ABSTRACT

Objective The aims of the study were to examine current reporting standards of health state utilities (HSU) using a review of published cost-effectiveness analyses in cardiovascular disease and to explore the impact of variation in model inputs used in these on estimated quality adjusted life years (QALYs) and cost-effectiveness.

Method Key health /economics bibliographic databases were searched to identify relevant articles published after 2014. Any narrative and values relating to the HSU used in the model were extracted and reviewed. The HSUs were systematically applied to an existing model to explore the influence of different values on QALYs and incremental cost-effectiveness ratio (ICER).

Results 24 peer reviewed articles were identified. Only two studies referred to a literature review for the HSUs. The majority (18/24) referenced previously published economic studies (as opposed to the original source) for at least one of the HSUs. Only four studies referenced the original sources and reported all the HSUs accurately, and several did not provide all the HSUs. Little information was provided on methods used to calculate QALYs. For example, the duration of time for acute HSUs, what the baseline HSU was, the method that was used to assign HSUs for subsequent different events, or how constant HSUs for clinical events were combined with age-adjusted baseline values. The huge differences in HSUs used in the studies produced substantial variations in the QALYs and ICERs generated from the cost-effectiveness model.

Conclusion Current standards are poor and there is a need for greater transparency in reporting the HSUs used in cost-effectiveness models.

Introduction

Agencies throughout the world produce national guidance on the provision of new health technologies using results generated from cost-effectiveness models to inform the allocation of health care resources[1]. Many policy decision makers now prefer that results generated by these models are presented as a cost per quality adjusted life year (QALY), where the health related quality of life (HRQoL) is calculated using heath state utilities (HSU) derived from preference studies[2-3]. The use of the QALY ensures that the results generated from these models can be compared across disparate conditions and interventions. However, inconsistencies and discrepancies in the methodologies used when selecting and applying HSUs in these models could produce sub-optimal allocation of resources which undermines the aim for consistent decision making.

Different samples and estimation methods produce incomparable HSUs, even when obtained from the patients with the same health condition at the same point in time[4-5], and a QALY generated using evidence obtained from one measure is not equivalent to a QALY generated using evidence obtained from another measure. Even evidence collected using the same measure in the same sample can produce different HSUs depending on the specific country preference-weights that are applied. Consequently, for internal consistency and comparability with other evaluations, it is self-evident that all health states within a single model should be informed by HSUs generated from the same measure using the same source of preference weights when possible. There will always be exceptions to this, for example it may be challenging to capture the utility effects for acute or rare adverse events within the main study but this does not imply that the use of evidence from a quick vignette study is appropriate and factors such as whether a specific HSU influences the ICER should be considered. Combining evidence obtained from different sources in an ad hoc manner is unjustifiable, and the results from cost-effectiveness models may not be directly comparable[5].

Historically, analysts have often struggled to identify preference-based utility data and have simply referenced values used in previous models, or have used values with no transparency or justification of choice. However, the evidence base in this area has increased substantially over recent years and it is

no longer appropriate to use dated evidence simply because it has been accepted in a previous evaluation or is known to the author. Increasingly analysts may be forced with a choice of different values and analysts should treat this form of evidence as they would any other and undertake a review of the literature to avoid the suspicion of 'cherry picking'.

The primary aim of this project was to review the reporting standards associated with the HSUs used in recently published cost-effectiveness analyses and to explore the impact of variation in model inputs on estimates of QALYs and incremental cost per QALY. More specifically this review identifies previous models in cardiovascular disease (CVD) primary and secondary prevention. The HSUs from these models were then harvested and systematically applied to an existing model (developed to assess the cost-effectiveness of lipid lowering interventions[6]) to explore the influence of different utilities on QALYs and ICER estimates. A case study in CVD was used because this enabled us to explore many of the issues frequently encountered when using HSUs in cost-effectiveness models. For example, pharmaceutical interventions can be offered as prophylactic treatment or secondary prevention thus patients can enter the model either in a CVD free health state or in a health state representing patients with a history of cardiovascular disease respectively. These two analyses will require different 'baseline' HSUs for patients entering the model. CVD models generally comprise of multiple health states describing clinical events such as angina, heart attack, or stroke. The HSUs associated with these may vary over time, representing the short acute phase of the clinical event and the chronic follow-on period when HRQoL may improve. In addition, as a history of CVD increases the risk of other CVD events (e.g. a person with a history of stroke is at increased risk of having a myocardial infarction (MI)) the combined effect on HRQoL associated with these sequelae or comorbidities should be captured.

Method

Search strategy

Key health /economics bibliographic databases (Medline and Medline in process via Ovid SP, Embase via Ovid SP, Econ Lit via Ovid SP, NHS EED via Wiley) were searched using free text and subject

heading terms (e.g. MeSH). Terms for lipid lowering interventions (e.g. CETP inhibitors) were combined with terms for cardiovascular disease (e.g. ischaemic heart disease) and cost-effectiveness models (e.g. quality adjusted life-year). The search was conducted during July 2017 and was limited to articles published after 2014 as we were interested in reporting standards in recently published manuscripts. An example search strategy and list of data sources is provided (online materials).

Review and data extraction

Titles and abstracts were reviewed against the pre-determined inclusion and exclusion criteria (online appendix) by one reviewer, while a second reviewer checked a random sample. The full text of all articles provisionally accepted on the title and abstract screen were then examined. The bibliographies of the articles selected for the review were examined to identify any relevant additional studies. For the studies that satisfied the inclusion criteria, data (author, year, setting, intervention(s), model type, health states, health state utility values, relevant references for the HSUs reported to be used, any narrative directly associated with the HSUs sources or their use in the model) were extracted by one reviewer and checked by a second. The HSUs were checked against the cited source to determine: a) if the cited source was the original source of the HSUs (e.g., if the cited source was found to cite an earlier article for a specific HSU, the full text of the earlier article was retrieved and reviewed). This form of backward tracking was undertaken until the original source of the specific HSU was identified. b) if the values in the included article matched those in the original source, c) the actual preference-based measure(s) used to obtain the HSUs (e.g. indirect such as EQ-5D, or direct such as time-trade off (TTO)), and d) the setting of preference weights if applicable (e.g. UK based tariff for the EQ-5D[7]). Any narrative relating to the application of the HSUs was reviewed including the baseline values (the health state that patients enter the model – for primary prevention this is likely to be defined as 'event free', 'healthy' or 'no history of CVD'; for secondary prevention this is likely to be a health state defined as 'history of CVD', or history of a specific CVD event type such as 'previous MI'), the duration of effect (to account for any acute versus chronic period), any adjustments made (e.g. the HSU associated with the comorbid health state MI in patients with a history of stroke).

Case study

An existing peer-reviewed cohort (n=1,000) Markov model was utilised to explore the implications of using the actual HSUs and methods reported in the articles included in the review. The model was initially constructed to explore the cost-effectiveness of a lipid lowering intervention (compared to standard care) for both primary and secondary prevention[6]. The model includes non-fatal health states representing patients who have no history of CVD (primary prevention), the acute or chronic stages of the CV events (angina, MI, stroke), and two absorbing health states representing death (either CV events or from other causes). For primary prevention, patients enter the model in the CVD free health state, whereas for secondary prevention, patients are distributed across the three 'chronic' CVD health states using age and gender adjusted prevalence data. Annual probabilities of initial and subsequent events are applied using age-adjusted risks. Costs and benefits are discounted at 3.5% and half cycle correction is used to assess the cost and benefits accrued over a lifetime (up to age 100). The potential disutility associated with medication was not modelled explicitly in this model as it was assumed that patients withdrew from treatment (high dose or lower dose statin) if they experienced an adverse reaction, and a series of analyses were undertaken to examine the economic implications of different levels of adherence. A detailed description of the model is published elsewhere and a diagram is provided in the online material[6].

The HSUs reported in the studies included in this review were input into the model using the methods described by the authors (online materials). All other parameters remained unchanged. Data from studies that reported HSUs representing at least two different cardiovascular events from the three included in the case-study model were used. For studies that did not report HSUs for angina, the HSU they reported for MI was used. If only one HSU was reported for a particular event, this was used for both the initial acute and corresponding chronic health state. The method described to account for any additional decrement due to sequelae (e.g., an MI following a stroke) was replicated. If this information was missing, it was assumed the analyst had applied no additional detriment and the HSU reported for a particular health state was retained irrespective of history. Deterministic ICERs were generated for

cohorts of 1,000 patients entering the model at the age of 45, or 75 years. Full probabilistic analyses were not generated as the information reported in the articles was insufficiently detailed to replicate the approaches taken.

Results of the literature review

A total of 24 studies were included in the review (Table 1)[8-31]. Half of the studies were set in the US (N=12), and a third in Europe (N=8). The balance were set in Iran (N=2)[10-11], Singapore (N=1)[25], and Brazil (N=1)[28]. While the majority compared lipid lowering interventions, two assessed the cost-effectiveness of screening mechanisms[15,29], and one assessed the effect of risk stratification[18]. The treatment strategies were for primary prevention (N=10), secondary prevention (N=7), both primary and secondary prevention (N=3)[23-24,28], both primary and secondary in populations with heterozygous familial hypercholesterolemia (N=3)[15,19,23], and in patients with chronic kidney disease (N=1)[26]. The vast majority of studies reported using a Markov model (N=20/24) with an annual cycle. Costs and benefits were extrapolated over a lifetime horizon in almost three-quarters (N=17/23) of the studies, although some used shorter horizons of 5 years (N=3)[22,26,30], 10 years (N=3)[8,13] and 30 years[18].

INSERT TABLE 1

Reporting standards

Literature review

Only two of the studies referred to a literature review in reference to HSUs. One conducted a systematic search of the literature to identify appropriate HSUs but limited details were provided[14]. The second stated their evidence was based on the results of the former review[13]. The vast majority of studies provided no description of the heath condition of the patients the HSUs were obtained from. None of the studies reported all basic details of the original source of the HSUs that are required to enable the reader to judge the appropriateness of the evidence (e.g. study type, patient characteristics (e.g. age, sex, comorbidities, diagnosis, condition severity), time since event/time of data collection, preference

measure used, completer of measure, the appropriateness of the measure for the population, sample size, missing data (or loss to follow-up), mean and uncertainty.

Original source of HSUs

Three quarters of the studies (18/24) referenced previously published economic studies as opposed to the original source for at least one of the HSUs. Only six of the studies referenced the original sources for all the HSUs[12,19,25,27,28,31]. Three iterations were required to obtain the original sources for almost a third of the studies[10,11,13,14,22,24,30] and over half of the studies utilised evidence collected in the 1990s[9,10,11,13,14,15,16,18,21,26,27,29,30].

Just four studies reported all the HSUs accurately when compared to the values in the original source studies[16,19,25,27]. For the remaining twenty studies, at least some of the reported HSUs could not be found in the referenced studies or the original source studies; or, the original source could not be identified due to incorrect referencing[18,20,21,22,24].

Preference based measures

Half (12/24) of the studies did not mention the measure (e.g. EQ-5D) or method (TTO/clinical judgement) used to obtain the HSUs[9,10,11,13,14,18,22,24,26,28,29,30]. Of the remaining studies, just six mentioned the measure or method used for all the HSUs[12,16,21,23,25,27]. Several authors stated they used data obtained from the EQ-5D but, some of their HSUs was obtained from the 15D[8], TTO studies[15,17], or were disability weights/lifeyears[20,22,31].

It was not possible to determine all the measure(s) or methods used to collect the HSUs in several of the studies even when tracing the original source studies[13,14,17,22,26]. For example, one referenced a source reporting evidence collected from the SF-36 and the WHOQOL but there were no HSUs in the article[28]. Only two of the studies used evidence obtained from the same measure for all the HSUs[12,16]. The remaining studies used HSUs obtained from two[8,10,11,15,19,23,29,30,31] or more[9,17,18,21,25,27] different measures and methods.

HSUs used for baseline and clinical events

It was unclear what baseline HSUs were used in several of the studies due to lack of detail. For the primary prevention strategies (i.e. patients enter the model with no history of CVD), seven studies used age-adjusted HSUs for the health state 'healthy/no history of CVD'[8,10,11,16,17,23,29] while six assumed the baseline HSU was full health (e.g. EQ-5D=1) irrespective of age[18,22,24,25,27,30]. Of those using age-adjusted data, the actual HSUs used were not provided in four of the studies[10,11,16,23]. For the secondary prevention analyses (i.e. patients enter the model with a history of CVD), the baseline HSU for patients with a history of CVD was constant (range: 0.76 to 0.85)[14,21] in all the studies where it was possible to determine what data were used. The two studies assessing interventions in patients with a history of heterozygous familial hypercholesterolemia (HeFH) or CVD used constant baseline values of 0.824[19] and 0.996[15].

Comparing across all studies, the HSUs reported for the CV events covered a very broad range. For example, angina first year HSUs ranged from 0.63[12] to 0.8351[29], MI first year HSUs ranged from 0.58[12] to 0.8351[29], and stroke first year HSUs ranged from 0.327[19] to 0.8272[29]. Approximately half of the studies modelled different HSUs for the acute (<1 year) and chronic (≥2 year) periods following events and there was substantial differences in the HSUs assigned for the chronic periods: angina ranged from 0.68[15] to 0.9064[22], MI ranged from 0.68[15] to 0.9648[22], and stroke ranged from 0.39[9] to 0.8835[22].

It is possible that patients may experience an MI after they have earlier had a stroke. Markov models do not retain history of events and as the HSU for MI is greater than that for stroke, unless this is taken into account, patients will experience an increase in QOL within the model. However, not all the studies provided information on how this was handled within the model. Two reported they used the minimum method (i.e. used the smallest HSU of stroke and MI and thus ignored any additional decrement due to the comorbidity)[19,27]. One reported the HSUs for MI and stroke were multiplied together[21]. One provided a HSU for the chronic period for patients who experienced two or more events within the same

year but did not explain how the acute period was modelled[31]. Two provided a single HSU for a subsequent different event but neither explained how the acute period was modelled[22,30].

In addition to the HSUs extracted (see online materials), several of the studies reported they assigned an additional burden on HSUs to account for the disutility of taking medication, or treatment related adverse events. However, the methodology used (e.g., duration of decrement or method used to combine with other HSUs) was not described clearly in these studies[15,17,18,20,22,25,26,27,29,30], and the original source data was sometimes based on clinical judgement[18,25,29].

Uncertainty

Uncertainty around the HSUs was explored in most of the studies and the vast majority used Beta distributions to characterize the uncertainty in the mean, although insufficient details were provided to replicate this. Several authors reported the model results were sensitive to variations in HSUs used in univariate sensitivity analyses[14,15,16,17,25].

Implications of the different health state utility values associated with avoiding a single event

The implications of the differences in the HSUs used for the baseline and the individual events was explored by generating the absolute and incremental QALYs accrued over a lifetime (50 years) for a single event occurring at the age of 45 years (Table 2). For primary prevention, the baseline values represent individuals who have no history of CVD and remain event free, while in the secondary analyses, the baseline values represent individuals who have a history of CVD. The total QALYs accrued for remaining in this health state for primary prevention range from 40.00 for an analysis using a HSU of 0.80[28], to 50.00 for those that assume HSUs are equal to full health irrespective of age[25,27,30]. For secondary prevention, they range from 39.00[31] when using a HSU of 0.78, to 50.00 when assuming the HSUs are equal to full health irrespective of age[22]. There are also substantial differences in the QALYs accrued for the individual CV events. For example, QALYs accrued when experiencing a non-fatal stroke and remaining in that health state range from 26.00 (HSU: 0.327 acute, 0.524 chronic[19]) to 44.16 (initial decrement of 0.0113, 0.8835 chronic[22]).

The ranges in incremental QALYs associated with avoiding these events vary substantially. For example, the incremental QALYs accrued for avoiding an MI range from 0.08[13] to 15.80[15]. The large difference is due to the fact that for the latter, Chen et al use one of the highest HSU for the baseline (0.996) and apply one of the lowest HSU for MI (0.68 for both the acute and chronic periods). The potential incremental QALY gains demonstrate that the HSUs used for the baseline and the events are equally important. For example, although Kazi et al. apply relatively small disutilities for the CV events for the acute periods, as they assume full health for the baseline and apply relatively large disutilities for the chronic period, the incremental QALY gain associated with avoiding events are relatively large compared to the other studies. Looking at the secondary prevention analyses, although Stam-Slob et al accrue the least QALYs for the baseline (39 QALYs[31]), as they have the smallest HSU for MI (0.65), the difference between the baseline and MI HSUs produce the largest potential gain for avoiding an MI (6.50). Conversely their potential gain from stroke is one of the lowest at 7.00 QALY.

INSERT TABLE 2

Results from the cohort (1,000 patients) cost-effectiveness model

Fifteen studies provided data for at least two of the CV events in the case-study model and the reported HSUs and methods were used to generate seven results for primary prevention and eight results for secondary prevention. The discounted incremental QALY gains (Figure 1) and the corresponding lifetime ICERs (Figure 2) were generated for cohorts of 1,000 patients entering the model with no history of CVD at the age of either 45 or 75 years. Similar results were generated for the studies assessing secondary prevention (Figure 3-4).

For the primary prevention analyses, commencing treatment at the age of 45 years, the discounted incremental QALYs ranged from 211[15] to 308[25] (Figure 1), and the corresponding ICERs ranged from

£28.0k to £19.2k respectively (Figure 2). Commencing treatment at the age of 75 years, the discounted incremental QALYs ranged from 67[15] to 104[25], and the corresponding ICERs ranged from £40.2k to £25.9k respectively.

The baseline HSUs influence the results and the three analyses using a baseline of full health (e.g. EQ-5D = 1) have comparable ICERs (c£20k at age 45; c£26k at age 75)[25,27,30]. These results are not surprising as the HSUs used for the events are comparable, thus incremental QALY gain and ICERs would be expected to be similar. These ICERs are lower than those for the analyses that do not use a baseline of full health (age 45 ICERs>£25k, age 75 ICERs>£32k) as the potential QALY gain due to avoiding events is substantially lower for those. While there is not a great deal of difference in the ICERs for the aged 45 year analyses not using full health as the baseline (£25k<ICER<£28k), there is greater variation for the cohorts aged 75 years (£32k<ICER<£40k). In the older cohort, the model is more sensitive to the absolute HSUs used for the events as there is less time to accrue the QALYs associated with events avoided[15,17,19,23,28,29].

The results for the secondary prevention range from 242 to 307 incremental QALYs for cohorts aged 45 years, and from 121 to 151 incremental QALYs for cohorts aged 75 years (Figure 3-4). The corresponding ICERs range from £19.9k to £25.3k and from £16.6k to £20.7k for cohorts aged 45 and 75 years respectively. As in the primary prevention analyses, the ICER generated using a baseline of full health is lower than those generated using lower baseline values irrespective of age[22].

INSERT FIGURES 1-4

DISCUSSION

This study has served two purposes. At one level the review highlights the importance of differences in model inputs on the overall cost effectiveness of an intervention in CVD. The figures show how sensitive a model can be to differences in HSUs. While it is likely that the confidence intervals of the ICERs would overlap for some results (if we had been able to undertake PsA), the observed differences

in the deterministic results suggest that this would not be the case for all. These results reinforce the importance of robust and transparent methods for the selection, appraisal and possibly synthesis of this evidence. This is particularly marked in a disease area like CVD where the impact of CV events can be experienced for months and years. The implications of this study will be very relevant for other chronic diseases.

It is clear that the baseline utility will have a large effect on the ICER and we recommend that decision makers pay specific attention to the quality or appropriateness of these values. We recommend it is impossible to justify the use of full health (i.e. 1.0) as a baseline in the absence of other data. It is also clear that special attention needs to be paid to instances where patients can experience multiple clinical events (e.g. an MI and a stroke), especially when Markov style models are used. In the absence of data the modelling team should consider the influence of different approaches to combining the effects. Clearly also for certain events (e.g., stroke) there is huge variation in their impact on HRQL and it's important not to simply select one value without justification. Utility data graded by clinical markers (e.g. modified Rankin scale in stroke) may help ensure data are more representative.

The review has highlighted some significant problems regarding how HSUs are incorporated into different models in the same clinical area. There are very large discrepancies between the estimates for the same health states. There are also substantial differences between estimates for baseline states with some models simply assuming that everyone at baseline is in a state of full health. The most concerning finding is that of the 24 studies that were reviewed only four accurately and consistently referenced the source material. Twenty of the studies failed to correctly reference and cite the values used in the model. The study has highlighted examples of very poor practice in the reporting of model inputs. In addition to this, several of the models also reported adjustments to utilities related to issues such as mode of administration, or the effect of taking daily medications, where the adjustments were based on no empirical data.

These results support the need for greater transparency in reporting standards. Researchers need to be systematic in their selection of model inputs from the literature and where multiple values are available then model developers can consider the use of evidence synthesis. These methods are described in the recent ISPOR TF report on sourcing utilities[32]. In developing this guidance paper, it became apparent that there are a large number of issues to be considered and even in this focused TF report there was insufficient room to go into detail on everything. This suggests that the methodological area is still somewhat under-developed and more work is needed. HSUs are important model inputs, and as this study highlights can have a very substantial effect on the model results.

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