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# Letters to the Editor

## WHO SHOULD CONDUCT MODELING AND COST-EFFECTIVENESS ANALYSIS?

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Dear Dr. Mäkelä,

In some countries, reimbursement of drugs is based on cost-effectiveness analysis (CEA), in others not. In times of ageing populations, increasing number of possible interventions, and limited resources, it seems likely that CEA will be more and more important as a basis for decision making.

SBU has conducted systematic reviews for more than 25 years, and our experience is that it is very difficult to draw any conclusions from the literature on cost-effectiveness due to the variability in organizations, contexts, and costs between countries. According to CHEERS (1), economic evaluations have no widespread mechanisms for warehousing data to allow for independent interrogation and thereby creating transparency.

In most countries where CEA plays a role in drug reimbursements, industry delivers the CEA which then are scrutinized by regulatory bodies. These public agencies can ask for complementary information within a short time period. However, models are usually not transparent for others or available for public use. The problem is that CEA studies funded by industry are more likely to report lower ratios than nonsponsored studies (2–5), that is, they are biased. Approximately 70 percent of all CEA were sponsored, and those studies were much more likely to report favorable conclusions and showed more favorable incremental cost-effectiveness ratios than nonsponsored studies (2;5). To minimize this bias, actions have been taken, for example, developing methodological guidelines (1), improving the peer review process and clarifying relationships between sponsors and analysts (6). Still, the problem persists and is well in line with standard economic theory, which postulates that the behavior of private firms is driven by the objective of profit maximization (7).

With the present decision-making process, society will not optimize health within limited resources. An alternative approach is thereby to let public organizations or independent university departments conduct CEA financed by fees from industry. The benefit is more unbiased CEA without increasing costs for involved parties. There would be a parallel to the legislation where industry pays a fee to the European Medicines Agency (EMA) for their services.

To deal with the problem of biased CEA, Barbieri and Drummond suggested increased public funding for economic evaluation of medicines (8). Garattini et al. took one step further and concluded that the best way of limiting confounding factors is by clearly distinguishing assessors from manufacturers and marketers of any new technologies (5). However, no actions have been taken so far and the reasons could be discussed. Hampering factors are that economic modeling is a demanding and time consuming task and that strong stakeholders like industry would oppose. It may even not be in the interest of health economists depending on assignments from industry. For drugs, decisions on reimbursement must usually be made with limited resources and within a limited time period. Most health technology assessment (HTA) organizations or reimbursement bodies, except NICE, lack the economic resources to conduct modeling on their own. Open and transparent economic modeling where each country can put their own data on incidence and costs is a more appealing approach.

Because economic modeling is a demanding task, international collaboration would be needed and cost-effective. How such a system would be organized is a later question. Maybe member states interested could join in a consortium. The models should be transparent with open-access and possibilities to adjust according to local conditions. For example, organization, costs, and incidence vary between countries. Each regulatory

body could then incorporate relevant figures for their own country. Initiatives within Europe and the HTA society would be very welcome.

**Måns Rosén, Professor, Executive Director**
*Swedish Council on Health Technology Assessment (SBU) Karolinska Institutet, Department of Learning, Informatics, Management and Ethics*

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# UPDATE ON ROMIPLOSTIM AND ELTROMBOPAG INDIRECT COMPARISON

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Dear Dr Mäkelä,

In our article "Romiplostim and eltrombopag for immune thrombocytopenia: methods for indirect comparison" published in the *Journal* (1), we presented an indirect comparison of the effectiveness of eltrombopag and romiplostim in raising platelet counts in patients with immune thrombocytopenia (ITP). Indirect comparison analyses are recommended by the National Institute for Health and Care Excellence (NICE) in cases where randomized head-to-head studies do not exist, and were used by NICE in their guidance for the eltrombopag Single Technology Appraisal submission (2).

Following publication of our study, updated data from the eltrombopag RAISE study were included in the evidence package to support the NICE final guidance regarding eltrombopag for the treatment of ITP (2;3). These updated data included fourteen additional patients receiving eltrombopag and one additional patient receiving placebo assessed as having an overall platelet response, and six additional eltrombopag patients and no additional placebo patients assessed as having a durable platelet response (Table 1). We would like to describe the relevance of our original analyses in light of these new data, such that readers of *International Journal of Technology Assessment in Health Care* are aware of the full range of evidence available for informing health policy decisions on the use of eltrombopag and romiplostim.

Several alternative methods are available for conducting an indirect treatment comparison. Our original article presented analyses using five methods, incorporating either a Bayesian or Bucher approach, and in each case the results indicated that romiplostim significantly improves overall platelet response compared with eltrombopag. We consider the Bayesian method to be a more robust approach than the Bucher method, because the Bayesian method includes all data in a single model that accounts for the heterogeneity between studies and preserves the within-trial randomization. The NICE Evidence Review Group (ERG) also considered the Bayesian analysis to be most appropriate, and used this approach in their review of the NICE eltrombopag submission (4). Including the new eltrombopag response data, and using the same Bayesian methodology as previously used by us, the ERG found that the results remained consistent with our original analysis (Table 1): the overall platelet response was significantly higher in patients receiving romiplostim than in those receiving eltrombopag (odds ratio [OR], 0.15; 95 percent confidence interval [95%CI], 0.02–0.84), assuming medium heterogeneity. Also consistent with our original analysis, the ERG found that while the point estimate favored romiplostim, there was no statistically significant difference in durable response between eltrombopag and romiplostim (OR, 0.20; 95% CI, 0.01–2.13).

Results from indirect treatment comparisons between eltrombopag and romiplostim should be interpreted with caution due to heterogeneity between the study designs, patient populations, and response definitions. Nonetheless, in the absence of head-to-head studies these analyses provide important evidence on the relative efficacy of the two currently available thrombopoietin-mimetics in patients with ITP. Using the same Bayesian approach as in our original study, an independent research group on behalf of NICE (the ERG) have used updated evidence to demonstrate that the overall platelet response remains statistically significantly greater with romiplostim than with eltrombopag.

**Katy Cooper**
*University of Sheffield, UK*

**James Matcham**
*Amgen Ltd, Cambridge, UK*