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Dear Natalie,

Medtronic comments on Economic Model for Review of Guidance on Use of Coronary Artery Stents

Thank you for the opportunity to review the electronic copy of the assessment group's model for the appraisal of drug eluting stents (DES). We believe it has added value to the consultation process.

Medtronic's comments are based on the protected version of the economic model provided by NICE and the NICE TAR 04/42 Version 3 and associated appendices. We would like to address our concerns on the technical aspects of the model under eleven key headings in line with the core principles of economic modelling and HTA: Model design, replicability of the model, structural assumptions, strategies/comparators, time horizon, data inputs, model layout, uncertainty, internal consistency, external consistency and specific DES issues.

1. Model design

The spreadsheet shows the model to be a very basic decision tree model. It is described within ten formulae in the TAR (page 104). Whilst we agree that models should not be unnecessarily complicated, we do not believe that the assessment group's model is sufficiently sophisticated to allow adequate analysis of the cost-effectiveness of DES.

2. Replicability of the model

As previously mentioned, the model provided was protected and it was therefore not possible to examine the formulae. We believe that as independent assessors, the Liverpool group's model should be subject to the same level of scrutiny as the models of other stakeholders who are required to submit unlocked versions which can be independently replicated to ensure there are no errors.

Despite the model being locked down, it has been possible to replicate the model via referral to the assessment report and through trial and error of including and excluding variables to match the results in the protected model. On the basis of this replication we do not believe that the report description accurately reflects the apparent formulae used in the Liverpool model. We request that the Liverpool group check the report wording in case of any potential errors.

3. Structural assumptions

Through our replication of the model, we believe that the structural assumptions are not as transparent as they appear in the TAR. The structural assumptions appear only to be relevant if a twelve month time horizon is deemed appropriate.

Mortality does not appear to be taken into account within the model. The justification for this is that three year data is inconclusive between DES and BMS. However, if this had been incorporated it would have allowed the appraisal committee to see whether any short-term mortality data or future mortality data would have an effect on the guidance being proposed.

Other clinical outcomes evaluated in trials submitted to the Institute included acute MI, other coronary events and vessel failure. These have not been modelled as the authors found no difference between DES and BMS in a meta-analysis. We believe that the appraisal committee should consider whether these outcomes are relevant. By excluding them, the validity of the model from a clinician perspective may be compromised. It should be noted that meta-analyses do provide uncertainty over the point estimate and that this can be examined through probabilistic sensitivity analysis (PSA) within a modelling framework (the authors do not do this).

4. Strategies/comparators

The Liverpool model has been built based on immediate data constraints (some of which have now been overcome due to the delays in the appraisal process and newly available data). The critical appraisal of decision-analytical models for HTA (Phillips et al. 2004) clearly states that options should not necessarily be constrained by data availability. We suggest that due to process delays a re-evaluation of data currently available and its appropriateness for inclusion in the model should be mad and assumptions tested.

5. Time horizon

A twelve month time horizon has been chosen by the assessment group, however, the clinical literature suggests that differences in the effect and consequences between the comparators may extend beyond this.

The authors note that there is limited long term data available, however make no attempt to handle this within the model and therefore the model has limited applicability to HTA decision-making. One of the powerful uses of pharmacoeconomic modelling is being able simulate what may happen over time. The design of the Liverpool model would need to be changed to allow this level of analysis which we believe is required.

It is surprising that, given uncertainty of long term effects, the assessment group did not attempt longer term modelling and employ value of information techniques to see if collecting longer term outcome data (possibly through a multi-centre registry) was of value.

By not modelling over the longer-term, the model is in essence inflexible and cannot provide a benchmark to show what DES has to achieve to be deemed cost-effective. Lack of data (particularly with new technology) does not necessarily mean no effect. We believe that models developed as part of a NICE appraisal should have the capacity to be able to simulate potential future benefits.

6. Data

Comprehensive data input information is included in the BCIA model comments with which Medtronic concur. Top-line, despite the numerous RCTs available at the time of review, the assessment report authors have consistently relied heavily on observational, single centre audit data. As previously commented to the Institute, such data is prone to bias and we believe does not accurately reflect the true effect of DES:

A. Patient selection bias – treatment with DES or BMS may be based on patient characteristics and this can affect the reason for differences in effect
B. Single centre – treatment may not accurately reflect that of other centres and therefore applying the effect from this centre to others may be inappropriate.

Again, we would also like to highlight that due to delays in the appraisal process valuable new data is available which should be considered as part of this appraisal.

7. Model layout

Medtronic is disappointed with the quality of model lay out and the fact that no referencing is presented.

It would seem that some of the inputs may be hard coded rather than derived from other clearly inputs (for example, derivation of disutility values). However, as the model was locked down, this is not possible to confirm conclusively.

It is also disappointing to see that the model does not clearly show the total costs and total QALYs for each strategy before concluding the incremental costs and benefits. Although the ICER only relies on incremental results, good modelling practice recommends that costs and QALYs should be reported separately for each strategy.

8. Uncertainty

The authors rely heavily on the use of basic deterministic sensitivity analysis. They have made limited attempts in handling uncertainty:

1. Changes in methodological assumptions
2. Structural uncertainty e.g. long term effect/modelling has not occurred
3. Heterogeneity – sub group analyses (published literature suggests that there are specific sub-groups where DES are more cost-effective)
4. Parameter uncertainty is not appropriately handled through PSA

Contrary to NICE guidance and current thinking within the pharmacoeconomic field, the authors have not addressed parameter uncertainty through PSA. It is of concern that the independent assessment group are not following NICE guidance on this.

9. Internal consistency

It has not been possible to conclusively confirm internal consistency of the mathematical logic – although replication of the model has been done, there seems to be differences between reported structural equations in the report and the equations in the model.

10. External consistency

It is not clear whether the authors have included all relevant data within their model. It would appear that the main data incorporated is that of the single centre audit in Liverpool.

It has not been possible in the time constraints to test external consistency fully with other data sources. However, it is likely that the model structure is not sufficient to model some of the other data available, particularly that showing effects beyond 12 months.

Additionally, the assessment group has only examined data for two stents. This is out of line with the current evidence base

11. DES issues

The authors do not use list prices for the stents. The average number of stents used also differs between manufacturer's submissions and the assessment group submission. It would appear that there is uncertainty around this assumption which should be tested.

Conclusion

In conclusion, despite the concerns regarding the lack of modelling techniques employed by the assessment group, the applicability of the results to national policy making relies mainly around the findings from a non-randomised, single centre audit. Where there is any concern about the generalisability of this data (including average number of stents), particularly when RCT data is available, extreme caution should be placed on the results provided by the model.

With regards to the modelling techniques employed, it would appear that the simple model may be appropriate for evaluating short term effects. However, if the clinical community believes that there are potential long term benefits of DES (particularly if revascularisation differences are likely to occur in the future), the model has limited use.

It is also noted that the model does not fully comply with current NICE guidance and good practice guidelines, particularly in the handling of uncertainty and ability to validate the structure.

On the basis of this model review and in view of the fact that new data is available on DES which would add value to the appraisal if considered, we would like to reiterate our suggested next steps submitted to the Institute as part of the ACD consultation. We maintain that the most appropriate solution would be for a complete re-analysis of the clinical and cost-effectiveness sections of the AR. Due to the conflict of interest of the Liverpool group regarding DES and their publication record we believe an alternative group would be most appropriate to conduct any new assessment.

As an alternative, as previously suggested to the institute, the Decision Support Unit (DSU) could be engaged to objectively review the work of the Liverpool group.

Thank you again for the opportunity to comment on the model. Please don't hesitate to contact me if you have any further queries.

Kind regards,

[redacted]

Medtronic Ltd.