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Difficulties arising in reimbursement recommendations on new medicines due to inadequate reporting of population adjustment indirect comparison methods

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Abstract: Indirect treatment comparisons are useful to estimate relative treatment effects when head-to-head studies are not conducted. Statisticians at the National Centre for Pharmacoeconomics Ireland (NCPE) and Scottish Medicines Consortium (SMC) assess the clinical and cost effectiveness of new medicines as part of multidisciplinary teams. We describe some shared observations on areas where reporting of population-adjustment indirect comparison methods are causing uncertainty in our recommendations to decision making committees when assessing reimbursement of medicines.

As patients and clinicians desire quicker access to new medicines, the assessment of the efficacy and safety relative to comparator medicines may rely on evidence other than traditional head-to-head studies. Population-adjustment indirect comparison methods use statistical modelling approaches and consider common sets of outcomes and covariates between studies. But these estimates may not provide the evidence that national healthcare organisations require to make recommendations about reimbursement.

Statisticians at the National Centre for Pharmacoeconomics Ireland (NCPE) and Scottish Medicines Consortium (SMC) assess the clinical and cost effectiveness of new medicines as part of multidisciplinary teams of clinicians, pharmacists, statisticians, health economists and health service researchers. One of the aims of the statisticians is to ensure our decision-making committees are aware of any areas of uncertainty presented within the submission documents for new medicines. It is extremely difficult to provide clear advice on the statistical components when there is a lack of transparency in the methodology used for the statistical analysis. We acknowledge that the excellent series of the National Institute for Health and Care Excellence (NICE) Decision Support Unit Technical Support Documents (DSU TSD)[1] has seen an improvement in the quality of methods used for indirect treatment comparisons (ITCs) and cost effectiveness analyses. Recent discussions between the NCPE and SMC statisticians highlighted a shared concern with the reporting of population-adjusted indirect comparisons methods, primarily those from matching-adjusted indirect comparisons (MAIC) and simulated treatment comparisons (STC), even though guidance documents are available [2,3].

There are two commonly used methods: MAIC which applies propensity score weighting and STC which uses outcomes regression. These analyses may be “anchored”, i.e. have a common comparator arm (often a placebo or “standard of care” group), or “unanchored”. Unanchored analyses would be expected to have greater uncertainty than anchored analyses.

An unanchored comparison requires the assumption that all prognostic variables and effect modifiers have been included in the model, while anchored analyses only require the assumption that all effect modifiers have been included.

The treatment effect estimates allow clinical assessment of relevant comparator medicines. These estimates are often then used in a cost effectiveness analysis, in particular as a component of the incremental cost effectiveness ratio (ICER), which is the difference in the cost between two medicines divided by the difference in their effect. Although NCPE and SMC are primarily interested in the best estimate of the relative treatment effect, we also need to understand the potential uncertainty arising from modelling assumptions. Therefore, sensitivity analyses are very important in shaping our recommendations.

We are often presented with little information on the modelling strategy and results, and there are six areas where we routinely have to request more information from companies.

1. **Covariate selection:** A key assumption of MAIC and STC is that the outcomes can be predicted from the covariates in the model. In practice this may be limited by the availability of data (collected or reported) and more complex models may mean lower sample sizes due to less matching between heterogeneous patient populations. Generally good predictions require large numbers of clinically relevant predictors [4]. We are not looking for a parsimonious model, we want the one with the highest predictive power and the usual arguments of "statistical significance" for inclusion/exclusion are usually not helpful. Clinical *and* statistical justification should be given for the selection of covariates. The predictive power should be presented and if the predictive power is low, this will suggest greater uncertainty in the estimated treatment effect which we need to consider in our assessment.
2. **Assessment of model fit:** We want to see model fit statistics like R^2 value, predictive ability and area under the ROC curve [4] but often these are not reported, even after being requested.
3. **Summary of weights:** NICE DSU TSD 18 [5] recommends presenting numerical summaries and histograms of rescaled weights from an MAIC analysis, but these are often not included in the submissions to NCPE and SMC. The effective sample size allows some evaluation of degree of matching, but it is important to see the distribution of the rescaled weights and in particular if the analysis may be influenced by a few observations with large weights. The assessment teams will regard the omission of these summaries as a weakness in the submitted evidence.
4. **Anchored analysis:** When anchored analyses are possible then an unanchored analysis should not be presented.
5. **Sensitivity analyses:** In a scenario when only an unanchored comparison can be made, treatment effects estimated from models with reduced sets of covariates should also be investigated. In the case of an anchored comparison, the treatment effect estimates from standard NMAs should also be presented, such as from the Bucher [6] method or the Bayesian methods described in Dias et al [7]. These treatment estimates

could also be included in cost effectiveness sensitivity analyses and we would expect little difference in the ICER from the base case if the treatment estimates are robust.

6. **Study design is important:** MAIC and STC only account for differences in patient populations between trials by inclusion of covariates in the model but they do not take differences in study design, such as phase of study, into account. Any potential biases due to study design should be described [8].

Appendix D of NICE DSU TSD 18 [5] is a worked example of MAIC and STC. We accept that it is impossible to address all potential sources of uncertainty and more research would be useful in most of these areas. For example on suitable levels of predictive power for MAIC and ITC or the impact of including studies which contribute a few patients with very large weights.

Earlier access to medicines has resulted in EMA approval for some medicines based on single arm, phase II studies. However, reimbursement is not part of the EMA remit. Therefore, companies need to consider the effects of comparator medicines or treatment pathways when submitting to individual country HTAs. The comparative treatment effects may then be based on unanchored indirect comparison from an MAIC/STC analysis. We agree with the concerns of Grieve et al. [9] regarding the use of observational studies, or "real world" data, after interim approval has been given and this will be exacerbated where there is a lack of clarity in the modelling of the original estimate of the treatment effect. The requirement to share details of methods and results is important in all statistical analyses but, for us, it is imperative. Otherwise the answer to the question "Is this new medicine good value for money and should patients have access to it?" may just be "We don't know".

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