Bone Research Society Subcommittee on Economic Models

13 September 2009

Dr Elisabeth George
Associate Director, Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
Midcity Place
71 High Holborn
WC1V 6NA

Dear Dr George

Bone Research Society's comments on the Decision Support Unit (DSU) report for Technology Appraisals (TA) 160/161

Thank you for inviting the BRS to comment on the contents of the (DSU) report.

We read the DSU's response to our original points with dismay because we feel that the DSU and NICE have not entered into a meaningful exchange. Indeed the offhand way in which several of the points have been dealt with undermines confidence in the whole process. Our concerns have not been adequately addressed and we do not concur with the assertion by the DSU report's authors that *"none of the consultee comments relating to the modelling approach would lead to significant improvements in the cost effectiveness of the interventions, either cumulatively or in isolation"*. Most reasonable observers would regard a potential decrease in the ICER for treatment of a 60 year old woman from £267,461 to £27,534 as a significant improvement. And this is in isolation from the further 50% decrease in the cost of generic alendronate to the NHS.

The openness with which the process has been approached remains questionable and undemonstrated. Several aspects of the process including the DSU report

could easily be interpreted as a deliberate attempt to hinder interrogation of the NICE model. Inconsistencies in terminology by the authors of the NICE model have caused a large amount of extra work for the BRS in validating the DSU's claim that the Holt data was sufficiently well simulated by the NICE modellers.

Our major objection remains the handling of disutilities for bisphosphonates in the model (see below). We maintain that the DSU response is misleading and damaging to the credibility of both the DSU and NICE. To simply dismiss this as beyond consideration deeply undermines confidence in the whole approach of NICE to improving the management of patients with osteoporosis. Indeed, the response of the DSU to the BRS could be interpreted as an attempt to circumvent the High Court Judgement by claiming that a crucial part of the model structure is outside the scope of the Court's ruling. In truth, a genuine DSU response appears to have been deliberately avoided because there is nothing they could say in NICE's defense.   We insist that the NICE model should employ real scientific data rather than irrational whims and the disutility multiplier removed. Following the resolution of this issue, the other issues identified by the BRS should be resolved collaboratively by the NICE and NOGG modellers (who both already have access to the Kanis copyright data).

We feel strongly that any continued avoidance of sensible collaborative and science-based dialogue between NICE, the DSU and bodies such as the BRS will seriously damage people's belief in the openness of both Government and NHS.

Our specific comments on the DSU report are set out below.

BRS Issue 1

The DSU response to the first point of criticism made by the BRS misleads. The BRS Issue 1 was stated as follows:
"The disutility associated with bisphosphonate use (eg alendronic acid) was over-estimated by a factor of 10 compared to the published literature."
For those not familiar with the terminology of health economic modelling, disutility refers to the extent to which taking the drug is useless or counterproductive. It is quantitated according to the associated add-on costs of dealing with the disutility plus the reduction in quality-adjusted life years (QALYs) resulting from treatment that is attributable to the disutility.

Thus, when the disutility factor is increased for alendronic acid by a factor of 10, the benefits of treating those who receive treatment and still suffer no ill effects remain the same, while the numbers suffering disutility (or alternatively the impact of the disutility on the individual) are/is amplified ten-fold. The effect is to remove and sometimes reverse the benefit of treatment in those who stand to gain moderately from treatment in terms of fractures avoided."

The response of the DSU was as follows

"As this is a comment on an input parameter, previously known to consultees and commentators, and agreed upon by the Committee, and therefore one on which consultees have previously been able to make representations, no DSU response is provided."

The error in this response is the assertion that this factor of 10 is an input parameter: it is not, it is embedded in the model in Excel Workbook CPQ CALC Prev.xls <variables> cell C14 that is multiplied with the actual disutility coefficients summarised from the published literature (in cells C15 through C20 for each 5 year age band) to supply the grossly exaggerated values employed in the TA 160/1 version of the model. It is incontrovertibly part of the model's STRUCTURE. In consequence, its effect on cost effectiveness could not previously have been assessed prior to the release of the unlocked model because there was no way before we received the unlocked model to restore cell C14 to the value 1 which restores the model to compliance with the published scientific literature. Accordingly there was no basis on which informed representations could have been made prior to the BRS response quoted above.

BRS Issue 2

After a great deal of investigation, that was in no way shortened by the DSU report, we have discovered that the ScHARR modellers have been inconsistent in their nomenclature and moreover provided no useful comments or other model documentation that would have enabled us or any other scientists investigating the model's properties to confirm the validity of the simplified distributions Dr Stevenson and colleagues used to model the Holt et al data.

After at least 40 hours of investigative modelling work by our Society's statistician advisor, that could have been avoided if NICE had used decent standards of scientific documentation, we have now discovered that the shorthand used to describe 5 year age bands and the shorthand used to describe 0.5 SD unit T-score bands counter-intuitively run in opposite directions. ScHARR age-bands are identified by their lower bound while T-score bands are identified by their higher bound. This was never made clear by the ScHARR modellers. Thus with respect to age, "55" refers to a 55 to 59.9 year age band. In contrast, for BMD T-scores "-2" does not refer to a -2.0 to -1.51 T-score band but to a -2.49 to -2.0 T-score band. When this was corrected so that we were simulating the same data as ScHARR, we obtained the following results.

We have established that there is no constancy of variance in BMD across age-bands in the UK population (p=0.000323), ie there was one chance of it being true in 3,000. Secondly, in no age band was it true that the distribution of BMD was statistically normal (less than one chance of this being true in a million at any age). In Annex 4 the authors of the DSU report argue otherwise without giving details of their statistical test (there are several tests of normality) and having, unforgivably by the standards of most scientific journals, trimmed "outliers" from the data beforehand without giving details of how they chose the outliers to be trimmed or even if the cut-offs for trimming were pre-specified. These results (Table 1 p105) had from a scientific perspective therefore to be completely re-run by ourselves because of the grossly inadequate nature of how they were presented by the DSU. It is only after completing this time-consuming and unnecessary activity that we can conclude women are not disadvantaged by the simplifications adopted to describe the Holt et al data by the NICE modellers. The lack of adequate and clear documentation of the model remains a very valid criticism. Without better documentation of their models NICE will cause confusion among scientists and damage its own reputation and utility to the NHS. The issues are simply those that led to the present system of scientific peer review: scientists must be constrained to present their results in a way that allows other scientists with equivalent expertise to reproduce them.

BRS Issues 3-9

In the various annexes, the DSU modellers have considered most of our other points of criticism and come up with various conclusions. In the main our suggestions were designed to make the NICE model operate as similarly as possible to the NOGG model while representing the current state of scientific knowledge as accurately as possible (which was we understand NOGG's intention). To bridge the divide between the two models, that has already led to many practising specialists and generalists losing confidence in NICE and its models, seems still both practical and potentially highly reassuring to clinicians. Unfortunately the DSU's current results and conclusions have to be regarded as unreliable because of the disutility issue. They require re-confirmation after the DSU have corrected the central error in multiplying the disutility of alendronate (and by implication other bisphosphonates) by a factor of ten. Until this is done, the NICE model must be regarded as unfit for purpose and therefore unsuited to the clinical task NICE has set for it. We would be happy to comment again when further work has been done to make the model operate properly.

Conflict of Interest

It is noted that the DSU report was signed by at least one of the scientists responsible for the Economic Model underpinning TA 160/1. The DSU Report lacks some authority in consequence because of this conflict of interest.
We trust that our comments will be of use in achieving the ultimate aim we must all espouse: to achieve fairness in the allocation of NHS resources for managing patients at high risk of osteoporotic fractures. This is both for their own benefit and for the benefit of society as a whole, which gains immeasurably from the positive contribution to the national life of patients with osteoporosis when they are freed from the distressing and sometimes fatal consequences of an excessive burden of osteoporotic fractures.

Yours sincerely,