INCORPORATING WIDER SOCIETAL BENEFITS INTO ESTIMATES OF COST PER QALY: CASE STUDIES

REPORT BY THE DECISION SUPPORT UNIT

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Susan Griffin, Stephen Palmer, Marta Soares, Eldon Spackman, Paul Tappenden, Allan Wailoo and Sophie Whyte

Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street Sheffield, S1 4DA

Tel (+44) (0)114 222 0734

E-mail dsuadmin@sheffield.ac.uk

www.nicedsu.org.uk

ABOUT THE DECISION SUPPORT UNIT

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1. INTRODUCTION

This is the second of two reports from the DSU which consider issues around the implementation of values intended to reflect "Wider Societal Benefits" (WSBs) within NICE assessments of cost effectiveness. The full background to this project is outlined in the first report. The first report also considered a number of potential challenges to incorporating WSBs into existing estimates of cost per quality adjusted life year (QALY), and provided some potential solutions to those challenges.

Two specific issues were identified. First, WSBs are calculated as a function of age, sex, International Classification of Diseases (ICD) code and quality of life. The relationship between WSB and both age and quality of life is non-linear in nature. This means that the calculated value for a patient (or group of patients) with mean characteristics for the relevant cohort will be a biased estimate of the mean WSB for the cohort. Second, in many cases the value of age and quality of life will change throughout the time period for which costs and benefits are assessed. Both of these issues mean that simple adjustments to summary estimates of costs and QALYs are unlikely to lead to unbiased estimates of WSBs.

Four potential methods were suggested to incorporate WSBs into cost effectiveness models, in addition to more simple adjustments of summary output statistics.

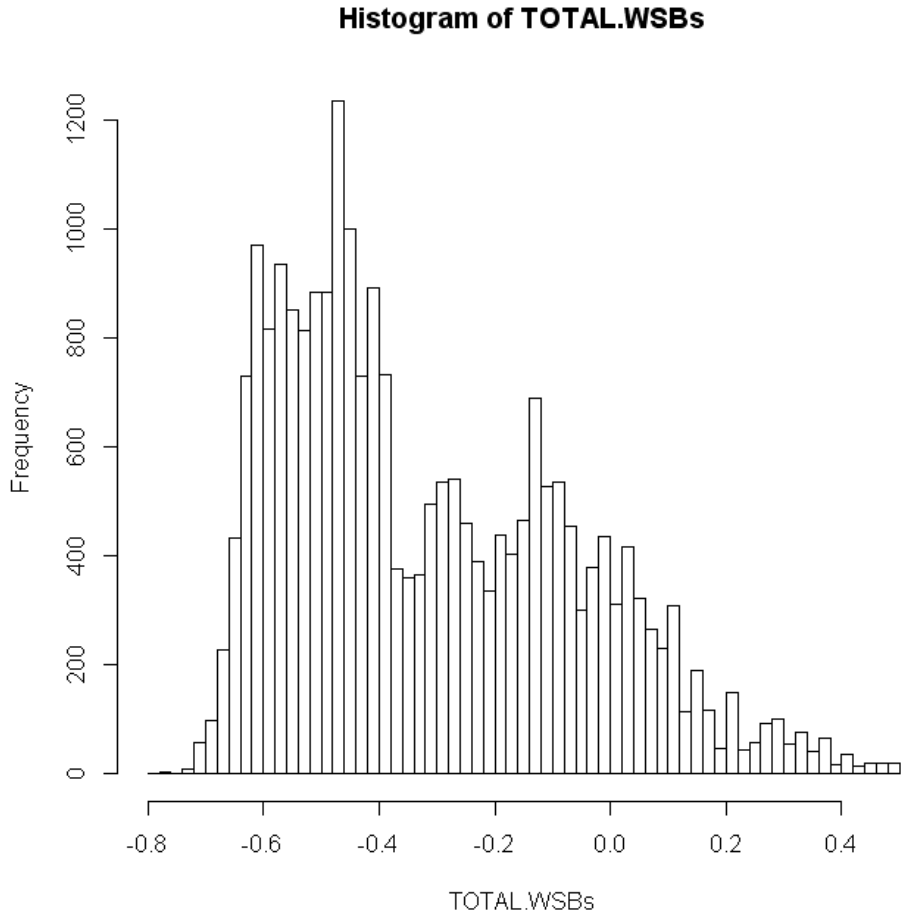
1) Incorporation of WSBs within an existing full patient level simulation,
2) Running cohort models as "pseudo" patient level simulations
3) Use of age/quality of life subgroups to approximate the distribution of the patient population for use in cohort models.
4) Making estimates of WSBs outside the decision model by making use of a statistical model, linear in parameters, to approximate the full set of WSBs.

The purpose of this second report is to attempt to implement these options in three case study models. Cases studies selected were for treatments in rheumatoid arthritis, asthma and metastatic colorectal cancer. We report on the feasibility of implementing each method, other practical considerations, the requirements for data exceeding those normally required in the course of a technology appraisal and the impact on results from those methods that were implemented.

2. ESTIMATING A STATISTICAL APPROXIMATION TO THE SET OF WSBS

We attempted to estimate WSBs, as a linear function of the parameters age, sex, ICD code and Quality of Life (QoL), or their squared and cubed terms, based on values supplied by the Department of Health in an Excel table. The table comprises 23,902 WSBs expressed in terms of QALYs based on 17 categories for QoL, 19 for ICD, 37 for age and 2 for gender. 1,075 of these are unique values. The distribution of the WSBs is shown in figure 1.

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



We ran various linear models in R starting with age, QoL, gender and ICD as explanatory variables. We inspected model results in terms of fit, significance of each of the covariates and model diagnostics such as the degree of normality in the distribution of the residuals. Additional parameters were added in response to considerations of these issues. We did not include any interaction terms because of the additional complexity this would imply for using

the results alongside cost effectiveness models. Similarly we restricted the models to the inclusion of cubic terms.

We found that ICD codes B, D, E, G, J, Q and Z gave near equivalent results and these were therefore merged.

The best fitting model included squared and cubed terms for Age and QoL, as well as ICD codes (merged as described above) and gender. Whilst in many settings the value of summary measures of fit is questionable, and what constitutes "good" fit is also unclear, in the current situation the fit of the model would seem to be of particular interest. The R^2 for this model was 0.68 and a mean absolute error of 0.11. Given that the total range for these values lies from approximately -0.8 to 0.4, this is a relatively large error. The model also suffered from substantial heteroskedasticity. We therefore conclude that no acceptable linear approximation to the WSBs can be estimated and did not pursue this method further.

3. CASE STUDIES

3.1. OMALIZUMAB FOR THE TREATMENT OF SEVERE PERSISTENT ALLERGIC ASTHMA

3.1.1. Background and methods

This case study relates to a health economic model developed to inform the review of Technology Appraisals 133 and 201 - omalizumab for the treatment of severe persistent allergic asthma.[1] The draft guidance was that omalizumab should not be recommended for treating severe persistent allergic asthma
http://guidance.nice.org.uk/TA/WaveR/110/Consultation/DraftGuidance.

The patient population comprises individuals with severe persistent allergic asthma aged 6 years and older. The authors report the cost-effectiveness of children and adults; the results for the adult population were used for this analysis. The ICD code for the disease is J. The trials considered patients aged between 6 and 11 years (mean age 9), and aged 12 and above (mean age 43). The characteristics of the disease change with age but it is largely a chronic, incurable condition. The treatment, omalizumab, is an add-on therapy to standard treatment,

assumed to be taken for 10 years in the model used in the appraisal. The aim of treatment is to treat symptoms and to reduce exacerbations which can lead to hospitalisation and death.

The cost-effectiveness analysis was performed using a Markov cohort model which followed the NICE Reference Case. The assumed treatment duration was 10 years, after which the patients who had received omalizumab revert to the risks, utility and costs associated with standard treatment. The model was probabilistic, with probabilistic sensitivity analysis performed by means of Monte Carlo simulation executed via visual basic macro.

The basic model structure consisted of two health states: alive with severe asthma and dead. The cycle length was three months. Patients who were alive could experience exacerbation events, which were associated with a quality of life decrement and cost. Exacerbation events were assumed to be of four weeks duration. The Markov trace recorded the number in each health state and the number of events separately for men and women before summing to provide total costs and total QALYs for the whole cohort. The model considered different subgroups of patients according to age and severity of disease but each cohort contained the same proportion of men and women.

Table 1 Summary of asthma case study

Population	Children and adults with severe persistent allergic asthma (ICD code first letter J)
Intervention	Omalizumab add-on therapy (for 10 years)
Comparator	Standard care
Perspective	NHS and Personal Social Services
Model type	Markov cohort model
Software	Excel
Time horizon	Lifetime (until age 100)
Discount rate	3.5% for costs and health outcomes
Parameter uncertainty	Probabilistic sensitivity analysis - conducted by Monte Carlo simulation using Visual Basic
Model results	Total discounted costs and total discounted QALYs (based on probabilistic analysis)

3.1.2. Incorporation of WSBs

We developed alternative analytic approaches to calculate WSB within a cohort model. We began by considering the most aggregate form of analysis based on the summary model results and Assessment Report without requiring access to the electronic model or additional searches for data. We then considered what could be done with access to the model and the challenges faced in interpreting a model appropriately in order to calculate WSB at the most disaggregate level. We then extend this approach to consider subgroups of age (A), gender (G) and starting QoL (Q). Note that given the cohort nature of the decision model, we will not have the 'correct' WSB estimate, which would need patient level estimates. The application of alternative methods to the case study results will allow us to point to where there are big differences in the WSBs we estimate but we will not be able to say which is best.

We will not evaluate comprehensively how parameters of the model may differ with Age, Gender, ICD, and Quality of Life over and above what is already being considered in the current model.

3.1.2.1. Implementation and Results using Summary Statistics

The first level of calculation will use only information presented in the manufacturer's, Assessment Group's or Evidence Review Group's report.

The minimum level of summary statistics available in cohort models submitted to NICE will include the total costs and total QALYs for each treatment. These will incorporate any discounting that was applied in the model.

Age	Starting or mean age of the cohort (depending on how accrual of WSB over time is calculated)
Gender	Reported ratio of men:women in starting cohort
ICD	As per disease area
Quality of Life	QALYs/Lys
Discounting	As per the summary statistics

Information should be provided on the starting age and assumed gender (or ratio of genders) of the cohort model. In this first analysis the gender ratio will be assumed constant over time. The effect of age and ageing will be considered in two alternative ways; these will be detailed below. In what concerns QoL scores, and given we are here only using summary statistics, it is not possible to track their evolution over time. Thus an average absolute QoL score for each arm will need to be calculated, and this will determine the WSB gains due to treatment. If life year estimates are available within the model then the average quality of life weight could be calculated as QALYs/LYs. However, if the available information from the model does not include LYs, an approximation can be used. If QALYs are discounted then LYs or their approximation should be discounted at the same rate.

Applying the values for AGIQ assigned above will provide a single estimate of WSB weight. In practice these WSBs would accrue (and vary) over time. Three ways of accumulating WSB over time are here considered:

1) The simplest way is to simply multiply the WSBs by the number of expected life years.
2) WSB could be alternatively calculated over time by varying the age across the age range that patients are expected to be alive (G, I and Q are here constants), i.e. from initial age to life expectancy. WSB can then be summed across the ages.
3) WSB could be alternatively calculated over time by varying the age across the age range that patients are alive (G, I and Q are here constants), e.g. from initial age to 100 years old. The expected proportion of patients alive at each age would need to be considered to obtain an overall WSB estimate. The LY value (or estimate) can be used to calculate an expected proportion of patients alive at each age. A simple method by which to achieve this would be to define an exponential survival function, though this may not match actual survival in the model.

Results

We used the QALYs for each treatment estimated from the probabilistic analysis as reported in the MTA. No life-year estimates were reported in the case study. We used the life expectancy from life tables associated with the starting age of the model cohort to estimate life-years. This assumption ignores all possible mortality effects of the disease or treatment. As we would expect asthma to have a life-expectancy similar to the general population this

may be a reasonable assumption. Any mortality benefits from treatment will mean our estimates overestimate the difference in quality of life and bias the WSB.

The starting age in the model is 43 years old; from the UK life tables we weighted the life expectancy of males and females by the proportion in the population and estimated the population life expectancy and therefore life-years to be 39 years (http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables). Life-years were discounted at the model's 3.5% discount rate for health benefits to give a discounted life expectancy of 22.1 years. The reported QALYs were divided by the discounted estimate of life-years to calculate an average quality of life for each treatment. If the QALYs had been reported by male and female then gender specific quality of life could be estimated using gender specific life-years.

The age used to calculate the WSB was the average age in the model. The starting age of the model is 43, with a life expectancy of 39 the expected age of death is 82. The average age in the model was estimated to be 62, the midpoint between 43 and 82.

The annual WSBs were estimated for an average age of 62 using the quality of life as calculated above for both treatments and genders. A WSB representing the average patient was calculated by weighting the male WSB and female WSB for each treatment by the proportion of males and females in the starting population. The annual WSB was then, in a first analysis, multiplied by the life-expectancy to calculate the discounted WSB over the patients expected life-time.

Table 2 Results using summary statistics

Treatments	Costs	WSB	QALY	Total	Multiplier*
Standard therapy	£ 33,218	-4.67	13.66	8.99	
Omalizumab	£ 72,938	-4.33	14.13	9.80	
Difference	£ 39,720	0.34	0.47	0.81	1.72
ICER	£ 48,944				

* The Multiplier is Total/QALY

The results of this analysis suggest that the WSB of omalizumab are 0.34 QALYs higher than standard therapy compared to a 0.47 QALY improvement in health. This results in a 0.81 QALY improvement with an ICER of £48,944 per additional QALY.

These results do not consider that the WSB were accumulated at different ages, but assume the average age. To correct for this we use the quality of life estimates for each treatment as calculated above but calculate a WSB for each gender at each age starting at the model starting age of 43 and summing these WSB to the life expectancy of 82. Again WSB have been discounted at the discount rate for health.

Table 3 Results using summary statistics accounting for age over time

Treatments	Costs	WSB	QALY	Total	Multiplier
Standard therapy	£ 33,218	-3.25	13.66	10.41	
Omalizumab	£ 72,938	-2.91	14.13	11.22	
Difference	£ 39,720	0.34	0.47	0.81	1.72
ICER	£ 49,005				

The results of accounting for age overtime in the estimation of the WSB change the difference between treatments in WSB only slightly resulting in an ICER of £49,005 per additional QALY. Summing across the WSB from age 43 to age 82 assumes that all patients are alive at each age. To correct for this we weight the WSB by an exponential function. The full cohort (100%) is alive at the starting age of 43. The mean life expectancy of 82 is converted to a constant hazard for an exponential in order to predict the proportion of the cohort alive each year until the model time horizon of age 100 years. The WSB at each age is multiplied by the proportion of the cohort still alive and summed to the model timeframe of 100 years.

Table 4 Results using summary statistics accounting for age and death over time

Treatments	Costs	WSB	QALY	Total	Multiplier
Standard therapy	£ 33,218	-3.06	13.66	10.60	
Omalizumab	£ 72,938	-2.74	14.13	11.39	
Difference	£ 39,720	0.31	0.47	0.78	1.66
ICER	£ 50,600				

This results in the difference in WSB decreasing and the ICER increasing to £50,600 per additional QALY.

3.1.2.2. Implementation and Results calculating WSBs per model cycle

The second level of calculation will involve calculating WSBs in each cycle of the model. This necessitates using information available from the Markov trace.

In order to reflect differing quality of life weights over time WSBs can be calculated per cycle and then summed according to the proportion of the cohort in each health state. Two alternative procedures can be used:

1) The simplest way is to use QALY and patients alive per cycle to evaluate an average QoL score per cycle, calculate WSB per cycle and sum across cycles weighting by the proportion of patients alive.
2) Alternatively, the QoL score per health state can be used to calculate WSB per health state per cycle and then summed appropriately.

If a single trace is run for a mixed cohort of men and women then this ratio will be used for the WSB calculation. If separate traces are available by gender then these will be used.

Age	Current age in cycle
Gender	Reported ratio of men:women in starting cohort or for each cycle (if available)
ICD	As per disease area and health state (where this confers change in ICD)
Quality of Life	Quality of life for each health state in current cycle
Discounting	By cycle

Probabilistic results are compared to deterministic results.

As described above the Markov trace was used to calculate a per cycle WSB. This was initially done by calculating the average quality of life per cycle by dividing the QALY by the life-years of each cycle. Ages at each cycle were rounded to the nearest age found in the WSB table provided by the DH. WSB were estimated for males and females at each cycle given the rounded age and the same quality of life. An average WSB for the population was estimated by weighting the male WSB and female WSB by the proportion of each in the population. WSBs were weighted by the length of the cycle and discounted.

Table 5 Calculating WSBs per model cycle - deterministic analysis

Treatments	Costs	WSB	QALY	Total	Multiplier
Standard therapy	£ 33,222	-2.99	13.66	10.67	
Omalizumab	£ 72,916	-2.78	14.14	11.36	
Difference	£ 39,694	0.21	0.48	0.69	1.44
ICER	£ 57,395				

Table 6 Calculating WSBs per model cycle - probabilistic analysis

Treatments	Costs	WSB	QALY	Total	Multiplier
Standard therapy	£ 34,636	-3.00	13.68	10.68	
Omalizumab	£ 74,544	-2.78	14.15	11.37	
Difference	£ 39,908	0.22	0.47	0.69	1.44
ICER	£ 57,832				

Probabilistic results are very similar to the deterministic results with the difference in WSBs being 0.01 higher in the probabilistic results. The probabilistic analysis took 8 hours to run due to the number of "lookups" necessary from the large WSB table provided by the DH.

The model was not set-up with quality of life for all the possible health states. Instead events were accumulated with quality of life decrements applied for each of two events. From the event counts and quality of life decrements it was possible to calculate quality of life values for the two events and treat the events as health states. Events were also calculated by the model for males and females separately. This allowed us to calculate a WSB for each health state or event by gender for each cycle. The model changes necessary for this analysis were time consuming due to a need to understand the model sufficiently to make the changes.

The results of this analysis are very different from previous results. Programming was double checked to assure that the calculations were correct, but no errors could be detected.

Table 7 Calculating WSBs per model cycle using health states - deterministic

Treatments	Costs	WSB	QALY	Total	Multiplier
Standard therapy	£ 33,222	-1.45	13.66	12.21	
Omalizumab	£ 72,916	-0.72	14.14	13.42	
Difference	£ 39,694	0.74	0.48	1.21	2.52
ICER	£ 32,720				

Table 8 Calculating WSBs per model cycle using health states - probabilistic

Treatments	Costs	WSB	QALY	Total	Multiplier
Standard therapy	£ 4,226	-1.46	13.67	12.21	
Omalizumab	£ 74,004	-0.72	14.14	13.42	
Difference	£ 39,778	0.73	0.48	1.21	**2.52**
ICER	£ 32,863				

3.1.2.3. Subgroups

The third level of calculation will involve calculating summary statistics for subgroups of the overall cohort and then using these results to calculate WSBs in each subgroup. The subgroup results can then be recombined to obtain the total costs, total QALYs and total WSBs for the population considered in the original decision.

Exploring subgroups necessitates re-running the model submitted to NICE with different starting characteristics. In many appraisals subgroup analyses may have already been conducted. Some models submitted to NICE will incorporate parameter values that differ by gender or age, and may allow the starting gender or age of the cohort to be varied. However, the information used to parameterise the model may pertain to a particular age or gender group and so consideration will have to be given to whether this is appropriate.

The quality of life weights applied in the model may be derived from a sample of patients with an underlying distribution of disease severity, age and gender and the appropriateness of amending these should be considered carefully. Further consideration must be given to consistency of quality of life weights across all of the health states in the model. If the quality of life weight of the starting state is to be amended it may be necessary to maintain fixed absolute differences between the remaining health states but bound by the maximum and minimum values possible (e.g. 1 and -0.57 for EQ-5D).

In order to define subgroups by age, gender and quality of life some information will be required as to the starting distribution of all three characteristics for each of the patient groups considered. For example, some information may be available on the mean and standard deviation of age and the ratio of males to females for patients analysed in the clinical trials used to inform the decision model. Consideration must be given to correlation, for example whether the distribution of starting age would differ by gender.

To explore the impact of the number of subgroups explored we will begin with a minimum of four age bands for each gender (as appropriate). It may not be possible to recombine the results of the subgroups in order to replicate the original totals, especially when the starting quality of life has been amended such that ceiling or floor effects prevent the maintenance of differentials between health states. In these circumstances it may be necessary to consider whether the original total costs or QALYs or the recombined subgroup total costs and QALYs should form the basis of VBP decisions.

Age	Median age of the subgroup
Gender	As per subgroup
ICD	As per subgroup disease area
Quality of Life	Average quality of life weight: QALYs/LYs
Discounting	Discounted to median survival of the subgroup

Additional reasonable alternative assumptions can then be explored. We will evaluate the impact of correlations between age, gender and/or quality of life weights. For example, in the asthma model we could assume that starting quality of life declines with age and utilise information from UK population norms to amend the quality of life weights in the model accordingly. These amended quality of life weights could remain constant over the duration of the model (as with the original submission).

These can then be combined to calculate WSBs in each cycle of the model for subgroups.

Age	Current age in cycle
Gender	As per subgroup
ICD	As per disease area and health state
Quality of Life	Quality of life in for each health state in current cycle
Discounting	By cycle

Probabilistic models will propagate uncertainty through to the estimate of WSBs. We may wish to compare results with calculating WSBs based on a deterministic analysis, but this was not undertaken due to time constraints.

Results

Subgroup analyses were performed on age and gender. No information was found in the MTA report on the distribution of age. The EXALT trial[2] reported different age groups which were used to calculate the subgroups. For consistency gender distribution was also used from the EXALT trial, 64.8% female, this differs from the previously used 66.6% from the model. Subgroup results were calculated for both methods (average quality of life across health states versus quality of life by health state) calculating WSB per model cycle.

The difference in WSB across subgroups varied from 0.06 to 0.19 using the total QALY calculation and from -0.35 to 2.57 using the health state calculation. The weighted average difference in WSB was 0.16 using the total QALY calculation and 0.64 using the health state calculation (Table 10). The ICERs differ by more than £10,000 compared to the non-subgroup calculation in the case of the total QALY calculation and by less than £3,000 in the case of the health state calculation.

Table 9 Age distribution from EXALT

Age distribution	**Average Age**	**Proportion**
<18	14	1.3%
18-54	35	70.3%
55-64	60	21.8%
≥65	70	6.8%

Table 10 Subgroup results

Treatments	Costs	WSB (Total)	WSB (Health States)	QALY
Standard therapy	£ 32,447	-2.70	-3.78	13.34
Omalizumab	£ 71,758	-2.54	-2.09	13.81
Difference	£ 39,310	0.16	1.69	0.47
ICER		£ 62,397	£ 35,414	

Table 11 Subgroup results for females

Treatments	Costs	WSB (Total)	WSB (Health States)	QALY
Standard therapy	£ 32,968	-3.02	-4.51	13.56
Omalizumab	£ 72,404	-2.87	-2.46	14.03
Difference	£ 39,436	0.15	2.05	0.47
ICER		£ 62,871	£ 15,633	

Table 12 Subgroup results for males

Treatments	Costs	WSB (Total)	WSB (Health States)	QALY
Standard therapy	£ 31,490	-2.11	-2.43	12.95
Omalizumab	£ 70,569	-1.93	-1.40	13.41
Difference	£ 39,079	0.18	1.03	0.46
ICER		£ 60,677	£ 26,277	

A subsequent analysis included quality of life along with age and gender. The quality of life was estimated for the midpoint of each quartile from the mean and (standard error) reported in the model, 0.719 (0.026) and 0.767 (0.02) for standard therapy and omalizumab respectively. Quality of life was not correlated with age or gender as no information to do so was available. Age and gender distributions were used as above.

Table 13 Distribution of utilities for no event health states

	Percentile			
Treatments	**12.5**	**37.5**	**62.5**	**87.5**
Standard therapy	0.688904	0.711141	0.72774	0.748776
Omalizumab	0.743855	0.76098	0.773738	0.789886

The difference in WSB across subgroups varied from 0.05 to 0.23 using the total QALY calculation and from -0.56 to 2.71 using the health state calculation. The weighted average difference in WSB was 0.17 using the total QALY calculation and 0.65 using the health state calculation (Table 14). The ICERs differ by more than £10,000 compared to the non-

subgroup calculation in the case of the total QALY calculation and by less than £3,000 in the case of the health state calculation.

Table 14 Subgroup results by quality of life, age and gender

Treatments	Costs	QALY	WSB (Total)	WSB (Health States)
Standard therapy	£ 32,447	13.35	-2.73	-1.28
Omalizumab	£ 71,758	13.81	-2.56	-0.63
Difference	£ 39,310	0.47	0.17	0.65
Multiplier (Total vs. QALY)			**1.36**	**2.38**
ICER			£ 61,744	£ 35,238

3.2. RITUXIMAB IN METHOTREXATE-INTOLERANT PATIENTS WITH RHEUMATOID ARTHRITIS

3.2.1. Description of model

Patient population

This model considers a population with severe rheumatoid arthritis (RA) that has already failed on several previous lines of treatment and who are intolerant to methotrexate.[11] As this is a patient level model it incorporates male and female patients and a range of ages appropriate for the population with disease. Patient age is sampled from a normal distribution (with mean 54 and standard deviation of 10) whilst patient gender is sampled so that 80% are female.

Characteristics of treatment

An economic model was developed based on the economic model used in the previous NICE appraisal of Rituximab (RTX). The model compares RTX monotherapy with leflunomide and estimates the costs and effects of treatment over a patient's lifetime. Following initial treatment (leflunomide or one course of RTX), patients are assumed to receive palliative care on disease progression. The first two years of the analysis of patient response and time spent on treatment are based on clinical trial data and extrapolated beyond this.

Decision model

The cost-effectiveness analysis was performed using a patient level simulation excel model. The cost-effectiveness of rituximab versus DMARDs is evaluated. Health outcomes are expressed using quality adjusted life years (QALYs) in the economic analysis. Both costs and QALYs are discounted at 3.5%, as per current NICE guidance. The ICER for rituximab versus DMARDs in the base case model (excluding all WSBs) was approximately £16,000 per QALY. The model was probabilistic, with probabilistic sensitivity analysis performed by means of Monte Carlo simulation executed via visual basic macro. The original analysis was run for 1,000 patients for 1,000 second order Monte Carlo simulations. The WSB were estimated running the model deterministically for 10,000 patients.

3.2.2. Implementation of the methods

WSB lookup table

The VBP WSB table provides the wider societal benefits in £'s by patient age, ICD code, gender and QoL (to nearest 0.1). A copy of the WSB lookup table was included within the model as an additional sheet. For each patient in the simulation the 'code' was calculated and this was used to lookup the appropriate WSB from the table. The code is of the form '1+QoL' ICD age gender, for example 1.3M54F for QoL=0.3, ICD=M, age=54, gender=female.

Not all ages were provided in the WSB table (and the intervals between included ages varied from 2 to 5 years). The patients exact age was rounded down to an age included within the WSB table and this was used for the analysis. A WSB table which included and entry for each possible age would improve accuracy. The WSB lookup table had granularity of 0.1 for QoL so linear interpolation was used to estimate precise WSBs for the utility values.

The combination of generating the codes, looking up in the WSB table and linear interpolation makes the formulae relatively complex.

Analysis population

Firstly the analyses were undertaken with age sampled from a normal distribution (mean=54, sd=10). Secondly, subgroup analyses were undertaken for 10 year age bands (30-39, 40-49, 50-59, 60-69, 70-79, 80-89). This was implemented by modifying the distribution from which

patient age is sampled to be a uniform distribution over a given decade. A short VBA macro was written to run the analyses over each of these age subgroups and to store the results in the new WSB results sheet.

Method 1- Patient level analysis using average QoL and age at start of treatment

For each patient WSBs were calculated based on patient age at the start of treatment and average QoL over the remainder of their lifetime. The average QoL was calculated on the two model sheets which estimate QALYs. The QoL values available in the model were discounted so these were first converted to undiscounted values. To un-discount the QALYs each 6 month QALY gain was multiplied by (1+0.035)^years. The total undiscounted QALY gain was then divided by the total life years accrued to give the average QoL for each patient.

The average QoL for a patient was combined with the patient's gender, age and ICD to form a 'code'. The WSB value was multiplied by the discounted life years gained to obtain the total WSB contribution for the patient.

Method 2 – Patient level analysis calculating WSB for each model cycle

For each patient the WSBs were calculated for each 6 monthly cycle of the model separately. This was implemented on the two model sheets which estimate QALYs. For each cycle the WSB contribution was discounted then added to the expected QALYs for that cycle (note that the expected QALYs were already discounted).

Model outputs

The inclusion of WSBs (using either method) resulted in a significant change to both expected QALYs and incremental QALYs associated with the treatment but the impact was greatest with method 2. The difference between the population estimates and the estimate for the age subgroup containing the mean age was only slight. As the QoL values are often below 0.5 in this model the expected QALYs together with the WSB contribution were regularly negative. Although the value of the expected QALYs changes dramatically with the inclusion of WSBs the impact on the incrementals is less significant. However the impact on the incrementals varies between methods 1 and 2 suggesting that the results are certainly sensitive to the calculation methods employed.

Table 15 WSBs from Rituximab model: Patient level analysis using mean QoL (Method 1)

Treatments	Costs	WSB	QALY	Total	Multiplier
DMARD therapy	£12,847	-5.95	1.945	-4.005	
Rituximab	£14,804	-6.04	2.07	-3.97	
Difference	£1,957	-0.09	0.125	0.035	0.28
ICER	£55,914				

Table 16 WSBs from Rituximab model: Full patient level analysis (Method 2)

Treatments	Costs	WSB	QALY	Total	Multiplier
DMARD therapy	£12,847	-10.137	1.945	-8.192	
Rituximab	£14,804	-10.042	2.07	-7.972	
Difference	£1,957	0.095	0.125	0.22	1.76
ICER	£8,895				

Table 17 WSBs from Rituximab model: Patient level analysis using mean QoL by age subgroup (Method 1)

Treatments	Costs	WSB	QALY	Total	Multiplier
DMARD therapy	£12,847	-5.888	1.945	-3.943	
Rituximab	£14,804	-5.975	2.07	-3.905	
Difference	£1,957	-0.087	0.125	0.038	0.304
ICER	£51,500				

Table 18 WSBs from Rituximab model: Age subgroups in patient level analysis (Method 2)

Treatments	Costs	WSB	QALY	Total	Multiplier
DMARD therapy	£12,847	-9.954	1.945	-8.009	
Rituximab	£14,804	-9.881	2.07	-7.811	
Difference	£1,957	0.073	0.125	0.198	1.584
ICER	£9,884				

3.3. BEVACIZUMAB FOR THE FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER

3.3.1. Methods

Description of model

This case study relates to a health economic model developed to inform Technology Appraisal 118 – bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.[3] Within this appraisal, two separate decision-analytic models were developed by the Assessment Group as the two interventions under appraisal were not competing therapies at the same point in the pathway.[4] This case study *only* concerns bevacizumab in combination with chemotherapy for the first-line treatment of metastatic colorectal cancer. As part of the appraisal, the Assessment Group undertook comparisons of bevacizumab plus chemotherapy versus chemotherapy alone across two different indications: (1) in combination with IFL (irinotecan plus 5-fluorouracil plus folinic acid [5-FU/FA]) and (2) in combination with 5-FU/FA alone. These analyses were presented as separate comparisons due to heterogeneities between the trial populations from which the efficacy evidence was drawn. For the purpose of this case study, we concentrate only on bevacizumab plus IFL versus IFL.

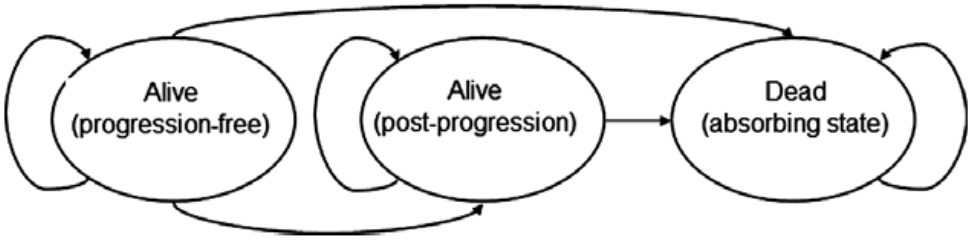
The model follows the current NICE Reference Case[5] in all respects with the exception that discounting is not included the model. This was due to (a) the short time horizon employed within the model (mean survival <2 years) and (b) uncertainty with respect to the timing of resource consumption within the available trial data. The scope of the economic analysis used in the case study is summarised in Table 19:

Table 19 Summary of economic evaluation scope for colorectal cancer case study

Population	Patients with untreated metastatic colorectal cancer
Intervention	First-line bevacizumab in combination with irinotecan, 5-fluorouracil and folinic acid (IFL)
Comparator	Irinotecan, 5-fluorouracil and folinic acid (IFL)
Economic outcome	Incremental cost per quality adjusted life year (QALY) gained
Model type	Decision-analytic survival model
Perspective	NHS & Personal Social Services
Handling of parameter uncertainty	Fully probabilistic
Discount rate	Not applied
Time horizon	Remaining lifetime

The model was implemented as a decision-analytic survival model – an approach sometimes referred to as a partitioned survival model. The model uses three mutually exclusive health states – (1) Alive – progression-free; (2) Alive - post-progression, and; (3) Dead (Figure 2).

Figure 2 Model structure



This modelling approach is similar to a time-varying Markov process, except that transitions between states are not modelled directly, as the clinical endpoints used to inform transitions between states are not sufficiently specific (progression-free survival [PFS] curves tell us about progression from a state without progression to *either* post-progression or death, and [OS] overall survival curves tell us about progression from *either* a state without progression or a state of post-progression to dead). Instead, the model simply captures mean sojourn time

(MST) in each state for a given Treatment *i* as $MST(OS_i)=\int OS_i\, dx$; $MST(PFS_i)=\int PFS_i\, dx$ and $MST(PPS_i)=\int OS_i\, dx - \int PFS_i\, dx$.

Whilst the model *could* capture a Markov trace, this is unnecessary as the estimated MST in each state can be calculated exactly by integrating over the relevant survival curves. All MST estimates were generated by extrapolating censored OS and PFS curves from the trials using parametric Weibull survival curves. Different levels of HRQoL are applied to the living health states, with a higher health utility score assigned to the progression-free state. The model does not include any adjustment of HRQoL according to age, sex or treatment received. The model was implemented on a cohort basis and was programmed in Microsoft Excel (including some Visual Basic for Applications [VBA] routines).

Methods for estimating wider societal benefits in the case study

Time-to-event curves for PFS and OS were drawn from a single trial reported by Hurwitz *et al*.[6] No adjustment was made for competing risks associated with age - age itself is not explicitly included in the model as the OS endpoint includes death from cancer and death from other causes. In other words, the risk of death from non-cancer causes is already encapsulated within the available OS curves. Consequently, the model does not explicitly include any other characteristics or covariates relating to the distribution of patients with metastatic colorectal cancer who may be eligible to receive bevacizumab. No subgroups were identified within the appraisal and time-to-event data were available only for the intention-to-treat (ITT) population.

For the purposes of estimating the potential impacts of capturing additional impacts of wider societal benefits (WSBs), other information was necessary to estimate the distribution of age- and sex- across the relevant population. As is common for trials of active chemotherapies and biologics, the Hurwitz et al trial[6] was undertaken in a comparably younger patient population to that of the UK colorectal cancer population, and the trial publication did not report the age-distribution of the recruited cohort. Instead, the distribution of age- and sex- specific diagnoses of colorectal cancer was taken from the Office for National Statistics (ONS) publication Cancer Statistics Registrations, England (Series MB1), No. 41, 2010.[7] This report gives frequencies of cancer registrations (ICD code C) for England by gender and 5-year age band.

Table 20 Age-and sex- distribution weights

Age band	Observed number of cases registered		Adjusted weighting within band for individual starting year*		Comment
	Male	Female	Male	Female	
Under 1	-	-	0.000	0.000	Outside of licensed indication
1-4	-	-	0.000	0.000	
5-9	-	-	0.000	0.000	
10-14	7	1	0.000	0.000	
15-19	7	7	0.000	0.000	Some patients in the 15-19 age group may receive treatment
20-24	17	28	0.000	0.000	
25-29	39	55	0.000	0.000	
30-34	70	75	0.001	0.001	
35-39	82	90	0.001	0.001	
40-44	215	208	0.002	0.002	
45-49	434	364	0.004	0.003	
50-54	739	570	0.006	0.005	
55-59	1173	837	0.010	0.007	
60-64	2526	1510	0.021	0.012	
65-69	2970	1876	0.024	0.015	
70-74	3080	1999	0.025	0.016	
75-79	2969	2318	0.024	0.019	
80-84	2377	2202	0.000	0.000	Unlikely to receive active treatment
85 +	1885	2488	0.000	0.000	

**The weights presented in the table reflect those for a patient with a discrete starting age rather than for the band. This assumes an equal distribution of patients within each 5-year age band.*

Two limitations should be noted with respect to the use of this source: (1) the distribution reflects the broader population of patients with a diagnosis of colorectal cancer rather than those patients specifically with *metastatic* disease, and; (2) the distribution does not reflect restrictions on the use of bevacizumab or any other therapy. With respect to the latter point, the safety and efficacy of bevacizumab has not been established in paediatric or adolescent

populations and it is unlikely that patients would receive such active cytotoxic drugs or biologics beyond the age of 80 years. In order to reflect these other factors, we adjusted the distribution in an attempt to improve its representativeness to the decision problem (see Table 20).

Methods for implementing WSBs in the model

The original economic analysis was undertaken from the perspective of the NHS and PSS only. Wider societal benefits were estimated using two alternative methods: (i) estimating cohort-level WSB impacts using summary statistics only, and (ii) by estimating the additional WSB QALY impact according to age- and sex-specific subgroups within the model and weighting these impacts according to the proportion of the overall metastatic colorectal cancer population represented within each subgroup. Owing to the absence of any other information on covariates which are likely to influence cost or health outcome, the direct costs and health outcomes are not varied by WSB subgroup in either analysis. Further, we did not attempt to adapt the model into a patient-level simulation, as this would require considerable manipulation of the available survival curves to estimate the post-progression survival distribution conditional on progression for each group (see Discussion).

Method (i) Estimating cohort-level WSB impacts using summary statistics only

The first WSB calculation method was undertaken using the types of summary statistics that would be routinely available in a Technology Assessment Report or Manufacturer's Submission to NICE. This method involved estimating the proportion of the metastatic colorectal cohort eligible for treatment which is male/female and the mean starting age of the population according to gender. Table 21 shows the relevant information required for the analysis. In order to enable meaningful comparisons between methods, the values extracted were based on the point estimates of costs, life years and QALYs and thus do not reflect the expectation of the mean.

Table 21 Information used to estimate WSBs using summary statistics

Parameter/value	Bevacizumab +IFL	IFL	Comments
Total costs	£43,007	£23,646	Based on deterministic model analysis
Total QALYs	1.44	1.13	
Total LYs	1.98	1.57	
Proportion female p(F)	0.41	0.41	Based on MB1 for eligible population assuming equal distribution of patients within age bands
Mean age female	66.22	66.22	
Mean age male	66.68	66.68	
ICD	C	C	-
Utility progression-free	0.80	0.80	-
Utility post-progression	0.60	0.60	-
Mean PFS time (years)	0.98	0.68	Based on mean of extrapolation curves
Closest WSB lookup female PFS (concatenated WSB code)	0.8C66F	0.8C66F	-
Closest WSB lookup female PPS (concatenated WSB code)	0.6C66F	0.6C66F	-
Closest WSB lookup male PFS (concatenated WSB code)	0.8C66M	0.8C66M	-
Closest WSB lookup male PPS (concatenated WSB code)	0.6C66M	0.6C66M	-
WSB lookup female PFS (value)	-0.02238	-0.02238	-
WSB lookup female PPS (value)	-0.20716	-0.20716	-
WSB lookup male PFS (value)	-0.04274	-0.04274	-
WSB lookup male PPS (value)	-0.23064	-0.23064	-

Total WSBs for treatment group *i* were calculated as:

WSB_i=p(F).MST(PFS_i).WSB(F,PFS)+p(F).MST(PPS_i).WSB(F,PPS)+p(M).MST(PFS_i).WSB(M,PFS)+p(M).MST(PPS_i).WSB(M,PPS)

Where: M=male; F=female; MST=mean sojourn time; WSB=wider societal benefit impact

This method does not capture the distribution of WSBs across subgroups of the broader population - it only considers the estimated mean WSB for each treatment group. In addition, this approach does not include any assumptions about changes in WSB impacts as the patient's age increases. Given the short mean survival duration in the model and the size of the age intervals within the WSB lookup table, this latter simplification is unlikely to result in considerable bias. It should be noted that there are undoubtedly numerous other ways of generating WSB estimates using summary statistics, subject to which summary data are available and the acceptability of assumptions regarding the age of the cohort and changes in WSBs by patient age. Irrespective of which set of assumptions is selected, this approach is inevitably subject to a greater degree of bias than Method (ii).

Method (ii) Estimating WSB impacts according to age- and sex-specific subgroups within the model

The second method was undertaken within the model itself and overcomes some of the limitations of method (i).The additional WSB QALY impact for each treatment group in the model was calculated using the following steps:

1. Generate a Markov trace for each state and each treatment using the parametric survival curves employed in the original model. A cycle length of 0.01 years was used to ensure a smooth risk function for each survival curve.
2. Define WSB subgroups according to:
    a. starting age (range 18-79)
    b. gender (male/female)
    c. ICD code (C)
    d. HRQoL (PFS state utility =0.80, PPS state utility = 0.60)
3. Determine the WSB QALY impact for the given WSB subgroup at each age in the Markov trace by health state*
4. Generate estimates of direct QALYs, additional WSB QALY impacts and costs for each treatment for the given age- and sex-specific subgroup**

5. Repeat steps 3 and 4 for all WSB subgroups
6. Weight direct QALYs, additional WSB QALY impacts and costs according to the age- and sex-distribution from the MB1 report.

The process required an additional worksheet and a simple loop-based subroutine written in VBA.

* Note: We did not interpolate WBS weights according to the patient's precise age - instead we used direct lookup values (rounded down to nearest lower age bound)

** Estimated using point estimates of parameters rather than the expectation of the mean. We could have undertaken the analysis probabilistically without the need for considerable computational expense. Note also that the direct QALY gains and costs within both analyses are identical; only the WSB estimates differ between method (i) and method (ii).

3.3.2. Results

Table 22 presents the cost-effectiveness results for bevacizumab plus IFL versus IFL alone with and without WSB impacts. Based on the original economic analysis, the incremental cost-effectiveness ratio (ICER) for bevacizumab plus IFL versus IFL alone was approximately £63,000 per QALY gained.

It is evident that the additional impact of the WSBs is small in comparison to the direct health gains associated with treatment irrespective of which method is used. Importantly though, the two methods for estimating WSBs give different results. The summary statistics approach (Method i) favours the comparator group with an estimated difference of -0.04 WSB QALYs in favour of IFL. This results in a less favourable ICER for bevacizumab +IFL versus IFL of approximately £71,000 per QALY gained. The subgrouping method (Method ii) suggests the opposite impact – this produces a small incremental WSB gain of approximately 0.01 QALYs in favour of bevacizumab+IFL. This results in a more favourable ICER for bevacizumab+IFL versus IFL of around £60,000 per QALY gained.

Table 22 Cost-effectiveness results (with/without WSBs using both methods of computation)

Decision alternative	Bevacizumab+IFL	IFL alone	Incremental
QALYs gained	1.44	1.13	0.31
Estimated WSB QALY impact (method i)	-0.25	-0.22	-0.04
Estimated WSB QALY impact (method ii)	-0.11	-0.12	0.01
Cost	£43,000.62	£23,642.56	£19,358.05
ICER (Health)	-	-	**£62,857.10**
ICER (Health+WSB QALY impact – method i)	-	-	**£70,985.43**
ICER (Health+WSB QALY impact – method ii)	-	-	**£60,011.86**

3.3.3. Discussion

A large proportion of all appraisals undertaken by NICE relate to treatments for cancer, the majority of which concern metastatic or advanced cancer. This particular case study was selected as it adopts a general model structure which is often used for the evaluation of treatments for metastatic/advanced cancer. There are other similar examples of this type of approach including the appraisals of bevacizumab, sorafenib tosylate and sunitinib for renal cell carcinoma (TA178),[8] cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer (TA150/partial update of TA118),[9] and sunitinib for gastrointestinal stromal tumours (TA179).[10] There are also examples of this type of approach in non-metastatic cancer appraisals.

The impact of capturing additional WSBs in the case study was minimal and had only a fairly small effect on the ICER. It is reasonable to suggest that where a similar methodology is employed in evaluations of other metastatic cancer treatments, the impact of WSBs will often be very small due to the typically small impacts of treatment on progression-free survival and overall survival. Importantly, the two methods for estimating WSBs employed produce inconsistent results – the method based on the summary statistics favours the IFL comparator and produces a less favourable ICER for bevacizumab+IFL versus IFL, whilst the

subgrouping method produces an additional WSB QALY gain for bevacizumab+IFL and hence produces a slightly lower and more favourable ICER for bevacizumab+IFL versus IFL.

Both analyses were simple to undertake and required little additional programming or computational expense. Given the common use of this modelling method, it is likely that the same approach could be used to estimate additional WSB QALY impacts in a range of other cancer areas.

It should be noted that we did not convert the model into a patient-level simulation. This would imply a different set of evidence requirements which are unnecessary to estimate the direct health benefits and costs of the treatments under considerations. If there was an imperative to produce a patient-level simulation model solely for the purpose of estimating WSB impacts, this would require additional information on the post-progression survival distribution conditional on prior disease progression. This information is not commonly reported in oncology trials or manufacturers' submissions. Whilst this distribution could be estimated, either through direct analyses of patient-level trial data, or through the use of complex calibration methods or simple assumptions, this may introduce an additional layer of unnecessary uncertainty. However in this case study, the model did not include an age distribution, mortality was based solely on time-to-event curves from the trial and HRQoL impacts were state-dependent rather than age-dependent, hence a patient simulation model would be expected to produce virtually the same results (the only difference would be a result of Monte Carlo sampling error).

One additional simplification should be noted; the original model included assumptions about the sequence of treatments received after cessation of first-line therapy – a proportion of patients in each group accrue additional PFS gains due to second- and third-line treatments, based on efficacy data from other trials. Whilst these additional treatments have virtually no impact on the direct QALY gains in each group (as they are roughly proportional in each treatment group), they were part of the original model. In order to estimate the Markov trace, these assumptions had to be removed. The consequence is a mismatch between the Markov trace used to estimate direct QALY gains and that used to estimate the additional WSB QALY gains. It is unclear how this problem could be resolved by other means.

One final point that should be noted is that the age intervals for the WSB QALY gains are not set at equal intervals. This introduces some unnecessary complexity to the process of looking up WSB QALY impacts at each age. Unless there is some rationale underpinning the use of these uneven intervals, it may be beneficial to present the WSB lookup table a higher level of resolution (e.g. annual age increases).

4. DISCUSSION

It is difficult to draw firm conclusions about the best method for incorporating WSBs into existing cost effectiveness estimates based on a limited number of case studies. Whilst we selected these three case studies in order to highlight a range of model types typically encountered by the NICE Technology Appraisals programme, there are issues about the degree of comparability between model results. Since each is programmed in a different manner, and used differing modelling approaches, the implementation of potential methods identified in DSU report 1 inevitably has some variation in practice and not all methods can be implemented in all model types. Further investigation of methods is warranted, perhaps focussing exclusively on a range of individual patient level simulation models. In many situations, it is only possible for us to highlight differences in results from the implementation of different methods. It is often the case that we are unable to state which set of results are most accurate because it is only the full patient level simulation that provides this "correct" estimate. It should be noted that the omalizumab case study is based on a newer set of WSB estimates than the other two case studies. However, this does not affect the conclusions made across case studies.

The results presented here do demonstrate that it is not feasible to estimate WSBs as a linear function of parameters based on age, sex, QoL and ICD codes to an acceptable degree of accuracy. This makes it unlikely that adjustments made to summary output statistics, rather than estimates made within the decision model, will be appropriate. The dangers of implementing any simplistic approach based on summary output measures is demonstrated in the asthma example by the large differences between such approaches and those that we might think a priori are more likely to be closer approximations to the unbiased estimate.

The magnitude of the differences in WSB adjusted QALYs is variable. In the cancer model example, all methods result in only minor adjustments to the incremental QALYs generated.

In both the RA and asthma model examples the incorporation of WSBs, by any method, results in very large changes in incremental benefits. This is likely to be due to the short time horizon in the cancer model example.

The RA example does provide an estimate that is "correct" from a theoretical point of view: the full patient level model adjustment method. This differs substantially from approaches which are based on approximations of QoL changes throughout the course of the model. The example also demonstrates that the estimates gained from considering patient subgroups, defined in terms of age in 10 year bands, provide very similar results to the patient level analysis.

It is obvious that implementation of methods will require estimates of the distribution of the relevant patient populations in terms of age. In these case studies we have used various trial populations and registry as information sources for this distribution, which may not be ideal. In addition, none of the subgroup examples have considered the potential correlations between age, gender and QoL. This may be an important omission for any analysis based on subgroups and may be more difficult to identify from standard data sources.

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