INCORPORATING WIDER SOCIETAL BENEFITS

INTO ESTIMATES OF COST PER QALY:

IMPLICATIONS OF VALUE BASED PRICING FOR NICE.

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1. INTRODUCTION

From January 2014, reimbursement of new drugs in the NHS will be governed by a new system referred to as "Value-Based Pricing" (VBP), when the current Pharmaceutical Price Regulation Scheme (PPRS) expires. The key features of this approach were set out in the consultation document "A new value-based approach to the pricing of branded medicines" in 2010,[1] and further details of the proposed basic principles have been shared by the Department of Health since that time. What is now clear is that the assessment of costs and health related benefits, in terms of Quality Adjusted Life Years (QALYs), will remain central to the assessment of value. The methods currently employed by NICE to assess this element of cost effectiveness will remain largely unchanged, notwithstanding planned methods amendments in the forthcoming NICE methods guide update. The VBP framework will however involve a variety of additional considerations to be factored into the cost per QALY assessment of any new technology in a formal manner. Of course, NICE's guidance is not currently formulated strictly on the basis of cost per QALY and the Methods Guide[2] clearly sets out which other issues should be considered as relevant. However, these "additional factors" tend to be considered qualitatively via a deliberative process rather than a formal quantification of their value in the current Appraisal Process. One partial exception to this is the consideration of additional value assigned to therapies meeting the stated criteria for "end of life" treatments.

The first set of additional considerations to be incorporated into the assessment framework under VBP are referred to as "Wider Societal Benefits" (WSBs): these refer to the broader impacts on society that improved patient health may have via productive activity by the patient net of their consumption of resources, beyond those captured within the current NHS perspective operated by NICE. This requires estimates of the value of paid labour and unpaid production such as childcare and domestic housework on the production side, and the value of care, public and private goods and services on the consumption side. This set of considerations might therefore be thought of as additional efficiency based elements of value.

The second set of additional benefits are those intended to reflect the possibility that society may place greater or lesser value on the health benefits accrued from different therapies based on the characteristics of the patients receiving those health gains. Under VBP it is envisaged that QALYs may be weighted according to size of the therapeutic improvement and burden of disease of patients. Such weights are often considered to reflect "equity" considerations, though it should be noted that there are many other reasons why members of the public may

hold such preferences, including those that overlap with those intended to be reflected via WSBs.

The purpose of this paper is to consider how the values calculated in relation to WSBs should be incorporated into, or alongside, the existing cost effectiveness (CE) models submitted to NICE which are designed to calculate the incremental cost per QALY of technologies in most cases. The paper will set out our understanding of the data that will be available for such a calculation, different options for incorporating that data into decision models designed to estimate cost per QALY and consider the advantages and risks associated with different options. It concentrates solely on the incorporation of WSBs. It does not consider the incorporation of QALY weights, though there is likely to be a degree of overlap in terms of the challenges posed. The paper makes no comment on the merit of the VBP framework more broadly or the sources of evidence used to estimate the WSBs.

It is planned that the issues highlighted here will be further explored and illustrated using a series of real-life case studies.

2. IN WHAT FORM ARE WSBs TO BE CONSIDERED?

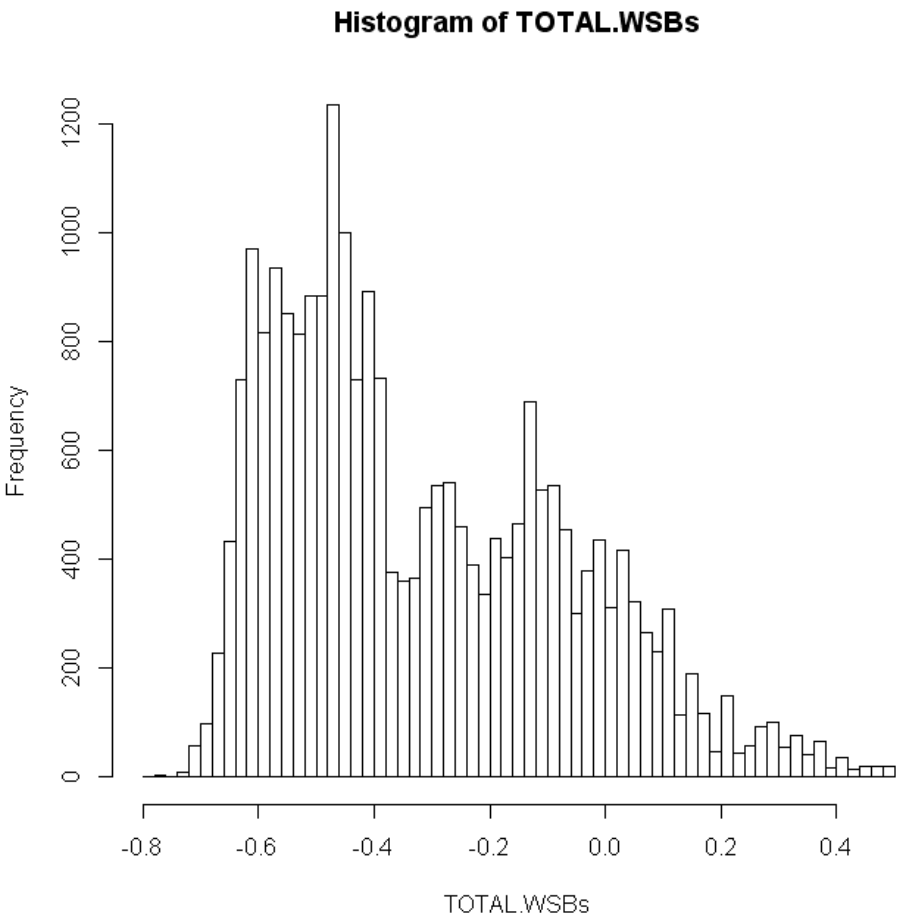
The Department of Health (DH) has produced a series of calculations which are combined to estimate a single monetary value reflecting the net WSB as a function of age, sex, ICD code and quality of life. These net WSBs are derived from a series of calculations which collectively are intended to reflect the value of the productive contribution of an individual less the value of that individual's consumption.

A table of WSB values provided by DH are considered here, though these are not yet definitive and are subject to change. Age can be calculated from 1 to 100yrs with different values for each year, ICD codes are based solely on the first letter code (B-O,Q-T, Z), and quality of life is based on the full range of the EQ-5D UK tariff in 0.1 increments (-0.6 to 1). There are thus 64600 (100x2x19x17) unique combinations which each lead to an estimate of the WSB for any set of patient characteristics.

The WSBs are calculated in the form of a monetary benefit per month which in turn are converted to annual QALY equivalents according to the assumed value of a QALY (£60k in the data provided to DSU). Therefore, to incorporate these values alongside those calculated as part of the standard cost effectiveness estimates currently submitted to NICE requires an addition to the QALYs estimated from the original economic evaluation (note however that the WSBs are not limited to positive values).

The distribution of WSBs is shown in figure 1. Values range from -0.789 to 0.492 QALY equivalents per year in the entire set of weights and that range is the same or similar across ICD codes. There is therefore the potential for treatments to generate benefits of a substantial magnitude relative to QALY gains.

Figure 1: Histogram of Wider Social Benefits (in QALY equivalents)



3. DIFFERENT MODEL TYPES USED FOR ESTIMATING COST PER QALY

The current NICE approach to estimating cost effectiveness compares the costs and QALY benefits of alternative treatments over a time period where these may be expected to differ. For most technologies this time horizon is more than a single year, often extends beyond the period in which clinical study outcomes are observed, and in numerous cases may comprise the rest of a patient's life. In order to make such estimates, it is almost always the case that evidence must be drawn together from many different sources: clinical trials, observational databases, studies of health state utility values, resource use studies, as well as clinical and other judgments and assumptions. This is done within a mathematical framework that intends to provide a simplified representation of the real world, referred to as a decision model.

There are a variety of model techniques that can be used in this setting. For the NICE setting, the most commonly observed techniques are decision trees, state-transition models and discrete event simulations and within these three broad model types it is the state-transition type that is most commonly observed.

Detailed accounts of these model techniques can be found elsewhere.[3,4] Decision tree models are particularly suitable where the time period for which the model needs to be run is short, where there are not a large number of different events of interest and where the costs and outcomes associated with each set of options are straightforward to calculate. An example of the use of such a kind of model is in the assessment of drug treatments for influenza. Here the time period is short, representing the time from presentation at the GP surgery to the development of flu symptoms and their potential complications. There are a limited number of "paths" based on the combination of developing flu or not, and the presence or absence of complications such as pneumonia for those who do develop flu. Note that whilst the complications of flu may last for a longer time period the costs and outcomes associated with this can be summarised easily within a decision tree that itself adopts only a short analytical period. This is therefore different from the concept of "time horizon".

Transition state models are better suited to longer time horizons than decision tree models and operate by defining a number of distinct health states which patients move to and from over the time period of interest. States are mutually exclusive and each is associated with a cost and health outcome with the expected value being calculated by summing these costs and outcomes over time. The health impact of different treatments (e.g. delayed disease progression) is most commonly represented by different transition rates between states and hence different trajectories through the model over time.

The state transition model allows a simple representation of a large number of potential pathways that would otherwise become unmanageable to reflect via a decision tree approach. The design is based on defining a series of mutually exclusive states and using a series of starting values, transition probabilities and a set time period to track which state any member of the patient cohort is in at any stage of the analysis. This approach is particularly widely used in models of therapies for various types of cancer, where health states corresponding to different stages of disease such as local disease, progression and death can often be sufficient. Because patients can transit between some of these states, representing this as a recursive decision tree would require a very large number of branches. It should be noted that the terms "Markov" and "transition state" models are often used interchangeably, though strictly speaking the term "Markov" is aligned to the assumption of memorylessness: that all patients in a given state at a given time period have the same prognosis regardless of their previous history. Since this assumption can be relaxed whilst still maintaining the same general structure leads us to favour the use of the term "state transition".

Discrete Event Simulation (DES) is an approach that remains little used in economic evaluation though its use is growing.[5] As the name suggests, the general approach is based around identifying the time to a series of different occurrences for individual entities (usually patients). In principle, time can be treated in a continuous manner rather than being artificially restricted to set time intervals as with a state transition model.

Much more detail relating to these, and other, model approaches is available elsewhere.[3] For the purposes of how to incorporate WSBs alongside estimates of costs and QALYs, we believe these features are unlikely to be of fundamental importance *per se*. What is likely to be relevant is the difference in methods used to estimate the expected costs and benefits for a patient population within these broad modelling approaches. A distinction can be drawn between models that operate by simulating a cohort of homogenous patients, with the expected value simply equal to the sum for that cohort, versus those that simulate individual patients and calculate the expected value by simulating over many such individuals. Again terminology can be variable and confusing in this regard – the terms "individual patient", "individual sampling", "microsimulations" and "first order trials" are often used interchangeably.

Decision tree models and transition state models are typically analysed as cohort level models, though both can be analysed at the individual patient level. For example, a transition state model structure can reflect patient history and allow other patient level covariates to determine transition probabilities and payoffs. DES's are based on individual entities, which

in the health economic setting almost always equates to the individual patient. DES and patient level simulation are not however coterminous.

4. ISSUES AND OPTIONS FOR INCORPORATING WSBs

There are two potentially important issues that may make it less than straightforward to incorporate WSBs into the types of models typically submitted to NICE. These have been previously identified in relation to the incorporation of proposed "equity weights".[6]

First, it is important to define precisely the characteristics that determine the WSBs to be applied. "Age" is the age in years for the period (year) in which the treatment benefits are realised. Similarly, "Quality of life" refers to the period (year) in which the treatment benefits are realised. Both of these characteristics will vary across the period being assessed in almost all examples of models submitted. Even in models that have an analytical time horizon of one year or less, it will still likely be the case that some of the benefits and costs arising from the events which occur in that first year accrue in future periods. For example, in the case of drug therapies for influenza, models may wish to reflect the risk of long term adverse events associated with the drug.[7]

The total benefits generated, the sum of QALYs and relevant WSBs, are unlikely to be related to either "age" or "quality of life" in a straightforward manner and therefore summary outputs generated by the cost effectiveness model cannot be manipulated to allocate the appropriate WSBs. Of course, age will progress in an entirely obvious manner throughout the course of a model, given a specified starting age and the way in which time is reflected in the model. But summary outputs will not directly indicate what proportion of benefit accrued at which age.

Second, the relationships between the WSB adjustment and both age and quality of life are extremely non-linear in nature (as illustrated in Figure 2 for age). In this situation, the mean WSB adjusted QALYs across all patients (the correct value) is not equivalent to the WSB adjusted QALYs for the average patient. To illustrate this issue, consider Table 1 which shows a hypothetical set of WSBs for three different age groups. In part a) the relationship between age and the WSB weight is assumed linear. For the three patients comprising the population it can be seen that the mean adjusted QALY, $E(X)$, is equivalent to the adjusted QALY for the average patient, $E(X_{\bar{a}})$. In part b) a non-linear relationship is assumed and in this situation it can be seen that the two methods of estimation lead to differing results (0.7 and 0.683 respectively). This issue is entirely equivalent to that faced by analysts in relation to uncertainty in parameter inputs to cost effectiveness analyses. Where the relationship

between an uncertain parameter and estimates of cost effectiveness (more precisely net benefit) is non-linear then simply setting the parameter value to its expected value leads to a biased estimate of the expected cost effectiveness. For this reason, simulation methods that sample from the distribution of the uncertain parameter are widely advocated. NICE have specified the use of Probabilistic Sensitivity Analysis (PSA) for this reason, *inter alia*, since the publication of its methods guide in 2004.

Figure 2: Distribution of WSBs by age for a) Males and b) Females

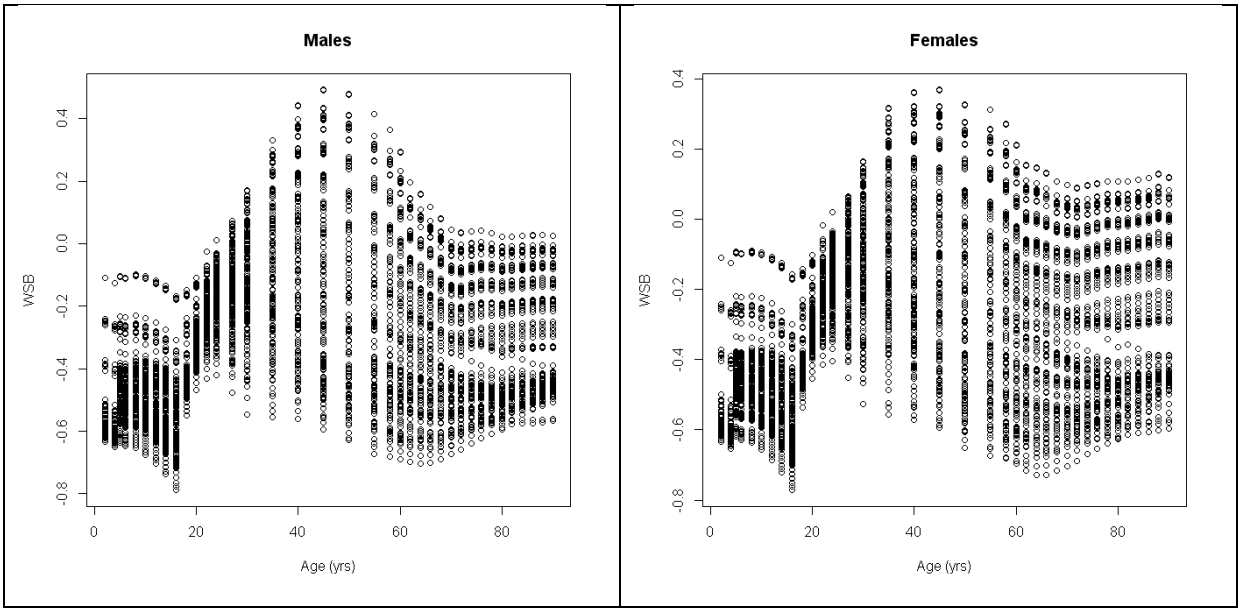


Table 1: Comparison of methods for incorporating WSBs with linear/non-linear relationship to age.

Patient number	*Age*	*QALYs*	*WSB*	*Adjusted QALYs*[1]		
(i)	*(a)*	*(Q)*	*(W)*	*X*	$E(X_{\bar{a}})$	$E(X)$
a) Linear Relationship between age and WSB						
1	40	0.5	0.1	0.6	0.7	0.7
2	50	0.5	0.2	0.7		
3	60	0.5	0.3	0.8		
b) Non-linear relationship between age and WSB						
1	40	0.5	0.1	0.6	0.7	0.683
2	50	0.5	0.2	0.7		
3	60	0.5	0.25	0.75		

[1] $X=Q+W$

In the context of WSBs, it is not uncertainty that results in the need to avoid simple methods, but heterogeneity in the population to be treated that needs to be reflected in the analysis (though uncertainty in the estimates of WSBs is an issue for consideration in addition to this). For both of these reasons, it will not be feasible to obtain unbiased estimates of weighted QALY gain for any technology without undertaking additional analysis within the economic model used to generate estimates of cost effectiveness. Simply adjusting the outputs of those models i.e. the expected costs and QALYs of alternative technologies, will result in biased estimates of the WSB adjusted cost effectiveness. The magnitude of this bias will be considered in the case studies planned as Part 2 of the DSU project.

4.1 Alternative methods for incorporating WSBs – patient level simulation models

Cost effectiveness models that simulate individual patients offer the opportunity for WSBs to be calculated without further approximation beyond those already embodied in the supplied matrix of WSB values. For each patient, and for each time period, where the model is already calculating costs and benefits accrued, the required adjustment could be made in a relatively simple manner in many cases, though this will depend on precisely how the model has been programmed. The analyst would have the information on current age, quality of life at the start of the period, ICD and sex for each patient as part of the structure of the existing model and would therefore only require additional programming to look up the correct WSB from

the supplied table of values. It is difficult to conceive of any model that would not track these variables as a matter of course since they would almost always be pertinent factors in determining the course any individual patient took through the model.

So far, such model types have not been submitted frequently to NICE, but their use is increasing.. In the absence of the requirement to factor in WSBs, there is substantial disagreement about the frequency with which such model types are required and the potential for more complex model structures and first order simulations to reduce the ability of analysts to reflect uncertainty using PSA (which is performed via "second order" Monte Carlo simulation), simply because of the computational demands.

In the current context of WSBs, there is no requirement for more complex models than would otherwise be the case, just for their analysis to be undertaken using patient level simulation rather than cohort analysis. We return to this point later.

On a more pragmatic note, it is also often the case that those models which do sample individual patients in fact have elements of cohort analysis in them. For example, vocal proponents of DES type models have been particularly strong critics of cohort analysis in Alzheimer's disease, including at judicial review. Yet the sponsor submitted DES models included key elements of costs and benefits calculated on a cohort basis. For example, the utility value assigned to any individual patient is a function of whether they were institutionalised or not. However, the model does not actually assign individual patients to institutional care or not, rather it assigns a probability of being institutionalised and the utility assigned is thus an average value weighted according to that probability (see DSU report p.9). The true distribution of health status, required to assign the appropriate WSB each period, is not necessarily captured even in models that are predominantly individual simulation models.

4.2 Approximations using cohort models

The majority of cost effectiveness models received by NICE are based on cohort analyses: the estimates of costs and QALYs are based on simulating a hypothetical group of homogenous patients. They therefore ignore the distribution of patients in terms of age and quality of life which, given the non-linear nature of the WSBs, will result in biased estimates of the true adjusted QALYs from treatments.

An approximation to the patient level analysis can potentially be achieved by performing multiple subgroup analyses. Subgroups can be specified in terms of patient age and starting quality of life, and for each subgroup analysis the appropriate WSB adjustments made within the model QALY calculations. The estimate of adjusted QALYs is then equal to the mean for

all those subgroups weighted according to their size relative to the relevant population. Of course, how many subgroups are required to achieve a sufficiently precise approximation will vary according to the specific disease, technology and the "lumpiness" of the range of relevant WSBs (for example whether values are defined for broad age categories or for every single year of age). At the limit, this reduces to the patient level simulation, where the subgroup size is 1 (with potential for replication of patients).

There are two further issues relating to this subgroup analysis. The first is where subgroups have been specified in any case for the submitted cost effectiveness analysis. In this situation it would be expected that certain parameter values are subgroup specific. However, in the case of subgroups solely for the incorporation of WSBs it is unlikely that adjustments to other parameter values would be a realistic option. We would therefore be left in the situation where a model has been designed to run as a cohort analysis, with evidence relevant to that approach incorporated, that is now being analysed as a patient level simulation. Whether this yields credible results will require testing in case studies.

4.3 Methods to Approximate WSB estimates

Simplistic approaches to incorporating WSBs, based on the standard outputs from cost effectiveness models (mean costs and QALYs for competing alternatives), are inappropriate in part because of the non-linear relationship between patient characteristics and the associated WSBs .

Whilst the approaches above are based on incorporating the existing set of WSB estimates into CE models, an alternative approach for consideration involves making an approximation to the WSBs themselves and may be an acceptable solution for incorporating WSBs for cohort models.

If a simple linear relationship between input values and WSBs could be specified that approximated the true relationship, then the task of combining CE models with the WSBs becomes much more straightforward. How close such a linear approximation needs to be is an empirical issue but it is immediately apparent that the WSBs are currently not amenable to such an approximation (see Figure 2 for example).

However, it may be the case that a statistical model or relationship that is linear <u>in parameters</u> is able to be applied in this manner. To illustrate this point, let us assume that the relationship between age and WSBs is indeed non-linear and is in fact given by:

$$W = age^2/1000$$

In this situation, the relationship is linear in terms of the parameters where one (the only) parameter is age-squared. It is then possible to compute a) the mean QALYs for the strategy based on a patient of mean age and b) the mean WSB to be applied to a) based on a patient of mean age-squared. Table 2 provides such an example. As illustrated in Table 1, the crude approach is to calculate the mean adjusted QALY as that for the patient of mean age of the cohort, $E(X_{\bar{a}})$, which in this case corresponds to 50yr old patient 3. Calculating the adjusted QALYs for each individual patient and averaging, $E(X)$, obviously gives a different value because of the non-linear relationship between WSBs and age. The third approach estimates the mean QALYs based on the patient of average age and then calculates the WSB adjustment to be made based on the patient of average age-squared $E(X_{\bar{a}}) + E\left(X_{\overline{a^2}}\right)$, where $Q_{\bar{a}}$ is the QALY for patient of mean age, *a*, and $W_{\overline{a^2}}$ is the WSB for a patient of mean age-squared.

Table 2

Patient number	**Age**	**Age-squared**	**QALYs**	**WSB**	**Adjusted QALYs**			
(i)	*(a)*	*(a^2)*	*(Q)*	*(W)*	*X*	$E(X_{\bar{a}})$	$E(X)$	$E(Q_{\bar{a}}) + E\left(W_{\overline{a^2}}\right)$
1	30	900	0.5	0.9	1.4	3	3.2	3.2
2	40	1600	0.5	1.6	2.1			
3	50	2500	0.5	2.5	3			
4	60	3600	0.5	3.6	4.1			
5	70	4900	0.5	4.9	5.4			
Mean	50	2700						

In the simple case where age is the only characteristic defining WSBs, the approach requires information on both the distribution of patient ages at the start of the model AND the distribution of health benefits by age within the model where the time horizon exceeds one year. Those informational requirements grow given the reality that WSBs are weighted according to the combination of four factors, and quality of life also changes within the course of the model. Nevertheless, these types of information are readily available (or easily made available depending on the software) from most state transition models. Indeed, dedicated software packages such as Treeage Pro produce this output by default and, in any

case, it would be good modelling practice to consider these “Markov traces” as one means of checking the validity of the decision model.

Another alternative might be to make further approximations by ignoring the issue of changing age and quality of life throughout the model time horizon. The WSB adjustment using this method might be made using some estimate of the mean age and mean quality of life over time in the model, avoiding the need to make adjustments to the decision model itself entirely. Again, whether such a series of approximations yield acceptable results is an issue for further investigation.

The approach also requires that a suitable approximation to the WSB calculations can be established that is linear in parameters, though how one might define “suitable” in this setting is unclear. It may be expected that the WSB calculations are updated on an almost continuous basis, given the nature of the datasources and estimation techniques that underpin the current values. If this is the case then this introduces a further risk of adopting this method of implementation.

5. DISCUSSION

There are two key features of the proposed WSBs element of VBP that pose challenges for how they are combined with estimates of cost per QALY derived from decision analytic models. Firstly, WSBs are determined by current age and current quality of life, both of which change throughout the course of the period of time modelled. Secondly, the relationships between WSB and age and quality of life are not linear meaning that estimates based on the mean patient(s) will be biased.

These problems can both be overcome with relatively little additional complexity where a decision model based on individually simulated patients is available. But models of this type have been seen relatively infrequently in economic evaluations submitted to NICE so far.

When faced with cohort models there are a range of options available which all amount to approximations to the true unbiased estimate of adjusted cost per QALY. The degree of bias associated with these approximations requires further exploration in case studies. It will also be important to try to establish the characteristics of diseases and/or technologies that may influence the degree of bias in different settings.

In all these cases there are additional informational requirements that may exceed those currently in existence for the purposes of NICE appraisals based on cost per QALY estimates. Obtaining appropriate estimates of the joint distribution of patient ages and quality of life, at the point at which the health technology is to be considered will be required. The

most appropriate sources for these estimates will be case specific but it may be that disease registries or clinical trial populations are appropriate.

The methods by which uncertainty is considered and conveyed to decision making committees is central to current methods of NICE appraisal. In particular, the reflection of the joint uncertainty in model parameter estimates using probabilistic sensitivity analysis is an important element of the NICE approach. VBP and the estimates of WSB introduce several additional layers of uncertainty and, at the very least, the parameter uncertainty element of WSBs ought to be reflected with the same degree of rigour as is currently the case for direct health effects and costs. Parameter uncertainty exists in every component of the calculations used to estimate the table of WSB values. Estimates are made using statistical models fitted to samples of data for issues such as the sick rate, the number of days worked at full health, the number of hours of childcare provided – all are uncertain and that should not be ignored. This could be integrated into the same Monte Carlo simulation routine used to account for other sources of parameter uncertainty in the cost per QALY estimates.

An approach to incorporating WSBs that is based on a statistical approximation to the current set of circa 65,000 values itself should really recognise as part of the analysis that those 65,000 values are not datapoints but are themselves estimates AND the resulting statistical model itself is estimated with uncertainty, both of which should not be ignored.

Proposed next steps

We will select a range of cost effectiveness models that combined reflect the key modelling approaches typically seen in submissions to NICE. These will include a standard state transition cohort model and a patient level simulation model. We will compare the results of implementing the following methods in each of the selected case study models, though it may be the case that some approaches prove to be unfeasible given the required degree of reprogramming;

1) Incorporation of WSBs within an existing full patient level simulation,
2) Investigation of the feasibility and results from converting cohort models to patient level simulations and incorporating WSBs directly
3) Use of age/quality of life subgroups to approximate the distribution of the patient population for use in cohort models.
4) We will investigate the possibility of estimating a multivariate regression model of WSBs as a function of age, quality of life, sex and ICD code. If an acceptable

statistical model can be estimated we will combine this with summary outputs from the models.

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