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# Using tracker variables to overcome Markov restrictions: a cost-effectiveness model for rheumatoid arthritis

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## Introduction

This paper is concerned with a novel use of the TreeAge DATA package for modelling chronic conditions. The approach used has been applied to a model for rheumatoid arthritis constructed as part of a technology assessment review (Jobanputra *et al*, 2001) on behalf of the National Institute for Clinical Excellence (NICE). Since this paper is being presented before the completion of the NICE process, and since the purpose is to describe the modelling approach, a simplified version of the model is described which omits the drugs under consideration by NICE. This model will be referred to as the HESG Illustrative Rheumatoid Arthritis Model or HIRAM for short.

Rheumatoid arthritis (RA) is a chronic condition which can be treated by a class of drugs known as disease-modifying anti-rheumatic drugs (DMARDs). A patient on a DMARD may have to stop taking that DMARD as a result of either toxicity or loss of effectiveness. In the case of toxicity, the DMARD must be stopped and replaced by a new DMARD; in the case of loss of effectiveness, a new DMARD may be used in addition to, or in place of, the previous DMARD. This paper only considers the case where DMARDs are used one at a time: therefore the reason for quitting is not important in the model described. It is assumed initially that DMARDs improve quality of life, but have no effect on mortality; incorporating mortality effects will be considered in a later section of the paper.

In the HIRAM the following four DMARDs only are considered:

1. sulphasalazine (SSZ);
2. methotrexate (MTX);
3. parenteral gold (GST);
4. leflunomide (LEF).

If a patient has tried and quit all DMARDs, then palliative therapy is given for the remainder of the patient's lifetime. (In reality there are more DMARDs which can be tried.)

It is assumed for illustration that established practice is to use the first three of these DMARDs in the sequence SSZ – MTX – GST, and the question is whether to include leflunomide either before or after GST.

**Basic structure of the model**

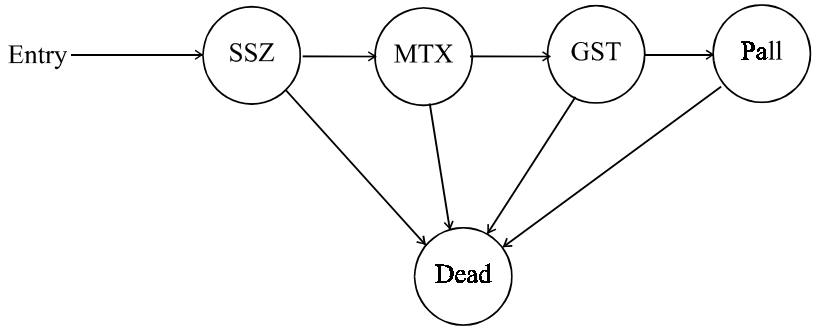


Figure 1. Pathways in the "3 DMARDs only" arm of the model
(Pall = palliative treatment)

Figure 1 shows the pathways in the "3 DMARDs only" arm of the model. For each simulated patient, the patient's lifetime is drawn from an appropriate distribution, as are the times spent on each DMARD. Patients enter the model and start on SSZ. SSZ may last the patient's remaining lifetime, or the patient may move on to MTX, and so on.

***Variance reduction***

The model is run for a large number of simulated patients. Because of the essentially stochastic nature of the model, the result in each arm is an estimated population mean, with a standard error around it. To reduce the standard error in the differences between arms of the model, it is helpful to run the model in such a way that the results can be treated as paired data. This can be done by ensuring that the same sequence of random numbers is used in each arm. For example, if a patient is given a remaining lifetime of 12 years, with 2 years on SSZ, 5 years on MTX, 4 years on GST and 3 years on LEF, then the patterns used for that patient are as shown in Table 1.

| Arm of model | Patient pathway |
|---|---|
| 3 DMARDs only | 2 yrs SSZ, 5 yrs MTX, 4 yrs GST, 1 yr palliation |
| LEF in 3rd place | 2 yrs SSZ, 5 yrs MTX, 3 yrs LEF, 2 yrs GST |
| LEF in 4th place | 2 yrs SSZ, 5 yrs MTX, 4 yrs GST, 1 yr LEF |

Table 1. Examples of possible pathways for the
same patient in different arms of the model

***Lifetime distributions***

Although it is assumed that DMARDs have no effect on mortality, the RA population has a higher mortality than the population as a whole. For the base-case analysis, a standardised mortality ratio (SMR) of 1.5 was applied to a set of standard life tables.

For example, the probability of a 45-year-old male in the general population surviving to the age of 60 is taken as 0.918. This converts to a probability of $0.918^{1.5} = 0.880$ for a 45-year-old male with RA. The distribution given in Table III of Symmonds *et al* (1994) was taken as a distribution for an incident RA population to provide appropriate weightings for a weighted average of survival for any length of time. A slight simplification was introduced in that the survival probabilities were calculated in 5-year bands as shown in Table 2 and it was assumed that survival was evenly distributed within each 5-year band.

| Survival (years) | 0-5 | 5-10 | 10-15 | 15-20 | 20-25 | 25-30 | 30-35 | 35-40 |
|---|---|---|---|---|---|---|---|---|
| probability | 0.117 | 0.118 | 0.114 | 0.108 | 0.099 | 0.089 | 0.079 | 0.070 |
| Survival (years) | 40-45 | 45-50 | 50-55 | 55-60 | 60-65 | 65-70 | 70-75 | |
| probability | 0.059 | 0.048 | 0.037 | 0.027 | 0.018 | 0.011 | 0.006 | |

Table 2. Assumed survival probabilities for an incident RA population

***Time on each DMARD***

For SSZ, MTX and GST, "survival curves" were published in Maetzel *et al* (2000); for leflunomide, data were taken from Crnkic *et al* (2001). Weibull distributions were fitted to these curves as shown in Table 3. (A random variable $X$ follows a Weibull distribution with shape parameter $a$ and scale parameter $b$ if $\left(\frac{X}{b}\right)^a$ follows a negative exponential distribution with unit mean.) The shape parameters are all between 0 and 1, indicating a hazard rate declining with time.

| DMARD | shape | scale |
|---|---|---|
| SSZ | 0.71 | 2.76 |
| MTX | 0.77 | 4.62 |
| GST | 0.71 | 3.08 |
| LEF | 0.67 | 3.10 |

Table 3. Survival times on each DMARD
(scale parameter in years)

***Costs of treatment***

Costs of treating an RA patient with a particular DMARD include drug and monitoring costs. Typically, more intensive monitoring is required at the beginning of the time spent on a particular DMARD. The cost of treatment was taken as a constant annual cost to reflect long-term usage, together with a "start-up" cost reflecting the

additional monitoring required initially. For discounting purposes, the start-up cost was taken to apply at the time of starting the DMARD. Table 4 shows the costs used.

| DMARD | start-up | use |
|---|---|---|
| SSZ | 458.13 | 575.96 |
| MTX | 381.36 | 1184.92 |
| GST | 2532.16 | 1547.64 |
| LEF | 839.52 | 1130.04 |
| (Palliation) | 0.00 | 312.00 |

Table 4. Costs used in the model
(currency sterling, price year 2001)

***Quality of life calculations***

It is characteristic of rheumatoid arthritis that patients experience considerable fluctuations in quality of life, particularly in the early stages of the condition. It is assumed that these fluctuations can be adequately represented by a smoothed curve showing a decline over time. The basic curve is taken to be that which a patient would follow without DMARD use. It is assumed that patients start a DMARD at a point below this curve, but improve over a short time to an improved state of life. The improvement is taken to remain constant relative to the basic curve until the DMARD loses effectiveness or becomes toxic, at which time it declines to a point below the basic curve. Figure 2 illustrates the pattern assumed.

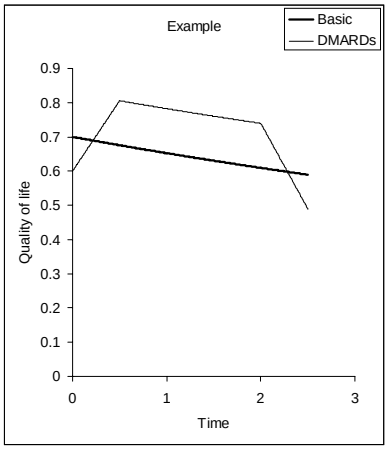


Figure 2. Assumed quality of life pattern for a single DMARD

***Simplifying QALY calculations***

As described above, the QALY calculations require data on the typical pattern on quality of life without DMARD use under palliation. As it is assumed that the effect of DMARDs is additive to the general pattern of quality of life, it can be shown that

such data are not in fact necessary. The two parts of Figure 3 compare the quality of life patterns for an individual in a (hypothetical) simplified version of the model, in which an additional DMARD is introduced between two other DMARDs. The two parts of Figure 4 show the quality of life patterns relative to the basic curve. It can be seen that the difference between the quality of life estimates in Figure 4 is the same as in Figure 3. This remains true regardless of discount rate, shape of assumed basic curve and lifetime of patient.

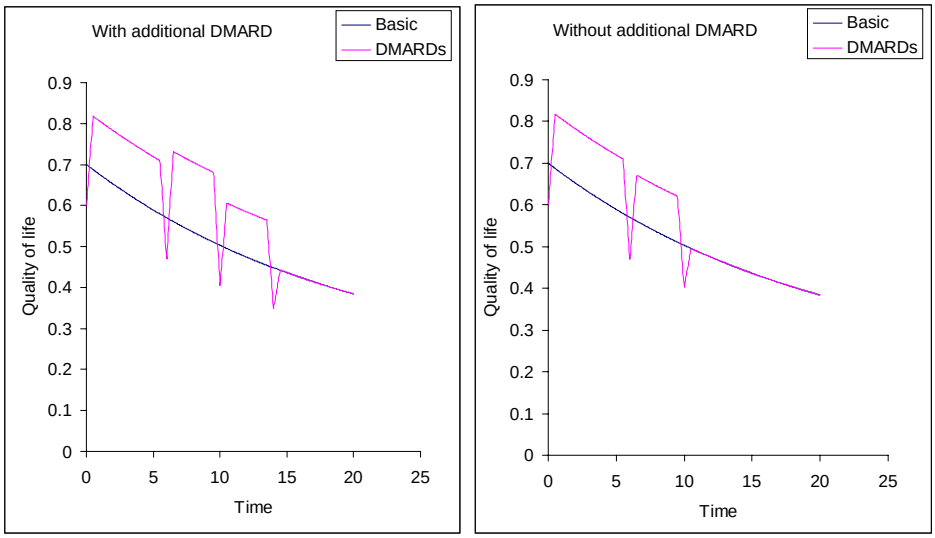


Figure 3. Quality of life patterns for an individual

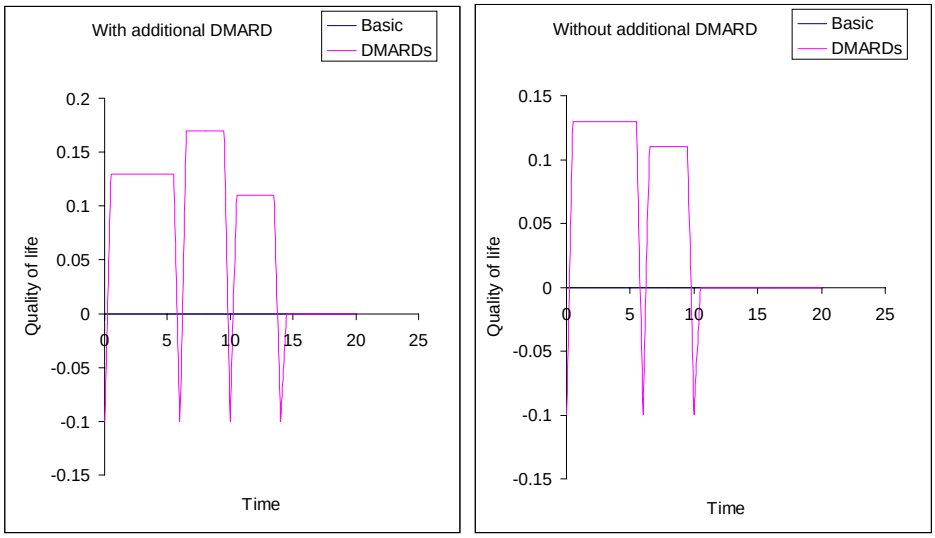


Figure 4. Quality of life relative to basic curve

The basic effect of each DMARD can then be modelled as a constant increase in quality of life per unit time. The "end effects" can conveniently be simplified to a fixed reduction in total QALYs for starting each new DMARD and a fixed reduction in total QALYs for finishing any DMARD. The reduction does not apply if the patient

remains on the DMARD for the remaining lifetime. For discounting purposes, the end effects are taken at the time of starting and finishing the DMARD in question. Note that this method has the advantage of being workable when the DMARD is only used for a very short time.

Table 5 shows the increased QALYs per year assumed for each of the DMARDs used in the HIRAM. End effects were taken as a deduction of 0.2 years' worth of QALY gain.

| DMARD | QALY change |
|---|---|
| SSZ | 0.050 |
| MTX | 0.066 |
| GST | 0.050 |
| LEF | 0.098 |

Table 5. QALY gains (per year) associated with use of DMARDs

## Implementation

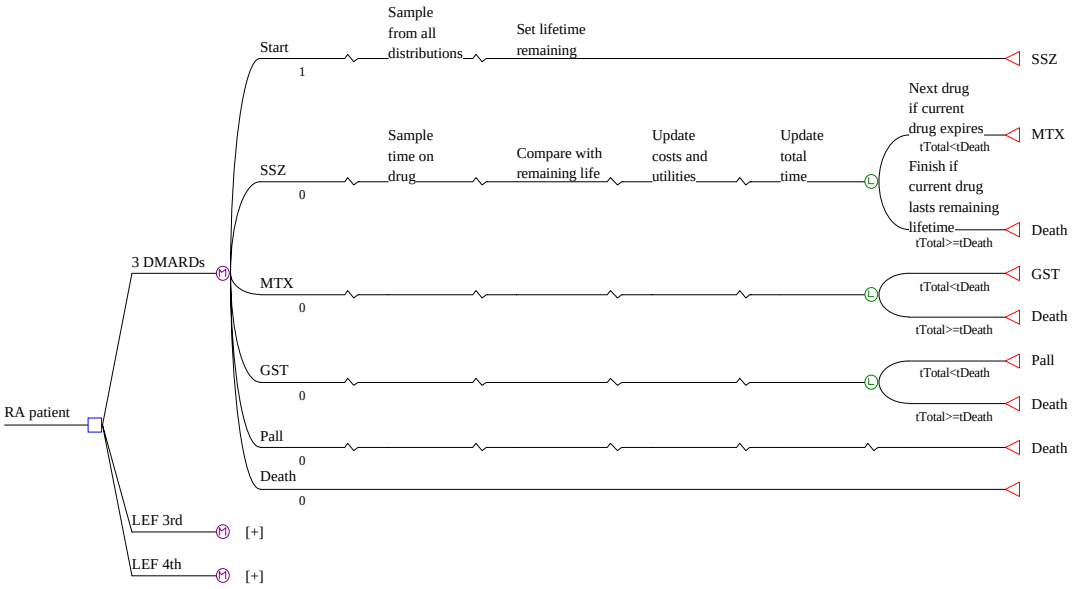


Figure 5. Basic structure of the model

The basic structure of the model is shown in Figure 5. The "3 DMARDs only" arm of the model is shown in full; the other two arms are similar, but include LEF in the appropriate place in the sequence.

### *Tracker variables*

Within its system of implementing Markov models under Monte Carlo simulation, the DATA software package allows the use of "tracker variables". These allow individual characteristics to be maintained and effectively allow most of the restrictions implicit in a Markov model to be overcome. Tracker variables can be updated at any point in a model. It is not, however, possible to control the order of calculation at a particular node. Accordingly, a sequence of label nodes are used to ensure that the calculation sequence is correct.

### *Model cycles*

Instead of each cycle representing a fixed period of time, each cycle in the HIRAM represents the whole time spent on a DMARD. The tracker variable *tTotal* is used to accumulate time within the model. By default it takes an initial value of zero, and is updated at the end of each cycle.

### *Sampling distributions*

The DATA package allows sampling from any number of statistical distributions. Six are used in this model. Numbers 1 to 4 are set as exponential distributions with unit

mean, to be adjusted to give the times on each DMARD, number 5 is set to sample from the probability distribution given in Table 2 above, and number 6 gives a uniform number between 0 and 5.

***Costs and utilities***

Four tracker variables are used to keep total costs and QALYs to date, with and without discounting. These are updated as necessary during the model from the default starting value of zero. The term for a given cost is as shown in Table 6, where $\lambda = \ln(1.06)$, representing a 6 per cent annual discount rate applied continuously. Similar principles apply for QALYs, but with a 1.5 per cent discount rate.

| Type of cost | Undiscounted term | Discounted term |
|---|---|---|
| One-off cost *c* at time *t* | *c* | $ce^{-\lambda t}$ |
| Cost *c* per year for period *s* starting at time *t* | *cs* | $ce^{-\lambda t}\frac{\left(1-e^{-\lambda s}\right)}{\lambda}$ |

Table 6. Calculations for updating total costs

***The Start cycle***

The value 1 below the state-name Start in Figure 5 ensures that all simulated patient records are correctly initialised by the use of the Start cycle. At the first node (Sample from all distributions), tracker variables *samp01* to *samp06* are set to values sampled from distributions 1 to 6 respectively. It is necessary to sample from all six distributions in each arm of the model to ensure that the results can be treated as paired data for analysis. At the next node (Set lifetime remaining), the tracker variable *tDeath* is set to the value of *samp05* + *samp06*, to give the time to death for the individual simulated patient. The terminal note is linked to the state SSZ, indicating that all patients start with sulphasalazine.

***The SSZ cycle***

The actions taken at the various nodes are as follows.

Sample time on drug: The tracker variable *samp01* is raised to an appropriate power and scaled so that the result (*tSSZ*) comes from the correct Weibull distribution to represent the time for which the patient will be able to remain on sulphasalazine.

Compare with remaining life: The value of *tSSZ* is compared with the patient's remaining lifetime, calculated as $tDeath - tTotal$. The new value of *tSSZ* is the lower of these two numbers, so that *tSSZ* now represents the time for which the patient actually takes sulphasalazine.

Update costs and utilities: The cost and QALY totals are updated to take into account start-up and usage costs and effects. Note that the start-up effect for QALYs is negative, and that the reduction at the end is not applied yet.

Update total time: The value of *tTotal* is increased by *tSSZ* to represent the time up to the end of sulphasalazine use.

Splitting at the logic node: If the value of *tTotal* is less than *tDeath*, that means that the patient has stopped using sulphasalazine and needs to move on to methotrexate. In that case, the QALY reduction for end of drug use is applied. If *tTotal* equals *tDeath*, then sulphasalazine has lasted the patient's remaining lifetime, so there is no QALY reduction to apply, and the patient moves to the state Death.

***Cycles for other DMARDs***

These work in exactly the same way as for sulphasalazine.

***The Pall cycle***

The patient can only reach the state Pall if all DMARDs have been tried and failed. It works in the same way as for DMARDs, except that the variable *tPall* is not based on any sampling but simply set to the patient's remaining lifetime at the start of the cycle, and there is no QALY deduction at end. (In fact, since QALYs are calculated relative to palliation, the QALY values added in this cycle are all zero.)

***Stopping condition***

The process is set to stop after a fixed number of cycles. The number chosen must be high enough to ensure that all patients reach the state Death. The only loss from an excessively high number is a small increase in running time.

***Running the model***

To run the model, select each Markov node in turn and perform a Monte Carlo simulation. For comparability between arms, the check box "Use predictable random sequence" must be checked. For the results shown here, the key value was left at 1000.

## Output and analysis

DATA(tm) Monte Carlo Simulation
Ordered List of 5 Outcomes

| Trial | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Outcome | 3 DMARDs | 3 DMARDs | 3 DMARDs | 3 DMARDs | 3 DMARDs |
| Value | 17298.97 | 129391.2 | 9846.099 | 82075.22 | 15644.99 |
| Cost | 13242.1 | 6299.3 | 4008.783 | 1692.93 | 7405.58 |
| Effect | 0.765485 | 0.048684 | 0.407144 | 0.020627 | 0.473351 |
| cTotAbsolute | 22631.76 | 6624.565 | 4857.324 | 1720.013 | 9115.93 |
| cTotDiscount | 13242.1 | 6299.3 | 4008.783 | 1692.93 | 7405.58 |
| samp01 | 1.428144 | 0.038324 | 4.290154 | 0.14342 | 0.51911 |
| samp02 | 0.427808 | 0.130297 | 0.881929 | 1.355492 | 1.468404 |
| samp03 | 1.548094 | 0.506775 | 0.131202 | 2.431979 | 0.782973 |
| samp04 | 1.170964 | 0.36644 | 0.151839 | 0.421229 | 0.102662 |
| samp05 | 30 | 0 | 5 | 0 | 5 |
| samp06 | 1.008789 | 4.803003 | 2.63802 | 0.835139 | 2.548143 |
| tDeath | 31.00879 | 4.803003 | 7.63802 | 0.835139 | 7.548143 |
| tGST | 5.699946 | 1.18249 | 0 | 0 | 0 |
| tLEF | 0 | 0 | 0 | 0 | 0 |
| tMTX | 1.533715 | 0.327497 | 0 | 0.656064 | 6.452003 |
| tPall | 19.21583 | 3.265104 | 0 | 0 | 0 |
| tSSZ | 4.559298 | 0.027912 | 7.63802 | 0.179075 | 1.09614 |
| tTotal | 31.00879 | 4.803003 | 7.63802 | 0.835139 | 7.548143 |
| uTotAbsolute | 0.844529 | 0.049738 | 0.431405 | 0.020935 | 0.503024 |
| uTotDiscount | 0.765485 | 0.048684 | 0.407144 | 0.020627 | 0.473351 |
| DISTSAMP(1) | 1.428144 | 0.038324 | 4.290154 | 0.14342 | 0.51911 |
| DISTSAMP(2) | 0.427808 | 0.130297 | 0.881929 | 1.355492 | 1.468404 |
| DISTSAMP(3) | 1.548094 | 0.506775 | 0.131202 | 2.431979 | 0.782973 |
| DISTSAMP(4) | 1.170963 | 0.36644 | 0.151839 | 0.421229 | 0.102662 |
| DISTSAMP(5) | 30 | 0 | 5 | 0 | 5 |
| DISTSAMP(6) | 1.008789 | 4.803003 | 2.63802 | 0.835139 | 2.548143 |

Table 7. Sample output from DATA

Table 7 shows the output that can be obtained from the package. The cost and effect are discounted totals and the “value” is the ratio of these for each individual. After this the final values of each of the tracker variables are shown, followed by the values

sampled from the distributions (as implemented, these are duplicated by the tracker variables *samp01* to *samp06*). It can be seen that patients 1 and 2 failed on all three DMARDs, patient 3 remained on sulphasalazine and patients 4 and 5 failed on SSZ but remained on MTX.

***Correct discounting point for comparison***

As shown in Table 7, the costs and QALYs are discounted to the start of the programme. For comparison between two strategies, the appropriate discounting point is the point at which the strategies diverge. Thus for comparing "LEF 3rd" with either of the other two strategies, the appropriate point is the time at which the patient fails on MTX, while for comparing "LEF 4th" with "3 DMARDs", the appropriate point is the time at which the patient fails on GST. Patients who do not reach the discounting point will have the same costs and QALYs in both arms and so contribute nothing to the incremental analysis.

***Calculations for incremental analysis***

| 3 DMARDs only | | | |
|---|---|---|---|
| Trial | 5 | 6 | 7 |
| Cost | 7405.58 | 12968.76 | 13654.55 |
| QALY | 0.473351 | 0.40729 | 1.238202 |
| | | | |
| LEF 3rd | | | |
| Cost | 7405.58 | 17841.8 | 12533.57 |
| QALY | 0.473351 | 1.667519 | 1.208583 |
| tStartLef | 0 | 3.361489 | 12.16788 |
| | | | |
| LEF 4th | | | |
| Cost | 7405.58 | 19547.03 | 13654.55 |
| QALY | 0.473351 | 1.661051 | 1.238202 |
| tStartLef | 0 | 6.141363 | 0 |

| | | | |
|---|---|---|---|
| LEF 3rd compared to 3 DMARDs only | | | |
| Discounted to start of programme | | | |
| Inc Cost | 0 | 4873.049 | -1120.98 |
| Inc QALY | 0 | 1.26023 | -0.02962 |
| Discounted to point of divergence | | | |
| Inc Cost | 0 | 5927.426 | -2277.81 |
| Inc QALY | 0 | 1.324906 | -0.0355 |
| | | | |
| LEF 4th compared to 3 DMARDs only | | | |
| Discounted to start of programme | | | |
| Inc Cost | 0 | 6578.27 | 0 |
| Inc QALY | 0 | 1.253761 | 0 |
| Discounted to point of divergence | | | |
| Inc Cost | 0 | 9408.582 | 0 |
| Inc QALY | 0 | 1.373805 | 0 |
| | | | |
| LEF 4th compared to LEF 3rd | | | |
| Discounted to start of programme | | | |
| Inc Cost | 0 | 1705.221 | 1120.981 |
| Inc QALY | 0 | -0.00647 | 0.02962 |
| Discounted to point of divergence | | | |
| Inc Cost | 0 | 2074.178 | 2277.809 |
| Inc QALY | 0 | -0.0068 | 0.035502 |

Table 8. Calculations for correctly discounted incremental analysis

Table 8 shows the calculations necessary for incremental analysis. The first three parts of the table are extracted from an equivalent to Table 7 for each of the three strategies. The extra tracker variable *tStartLef* is set to the time at which the patient started leflunomide (or zero if the patient did not start leflunomide). In each of the remaining three parts, the incremental costs and QALYs discounted to the start of the programme are obtained by subtraction. These are then converted to the correct discounting point by multiplying by $1.06^{tStartLef}$ and $1.015^{tStartLef}$ respectively, using the value of *tStartLef* for the "LEF 3rd" strategy if it is one of the comparators, but the value for the "LEF 4th" strategy when that strategy is compared to "3 DMARDs".

**Illustrative results**

The above analysis was extended to 10000 simulated patients. Incremental costs and QALYs were calculated for each patient in the manner illustrated in Table 8. Table 9 shows the overall results.

| LEF 3rd v 3 DMARDs | | |
|---|---|---|
| | mean | s.e. |
| Inc Cost | 1294 | 18 |
| Inc QALYs | 0.1838 | 0.0035 |
| ICER | 7043 | 166 |

| LEF 4th v 3 DMARDs | | |
|---|---|---|
| | mean | s.e. |
| Inc Cost | 2126 | 24 |
| Inc QALYs | 0.1919 | 0.0036 |
| ICER | 11082 | 241 |

| LEF 4th v LEF 3rd | | |
|---|---|---|
| | mean | s.e. |
| Inc Cost | 527 | 10 |
| Inc QALYs | -0.00015 | 0.00012 |

Table 9. Illustrative results

Note that the standard errors are driven by the number of simulated patients used. They can be reduced by increasing the sample size, at a cost of increased computation time. The recognised "counsel of perfection" is that the sample size should be large enough that the standard errors become negligible. The standard errors for the ICER were calculated using the formula on p.91 of Armitage and Berry (1987). For the comparison between LEF 3rd and LEF 4th there appears to be a dominance relationship in favour of LEF 3rd with the data set used.

The means were calculated from the full set of 10000 patients, including zero values for those patients who did not reach the point of divergence: omitting those zero values would not change the calculated values of the ICER.

***Sensitivity analysis***

All the usual methods of sensitivity analysis can be applied to the model. This issue is discussed further when considering the possible use of alternative software.

## Extension of the model

The HIRAM as it stands involves a number of restrictive assumptions. The next section of this paper describes some of these assumptions and how they might be overcome.

### *Use of combination therapy*

The strategy of using one DMARD at a time is not the only way of treating RA patients. Some strategies involve the use of DMARDs in various forms of combination therapy. However, a drug cannot form part of a combination if it has been quit for reasons of toxicity. Thus it may be necessary to distinguish between toxicity and loss of effectiveness as the reason for quitting a particular DMARD. Potentially this influences the model at two points. The cycle relating to that DMARD would be modified to incorporate modelling the reason for quitting, and the cycle immediately before the combination therapy would need modifying to divert the patient pathway away from combination therapy if it cannot be used for that patient.

Modelling the reason for quitting can be done in a number of different ways. The simplest is to retain the survival curve for the drug, but to have a probability of quitting for toxicity which may depend on the time spent on the drug. Then a chance node can be introduced immediately before the terminal node for transition as shown in Figure 6.

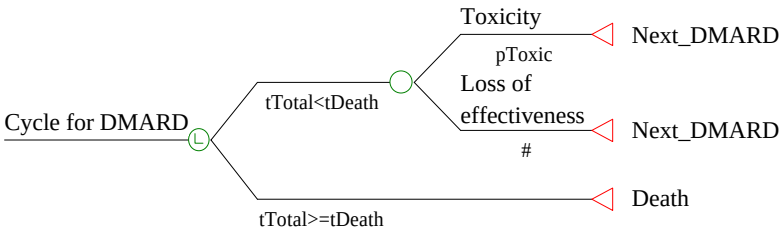


Figure 6. Modelling toxicity

In Figure 6, if the next DMARD is the combination therapy, then the transition would be set to bypass it; otherwise, a tracker variable would record the toxicity of the DMARD in question and be used at a logic node later in the model.

### *Assumption of independent survival times*

As the model stands, the distribution of survival time on any DMARD is independent of its position in the sequence, and of the time spent on previous DMARDs. This assumption is by no means essential to the structure of the model; it would be

perfectly possible for the survival time on any DMARD to depend in any desired way on the patient's history, if necessary by the use of additional tracker variables.

Incidentally, the Weibull distributions used in the HIRAM could be replaced by any other desired distribution.

***Effect of DMARDs on mortality***

It has been assumed that DMARDs have no effect on mortality. It would be perfectly possible to allow for such an effect. One way to do this would be to introduce a "mortality factor" *k* (which could be different for each DMARD if desired) and say that spending one year on a DMARD is equivalent to *k* years without the DMARD. For example, consider a DMARD with mortality factor 0.8 and a patient who would last 5 years on that DMARD. Then the time spent on the DMARD would count as $0.8 \times 5 = 4$ years of the patient's lifetime, so a patient starting the DMARD with 6 years left to live from the originally sampled lifetime would still have 2 years to live after failing on that DMARD. A similar patient starting the DMARD with only 2 years to live from the originally sampled lifetime would die after $2/0.8 = 2.5$ years without failing the DMARD. This particular method may be felt to be unrealistic, but any method that can be specified mathematically could be implemented within the basic structure of the model.

However, there is a price to pay for including mortality effects. The QALY calculations described above are assumed relative to a basic curve. This simplification would no longer work, and it would be necessary to include estimates of the (distribution of) actual patterns of quality of life.

***Age dependence and similar issues***

It would be possible to make any or all of the distributions of survival times on DMARDs dependent on age, gender, or any other relevant factors. The averaging process described earlier to give the survival distribution in Table 2 would then not be necessary, but age- and gender-dependent survival curves appropriate to RA patients could be used directly.

***Hospitalisation and joint replacement***

The model does not consider the effect of DMARDs on hospitalisation and joint replacement. The structure of the model could be expanded within its basic framework to include these issues; exactly how this would be done depends on the form of the data available.

**Alternative software**

The description above uses DATA for the modelling and Excel for the calculations. It would be possible to include all the conversions for correct discounting in the DATA version. However, care would need to be taken since the discounting point depends on which two policies are being compared. In any case, the incremental cost-effectiveness ratios would need to be calculated outside DATA.

It would equally be possible to implement all the calculations within Excel. Again, there is the problem that considerably more care would be needed to ensure that the logic of the model is followed correctly, especially if the issue of toxicity is handled. In the DATA version, the tracker variable *tTotal* is updated on every cycle: a separate cell would be needed for each update.

Another issue affecting the choice of appropriate software is the need for sensitivity analysis. As the model stands, it is necessary to intervene manually at each stage of running the model. This makes probabilistic (Bayesian) sensitivity analysis infeasible: the issue is not so much one of running time, more that the computer cannot simply be left to "get on with it". However, there is less difficulty in producing an extreme scenario analysis.

It would be much easier to produce a Bayesian sensitivity analysis if the model were coded in a generic programming language such as Borland Delphi: this would allow the whole process of sensitivity analysis to be automated within the program to run the model. Apart from requiring programming skill on the part of the modeller, this approach would also lead to an almost total loss of transparency in the model.

When choosing appropriate software for any model, it is necessary to consider both efficiency and transparency. The relative importance of these depends on the purpose for which the model is to be used. The original model, of which the HIRAM is a simplified version, was constructed as part of a technology assessment review commissioned on behalf of NICE: in such reviews, transparency of models is a high priority. Use of DATA software allows the model to be constructed transparently.

## Discussion

Markov models are well known to suffer from four restrictive assumptions:

1. transition probabilities do not depend on how long an individual has been in a given state;
2. transition probabilities do not depend on where an individual was before entering the current state;
3. transition times are only determined to within a multiple of a fixed cycle time;
4. no interaction between individuals is permitted.

Tracker variables were introduced into the DATA package to overcome limitations 1 and 2. This paper shows how limitation 3 may also be overcome. It is true that, without the method used here, timings can in principle be made as accurate as desired by reducing the cycle time. However, if an individual is undergoing a process which lasts a fixed time such as a course of drugs, reducing the cycle time requires a large number of linked states (known as "tunnel states") to represent such a process. In any case, if an individual spends a large number of cycles in the same state, conventional methods require a large number of samplings from the random number generator and possibly some rather artificial calculations of varying transition probabilities. The method suggested here allows any distribution of time spent in a given state to be sampled in a straightforward manner, with considerable gains in computational efficiency compared to standard Monte Carlo simulation.

The method has been illustrated in the case of rheumatoid arthritis: it is applicable to any chronic condition for which the Markov assumptions provide a significant restriction, but in which interaction between patients is not a consideration. Examples of situations where interaction between patients may be a consideration include infectious diseases, where the risk of an individual becoming infected depends on the number already infected, and resource constraints, where individuals may have to join a waiting list for some service or treatment. In such cases, the full power of discrete event simulation is necessary if individuals are to be tracked; otherwise cohort simulation methods such as system dynamics may be used.

**References**

Armitage P, Berry G (1987) *Statistical Methods in Medical Research*, 2nd edition. Blackwell Scientific Publications, Oxford.

Crnkic M, Teleman A, Saxne T, Geborek P (2001) Survival on drug as a tool for evaluation of drug tolerability. Initial experience in southern Sweden of infliximab, etanercept, and leflunomide in rheumatoid arthritis. *Rheumatology* 40 Suppl 1, 82-83.

Jobanputra P, Barton P, Bryan S, Fry-Smith A, Burls A (2001) The clinical effectiveness and cost-effectiveness of new drug treatments for rheumatoid arthritis: etanercept and infliximab. Report for the National Institute of Clinical Excellence.

Maetzel A, Wong A, Strand V, Tugwell P, Wells G, Bombardier C (2000) Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. *Rheumatology* 39, 975-981.

Symmons D, Barrett E, Bankhead C, Scott D, Silman A (1994) The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk arthritis register. *British Journal of Rheumatology* 33, 735-739.