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Populating an economic model with health state utility values: moving towards better practice

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Populating an economic model with health state utility values: moving towards better practice

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ABSTRACT

Background: When estimating health state utility values (HSUV) for multiple health conditions, the alternative models used to combine these data can produce very different values. Results generated using a baseline of perfect health are not comparable with those generated using a baseline adjusted for not having the health condition taking into account age and gender. Despite this, there is no guidance on the preferred techniques that should be used and very little research describing the effect on cost per QALY results.

Methods: Using a cardiovascular disease (CVD) model and cost per QALY thresholds, we assess the consequence of using different baseline health state utility profiles (perfect health, individuals with no history of CVD, general population) in conjunction with three models (minimum, additive, multiplicative) frequently used to estimate proxy scores for multiple health conditions.

Results: Assuming a baseline of perfect health ignores the natural decline in quality of life associated with co-morbidities, over-estimating the benefits of treatment to such an extent it could potentially influence a threshold policy decision. The minimum model biases results in favour of younger aged cohorts while the additive and multiplicative technique produced similar results.

Although further research in additional health conditions is required to support our findings, this pilot study highlights the urgent need for analysts to conform to an agreed reference case and provides initial recommendations for better practice. We demonstrate that in CVD, if data are not available from individuals without the health condition, HSUVs from the general population provide a reasonable approximation.

INTRODUCTION

A number of agencies, including the National Institute for Health and Clinical Excellence (NICE), require economic evidence to be presented in the form of cost-effectiveness analyses whereby health benefits are quantified by quality adjusted life years (QALYs).[1] QALYs are calculated by summing the time spent in a health state weighted by the health state utility value (HSUV) associated with the health state thus incorporating both length of survival and HSUVs into a single metric. Classification systems can produce a wide range of values for the same health state and the economic results generated using different systems are not always comparable.[1] Consequently, for submissions in the UK, the Institute advocate a preference for EQ-5D data with HSUVs obtained using UK population weights when available.[1]

However, this is not sufficient to ensure consistency across appraisals, as there is no guidance on appropriate baseline HSUVs.[1] If a baseline utility of perfect health (i.e. EQ-5D equals 1) is used to represent the absence of a health condition, the incremental QALYs gained by an intervention are inflated[2] and the results obtained using a baseline of perfect health are not comparable with those obtained when the baseline is adjusted for not having a particular health condition.[3] There is currently no consensus on baseline HSUVs used in economic evaluations.

In addition, there is currently no directive on the method that should be used to combine HSUVs for multiple health conditions. Analysts are increasingly exploring the benefits of interventions in individuals with several co-morbid conditions. For example, HMG-CoA reductase inhibitors (statins) reduce both cardiovascular (CV) risk and rheumatoid arthritis (RA) disease activity and an economic model exploring the benefits of statins in this population would include health states for patients with a history of both RA and cardiovascular disease.[4] Due to strict exclusion criteria preventing patients with co-morbidities entering clinical trials, it is unlikely that HSUVs will be available from patients with both health conditions.

When HSUVs for the multiple health states are not available, proxy scores are estimated by combining data collected from patients with the individual health conditions. Three methods are frequently used:

a) additive, b) multiplicative and c) minimum models. The additive and multiplicative models assume a constant absolute or proportional effect respectively while the minimum model applies a disutility that can vary depending on the baseline utility modelled. Research exploring the appropriateness of the techniques used to combine utility values is inconclusive. The additive and multiplicative models have been shown to produce similar results for individuals with both diabetes and thyroiditis;[5] the multiplicative model produced accurate utilities for several other co-morbid conditions;[6] and the minimum model was advocated as the preferred methodology in two other studies.[7-8]

While literature describing minimum requirements for probabilistic analyses is growing,[9] research exploring the basic principles involved in using HSUVs in economic models, and the implications for results generated from the models when using different techniques is scarce. The limited research undertaken in this area has explored the appropriateness of different baseline utilities and proxy HSUVs for multiple health conditions in isolation and there is currently no consensus on the preferred methodologies when the two adjustments are undertaken together.

We describe the results of a pilot study in which we explore the effect of using different baseline utility values and different techniques to estimate proxy HSUVs for multiple health conditions in combination. We use an existing economic model and data from the Health Survey for England to investigate the potential effect on policy decision making using cost per QALY thresholds. The primary objective of the study is to instigate additional research in this area to provide a foundation for better practice in economic evaluations used to inform health care decision makers in the UK and elsewhere.

METHODS

The following section provides a brief description of the economic model and a synopsis of the data used.

Cardiovascular model

An existing peer-reviewed Markov model[10] was modified slightly so the health states (Figure 1) matched the definitions of three cardiovascular conditions available from the Health Survey for

England which are angina (A), heart attack (HA) and stroke (Str).[10-11] An annual cycle is used for transitions between health states. Individuals enter the model in the event free health state (EF) and can move to a primary health state: angina (A), non-fatal heart attack (HA), or non-fatal stroke (Str), or remain in the EF health state. Individuals in the primary and post-event health states can move to a subsequent health state: subsequent angina (SA), subsequent non-fatal HA (SHA), subsequent non-fatal stroke (SStr); or remain in the primary or post-event health state. In each cycle all individuals are at risk of death through other causes (DoC), or fatal CVD (fCVD). Health state costs are taken from a recent HTA evaluation of lipid treatments in the UK.[10]

INSERT FIGURE 1: Health states in cardiovascular model

Health Survey for England

The Health Survey for England (HSE) is conducted annually using random samples of the population living in private households in England. The 2003 and 2006 surveys included questions about history of CVD and a random sample of participants (aged 16 to 98 years) were asked to complete the EQ-5D questionnaire (N=26,679).[11-12] These data were used to estimate preference-based HSUVs using the weights obtained (based on time trade off valuations) from the UK general public.[13]

INSERT TABLE 1: EQ-5D scores sub-grouped by health condition and time since event

We assumed that the data from individuals who reported a history of just one CV condition are representative of the HSUVs of individuals who have a first ever primary CV event; and that data from individuals who reported a history of more than one CV condition are representative of the HSUVs of individuals who have a subsequent event (Table 1). For example, the mean HSUV during the first 12 months after experiencing a primary (secondary) heart attack is 0.721 (0.431) and the corresponding mean HSUV for time periods after this is 0.742 (0.685).

The relationship between HSUVs, age, sex and history of CVD was explored using ordinary least square regressions. Model 1 (EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2, Figure 1) can be used to estimate the mean HSUVs for individuals in the general population and Model 2 (EQ-5D = 0.9454933 + 0.0256466*male - 0.0002213*age - 0.0000294*age^2, Figure 2) can be used to estimate the HSUVs for individuals with no history of CVD.[14]

INSERT Figure 2: Baseline utility for the event free health state: Relationship between HSUVs, age, sex and history of CVD

ANALYSES

The following section describes a worked example demonstrating the difference in incremental QALYs gained from avoiding a single event when using different baseline HSUV profiles, followed by results generated from the economic model demonstrating the potential effect on a policy decision using a cost per QALY threshold when using the different baseline HSUV profiles. We then provide a worked example using the three alternative models to estimate proxy scores for multiple health conditions, looking at the difference in incremental QALYs associated with avoiding a single event, followed by results generated from the economic model when combining the different baseline profiles and the techniques used to combine the utility data.

Baseline HSUV profiles

In a CV model, individuals who are at high risk of a CV event and have no prior history of CVD typically enter the model in an "event free" health state. The HSUV profile associated with this health state is then used as the baseline to estimate the health benefits accrued through avoiding CV events. Ideally, the health profile for the event free health state would be derived from long term registry data and would represent the HSUVs for individuals who are at high risk of a primary CV event but who have no existing history of CVD. In the absence of these data, analysts assume the baseline HSUV profile is either a) equal to perfect health (i.e. EQ-5D = 1 irrespective of age or gender), b) equal to the profile of HSUVs from the general population adjusted for age and gender (i.e. all individuals

irrespective of history of CVD), or c) equal to the profile of HSUVs from individuals with no history of CVD.

In the following example (Box 1), we illustrate the difference in QALYs accrued from avoiding a single event using the three alternative baseline HSUV profiles for the event free health state. The HSUV profile when assuming a baseline of perfect health (U^{PH}_{EF}) is constant at EQ-5D = 1. The HSUV profile when assuming a baseline from the individuals with no history of CVD (U^{NCV}_{EF}) is calculated using Model 2 and the HSUV profile when assuming a baseline from the general population (U^{GP}_{EF}) is calculated using Model 1 (Figure 1). The mean EQ-5D score for individuals who reported experiencing angina within the previous 12 months (U_A) is 0.6148 and the mean age for this subgroup is 68.8 years (Table 1). We assume the event occurs at the age of 50 years and examine the cumulative and incremental QALYs accrued over a 50 year time horizon. For the examples using the age-adjusted baseline profiles, the data for the individual health conditions are combined multiplicatively (see Box 2 for more details on this technique).

The cumulative QALYs for the event free health state are calculated by summing the life years weighted by the HSUV profile across the 50 year period (Cumulative $QALY^{PH}_{EF}$ =50*1, Cumulative $QALY^{NCV}_{EF} = \sum_{50 \le age \le 99} \text{Model } 2 = 39.27$, Cumulative $QALY^{GP}_{EF} = \sum_{50 \le age \le 99} \text{Model } 1 = 30.74$. The cumulative QALYs for angina are calculated by summing the life years weighted by the baseline profile multiplied by the multiplier associated with angina (Cumulative $QALY^{PH}_{A}$ =50*1*0.6148 =30.74, Cumulative $QALY^{NCV}_{A} = \sum_{50 \le age \le 99} \text{Model } 2 * 0.753 = 29.56$, Cumulative $QALY^{GP}_{A} = \sum_{50 \le age \le 99} \text{Model } 1 * 0.771 = 29.37$. The incremental QALYs associated with avoiding angina is calculated as the difference between the total cumulative QALYs for the event free health state minus the total incremental QALYs for angina (Cumulative $QALY^{i}_{EF}$ - Cumulative $QALY_A$). The technique used to obtain the multipliers is described in the next worked example.

Box 1: Comparing the incremental QALY gain from a single event when using different baseline HSUV profiles

Let $U^{PH}_{EF} = 1$

$U^{NCV}_{EF} = 0.9454933 + 0.0256466 * male - 0.0002213 * age - 0.0000294 * age^2$

$U^{GP}_{EF} = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$

$U_A = 0.6148$ (mean age = 68.8 years)

Where U^i_j = HSUV, and i = baseline: *PH* = perfect health

NCV = no history of CVD (regression Model 2)

GP = general population (regression Model 1)

j = health state: *EF* = event free, *A* = angina

multiplier for angina for U^{NCV}: male = 0.753 (= 0.6148/0.8167)

multiplier[#] for angina for U^{GP}: male = 0.771 (= 0.6148/0.7973)

([#] see example 2 for method used to obtain multipliers)

Results when assuming a baseline HSUV profile of full health:

Cumulative $QALY^{PH}_{EF} = 50$,

Cumulative $QALY^{PH}_{A} = 30.74$

Incremental $QALY^{PH} = QALY^{PH}_{EF} - QALY^{PH}_{A} = 19.26$

Results when using a baseline HSUV profile from individuals with no history of CVD:

Cumulative $QALY^{NCV}_{EF} = 39.27$

Cumulative $QALY^{NCV}_{A} = 29.56$

Incremental $QALY^{NCV} = QALY^{NCV}_{EF} - QALY^{NCV}_{A} = 9.71$

Results when assuming a baseline HSUV profile from the general population:

Cumulative $QALY^{GP}_{EF} = 38.08$

Cumulative $QALY^{GP}_{A} = 29.37$

Incremental $QALY^{GP} = QALY^{GP}_{EF} - QALY^{GP}_{A} = 8.71$

Comparing results when using different baseline HSUV profiles for the event free health state

For a male, the cumulative QALYs (Box 1) associated with remaining in the event free health state range from 38.1 when using a baseline HSUV profile from the general population to 50 when using a baseline HSUV profile of perfect health; and the cumulative QALYs associated with angina range from

29.4 when using a baseline HSUV profile from the general population to 30.7 when using a baseline HSUV profile of perfect health. The incremental QALY gain associated with avoiding angina range from 8.71 when using a baseline HSUV profile from the general population to 19.26 when using a baseline HSUV profile of perfect health. The incremental QALYs obtained using the baseline HSUV profile from the general population are comparable to those obtained when using the baseline HSUV profile from individuals with no history of CVD (8.71 versus 9.71).

Looking at the QALY gain associated with avoiding a single heart attack or a stroke (Table 2), the values obtained when assuming a baseline HSUV profile of perfect health are substantially higher than those obtained using the age adjusted data. Again the QALY gain obtained using the baseline HSUV profile from the general population are comparable to those obtained using the baseline HSUV profile from individuals with no history of CVD (heart attack: 4.30 versus 5.18; stroke: 8.33 versus 9.30).

INSERT TABLE 2: Cumulative and incremental QALYS associated with a single event using different baseline HSUV profiles

Cost per QALY results using different baseline HSUV profiles for the event free health state

The three alternative baseline profiles were applied in the CVD model and used to assess the lifetime benefits associated with avoiding primary events for cohorts of differing ages (Table 3). The results from the worked example show the benefits associated with avoiding a single event are considerably larger when using a baseline of perfect health compared to adjusting the baseline. When examining the effect on the results generated from the model, the cost per QALY obtained using a baseline of perfect health (Figure 3) is substantially lower than the corresponding results obtained using the age-adjusted profiles, particularly for the older aged cohorts. If a threshold of £20,000 per QALY is applied (Figure 3), using a baseline of perfect health could potentially induce a different policy decision than the one based on results generated when using a baseline HSUV profile that is adjusted for not having the health condition.

INSERT Table 3: Results generated from CVD model using the three alternative baseline profiles

INSERT Figure 3: Comparing the results generated from the CVD model using the three alternative baseline profiles

Estimating proxy HSUV for multiple health conditions

In the following example (Box 2) we use data from individuals who have a history of angina and no other CV condition (U_A) and data from individuals who have a history of a heart attack and no other CV condition (U_{HA}) to estimate a HSUV for the multiple health state "angina and heart attack" ($U_{A,HA}$). The additive, multiplicative and minimum models are used to estimate the HSUV profiles for the multiple health condition in conjunction with the two age-adjusted baseline HSUV profiles (no history of CVD and general population) using the disutility (δ^i_j), multiplier (φ^i_j) or minimum value (*min*) respectively. We compare the QALYs obtained from avoiding a single event when using the HSUV (U_{AHA}) from individuals who have a history of both angina and a heart attack with those obtained when using the estimated HSUV ($U_{A,HA}$).

A. Using the USUV obtained from individuals with a history of both angina and heart attack

The mean HSUV for individuals with a history of both angina and heart attack (U_{AHA}) is 0.6243, and the mean age for this sub-group is 68.2 years. When using the baseline HSUV profile from the general population, the HSUV for a male at the age of 68.2 years (U^{GP}) is 0.8000 (from Model 1). For the additive model, the disutility (δ^{GP}_{AHA}) is the absolute difference between the baseline utility at the age of 68.2 years and the HSUV associated with the health condition angina and heart attack (i.e. $\delta^{GP}_{AHA} = U^{GP} - U_{AHA} = 0.8000 - 0.6243 = 0.1757$). When summing the QALYs accumulated for the health condition, as the additive model assigns a constant effect irrespective of age, a constant value of 0.1757 is deducted from the age-adjusted baseline HSUV each year and the resulting values are summed to give the total cumulative QALYs ($QALY^{GP}_{AHA} = \sum_{50 \le age \le 99} \text{Model 1} - \delta^{GP}_{AHA} = 29.30$). The incremental QALYs are then calculated by deducting the total cumulative QALYS associated with the condition angina and heart attack ($QALY^{GP}_{AHA}=29.30$) from the baseline total cumulative QALYs for the event free health state ($QALY^{GP}_{EF}=38.08$).

For the multiplicative model, the multiplier (φ^{GP}_{AHA}) is the value that will give the HSUV associated with the health condition angina and heart attack (U_{AHA}) when multiplying the baseline utility at the age of 68.2 years (i.e. $\varphi^{GP}_{AHA} = U_{AHA}/U^{GP} = 0.6243/0.8000 = 0.7804$). When summing the QALYs accumulated for the health condition, the multiplicative model assigns a constant proportional effect which is dependent on the age-adjusted baseline HSUV. The total cumulative QALYs are calculated by summing the QALYs obtained when multiplying the age-adjusted baseline HSUV with the corresponding multiplier ($QALY^{GP}_{AHA} = \sum_{50 \le age \le 99} (\text{Model 1} * \varphi^{GP}_{AHA}) = 29.72$). The incremental QALYs are then calculated by deducting the total cumulative QALYS associated with the condition angina and heart attack ($QALY^{GP}_{AHA}=29.72$) from the baseline total cumulative QALYs for the event free health state ($QALY^{GP}_{EF}=38.08$). For the minimum model, the minimum HSUV for the multiple condition angina and heart attack, and the age-adjusted baseline is used. Consequently, the detriment associated with the health condition angina plus heart attack is not constant. The total cumulative QALYs is simply the sum of the minimum values each year ($QALY^{GP}_{AHA} = \sum_{50 \le age \le 99} \min(\text{Model 1}, U_{AHA}) = 31.21$). The incremental QALYs are then calculated by deducting the total cumulative QALYS for the health state angina plus heart attack ($QALY^{GP}_{AHA}=31.21$) from the baseline total cumulative QALYs for the event free health state ($QALY^{GP}_{EF}=38.08$).

B. Using the HSUV obtained from individuals with a history of either angina (with no other CV condition) or heart attack (with no other CV condition)

The mean HSUV for individuals with a history of just angina (U_A) is 0.6910 and the mean HSUV for individuals with a history of just heart attack (U_{HA}) is 0.7391. The mean ages for these sub-groups are 68.4 and 66.6 years respectively. When using the baseline HSUV profile from the general population, the corresponding HSUVs for a male at the age of 68.4 and 66.6 years are 0.7990 and 0.8076 (from Model 1). For the additive model, the total disutility ($\delta^{GP}_{A,HA}$) is estimated to be the sum of the absolute difference between the baseline utility at the age of 68.4 and the HSUV associated with the health condition angina (i.e. $\delta^{GP}_{A} = U^{GP} - U_A = 0.7990 - 0.6910 = 0.1080$) plus the absolute difference between the baseline utility at the age of 68.4 and the HSUV associated with the health condition heart attack (i.e. $\delta^{GP}_{HA} = U^{GP} - U_{HA} = 0.8076 - 0.7391 = 0.0685$), giving a total estimated detriment of 0.1765.

When summing the QALYs accumulated for the health condition, a constant value of 0.1765 is deducted from the age-adjusted baseline HSUV each year and the resulting values are summed to give the total cumulative QALYs ($QALY^{GP}_{A,HA}= \sum_{50\le age\le 99}(\text{Model } 1-\delta^{GP}_{AHA}) =29.25$). The incremental QALYs are then calculated by deducting the total cumulative QALYS ($QALY^{GP}_{A,HA}=29.25$) from the baseline total cumulative QALYs for the event free health state ($QALY^{GP}_{EF}=38.08$).

For the multiplicative model, the estimated multiplier for the health state angina and heart attack ($\varphi^{GP}_{A,HA}$) is calculated by multiplying the multiplier for angina (φ^{GP}_{A}) with the multiplier for heart attack (φ^{GP}_{A}). The single multipliers are calculated using the method described earlier i.e. the multiplier for angina is obtained using the HSUV for angina and the baseline HSUV for individuals at the age of 68.4 years ($\varphi^{GP}_{A}=0.6910/0.7790$) and the multiplier for heart attack is obtained using the HSUV for heart attack and the baseline HSUV for individuals at the age of 66.6 years ($\varphi^{GP}_{A}=0.7391/0.8076$). When multiplied together, the estimated multiplier for the combined conditions angina and heart attack ($\varphi^{GP}_{A,HA}$) is 0.7915. The total cumulative QALYs are calculated by summing the QALYs obtained when multiplying the age-adjusted baseline HSUV with the corresponding multiplier ($QALY^{GP}_{A,HA}= \sum_{50\le age\le 99}(\text{Model } 1*\varphi^{GP}_{A,HA}) =30.14$). The incremental QALYs are then calculated by deducting the total cumulative QALYS associated with the condition angina and heart attack ($QALY^{GP}_{A,HA}=30.14$) from the baseline total cumulative QALYs for the event free health state ($QALY^{GP}_{EF}=38.08$).

For the minimum model, the minimum HSUV for the individual conditions angina and heart attack, and the age-adjusted baseline is used. The total cumulative QALYs is simply the sum of the minimum values each year ($QALY^{GP}_{A,HA}= \sum_{50\le age\le 99}\min(\text{Model } 1, U_A, U_{HA}) =34.14$). The incremental QALYs are then calculated by deducting the estimated total cumulative QALYS for the health state angina plus heart attack ($QALY^{GP}_{A,HA}=34.14$) from the baseline total cumulative QALYs for the event free health state ($QALY^{GP}_{EF}=38.08$).

Comparing results when estimating proxy HSUVs for multiple health conditions

When using age-adjusted baseline utilities from the general population to represent the HSUV for the event free health state, and the HSUV for individuals with a history of both angina and heart attack, the incremental QALYs obtained using the additive and the multiplicative models are 8.79 and 8.37 compared with 6.88 when using the minimum model. The corresponding incremental QALYs obtained when estimating HSUVs for the combined health state are 8.85, 7.96 and 3.95 for the additive, multiplicative and minimum models respectively. If it is assumed that the values obtained using the data from individuals with both health conditions are correct, then the additive and multiplicative models produce much smaller errors in the incremental values than the minimum model.

Using age-adjusted baseline utilities from individuals with no history of CVD to represent the HSUV profile for the event free health state (calculations provided in Box 2), the additive and the multiplicative models again produce similar results with incremental QALYs of 10.72 and 9.60 respectively compared with 9.75 and 9.35 when using the data from individuals with a history of both conditions. The incremental QALY gain when using the minimum model is much smaller at 4.81 and 8.05 when using the HSUV from the individual health conditions and the HSUV from individuals with both health conditions respectively. Results for additional examples ($n \geq 20$) are provided in Table 4.

Box 2: Estimating a proxy HSUV for the multiple health state both angina and heart attack

Let j = health state and: *AHA* = both angina and heart attack, *A* =angina, *HA* =heart attack,

A,HA = proxy angina plus heart attack

δ^{i}_{j} = disutility; φ^{i}_{j} = multiplier; *min* =minimum

U_{AHA} @ mean age 68.2 =0.6243, U^{GP} @ age 68.2 =0.8000, U^{NCV} @ age 68.2 =0.8193

U_{A} @ mean age 68.4 =0.6910, U^{GP} @ age 68.4 =0.7990, U^{NCV} @ age 68.4 =0.8185

U_{HA} @ mean age 66.6 =0.7391, U^{GP} @ age 66.6 =0.8076, U^{NCV} @ age 66.6 =0.8260

Using a baseline HSUV profile from individuals with no history of CVD,

Additive: $\delta^{NCV}_{AHA} = U^{NCV} - U_{AHA} = 0.8193 - 0.6243 = 0.1950$

$\delta^{NCV}_{A,HA} = \delta^{NCV}_{A} + \delta^{NCV}_{HA} = (U^{NCV} - U_{A}) + (U^{NCV} - U_{HA})$

$= (0.8185 - 0.6910) + (0.8260 - 0.7391) = 0.2143$

Multiplicative: $\varphi^{NCV}_{AHA} = U_{AHA}/U^{NCV} = 0.6243/0.8193 = 0.7622$

$\varphi^{NCV}_{A,HA} = \varphi^{NCV}_{A} * \varphi^{NCV}_{HA} = (U_{A}/U^{NCV}) * (U_{HA}/U^{NCV})$

$= (0.6910/0.8185) * (0.7391/0.8260) = 0.7555$

Minimum: $U^{NCV}_{AHA} = \min(U^{NCV}, U_{AHA}) = \min(U^{NCV}, 0.6243)$

$U^{NCV}_{A,HA} = \min(U^{NCV}, U_{A}, U_{HA}) = \min(U^{NCV}, 0.6910, 0.7391)$

Assuming the event occurs at the age of 50 years,

Using the data from individuals with a history of both angina and heart attack:

Additive, incremental $QALYs^{NCV} = QALY^{NCV}_{EF} - QALY^{NCV}_{AHA} = 39.27 - 29.52 = 9.75$

Multiplicative, incremental $QALYs^{NCV} = QALY^{NCV}_{EF} - QALY^{NCV}_{AHA} = 39.27 - 29.92 = 9.35$

Minimum, incremental $QALYs^{NCV} = QALY^{NCV}_{EF} - QALY^{NCV}_{AHA} = 39.27 - 31.22 = 8.05$

Using the proxy scores from individuals with a history of either angina or heart attack:

Additive, incremental $QALYs^{NCV} = QALY^{NCV}_{EF} - QALY^{NCV}_{A,HA} = 39.27 - 28.55 = 10.72$

Multiplicative, incremental $QALYs^{NCV} = QALY^{NCV}_{EF} - QALY^{NCV}_{A,HA} = 39.27 - 29.67 = 9.60$

Minimum, incremental $QALYs^{NCV} = QALY^{NCV}_{EF} - QALY^{NCV}_{A,HA} = 39.27 - 34.46 = 4.81$

Using a baseline HSUV profile from the general population,

Additive: $\delta^{GP}_{AHA} = U^{GP} - U_{AHA} = 0.8000 - 0.6243 = 0.1757$

$\delta^{GP}_{A,HA} = \delta^{GP}_{A} + \delta^{GP}_{HA} = (U^{GP} - U_{A}) + (U^{GP} - U_{HA})$

$= (0.7990 - 0.6910) + (0.8076 - 0.7391) = 0.1765$

Multiplicative: $\varphi^{GP}_{AHA} = U_{AHA}/U^{GP} = 0.6243/0.8000 = 0.7804$

$\varphi^{GP}_{A,HA} = \varphi^{m}_{A} * \varphi^{m}_{HA} = (U_A/U^{GP})*(U_{HA}/U^{GP})$

$= (0.6910/0.7790)*(0.7391/0.8076) = 0.7915$

Minimum: $U^{GP}_{AHA} = \min(U^{GP}, U_{AHA}) = \min(U^{GP}, 0.6243)$

$U^{GP}_{A,HA} = \min(U^{GP}, U_A, U_{HA}) = \min(U^{GP}, 0.6910, 0.7391)$

Assuming the event occurs at the age of 50 years,

Using the data from individuals with a history of both angina and heart attack:

Additive, incremental $QALYs^{GP} = QALY^{GP}_{EF} - QALY^{GP}_{AHA} = 38.08 - 29.30 = 8.79$

Multiplicative, incremental $QALYs^{GP} = QALY^{GP}_{EF} - QALY^{GP}_{AHA} = 38.08 - 29.72 = 8.36$

Minimum, incremental $QALYs^{GP} = QALY^{GP}_{EF} - QALY^{GP}_{AHA} = 38.08 - 31.21 = 6.87$

Using the proxy scores from individuals with a history of either angina or heart attack:

Additive, incremental $QALYs^{GP} = QALY^{GP}_{EF} - QALY^{GP}_{A,HA} = 38.08 - 29.25 = 8.83$

Multiplicative, incremental $QALYs^{GP} = QALY^{GP}_{EF} - QALY^{GP}_{A,HA} = 38.08 - 30.14 = 7.94$

Minimum, incremental $QALYs^{GP} = QALY^{GP}_{EF} - QALY^{GP}_{A,HA} = 38.08 - 34.14 = 3.94$

N.B. any anomalies in the results are due to rounding in the decimal places in the calculations shown above

INSERT Table 4: Cumulative and incremental QALY gains from a single event using different techniques to estimate proxy scores for multiple health states

Cost per QALY results generated when combining the alternative baseline HSUV profiles with the three different models available to combine HSUVs

The three alternative techniques used to combine utility scores are applied in the CVD model and used to assess the lifetime benefits associated with avoiding primary events for cohorts of differing ages using a baseline from individuals with no history of CVD and a baseline from individuals from the general population (Table 5). The results from the second worked example showed the benefits associated with avoiding a single event are considerably smaller when using the minimum model to

combine the utility values. This has a larger effect on the results for older aged cohorts (Table 5) where the ratio of costs and QALYs are more sensitive to small differences in the number of incremental QALYs gained. Figure 4 shows the cost per QALY results generated from the model using the different techniques to combine the utility data. There is very little difference in the results for the additive and multiplicative models, with the baseline HSUVs having a larger effect than the technique used to combine the utility data.

INSERT Table 5: Results generated from the CVD model when combining different baseline utility scores and different methods to combine utility data

INSERT Figure 4: Comparing results generated from the CVD model when combining different baseline utility scores and different methods to combine utility data

DISCUSSION

We have demonstrated that the difference in QALY benefits accrued from avoiding a single CV event when using a baseline of perfect health are not comparable with those accrued when using a baseline that is adjusted for not having CVD. We have also demonstrated that in CVD, results generated using age-adjusted data from the general population are comparable to those obtained using a baseline from individuals with no history of CVD. Applying the different approaches in an economic model, we also show that assuming a HSUV profile of perfect health as the baseline could potentially influence a policy decision based on a cost per QALY threshold.

The HSE data show that both age and gender are independent predictors of HSUVs and these findings are observed in numerous other datasets.[13,16] Given that the mean EQ-5D score is never equal to full health irrespective of age or gender, using a baseline of perfect health overestimates the benefits associated with avoiding an event and biases the results in favour of the older age cohorts as it ignores the natural decline in mean HSUVs due to age and co-morbidities. Data obtained from individuals without the health condition under consideration is the ideal baseline profile and should be used where possible. However, if these data are not available, we show that in CVD, the results generated using

age-adjusted baseline data from the general population are comparable with the results generated using age-adjusted baseline data from individuals with no history of CVD.

We demonstrated that when combined with the age-adjusted utilities, the method used to estimate proxy scores for multiple health conditions can produce a large variation in the incremental QALY gain from avoiding a single event. When applying the techniques in the economic model we demonstrate that the method used to estimate the proxy scores could affect a policy decision based on a cost per QALY threshold. In particular, using the minimum model in combination with an age-adjusted baseline produces results that are not comparable to those generated using the additive or multiplicative models.

The existing literature describing the effect on results when combining HSUVs using the different methods is sparse and inconclusive. Both Dale and Fu suggest the minimum value should be used to approximate the HSUV for a multiple health condition.[7-8] By taking the minimum mean utility score of the individual health conditions that contribute to a multiple health condition, the minimum model assumes a co-morbidity has no additional detrimental effect on the HSUV of individuals with an existing health condition. This is counterintuitive and data from the HSE show that in CVD there is a statistically significant difference in the mean EQ-5D score for individuals with one condition compared with those with more than one CV condition (mean EQ-5D for individuals with a history of just angina = 0.691, mean EQ-5D for individuals with a history of angina and stroke = 0.596, $p<0.01$). In addition, when applying the minimum model in an economic model in conjunction with an age-adjusted baseline, the method fails. The HSUVs for individuals who experience a primary heart attack is 0.7213. In the primary prevention analyses where all individuals commence in the event free health state the age-adjusted EQ-5D score for males with no history of CVD at the age of 89 years is 0.718. Consequently, when using the minimum model there is no benefit in avoiding a non fatal heart attack in males over the age of 89 years. Similarly the post primary angina health state has a mean EQ-5D score of 0.775 thus there are no benefits for males aged over 78 as the corresponding baseline age-adjusted EQ-5D score for individuals with no history of CVD is 0.7748. As the minimum model does not apply a constant detriment the technique introduces a bias against older aged cohorts and the results from our

threshold analyses demonstrate this can be quite substantial. We therefore recommend that the minimum model is not used to combine utility scores.

Our results show that the multiplicative and additive models produce similar results both for the individual events and when applying the techniques in the economic model. Flanagan and colleagues found the multiplicative model was reasonably accurate in estimating both double and triple co-morbidities after "purifying" the mean HUI3 scores to adjust for not having 26 chronic conditions.[6] Bond and Freedburg concluded that the additive and multiplicative models produced very similar results, when using a baseline of perfect health.[5] However, the additive model applies a constant absolute detriment across all ages while the multiplicative model applies a constant proportional detriment. In real terms, this means that the additive model provides a greater absolute reduction in HSUVs than the multiplicative model and the magnitude of the detriment is constant across all ages irrespective of the number of co-morbidities. The findings from Dale and Fu, who advocate the minimum model for combining HSUVs outside of an economic model, support the hypothesis that the detriment associated with several co-morbidities may not equal the sum of the individual detriments.

Saarni reported that the mean number of co-morbid chronic conditions increases from 1.1 for the age group 30-44 years to 4.0 for those aged 75 years and older.[16] It is possible that as the number of co-morbidities increase, the detriment associated with an additional condition is smaller than that observed in an individual with just two co-morbidities. If this hypothesis is correct, then the detriment associated with additional conditions would not be constant across all ages due to the increasing prevalence of co-morbidities. In addition, health conditions can impact on the same health dimensions and it is reasonable to assume that an individual with two or more similar conditions will not necessarily have a reduction in HSUV that is equal to the sum of the reductions observed for each of the individual health conditions.

Although we found the additive and multiplicative models produced similar cost per QALY results this finding may not generalise to other health conditions. In health conditions with comparatively small gains in QALYs, for example when the intervention does not have an effect on mortality rates, the economic results are likely to be more sensitive to changes in the techniques used to combine HSUVs.

While additional research is required to support our hypothesis and findings, in the interim period, to facilitate comparison across results generated from models with multiple health states, we advocate the use of the multiplicative model.

The health care literature and policy decision makers such as NICE place a great deal of emphasis on both the methods used to obtain weights used in preference-based instruments and the particular preference-based instrument used to collect the HSUVs which are used to populate health states within economic models.[1] Evidence shows that the choice of instrument used to represent the HSUVs of a particular health condition can influence the results generated.[15] However, there is a great deal more to populating an economic model than the choice of instrument used to obtain the HSUVs and a consistent approach would improve comparability of results.

Conclusion

Our results re-enforce earlier recommendations and until guidelines are in place, we would recommend that data from the general population are used as proxy baseline utility measures for individuals without the health condition under consideration if the actual data is not available. While our findings demonstrate the additive and multiplicative models give similar results in CVD, additional research in other health conditions and datasets are required.

The underlying principle behind using the same preference-based instrument for all economic evaluations is to enable comparison across different interventions and health conditions. If this is to be realised, some consensus is needed on the most appropriate methods to populate the economic models. The methods used should be clearly described to inform policy decision makers who are comparing results generated from different evaluations.

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REFERENCES

1. National Institute of Health and Clinical Excellence. Guide to the methods of Technology Appraisal. 2008.

2. Fryback DG, Lawrence WG. Dollars may not buy as many QALYs as we think: A problem with defining quality of life adjustments. MDM 1997;17;276-284

3. Ward S, Lloyd Jones M, Pandor A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess. 2007 Apr;11(14):1-160, iii-iv.

4. Bansback N, Ara R, Ward S, Anis A, Choi HK. Statin therapy in rheumatoid arthritis: a cost-effectiveness and value-of-information analysis. Pharmacoeconomics. 2009;27(1):25-37

5. Bond DE, Freedberg KA. Combining utility measurements exploring different approaches. Dis Manage Health Outcomes 2001: 9(9):507-516

6. Flanagan W, McIntosh CN, Le Petit C, Berthelot JM. Deriving utility scores for co-morbid conditions: a test of the multiplicative model for combining individual condition scores. Population Health Metrics 2006. 4:13

7. Fu AZ, Kattan MW. Utilities should not be multiplied: evidence from the preference-based scores in the United States. Med Care. 2008 Sep;46(9):984-90.

8. Dale W, Basu A, Elstein A, Meltzer D. Predicting Utility Ratings for Joint Health States from Single Health States in Prostate Cancer: Empirical Testing of 3 Alternative Theories. MDM 2008;28:102-112.

9. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000;17:479-500.

10. Ara R, Tumur I, Pandor A, et al. Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. Health Technol Assess. 2008 May;12(21):iii, xi-xiii, 1-212.

11. Joint Health Surveys Unit of Social and Community Planning Research and University College London, Health Survey for England, 2003 [computer file]. 3rd Edition. Colchester, Essex: UK Data Archive [distributor], 2005. SN: 5098.

12. Joint Health Surveys Unit of Social and Community Planning Research and University College London, Health Survey for England, 2006 [computer file]. 3rd Edition. Colchester, Essex: UK Data Archive [distributor], 2008. SN: 5809.

13. Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population study. Health Econ. 1996;5(2):141–54

14. Ara R, Brazier J, Young T. Health related quality of life by age, gender or history of cardiovascular disease: results from the Health Survey for England 2003 and 2006. Discussion paper (http://www.sheffield.ac.uk)

15. Brazier J, Ratcliffe J, Salomon J, Tsuchiya A. Measuring and valuing health benefits for economic evaluation Oxford University Press 2007.

16. Saarni SI,, Suvisaaria J, Sintonenb H, et al. The health-related quality-of-life impact of chronic conditions varied with age in general population. Journal of Clinical Epidemiology 2007;60(12) :1288-1297

Figure 1: Health states in CVD model

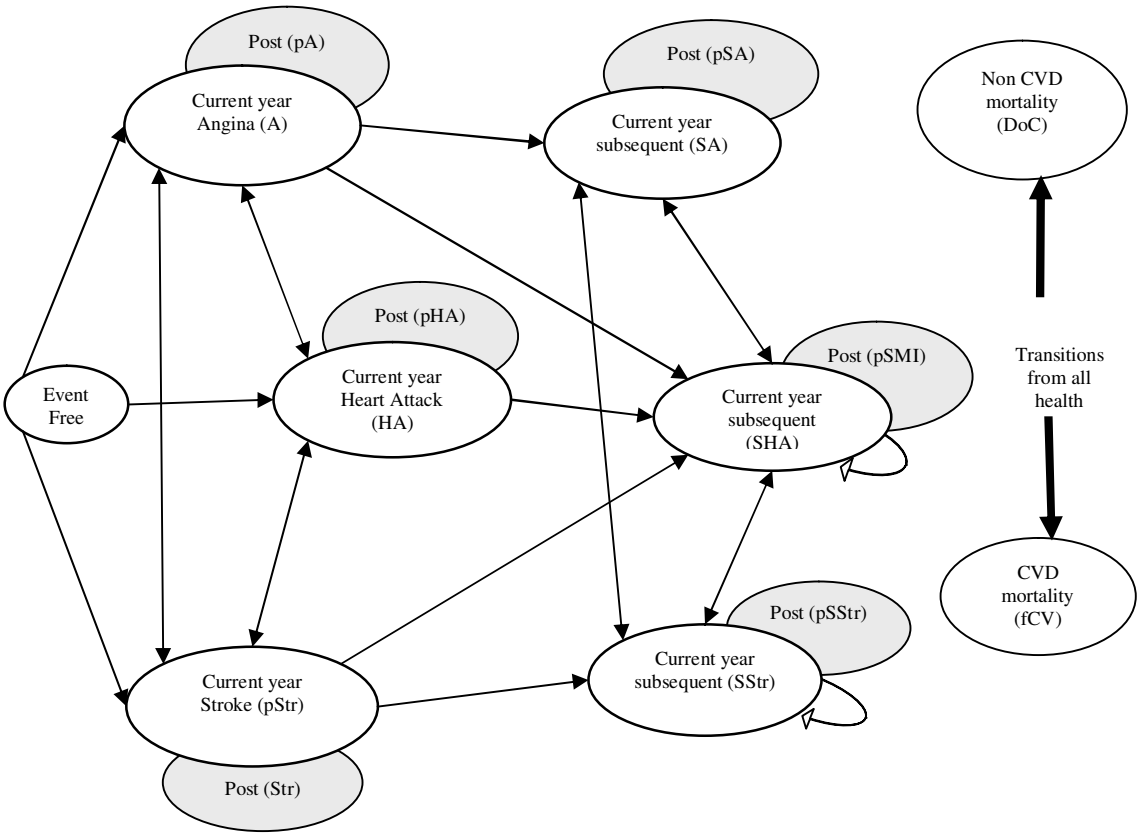


Figure 2: Baseline utility for the event free health state: Relationship between HSUVs, age, sex and history of CVD

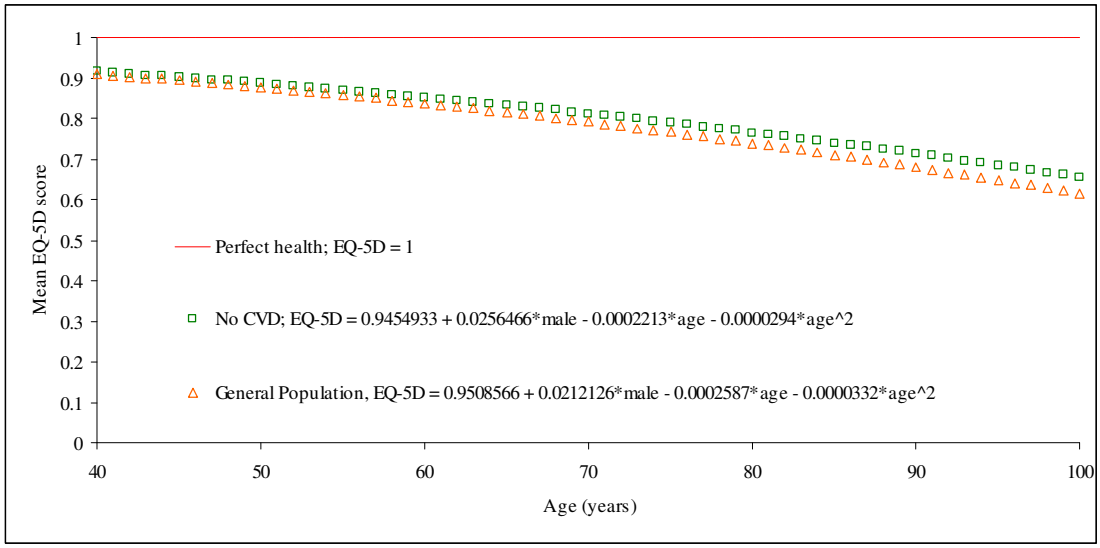
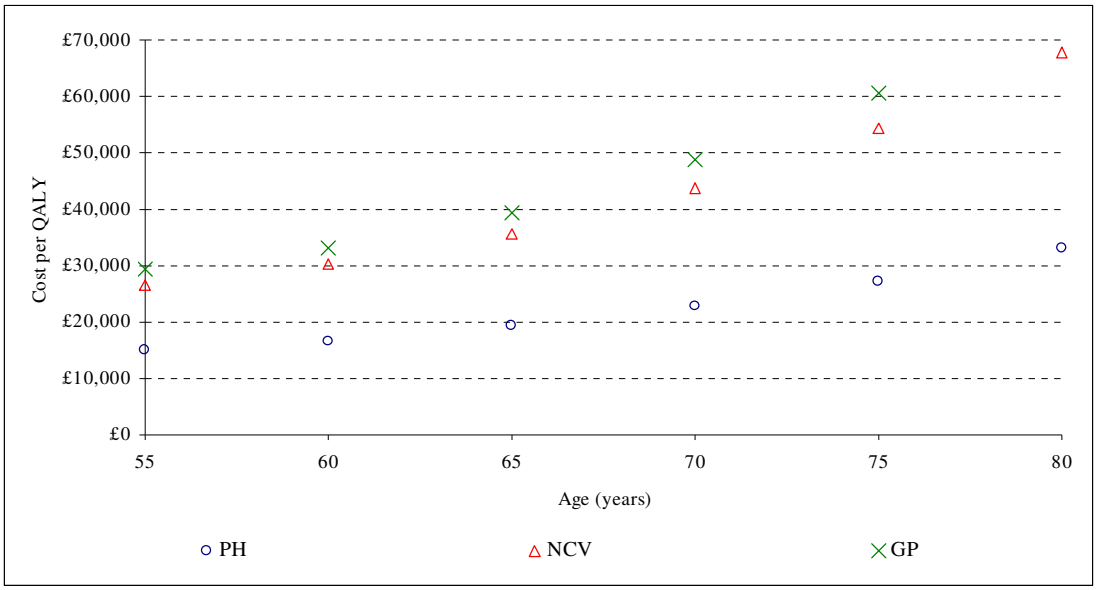
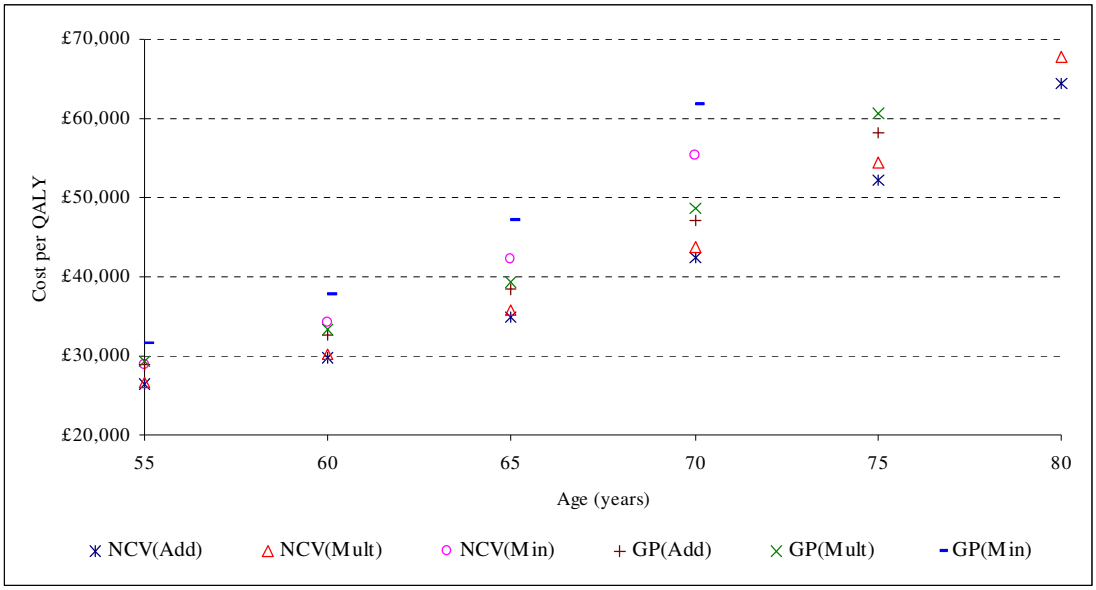


Figure 3: Comparing the results generated from the CVD model using the three alternative baseline profiles



PH = baseline of perfect health; NCV = baseline from individuals with no history of CVD; GP = baseline from the general population

Figure 4: Comparing results generated from the CVD model when combining different baseline utility scores and different methods to combine utility data



NCV = baseline from individuals with no history of CVD; GP = baseline from the general population; Add = additive model; Mult = multiplicative model; Min = minimum model.

Table 1: EQ-5D scores sub-grouped by health condition and time since event

Health condition	health state	N	Age mean	EQ-5D mean	se
Utility values used to populate health states in the economic model					
Event free	EF	25,080	47.0	0.872	0.001
Angina < 12 months, history of just angina	A	271	68.8	0.615	0.019
No event < 12 months, history of just angina	pA	246	68.0	0.775	0.015
Angina < 12 months, history of angina + other CV condition	SA	245	67.9	0.541	0.022
No event < 12 months, history of angina + other CV condition	pSA	184	69.4	0.715	0.022
Heart attack < 12 months, history of just heart attack	HA	31	65.4	0.721	0.045
No event < 12 months, history of just heart attack	pHA	206	65.1	0.742	0.020
Heart attack < 12 months, history of heart attack + other CV condition	SHA	36	66.7	0.431	0.066
No event < 12 months, history of heart attack + other CV condition	pSHA	184	69.2	0.685	0.024
Stroke < 12 months, history of just stroke	Str	76	67.9	0.626	0.038
No event < 12 months, history of just stroke	pStr	291	66.8	0.668	0.018
Stroke < 12 months, history of stroke + other CV condition	SStr	18	73.5	0.479	0.087
No event < 12 months, history of stroke + other CV condition	pSStr	77	70.4	0.641	0.037
Data used to compare methods for estimating proxy scores for multiple health conditions					
Angina (t=ever), history of just angina		517	68.4	0.691	0.013
Heart attack (t=ever), history of just heart attack		237	66.6	0.739	0.018
Stroke (t=ever), history of just stroke		367	67.0	0.660	0.016
Angina and heart attack (t=ever)		323	68.2	0.624	0.019
Angina and stroke (t=ever)		63	70.3	0.596	0.043
Heart attack and stroke (t=ever)		32	69.7	0.538	0.065

Angina < 12 months and heart attack < 12 months	23	63.1	0.400	0.073
Angina < 12 months and heart attack > 12 months	154	68.4	0.585	0.030

Table 2: Cumulative and incremental QALYs associated with a single event using different baseline utility data

	Multiplicative Model			
	Cumulative QALY		Incremental QALY	
	M	F	M	F
Baseline: perfect health				
Event free	50.00	50.00		
Angina	30.74	30.74	19.26	19.26
Heart Attack	36.07	36.07	13.94	13.94
Stroke	31.31	31.31	18.69	18.69
Baseline: from general population				
Event free	38.08	37.02		
Angina	29.37	29.33	8.71	7.69
Heart Attack	33.78	33.72	4.30	3.30
Stroke	29.75	29.71	8.33	7.31
Baseline: from individuals with no history of CVD				
Event free	39.27	37.99		
Angina	29.56	28.52	9.71	8.47
Heart Attack	34.09	34.02	5.18	3.96
Stroke	29.97	29.92	9.30	8.06

Table 3: Results generated from CVD model using the three alternative baseline profiles (combining utility scores multiplicatively)

	Baseline utility	Treatment A QALYs	Treatment B QALYs	Incremental QALYs	Cost per QALY
		Age 50 years			
Costs £(,000)		£4,216	£5,610	£1,394	
	Perfect Health	16,795	16,895	100	£13,887
	General Population	14,129	14,178	49	£28,324
	No history of CVD	14,363	14,417	54	£25,914
		Age 60 years			
Costs £(,000)		£3,660	£4,773	£1,113	
QALYs	Perfect Health	13,582	13,648	67	£16,711
	General Population	10,919	10,952	33	£33,957
	No history of CVD	11,197	11,229	32	£34,777
		Age 70 years			
Costs £(,000)		£2,609	£3,424	£815	
QALYs	Perfect Health	9,966	10,002	36	£22,849
	General Population	7,643	7,656	13	£62,195
	No history of CVD	7,866	7,880	14	£56,487

Table 4: Cumulative and incremental QALY gains from a single event using different techniques to estimate proxy scores for multiple health states

	Cumulative QALY				Incremental QALY				Error in Incremental QALY	
	Observed[a]		Proxy[b]		Baseline -Observed		Baseline- Proxy			
	GP	NCVD	GP	NCVD	GP	NCVD	GP	NCVD	GP	NCVD
Baseline										
event free	38.1	39.3								
Angina plus Heart Attack: EQ-5D just angina = 0.691; EQ-5D just heart attack = 0.739; EQ-5D angina plus heart attack = 0.624										
additive	27.4	29.5	25.4	24.7	10.7	9.8	12.7	14.6	2.0	4.9
multiplicative	27.9	28.1	26.8	26.4	10.2	11.2	11.3	12.9	1.1	1.7
minimum	29.3	29.3	30.8	30.8	8.8	10.0	7.3	8.5	-1.5	-1.5
Angina plus Stroke: EQ-5D just angina =0.691; EQ-5D just stroke =0.660, EQ-5D angina plus stroke = 0.596										
additive	28.4	28.5	25.4	24.7	9.7	10.7	12.7	14.6	3.0	3.9
multiplicative	28.7	28.9	27.0	26.5	9.4	10.4	11.1	12.7	1.8	2.3
minimum	29.8	29.8	32.9	33.0	8.3	9.5	5.2	6.3	-3.1	-3.2
Heart Attack plus Stroke: EQ-5D just heart attack = 0.739, EQ-5D just stroke = 0.660; EQ-5D heart attack plus stroke = 0.538										
additive	25.3	25.5	27.4	26.7	12.8	13.8	10.7	12.6	-2.0	-1.2
multiplicative	25.8	26.0	28.6	28.1	12.2	13.3	9.5	11.1	-2.7	-2.1

minimum	26.9	26.9	32.9	33.0	11.2	12.4	5.2	6.3	-6.0	-6.1
Angina < 12 months, Heart Attack < 12 months:										
EQ-5D angina < 12 months = 0.615; EQ-5D heart attack < 12 months = 0.721; EQ-5D angina < 12 months plus heart attack < 12 months = 0.400										
additive	16.9	17.3	24.4	23.7	21.2	22.0	13.7	15.6	-7.5	-6.4
multiplicative	18.5	18.7	26.1	25.7	19.6	20.6	12.0	13.6	-7.6	-7.0
minimum	20.0	20.0	30.8	30.8	18.1	19.3	7.3	8.5	-10.8	-10.8
Angina < 12 months, Heart Attack > 12 months:										
EQ-5D angina < 12 months = 0.615; EQ-5D heart attack > 12 months = 0.742; EQ-5D angina < 12 months plus heart attack > 12 months = 0.585										
additive	27.4	27.6	25.4	24.7	10.7	11.7	12.7	14.6	2.0	2.9
multiplicative	27.9	28.1	26.8	26.4	10.2	11.2	11.3	12.9	1.1	1.7
minimum	29.3	29.3	30.8	30.8	8.8	10.0	7.3	8.5	-1.5	-1.5

[a] using utility data from individuals with a history of both conditions; [b] using data from individuals with a history of a single condition to estimate the HSUV for the multiple health condition; GP = general population; NCVD = No history of CVD

Table 5: Results generated from the CVD model when combining different baseline utility scores and different methods to combine utility data

	General population			No history of CVD		
	additive	multiplicative	minimum	additive	multiplicative	minimum
			Age 55 years			
Treatment A, total QALY	12,530	12,535	12,565	12,790	12,794	12,827
Treatment B, total QALY	12,573	12,577	12,605	12,837	12,841	12,870
Incremental QALY	43	43	40	47	47	43
Cost per QALY	£29,109	£29,394	£31,742	£26,664	£26,927	£29,088
			Age 65 years			
Treatment A, total QALY	9,257	9,262	9,298	9,510	9,515	9,553
Treatment B, total QALY	9,282	9,286	9,318	9,537	9,542	9,576
Incremental QALY	25	24	20	27	27	23
Cost per QALY	£38,680	£39,553	£47,253	£35,235	£36,021	£42,767
			Age 75 years			
Treatment A, total QALY	6,038	6,042	6,067	6,251	6,256	6,284
Treatment B, total QALY	6,049	6,053	6,075	6,264	6,268	6,293
Incremental QALY	11	11	8	13	12	9
Cost per QALY	£58,521	£61,078	£82,287	£52,676	£54,892	£74,144