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News

How to measure life

Last week's BBC programme *The price of life* highlighted the plight of cancer sufferers awaiting a decision by NICE, the National Institute for Health and Clinical Excellence, on a new drug that could extend their lives. If approved by NICE, the drug, called *revlimid* and used to treat a cancer called *multiple myeloma*, could be prescribed freely on the NHS. If rejected, the prohibitive cost would mean that patients will miss out on those extra months or years. In the light of the suffering facing myeloma patients and their families, the main criterion for NICE's decisions cost−effectiveness seems almost inhumane. But, as the BBC programme revealed, NICE has to strike a next to impossible balance: the NHS budget is finite, and an extra year of life for a myeloma sufferer goes at the expense of others it could mean a baby's life in an area with high infant mortality, no decent palliative care for other terminally ill patients, or no new diagnostic equipment for a hospital. It's hard to make fair decisions without some sort of rational measure, but exactly what kind of mathematical considerations go into NICE's calculations?

Bitter pills: One capsule of revlamid costs over £200.

One of the bones of contention of NICE's strategy to appraising new drugs is the QALY: the *quality adjusted life year*. The QALY is designed to measure both the time a new treatment adds to a person's life and the quality of life the patient experiences in that extra time. The average quality of life is measured by a number

less than 1, with 1 standing for best possible health and 0 and below standing for worst possible health. Multiplying the quality rating and the extra life time a patient can expect, on average, from the drug gives the QALY. Thus, a drug which promises an extra 5 years, but has a quality rating of only 0.1, perhaps due to heavy side effects, gives a QALY of $5 \times 0.1 = 0.5$, which is less than that of a drug that only adds 1 year, but has a quality rating of 0.6, giving a QALY of $1 \times 0.6 = 0.6$. The QALY does of course represent an average it does not predict what an individual patient might experience, but describes what one might expect on average from a whole population.

The QALY forms the basis of NICE's cost−effectiveness measure, which is worked out as follows. First, compute the difference between the cost c_1 of a year's worth of treatment on the new drug and the cost c_2 of a year's worth of treatment of a standard existing drug. Then work out the difference between the new drug's QALY q_1 and the existing drug's QALY q_2. Now compute the ratio between the two differences:

$$(c_1-c_2)/(q_1-q_2).$$

This measures the cost per QALY of the new drug compared to existing treatments. It's called the ICER, the *incremental cost effectiveness ratio*. In general, NICE works with a £30,000 theshold: if a drug's ICER exceeds this, then there is a high chance that NICE won't approve it.

It looks like a chilling calculation. But the simple formula masks the sophisticated considerations that go into appraising a new drug considerations made not just by NICE's panel of experts, but also by the drug company for whom much profit hinges on an acceptance by NICE. The numbers that go into the QALY and ICER calculations the time a new drug adds to a patient's life and the quality of life are far from clear−cut and there is room for interpretation. They are based on large−scale clinical trials which compare patients on the new treatment with a control group on traditional treatments. Scientists fit a mathematical model to the data collected from the trials in other words, they try to find a mathematical equation which describes the data as closely as possible. By including information on the patients' well−being, the model predicts not just the expected survival time of a patient, but also the quality of life experienced by patients on the drug. It's on the basis of such a mathematical model that the QALY and ICER are calculated.

A course of revlimid for one patient could pay for important hospital equipment to treat many others.

But any model is only as good as its assumptions. In the case of revlimid, the manufacturer, Celgene, came up with an ICER of £24,584 per QALY gained for patients who had had two prior therapies for their cancer

that's below NICE's cut−off of £30,000. But NICE found Celgene's model wanting. Partly because it underestimated additional costs that come with treating a patient with revlimid, for example treatment to prevent deep vein thrombosis, and because it did not take account of side effects of the drug which would lower a patient's quality of life. But NICE also criticised a technical point that would escape anyone who's not a statistical expert. After the initial stage of the trial, patients in the control group had been given the option to cross over into the revlimid group, and many did. To make up for the resulting lack of data on long−term survival of non−revlimid patients, Celgene used data from other clinical trials on myeloma survival rates that had been done previously. It adjusted its model using the *median* of overall survival of patients in those trials.

This, according to NICE, was the wrong statistic to look at. The median represents the exact mid−point of the sample: 50% of patients in the trial survived longer than the median and the other 50% did not. It's a good summary statistic of survival rates, but it tells you nothing about the total number of years you can expect a group of myeloma patients to survive. That information is encoded in the *mean* (i.e. average) survival rate: you can work out the total number of years you expect a group of patients to survive by multiplying the mean by the number of patients. If you're interested in how many years of survival you can buy on a fixed budget, it's the mean you should be looking at. This small technical point turned out to have a huge impact on the ICER: when NICE ran an improved model calibrated to the mean, rather than the median, the ICER of people with two prior therapies almost doubled to £47,100 a difference between approval and rejection. For another subgroup in the trial involving patients with one former therapy the ICER increased by a factor of 30!

Celgene never did agree with NICE on the median issue, arguing that the mean can be skewed by *outliers*, patients who survive for unusually long or short periods, but it did present a revised model addressing some of NICE's criticisms. And it threw a deal into the bargain, promising to cover the cost of revlimid for all patients who remained on the drug after two years. This brought NICE's ICER projection down to £43,800 for patients who have had two or more previous therapies. According to NICE's model, these patients could expect to live 1.8 years longer, at a cost of £54,291 per patient. The 1.8 extra years corresponded to 1.24 QALYs, which means that the quality of life of revlimid patients is rated as 0.68 two thirds that of a person in full health.

How to divide a finite budget.

The £43,800 figure was still above NICE's threshold, but new rules came along just in time for the revlimid appraisal. Acknowledging the special plight of terminally ill patients, these rules allow NICE to exceed the threshold for end−of−life treatments. As a result, revlimid was approved for patients with two or more previous therapies. In the stark language of mathematics this means that each week spent at the end of life of

myeloma patients is worth 43,800/30,000 = 1.46 of an ordinary week, or ten days instead of seven days. A life−saving decision for myeloma patients, but, as the programme showed, one that provoked anger in people responsible for other public health issues because of the cut−backs it will bring along elsewhere.

Using maths to place a value on life seems distasteful, and it's natural to sympathise with patients who stand to lose out on account of an unfeeling measure like the QALY. But, as the revlimid case shows, far more expert and human judgment goes into the calculations than the simple equations suggest. It's not a matter of mechanically plugging made−up numbers into these equations, but of carefully assessing a drug's effectiveness and scrutinising the manufacturer's claims. Mathematics is the only way to do this objectively. The final equations, the QALY and ICER, are an attempt to summarise the results in order to make rational comparisons and to fairly divide a finite pie. They are controversial, and rightly so the important thing is that these measures are continually debated, and that there is flexibility to override the mathematical rule.

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Further reading

- NICE's appraisal of revlimid can be accessed on the NICE website;
- The NICE website also contains the findings of a Citizens Council on departing from the £30,000 threshold;
- And a brief introduction to the QALY.
- A recent play on BBC Radio 4 explored the issues surrounding QALYs. You can listen again until the 31st of July 2009.
- To put yourself into the shoes of a decision maker, take part in this online activity put together by the Peninsula Medical School, University of Exeter.

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Plus is part of the family of activities in the Millennium Mathematics Project, which also includes the NRICH and MOTIVATE sites.