to the error of not adjusting for baseline in a baseline balanced model.

Consequently the eight studies that assigned a fixed baseline value should have produced unbiased estimates of incremental benefit in the absence of baseline imbalance; the three studies starting estimation from post-treatment would similarly be adequate if the duration between randomisation and the timing of the first measurement is a small proportion of the overall follow-up period. In all circumstances the frequency of follow-up time points needs to be adequate to characterise the treatment effect, but has been simplified in Figure 2 for illustration.

4.2 Retrospective recall of the baseline health-related quality of life data

In the study by Bohmer and colleagues [18], “patients were carefully instructed to report health-related quality of life as it was experienced 14 days before the infarction (baseline value)”. The main appeal of retrospective recall is that baseline health-related quality of life data can be obtained from trial participants themselves. QALY estimates can also be adjusted to account for potential imbalances between groups [44]. The most obvious limitation is that it is not possible to obtain direct estimates from deceased or permanently incapacitated patients (who would not be missing at random). For example, in the PARAMEDIC 1 trial [35], only 6.6% of 1471 individuals experiencing out-of-hospital cardiac arrest recruited into the trial survived to 3 months post arrest, the first time point at which health-related quality of life data were collected. Asking patients to retrospective recall their baseline health-related quality of life would not be an option for the majority of this trial’s participants.

Another limitation of retrospective recall is the possibility of introducing recall bias in the final QALY estimation. The extent of any recall bias may depend on the clinical and demographic characteristics of patients and the length

of the recall period [45]; the longer this is, the more difficult it would be for patients to accurately recall and report on their baseline health-related quality of life. Wilson and colleagues [46] compared the use of retrospective recall of baseline health status versus population norms (New Zealand) in estimating change in health state valuations following acute-onset illness or injury. Their findings indicate a small but significant difference between pre- and post-injury health-related quality of life for people who had fully recovered, with recalled pre-injury health-related quality of life being higher than reported post-injury health. The reported health-related quality of life of the fully recovered patients was also higher than adult population norms. The authors concluded that “retrospective evaluation of health status is more appropriate than the application of population norms to estimate health status prior to acute-onset injury or illness, although there may be a small upward bias in such measurements.” Finally, provided that recall bias is similar in magnitude and direction across treatment arms, then it is unlikely to lead to a large effect on incremental QALYs.

4.3 Eliciting external evidence and using mapping techniques to derive baseline health-related quality of life data

Powell and colleagues [19] employed a more sophisticated technique to estimate baseline health-related quality of life based on a clinical outcome (Yung Asthma Severity Scores (ASS) in the context of acute severe asthma in children) measured at baseline. A physician panel comprising of two respiratory nurses and a consultant were asked to translate/map (not on the basis of a pre-existing association but rather their clinical opinion) ASS scores measured at baseline onto EQ-5D-3L health states from which baseline utility scores were estimated. More generally, ‘mapping’ techniques can be used to derive baseline health-related quality of life data if a condition-specific outcome measure that is better able to reflect changes to health status of individuals can be collected at baseline and at subsequent follow-up time points when individuals are able to provide information on their health-related quality of life. The relationship between the condition-specific outcome measure and the preference-based health-related quality of life measure can be derived using the data at follow-up time points when both outcome measures are collected. The mapping coefficients can then be used to derive baseline utility values based on responses to the condition-specific outcome measure at baseline.

As with the management of non-availability of baseline health-related quality of life data, the choice of external utility values elicited from experts is unlikely to have a significant effect on incremental QALY estimation if balanced trial allocation is achieved, and may not introduce significant bias where baseline differences are small, or subsequent health-related quality of life measurement is adequately informative.

5. Discussion

Summary

This review describes the conduct of cost-utility analyses alongside randomised controlled trials in emergency and critical care settings. In this context, the estimation of QALYs is problematic because of difficulties in collecting health-related quality of life data from acutely ill or injured patients around the time of recruitment into trials. Four approaches for handling the lack of baseline health-related quality of life data in QALY calculations were identified among the 19 studies included in the review: a) assigning a fixed health state utility value (typically assumed to be zero, a utility value for an unconscious health state, or stratified by important predictors of health-

related quality of life) to all patients at baseline; b) ignoring baseline health-related quality of life and estimating QALYs based on available data at later time points; c) retrospective recall of baseline health-related quality of life; and d) mapping from disease specific outcomes measured at baseline onto generic preference-based health-related quality of life outcomes. The results suggest that there is no uniformity in approach amongst researchers conducting trial-based economic evaluations regarding the most appropriate strategy for dealing with the problem of non-availability of primary baseline health-related quality of life data when estimating QALYs to inform trial-based cost-utility analyses within emergency and critical care settings.

Some implications of the methods used for dealing with the lack of baseline health-related quality of life data have been explored. To permit robust trial-based cost-utility analysis, a critical factor is whether the treatment arms are balanced with respect to the health-related quality of life of patients at baseline. By definition this is not observed directly but may be implied by measured baseline differences in trial covariates. In this circumstance, proxy covariate adjustment of health-related quality of life estimates should be explored. In terms of area-under-the curve QALY estimation, provided randomisation has resulted in balanced treatment groups at baseline and the first health-related quality of life assessment occurs early in the overall period of assessment (e.g. 2 weeks into a 52 week follow-up) then all methods are likely to give fairly similar answers, and estimated incremental QALYs will not vary significantly. However, use of a fixed baseline may reconstruct treatment arm QALY gains more faithfully and may be preferable to simply starting QALY estimation from the first post-randomisation measurement: the fixed baseline health state utility value cancels out in the calculation of incremental QALYs (Appendix D in the supplementary online material). In general, ignoring the baseline health-related quality of life measurement may increase potential biases, particularly if there is substantial delay to the first trial measurement point (Appendix E in the supplementary online material and Figure 2).

A potential limitation of the review is the omission of studies that meet the inclusion criteria in the review process (either at the search or screening and selection stages of the review). This can occur where eligible studies fail to report sufficient details in titles and abstracts to enable them to be identified as trial-based economic evaluations. For example, where trials fail to find difference in effectiveness between comparator interventions, there may be insufficient interest to include health economic outcomes within the main trial report or publish separate cost-effectiveness findings. The goal of the review was to characterise the types of approach used to compensate for unobtainable baseline utilities within the literature. Although some further eligible studies might have been obtained by more sensitive search methods, we have not identified any further approaches not already captured within this review.

Recommendations for design of future trial-based economic evaluations in emergency and critical care settings

- It is evident from the discussions above that an appropriate randomisation strategy should be employed to promote treatment groups that are similar in observable and unobservable patient characteristics. This in turn makes it likely that an unbiased estimate of incremental QALYs is produced irrespective of the strategy for dealing with the lack of baseline health-related quality of life data. It also limits the need for more complicated adjusted analyses to correct for the imbalances in baseline health utilities. It is

acknowledged that, as the outcome of randomisation is probabilistic, the best that randomisation can achieve is groups that are ‘similar’. It is thus possible that a perfectly valid strategy can still end up with a chance imbalance because there is a limit to the number of stratifying variables within randomisation, and blocking breaks down with low recruiting centres where these randomisation strategies are employed.

- It is also evident that when possible, the initial assessment of health-related quality of life of patients should be conducted at the earliest time possible post randomisation. This might mean the initial assessment of health-related quality of life is conducted at different time points as and when each patient is able to complete the health-related quality of life questionnaire. The differential times for the initial assessment would then be taken into account in the subsequent analyses. This is unlikely to cause problems if variation in first measurement time is random or small relative to the total follow-up. If, however, different treatments lead to substantially different durations to first measurement this might be an issue for incremental QALY estimation. Further research should be considered to investigate whether or not collecting data at early time points offers advantages over data collection at a fixed time point for all patients.
- Ignoring baseline utilities altogether in final QALY estimation is generally not preferable as this approach may result in biased estimates of incremental QALYs as demonstrated in section 4.1 and Figure 2.
- Identification and where possible collection of data on clinical variables (outcomes) that are strongly correlated with health-related quality of life and hence can be used to predict baseline health-related quality of life using mapping algorithms offers a route for further research enquiry.
- In the context of data collection, if the incorporation of health-related quality of life data is considered burdensome by trialists, it is important that health economists provide clear methodological guidance on best methods that balance the need to minimise respondent burden against the requirement for minimising analytical biases.

Concluding remarks

Baseline health-related quality of life measurement is problematic in trial-based economic evaluations conducted in emergency and critical care settings. Consequently, trial-based cost-utility analyses have used different methods that make different assumptions about baseline health utilities. Key messages that come out of this study include the need to employ appropriate randomisation strategies to ensure baseline comparability across treatment groups, initial assessment of health-related quality of life of patients at the earliest time possible post-randomisation and, where appropriate, inclusion of a constant or imputed baseline utility value rather than ignoring it. Further research is needed in order to determine the impact of different assumptions upon cost-effectiveness results, and to identify best methodological practice in this area.

Compliance with Ethical Standards

Melina Dritsaki, Felix Achana, James Mason, and Stavros Petrou have no conflicts of interest to disclose.

There was no research funding support for this study.

Author contributions:

The concept of this manuscript was jointly conceived by Melina Dritsaki, Felix Achana and Stavros Petrou. Melina Dritsaki and Felix Achana gathered and reviewed the literature and data and drafted the initial manuscript. James Mason drafted the initial work presented in Section 4. All authors participated in the interpretation of data and preparation of the final manuscript.

Data Availability Statement:

The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files

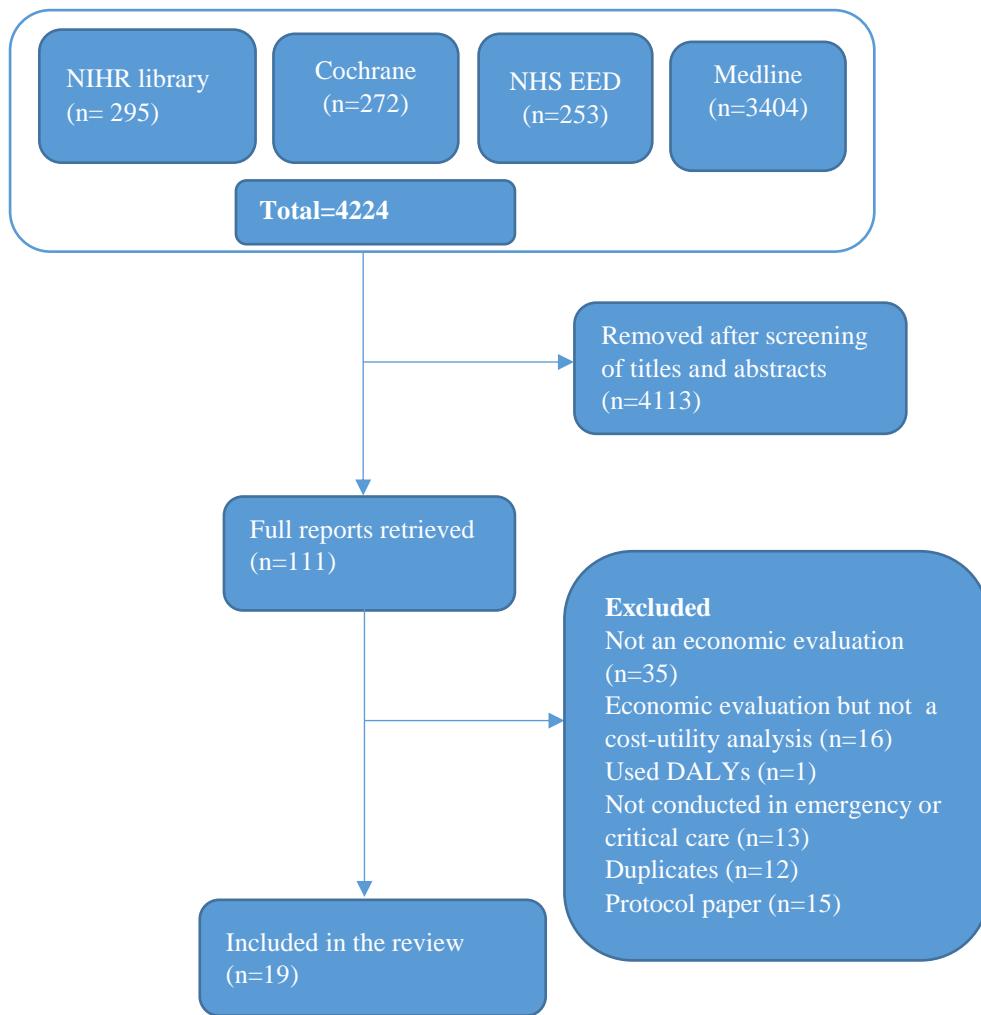


Figure 1: Flow chart of study identification and selection

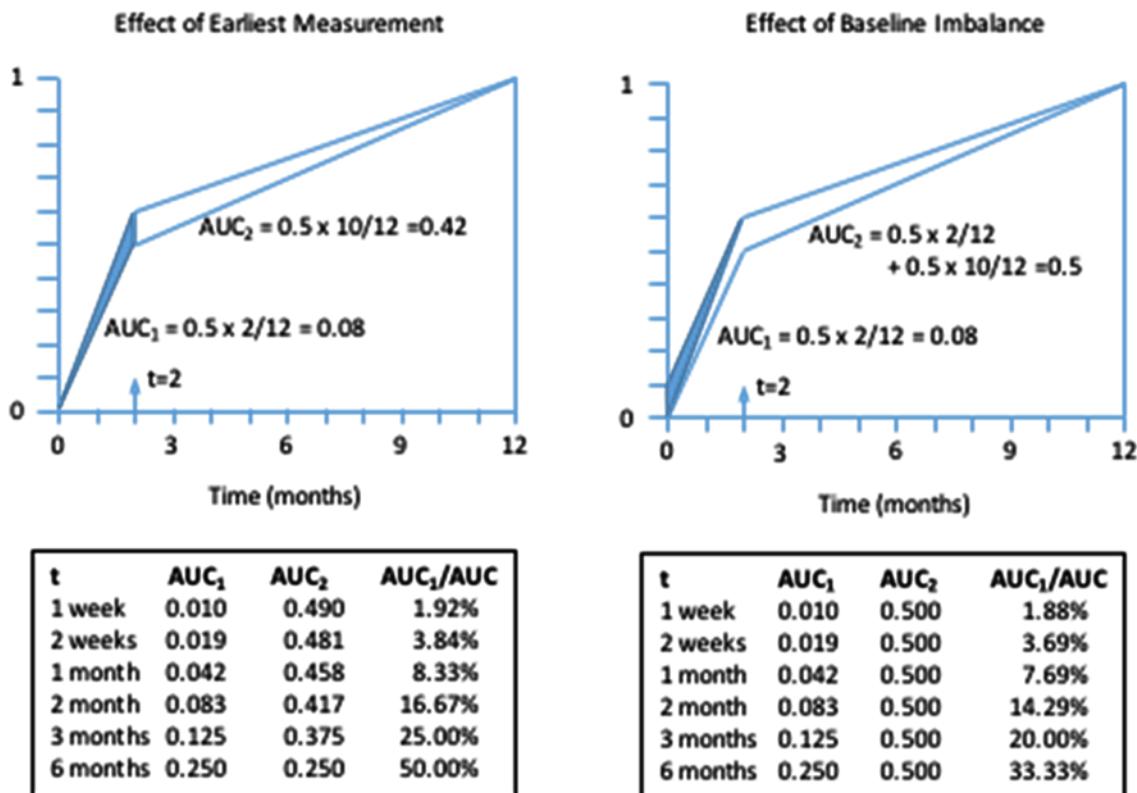


Figure 2: Effect of early measurement and baseline imbalance in health related quality of life on incremental QALY estimation using area-under-the-curve approaches. Health-related quality of life (utility) weight is displayed on the vertical axis and follow-up time on the horizontal axis. The left plot shows the effect of early measurement and right plot the effect of baseline imbalance on incremental QALY estimation. Assuming that the maximum follow-up is 12 months, there is no long term difference between treatment groups and that a difference of 0.1 at the earliest follow-up, time t. Assume further that t is a trial design choice and can be varied. Then error of taking the AUC from the earliest follow-up and not attempting a baseline estimate is minimal at 1 week and considerable at 6 months as shown in the box under left plot where $AUC = AUC_1 + AUC_2$. Similarly, having a baseline assessment is increasingly important the more delayed the first measurement. The right plot shows that when there is imbalance at baseline, ignoring it and choosing a common baseline value will have a minimal effect for an early first measurement.

Table 1. Summary of trial-based cost-utility analyses included in the review

First author (year), acronym	Country	Clinical setting	Disease/condition	Perspective	Time horizon (months)	Discounting costs and effects [†]	Sample size	Mean age (years)	% male
Goodacre (2005)[41]	UK	ED	Acute, undifferentiated chest pain.	NHS	6	No	972	50	64
Harvey (2006)[29]	UK	ICU	Critically ill patients in adult general intensive care.	NHS/PSS	12 ^a	Yes, 3.5%	1041	65	58
Dixon (2009)[43]	UK	ED	Care of older people following a call for an emergency ambulance	NHS/PSS	12	No	3018	78	43
Peek (2010), CESAR[33]	UK	ICU	Severe adult respiratory failure.	NHS, Societal	6 ^b	Yes, 3.5%	180	40	58
Bohmer (2011)[18]	Norway	ED	ST-elevation myocardial infarction	Societal	12	No	266	61	76
Goodacre (2011), 3CPO[17]	UK	ICU	Acute cardiogenic pulmonary oedema	NHS/PSS	6 ^a	Yes, 3.5%	1069	78	43
Goodacre (2011), RATRAC[16]	UK	ED	Acute myocardial infarction.	NHS	3	No	2243	55	58
Lamb (2012), MINT[42]	UK	ED	Acute whiplash injury	NHS	12	No	3851	37	43
Gates (2013), BALTI-2[13]	UK	ICU	Acute respiratory distress syndrome	NHS/PSS	12	No	326	55	65
Powell (2013), MAGNETIC[47]	UK	ED	Acute severe asthma in children	NHS	1	No	508	4	58
Goodacre (2014), 3Mg[40]	UK	ED	Acute asthma in adults	NHS/PSS	1	No	1084	36	30
Macrae (2014), CHiP[28]	UK	ICU	Blood glucose control in paediatric intensive care units	NHS/PSS	Life-time	Yes, 3.5%	1369	0.51 ^c	55
Gyrd-Hansen (2015), PHANTOM-S[25]	Denmark	ED	Acute stroke	Third-party ¹	3 ^b	Yes, 3.0%	6182	74	44
Lall (2015), OSCAR[26]	UK	ICU	Acute respiratory distress syndrome	NHS/PSS	12	No	795	55	62
Mouncey (2015)[15]	UK	ED	Early septic shock	NHS/PSS	12 ^a	No	1260	65	56
Perkins (2015), PARAMEDIC[35]	UK	ED	Out of hospital cardiac arrest	NHS /PSS	3	Unknown	4471	71	63
Rosenthal (2015)[27]	India	ICU	Nosocomial infections	Healthcare payer	Not stated	Not reported	1096	60	67
Schuster (2015), IABP-SHOCK II[31]	Germany	ED	Acute myocardial infarction	Healthcare (Germany)	12	No	600	70 ^c	69
Sierink (2016) REACT-2[32]	Netherlands, Switzerland	ED	Trauma patients requiring advanced life support	Healthcare	12	Unknown	1403	44	76

^aEtrapolated to lifetime; ^bExtrapolated to 60 months; ^cMedian age reported in original trial paper, Clinical settings (ED = Emergency department, ICU = Intensive care unit)

[†]Discount rate per annum

Table 2: Summary of health-related quality of life measurement and assumptions around how baseline health-related quality of life information was incorporated into QALY estimation

First author	Instrument	Data collection time points (months)	Source of baseline health related quality of life data	Methods used to estimate overall QALYs	Was the impact of baseline utility values used on cost-effectiveness results investigated and or reported through sensitivity analyses?
Goodacre (2004)[41]	EQ-5D	0.07 ^a , 1, 6	First time point data	EQ-5D data over 6 months were combined with survival data to estimate QALYs using the area under the curve methods.	No
Harvey (2006)[29]	None	None	UK valuation norms	EQ-5D age- and sex-specific health-related quality of life weights for UK adult population combined with survival estimates from the trial	
Dixon (2009)[43]	EQ-5D	1	Identical baseline scores assumed	Incremental QALYs estimated assuming a linear change in EQ-5D scores and that the two groups have identical scores at baseline.	No
Peek (2010)[33]	EQ-5D; SF-36	6	Zero score assumed	Linear interpolation	No
Bohmer (2011)[18]	15D instrument	0.5 ^b ,3,12	14 day retrospective recall	Linear interpolation	No
Goodacre (2011), 3CPO[17]	EQ-5D	1, 3, 6	Zero score assumed	Area under the curve	No
Goodacre (2011), RATPAC[16]	EQ-5D	1,3	Zero score assumed	“Data are reported assuming that EQ-5D was zero at baseline, although means for any baseline score between 0 and 1 can be estimated by adding a constant k/24, where k is the baseline EQ-5D score of interest. As 3 months is approximately one-quarter of a year, the maximum possible number of QALYs accrued is 0.25 (assuming EQ-5D was 1 at baseline).”	No
Lamb (2012)[42]	EQ-5D	0.5,4,8,12	UK pop norm assumed	Baseline utility were taken from Health Survey for England and matched on age.	No

Gates (2013)[13]	EQ-5D	6,12	Unconscious (-0.402)	An unconscious patient (-0.402) for the baseline utility	No
Powell (2013)[47]	Proxy EQ-5D, PedsQL	1	Delphi exercise followed by mapping	"A physician panel made up of two respiratory nurses and a consultant mapped the Yung Asthma Severity Score (ASS) scores on to EQ-5D health states from which baseline utility scores were estimated. In the base-case analysis, ASS scores of 1–3 were mapped on to an EQ-5D health state of 11111; ASS scores of 4–6 were mapped on to an EQ-5D health state of 22222; and ASS scores of 7–9 were mapped on to an EQ-5D health state of 33333."	Yes. This study reported varying the mapping algorithms used to estimate baseline utility as part sensitivity analyses. The results showed different assumptions about baseline utility values had little impact on the cost-effectiveness results (see page 55 of the HTA report).
Goodacre (2014)[40]	EQ-5D	0,1	Baseline data collected	Not reported.	Not applicable as study collected self-reported health-related quality of life data at baseline.
Macrae (2014)[28]	HUI-3	12	First time point	Health-related quality of life was collected from a subset of patients who had traumatic brain injury at 12 months from intensive care unit admission. The health-related quality of non-traumatic brain injury patients alive at 12 months post ICU admission was not assessed. Instead patients in this subgroup were assigned utility weights from another study. QALYs were then derived by applying the utility weights each life-year of lived predicted for trial participants from 12 months post ICU admission. Patients who died before the 12 months period were assigned zero QALYs.	No
Gyrd-Hansen (2015)[25]	None	None	External source	QALY estimates from external source (Oxford Vascular study) were stratified by stroke severity	
Lall (2015)[26]	EQ-5D, SF-12	6,12	Unconscious state (-0.40)	Area under the curve assuming unconscious state (utility of -0.40) at baseline.	No
Mouncey (2015)[15]	EQ-5D	3,12	First time point data	QALYs estimated by combining survival data with quality-of-life scores at 90 days	No
Perkins (2015)[35]	EQ-5D, SF-12	3,12	unconscious (-0.402)	Cost-effectiveness analysis not yet published. Personal communication with the trial health economics team indicate that the analysis will assume	Cost-effectiveness analyses and results not yet reported

				an unconscious state at baseline by applying utility score of -0.402.
Rosenthal (2015)[27]	None	None	External source	QALYs and QALY decrements were obtained from another study and assigned to individual patients stratified by age
Schuster (2015), IABP-SHOCK II[31]	EQ-5D	1,6,12	First time point	Area under the curve, starting from the first time point at which data were collected.
Sierink (2016)[32]	EQ-5D, HUI-3	3,6,12	Cost-effectiveness analyses and results not yet published	Cost-effectiveness analyses and results not yet published

^aRetrospective recall at 14 days post randomisation

Appendix A: Search strategy

Database searched	Timespan	Search Strategy
NIHR Journals Library	1991 to 2016	“intensive care” “economic evaluation” “critical care” “economic evaluation”
Cochrane	All years	#1 Medical subject heading (MeSH) descriptor Intensive Care explode all trees #2 MeSH descriptor Critical Care explode all trees #3 MeSH descriptor Intensive Care Units explode all trees #4 (“acute care” or “critical care” or “critically ill” or “critical illness”) #5 “high dependency care” or “high dependency unit” #6 high next dependency next unit* #7 “intensive care” #8 (ITU or ICU or CCU or CICU or CITU) #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) #10 (“cost effective*” or “cost benefit*” or “cost analys*” or “cost utili*”) ti,ab,kw #11(cost* or economic* or pharmacoconomic*):ti #12 (“health economic*” or “healthcare cost*” or “health care cost*” or “economic evaluation*”):ti,ab,kw #13 (economical):ti,ab #14 (#10 OR #11 OR #12 OR #13) #15 "randomized controlled trial":pt #16 "randomised controlled trial":pt #17 "controlled clinical trial":pt #18 randomized: ti,ab #19 placebo: ti,ab #20 randomly :ti,ab #21 trial :ti,ab #22 groups :ti,ab #23(#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22) #24(#9 AND #14 AND #23)
NHS EED	All years	(intensive care*) AND (economic evaluation*) AND (randomised controlled trial*) (critical care*) AND (economic evaluation*) AND (randomised controlled trial*) (intensive care*) AND (economic evaluation*) AND (randomized controlled trial*) (critical care*) AND (economic evaluation*) AND (randomized controlled trial*)
Ovid Medline/ Embase	All years	1.Critical Care/ or Intensive Care/ 2.exp Critical Care/ 3.acute care.mp. 4.exp Critical Care/ 5.exp Critical Illness/ 6.critical illness.mp. or Critical Illness/ 7.Hospital Units/ or Intensive Care Units, Neonatal/ or "Health Services Needs and Demand"/ or Intensive Care Units/ or Nursing Staff, Hospital/ or Intensive Care/ or Middle Aged/ or Critical Care/ or Esophageal Neoplasms/

	<p>8.Postoperative Care/ or Postoperative Complications/ or Intensive Care/ or "Length of Stay"/ or Intensive Care Units/ or Progressive Patient Care/ or Aged/ or Middle Aged/ or Hospital Units/ or Adult/</p> <p>9.Adult/ or Middle Aged/ or Thiourea/ or Pest Control, Biological/ or Bacillus thuringiensis/ or Thiouracil/ or Acute Kidney Injury/ or Critical Care/ or Intensive Care Units/ or Aged/</p> <p>10.Respiration, Artificial/ or Aged/ or Critical Illness/ or Nursing Staff, Hospital/ or Adult/ or Monitoring, Physiologic/ or Middle Aged/ or Cross Infection/ or Intensive Care Units/ or Intensive Care/</p> <p>11.Chest Pain/ or Aged/ or Patient Admission/ or Prospective Studies/ or Middle Aged/ or Coronary Disease/ or Coronary Care Units/ or Adult/ or Myocardial Infarction/ or Intensive Care Units/</p> <p>12.Postoperative Complications/ or Intensive Care Units, Pediatric/ or Heart Diseases/ or "Length of Stay"/ or Myocardial Infarction/ or Child, Preschool/ or Cardiac Surgical Procedures/ or Coronary Care Units/ or Heart Defects, Congenital/ or CICU.mp.</p> <p>13.CITU.mp.</p> <p>14.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13</p> <p>15.exp Fibroblasts/ or exp "Costs and Cost Analysis"/ or exp "Neoplasms, Glandular and Epithelial"/ or exp HIV Infections/ or exp Endometrial Neoplasms/ or exp Psychotic Disorders/ or exp Ovarian Neoplasms/ or exp Adult/ or exp Cost-Benefit Analysis/ or exp Neoplasm Recurrence, Local/</p> <p>16.cost benefit.mp. or Cost-Benefit Analysis/</p> <p>17.exp "Costs and Cost Analysis"/</p> <p>18.exp Quality-Adjusted Life Years/ or exp Cost-Benefit Analysis/ or exp Health Care Costs/ or exp "Quality of Life"/ or exp "Costs and Cost Analysis"/</p> <p>19.exp Economics, Pharmaceutical/</p> <p>20.exp Cost-Benefit Analysis/ or exp Health Services Research/ or exp Economics, Medical/</p> <p>21.exp Health Care Costs/</p> <p>Health Care Costs/</p> <p>23.economic evaluation.mp. or exp Cost-Benefit Analysis/</p> <p>24.economical.mp.</p> <p>25.15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24</p> <p>26.randomized controlled trial.mp. or exp Randomized Controlled Trial/</p> <p>27.controlled clinical trial.mp. or exp Controlled Clinical Trial/</p> <p>28.randomized controlled trials.mp. or exp Randomized Controlled Trial/</p> <p>29.random allocation.mp. or Random Allocation/</p> <p>30.double-blind method.mp. or exp Double-Blind Method/</p> <p>31.single-blind method.mp. or exp Single-Blind Method/</p> <p>32.clinical trial.mp. or exp Clinical Trial/</p> <p>33.clinical trials.mp. or exp Clinical Trial/</p> <p>34.Comparative Study/</p> <p>35.prospective studies.mp. or exp Prospective Studies/</p>
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		36.follow up studies.mp. or exp Follow-Up Studies/ 37.26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 38.14 and 25 and 37
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Appendix B: Study quality assessment

The quality of included studies was assessed using the following strategy reported in Kendrick et al (2012) (page 6):

1. “Quality of randomisation was considered to be adequate when study authors mentioned the use of sealed opaque envelopes, automated computerised randomisation programmes, minimisation programmes or independent researchers using a computer generated list of random numbers. It was considered to be inadequate where randomisation was based on coin tossing or drawing from packs of cards. If insufficient data were provided to judge the adequacy of randomisation, it was categorised as unclear”.
2. “Outcome assessment was considered to be blinded if authors stated this, and where it was not stated it was categorised as unclear.”
3. The percentage follow-up in each arm was calculated from the number allocated and the number with follow-up data for the primary outcome (including patients who have died) if they were included in the primary analysis. Completion rates were considered adequate if follow-up rate in each arm was more than 80%.

Results of study quality assessment are shown below:

First author (year), acronym	Primary outcome	Follow-up rates for primary outcome			Randomisation method	Study quality ¹
		Arm 1	Arm 2	Arm 3		
Goodacre (2004)	Proportion admitted	69.5%	69.6%		Block randomisation	A=A,B=N,F=N
Harvey (2006)	Hospital mortality	97.3%	97.6%		Central randomisation by telephone	A=A,B=N,F=Y
Dixon (2009)	-	-	-		Cluster randomisation	A=A,B=N,F=U
Peek (2010), CESAR	Death or severe disability at 6 months	57.8%	35.6%		Central randomisation by telephone	A=A,B=N,F=N
Bohmer (2011)	Composite of death, reinfarction, stroke, or new myocardial ischemia at 12 months.	97.1%	95.7%		Permuted block randomization	A=A,B=N,F=Y
Goodacre (2011), 3CPO	30 days mortality	94.8%	93.9%	96.6%	Central randomisation by telephone	A=A,B=N,F=Y
Goodacre (2011), RATRAC	Proportion of patients successfully discharged home after ED assessment.	99.4%	98.9%		Simple randomisation sequence	A=A,B=N,F=Y
Lamb (2012), MINT	Neck Disability Index (NDI)	71%	70%		Cluster randomisation	A=A,B=N,F=N
Gates (2013), BALTI-2	28 days mortality	98.1%	95.7%		Central randomisation by telephone	A=A,B=Y,F=N
Powell (2013), MAGNETIC	Asthma severity score after 60 minutes of treatment	90%	94.5%		Block randomisation	A=A,B=Y,F=Y
Goodacre (2014)	the proportion of patients admitted to hospital; and the patient’s visual	98%	97%	98%	blocked randomisation (block sizes of four or six),	A=A,B=Y,F=Y

	analogue scale (VAS) for breathlessness over 2 hours after initiation of treatment.				stratified by hospital,	
Macrae (2014)	numbers of days alive and free of mechanical ventilation within 30 days	63%	61%		central computerised randomisation	A=A,B=N,F=N
Gyrd-Hansen (2015), PHANTOM-S	Alarm-to-thrombolysis time	8.2%	6.4%		Block randomisation	A=A,B=N,F=N
Lall (2015), OSCAR	30 days mortality	100%	100%		Central randomisation by telephone	A=A,B=N,F=Y
Mouncey (2015)	90 days mortality	90%	90%		Central randomisation by telephone	A=A,B=N,F=Y
Perkins (2015), PARAMEDIC	Survival at 30 days following cardiac arrest	100%	99.9%		Cluster randomisation	A=A,B=N,F=U
Rosenthal (2015)	Rates of central line associated bloodstream infection	-	-		Block randomisation	A=A,B=N,F=U
Schuster (2015), IABP-SHOCK II	30 days mortality	100%	100%		Central randomisation	A=A,B=N,F=Y
Sierink (2016) REACT-2	In-hospital mortality	77.1%	77.3%		-	A=U,B=N,F=N

¹Study quality (A=Adequate allocation concealment; B=Blinded outcome assessment; F=At least 80% participants followed up in each arm; U=Unclear; N=No; Y=Yes)

Appendix C: List of included and excluded studies

First author	Year	Reference	Included / Reason for exclusion
Goodacre	2004	Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. <i>BMJ (Clinical research ed)</i> . 2004;328(7434):254	Included
Harvey	2006	An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial. <i>Health technology assessment (Winchester, England)</i> . 2006;10(29):iii-iv, ix-xi, 1-133	Included
Dixon	2009	Is it cost effective to introduce paramedic practitioners for older people to the ambulance service? Results of a cluster randomised controlled trial. <i>Emergency medicine journal : EMJ</i> . 2009;26(6):446-51	Included
Peek	2010	Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). <i>Health technology assessment (Winchester, England)</i> . 2010;14(35):1-46.	Included
Bohmer	2011	Health and cost consequences of early versus late invasive strategy after thrombolysis for acute myocardial infarction. <i>European journal of cardiovascular prevention and rehabilitation: official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology</i> . 2011;18(5):717-23.	Included
Goodacre	2011	The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. <i>Health technology assessment (Winchester, England)</i> . 2011;15(23):iii-xi, 1-102	Included
Goodacre	2011	Health utility and survival after hospital admission with acute cardiogenic pulmonary oedema. <i>Emergency medicine journal: EMJ</i> . 2011;28(6):477-82	Included
Lamb	2012	Managing Injuries of the Neck Trial (MINT): a randomised controlled trial of treatments for whiplash injuries. <i>Health technology assessment (Winchester, England)</i> . 2012;16(49):iii-iv, 1-141	Included
Gates	2013	Beta-Agonist Lung injury Trial-2 (BALTI-2): a multicentre, randomised, double-blind, placebo-controlled trial and economic evaluation of intravenous infusion of salbutamol versus placebo in patients with acute respiratory distress syndrome. <i>Health technology assessment (Winchester, England)</i> . 2013;17(38):v-vi, 1-87.	Included
Powell	2013	MAGNESium Trial In Children (MAGNETIC): a randomised, placebo-controlled trial and economic evaluation of nebulised magnesium sulphate in acute severe asthma in children. <i>Health technology assessment (Winchester, England)</i> . 2013;17(45):v-vi, 1-216	Included
Gyrd-Hansen	2015	Cost-effectiveness estimate of prehospital thrombolysis: results of the PHANTOM-S study. <i>Neurology</i> . 2015;84(11):1090-7.	Included
Lall	2015	A randomised controlled trial and cost-effectiveness analysis of high-frequency oscillatory ventilation against conventional artificial ventilation for adults with acute respiratory distress syndrome. The OSCAR (OSCillation in ARDS) study. <i>Health technology assessment (Winchester, England)</i> . 2015;19(23):1-177, vii.	Included
Mouncey	2015	Trial of early, goal-directed resuscitation for septic shock. <i>The New England journal of medicine</i> . 2015;372(14):1301-11.	Included

Perkins	2015	Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. <i>Lancet</i> (London, England). 2015;385(9972):947-55.	Included
Rosenthal	2015	Clinical impact and cost-effectiveness of split-septum and single-use prefilled flushing device vs 3-way stopcock on central line-associated bloodstream infection rates in India: a randomized clinical trial conducted by the International Nosocomial Infection Control Consortium (INICC) American Journal of Infection Control 43 (2015) 1040-5	Included
Schuster	2015	Economic implications of intra-aortic balloon support for myocardial infarction with cardiogenic shock: an analysis from the IABP-SHOCK II-trial. <i>Clin Res Cardiol</i> (2015) 104:566–573	Included
Sierink	2016	Immediate total-body CT scanning versus conventional imaging and selective CT scanning in patients with severe trauma (REACT-2): a randomised controlled trial. <i>The Lancet</i> Volume 388, No. 10045, p673–683, 13 August 2016	Included
Ducharme	2005	Impact of care at a multidisciplinary congestive heart failure clinic: a randomized trial	Not critical illness
Harrison	2002	Quality of Life of Individuals with Heart Failure: A Randomized Trial of the Effectiveness of Two Modelsof Hospital-to-Home Transition	Not critical illness
Hernandez	2014	Economic evaluation of nurse-led intensive care follow-up programmes compared with standard care: the PRaCTICAL trial	Not critical illness
Prinssen	2007	Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: Results of a randomized trial	Not critical illness
Rogers	2014	Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery: a randomised controlled trial (the CRISP trial)	Not critical illness
Sach	2012	Community falls prevention for people who call an emergency ambulance after a fall: an economic evaluation alongside a randomised controlled trial	Not critical illness
Sun	2013	Randomized Clinical Trial of an Emergency Department Observation Syncope Protocol Versus Routine Inpatient Admission	Not critical illness
Mastrigt	2006	Short-stay intensive care after coronary artery bypass surgery: randomized clinical trial on safety and cost-effectiveness	Not critical illness
Ghislaine	2010	health-related quality of life after fast-track treatment results from a randomized controlled clinical equivalence trial	Not critical illness
Macrae	2014	A clinical and economic evaluation of Control of Hyperglycaemia in Paediatric intensive care (CHiP): a randomised controlled trial	Not critical illness
Corbacho	2016	Cost effectiveness of surgical versus nonsurgical treatment of adults with displaced fractures of the proximal humerus	Not critical illness
Diwaker	2015	An economic evaluation of outpatient versus inpatient polyp treatment for abnormal uterine bleeding	Not critical illness
Moulaert	2015	Early neurologically-focused follow-up after cardiac arrest improves quality of life at one year: A randomised controlled trial	Not critical illness
Angus	2015	The cost-effectiveness of cardiac computed tomography for patients with stable chest pain	Not critical illness
Anis	2002	Economic Evaluation of Propofol for Sedation of Patients Admitted to Intensive Care Units	Not CUA
Barrientos-Vega	1997	Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs	Not CUA
Breslow	2004	Effect of a multiple-site intensive care unit telemedicine program on clinical and economic outcomes: An alternative paradigm for intensivist staffing	Not CUA
Cox	2008	An Economic Evaluation of Propofol and Lorazepam for Critically Ill Patients Undergoing Mechanical Ventilation	Not CUA
Desai	2008	Management of Acute Kidney Injury in the Intensive Care Unit	Not CUA
Harrison	2012	Cost-effectiveness of risk-based strategies for antifungal prophylaxis among non-neutropenic, critically ILL adult patients: The fire study	Not CUA

Hop	2015	Cost-Effectiveness of Laser Doppler Imaging in Burn Care in The Netherlands: A Randomized Controlled Trial	Not CUA
Park	2001	Trauma-specific intensive care units can be cost effective and contribute to reduced hospital length of stay	Not CUA
Plant	2003	Cost effectiveness of ward based non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease: economic analysis of randomised controlled trial	Not CUA
Raspall-Chaure	2014	Cost-effectiveness of buccal midazolam in the treatment of prolonged convulsive seizures in the outpatient setting in Spain	Not CUA
Turner	2000	A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma	Not CUA
Scawn	2012	A pilot randomised controlled trial in intensive care patients comparing 7 days' treatment with empirical antibiotics with 2 days' treatment for hospital-acquired infection of unknown origin	Not CUA
Schwebel	2012	Economic evaluation of chlorhexidine-impregnated sponges for preventing catheter-related infections in critically ill adults in the Dressing Study	Not CUA
Wheeler	2005	Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial	Not CUA
Wolf	2014	Prospective multicentre randomised, double-blind, equivalence study comparing clonidine and midazolam as intravenous sedative agents in critically ill children: the SLEEPS (Safety profiLe, Efficacy and Equivalence in Paediatric intensive care Sedation) study	Not CUA
Turunen	2015	Dexmedetomidine versus standard care sedation with propofol or midazolam in intensive care: an economic evaluation	Not CUA
Arora	2013	Trial to Examine Text Message-Based mHealth in Emergency Department Patients With Diabetes (TExT-MED): A Randomized Controlled Trial	Not economic evaluation
Bach	1998	Outcomes and Resource Utilization for Patients with Prolonged Critical Illness Managed by University-based or Community-based Subspecialists	Not economic evaluation
Bologna	1999	Hydrogel/silver ion-coated urinary catheter reduces nosocomial urinary tract infection rates in intensive care unit patients: a multicenter study	Not economic evaluation
Boom	2014	Insulin treatment guided by subcutaneous continuous glucose monitoring compared to frequent point-of-care measurement in critically ill patients: a randomized controlled trial	Not economic evaluation
Cronberg	2015	Neurologic Function and Health-Related Quality of Life in Patients Following Targeted Temperature Management at 33°C vs 36°C After Out-of-Hospital Cardiac Arrest A Randomized Clinical Trial	Not economic evaluation
David	2011	An open-labelled randomized controlled trial comparing costs and clinical outcomes of open endotracheal suctioning with closed endotracheal suctioning in mechanically ventilated medical intensive care patients	Not economic evaluation
Deliberato	2013	Clinical and economic impact of procalcitonin to shorten antimicrobial therapy in septic patients with proven bacterial infection in an intensive care setting.	Not economic evaluation
Denehy	2015	Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up	Not economic evaluation
Doig	2013	Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a full economic analysis of a multicenter randomized controlled trial based on US costs	Not economic evaluation
Finfer	1999	A prospective randomised pilot study of sedation regimens in a general ICU population: a reality-based medicine study	Not economic evaluation
FitzGerald	2000	Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a full economic analysis of a multicenter randomized controlled trial based on US costs	Not economic evaluation

Gastinne	1992	A controlled trial of intensive care units of selective decontamination of the digestive tract with non-absorbable antibiotics	Not economic evaluation
Goodacre	2014	The 3Mg trial: a randomised controlled trial of intravenous or nebulised magnesium sulphate versus placebo in adults with acute severe asthma	Not critical illness
Griffiths	1997	Six-Month Outcome of Critically Ill Patients Given Glutamine-Supplemented Parenteral Nutrition	Not economic evaluation
Henneman	2001	Effect of a collaborative weaning plan on patient outcome in the critical care setting	Not economic evaluation
Jackson	2010	Long-term Cognitive and Psychological Outcomes in the Awakening and Breathing Controlled Trial	Not economic evaluation
Johansen	2010	Predictors of Health Utility among 60-Day Survivors of Acute Kidney Injury in the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study	Not economic evaluation
Kollef	1997	A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation	Not economic evaluation
MacDonald	2011	Quality of Life and Healthcare Resource Use Associated With Angiographic Vasospasm After Aneurysmal Subarachnoid Hemorrhage	Not economic evaluation
Macrae	2014	A clinical and economic evaluation of Control of Hyperglycaemia in Paediatric intensive care (CHiP): a randomised controlled trial	Not economic evaluation
Marasco	2013	Prospective Randomized Controlled Trial of Operative Rib Fixation in Traumatic Flail Chest	Not economic evaluation
McCollam	1999	Continuous infusions of lorazepam, midazolam, and propofol for sedation of the critically ill surgery trauma patient: a prospective, randomized comparison	Not economic evaluation
Muellejans	2006	Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomised, open-label, pharmacoeconomic trial	Not economic evaluation
Nucifora	2009	Effect on Quality of Life of Different Accelerated Diagnostic Protocols for Management of Patients Presenting to the Emergency Department With Acute Chest Pain	Not economic evaluation
Orwelius	2010	Pre-existing disease: the most important factor for health related quality of life long-term after critical illness: a prospective, longitudinal, multicentre trial	Not economic evaluation
Sanchez Garcia	1998	Effectiveness and Cost of Selective Decontamination of the Digestive Tract in Critically Ill Intubated Patients A Randomized, Double-blind, Placebo-controlled, Multicenter Trial	Not economic evaluation
Sherry	1996	An economic evaluation of propofol/fentanyl compared with midazolam/fentanyl on recovery in the ICU following cardiac surgery	Not economic evaluation
Stiell	1998	The Ontario Prehospital Advanced Life Support (OPALS) Study: Rationale and Methodology for Cardiac Arrest Patients	Not economic evaluation
Trouillet	2011	Early Percutaneous Tracheotomy Versus Prolonged Intubation of Mechanically Ventilated Patients After Cardiac Surgery	Not economic evaluation
Walsh	2015	Increased Hospital-Based Physical Rehabilitation and Information Provision After Intensive Care Unit Discharge The RECOVER Randomized Clinical Trial	Not economic evaluation
Wang	2011	Effectiveness of a self-care program in improving symptom distress and quality of life in congestive heart failure patients: a preliminary study	Not economic evaluation
Baharoglu	2016	Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial	Not economic evaluation
Morris	2016	Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure A Randomized Clinical Trial	Not economic evaluation
ARISE Investigators	2014	Goal-Directed Resuscitation for Patients with Early Septic Shock	Not economic evaluation

PROCESS Investigators	2014	A Randomized Trial of Protocol-Based Care for Early Septic Shock	Not economic evaluation
Faux	2014	The ROARI project – Road Accident Acute Rehabilitation Initiative: a randomised clinical trial of two targeted early interventions for road-related trauma	Not economic evaluation
Barbar	2014	Impact on mortality of the timing of renal replacement therapy in patients with severe acute kidney injury in septic shock: the IDEAL-ICU study (initiation of dialysis early versus delayed in the intensive care unit): study protocol for a randomized controlled trial	Protocol paper
Bartels	2013	Design of COSMIC: a randomized, multi-centre controlled trial comparing conservative or early surgical management of incomplete cervical cord syndrome without spinal instability	Protocol paper
Bosch	2013	Implementing evidence-based recommended practices for the management of patients with mild traumatic brain injuries in Australian emergency care departments: study protocol for a cluster randomised controlled trial	Protocol paper
Drennan	2014	Expanding Paramedicine in the Community (EPIC): study protocol for a randomized controlled trial	Protocol paper
Fitzsimmons	2011	Preventative tele-health supported services for early stage chronic obstructive pulmonary disease: a protocol for a pragmatic randomized controlled trial pilot	Protocol paper
Hop	2013	Cost-effectiveness of laser Doppler imaging in burn care in the Netherlands	Protocol paper
Kandarian	2014	STUDY PROTOCOL Open Access Emergency department-initiated palliative care for advanced cancer patients: protocol for a pilot randomized controlled trial	Protocol paper
McAuley	2012	Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction (HARP-2) trial: study protocol for a randomized controlled trial	Protocol paper
Morello	2012	The 6-PACK programme to decrease falls and fall-related injuries in acute hospitals: protocol for an economic evaluation alongside a cluster randomised controlled trial	Protocol paper
Ruijter	2014	Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR): study protocol for a randomized controlled trial	Protocol paper
Sierink	2012	A multicenter, randomized controlled trial of immediate total-body CT scanning in trauma patients (REACT-2)	Protocol paper
Zeller	2014	IN.PACT Amphirion paclitaxel eluting balloon versus standard percutaneous transluminal angioplasty for infrapopliteal revascularization of critical limb ischemia: rationale and protocol for an ongoing randomized controlled trial	Protocol paper
Achten	2016	Protocol for a randomised controlled trial of standard wound management versus negative pressure wound therapy in the treatment of adult patients with an open fracture of the lower limb: UK Wound management of Open Lower Limb Fractures (UK WOLFF)	Protocol paper
Toft	2014	Non-sedation versus sedation with a daily wake-up trial in critically ill patients receiving mechanical ventilation (NONSEDA Trial): study protocol for a randomised controlled trial	Protocol paper
Thompson	2008	A randomized controlled trial of tea tree oil (5%) body wash versus standard body wash to prevent colonization with methicillin-resistant adults: research protocol Staphylococcus aureus (MRSA) in critically ill	Protocol paper
Downing	2015	Cost-effectiveness of the non-pneumatic anti-shock garment (NASG): evidence from a cluster randomized controlled trial in Zambia and Zimbabwe	Used DALYs

Appendix D: Equivalence of assigning same baseline utility weight to treatment and control groups on incremental QALY estimation

Let Y_{A0} , Y_{A1} and Y_{A2} represent 3 measurements of health-related quality of life of individual in treatment arm A at time points 0, 1 and 2, respectively, where measurements at time point 0 represents baseline (randomisation) and time point 2 equals 1 year post randomisation. Let l_1 represent duration of the time interval between the baseline and second time point measurements and l_2 the corresponding value for the interval between the second and third (final) measurements. Using the area under the curve approach [1] the total QALY accrued over the 1 year follow-up period is given by:

$$QALY_A = \frac{(Y_{A0} + Y_{A1})l_1}{2} + \frac{(Y_{A1} + Y_{A2})l_2}{2} \quad (1)$$

Using the same formulation as above, the corresponding QALY estimate in treatment group B is given by

$$QALY_B = \frac{(Y_{B0} + Y_{B1})l_1}{2} + \frac{(Y_{B1} + Y_{B2})l_2}{2} \quad (2)$$

The incremental QALYs between the two groups is

$$\Delta QALY_1 = QALY_B - QALY_A \quad (3)$$

$$\Delta QALY_1 = \frac{1}{2} [(Y_{B0} - Y_{A0})l_1 + (Y_{B1} - Y_{A1})l_1 + (Y_{B1} - Y_{A1})l_2 + (Y_{B2} - Y_{A2})l_2] \quad (4)$$

Setting the baseline health-related quality of life to be same for the treatment group A and B implies assumption $Y_{B0} = Y_{A0}$ and therefore:

$$\Delta QALY_1 = \frac{1}{2} [(Y_{B1} - Y_{A1})l_1 + (Y_{B1} - Y_{A1})l_2 + (Y_{B2} - Y_{A2})l_2] \quad (5)$$

Hence it does not matter what value the baseline utility value takes as this cancels out in the final estimate of the incremental QALYs.

Appendix E: Bias associated with ignoring baseline utility weight on incremental QALY estimation

For treatment A is $QALY_A = \frac{(Y_{A1} + Y_{A2})l_2}{2}$ and for treatment B is $QALY_B = \frac{(Y_{B1} + Y_{B2})l_2}{2}$ so that the incremental QALYs is given by:

$$\Delta QALY2 = \frac{1}{2} [(Y_{B1} + Y_{B2})l_2 - (Y_{A1} + Y_{A2})l_2] \quad (6)$$

$$\Delta QALY2 = \frac{1}{2} [(Y_{B1} - Y_{A1})l_2 + (Y_{B2} - Y_{A2})l_2] \quad (7)$$

The bias associated with not incorporating baseline health-related quality of life in the final estimates of incremental QALYs is given by:

$$\begin{aligned} \Delta QALY1 - \Delta QALY2 &= \frac{1}{2} [(Y_{B1} - Y_{A1})l_1 + (Y_{B1} - Y_{A1})l_2 + (Y_{B2} - Y_{A2})l_2] - \frac{1}{2} [(Y_{B1} - Y_{A1})l_2 + (Y_{B2} - Y_{A2})l_2] \\ \Delta QALY1 - \Delta QALY2 &= \frac{1}{2} (Y_{B1} - Y_{A1})l_1 \end{aligned} \quad (8)$$

Equation (8) implies that the magnitude of the bias is proportional to the difference between estimates of health-related quality of life at time point 1 and duration of the time interval l_1 (i.e. the time interval between the baseline measurement and first follow-up measurement).

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