TARGETED THERAPIES

Manufacturer sponsorship bias in economic analyses matters

David Kerr and Ahmed Elzawawy

A qualitative study indicates that there is a positive selection bias towards favourable economic analysis of targeted therapies, when these are funded by the manufacturer. At a time of increasing budgetary constraints and public scrutiny of the relationship between industry and the professions, we need a more mixed economy of funding for this field.

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In terms of the history of medicine and health care, the 19th century may be regarded as the century of Public Health, clean water, sewerage, and understanding the basis of infection; the 20th century might be regarded as the century of knowledge, when systematic clinical and laboratory research yielded extraordinary insights into the mechanism of disease; we predict that the 21st century will be driven by value. Considering the spiralling costs of health care and an often confused approach to how we define value in a societal sense, and given the global financial crisis and the likelihood that for many nations the health budget will flatline, it is obvious that we need more data on the relative cost effectiveness of innovative diagnostic or therapeutic agents if we are to make transparent and defensible judgements on their relative worth. This situation is set against a backdrop of increasing suspicion from policy and lawmakers and some patient groups that the relationship between practising clinicians and purveyors of these new technologies is not at sufficient arm's length.[1] In 2007, Djulbegovic *et al.*,[2] published a fascinating historical case study of the first conflicts of interest policy at the National Academy of Sciences. A fundamental debate in this case was whether one can simply declare a financial interest or whether one must also admit that this financial interest is a potential source of bias.

Now, a new study has been published by Valachis *et al.*[3] that addresses this question in a different way. One of the characteristic points of the study is that the authors tried to investigate the role of manufacturers' influence in various manifestations, such as the presence of any author affiliated

> "Does this sponsorship bias matter?"

with the manufacturer of the drug being assessed or the presence of direct funding from the manufacturer for the health-economic study—as shown in previous studies—the role of funding and its bias in economic evaluation of drugs in oncology,[4] and medical researchers in general.[5] Of the 81 eligible studies that they identified, the authors found that economic analyses that were funded by pharmaceutical companies were more likely to report favourable qualitative cost estimates than those without an expressed funding association with these companies (28 out of 34 studies [82%] versus 21 of out of 47 studies [45%]; $P = 0.003$). This phenomenon was seen to a similar degree for those studies that reported any financial relationship with the manufacturers, for example, author affiliation or author funding. Valachis *et al.*[3] discuss the weaknesses inherent in their study with candour: the linkage between the eligible studies and their financial aspects depended solely on published details as Valachis *et al.*[3] made no effort to contact authors directly to further verify these data; there may have been a publication bias towards positive reports that might have skewed results; certain study criteria were poorly represented, so the database was rather small (for example, affiliation with manufacturers); and finally, their analysis was based on qualitative data. Nevertheless, Valachis *et al.*[3] do seem to have demonstrated a consistent sponsorship bias towards the manufacturer of costly, targeted drugs with respect to economic analyses. It is concluded that the best way of dealing with perceptions of sponsorship bias is not increased rhetoric, but rather increased public funding for economic evaluation of medicines, thereby creating a true mixed economy for research funding in this field.

Does this sponsorship bias matter? If we are to adopt Michael Porter's definition of value,[6] then, yes it does.

"Value in any field must be defined around the customer, not the supplier. Value must also be measured by outputs, not inputs. Hence it is patient health results that matter, not the volume of services delivered. But all outcomes are achieved at some cost. Therefore, the proper objective is … patient health outcomes relative to the total cost (inputs). Efficiency, as well as other objectives such as safety, is subsumed in the concept of value."

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> "Do we think that there is some methodical misrepresentation of results? Of course not..."

Adoption of any new therapeutic agent in the current climate is likely to involve trade offs, comparing the value gained from the introduction of the targeted therapy relative to existing gold standards in cancer treatment, or, even more widely, comparing its value with that gained from hip replacements or cataract operations. The latter comparison might seem absurd, but within a finite health budget in which there is no ring-fencing of cancer funding then this could become an issue. So, an economic evaluation of the new drug will have an often critical role in whether the drug is made available to cancer patients by governments or payers.[7] If there are significant doubts about the veracity of the data, hanging over the analysis like the sword of Damocles, then this starts to undermine the validity of the data and even reduce the chances of a targeted therapy passing over whatever health-economic hurdles have been erected in its way.

So, is there a way to square this circle? In the same way that we now have mandatory listing of clinical trials[8] to offset publication bias, one might establish a register of pharmacoeconomic studies; approaches might be made to journal editorial boards to lower their threshold for publishing negative studies; and payers could establish independently funded analytical units to give an entirely unbiased view of the economic case for acceptance or not of the agent under investigation. If the workings of these analytical units were utterly transparent and open to public review, then this would further enhance their credibility and relevance to citizens. Do we think that there is some methodical misrepresentation of results? Of course not, however, the paper by Valachis *et al.*[3] is a timely warning of the subtle biases that can creep in unnoticed, and is perhaps doubly important given the wider economic challenges faced by all health-care systems and, therefore, the increasing scrutiny that will be applied to all such economic analyses.

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Competing interests
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HAEMATOLOGICAL CANCER

Gemtuzumab ozogamicin in acute myeloid leukaemia

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Gemtuzumab ozogamicin was withdrawn from the market after being evaluated in combination with chemotherapy in the frontline treatment of patients aged 18 to 60 years with acute myeloid leukaemia (AML). More-recent randomized trials demonstrate that low doses of gemtuzumab added to cytarabine and anthracycline-based chemotherapy benefit patients with better-risk AML.

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Treatment of patients with acute myeloid leukaemia (AML) has not changed significantly since studies in the 1980s established cytarabine and anthracyclines as the most-effective agents in this disease. Several randomized trials have demonstrated that the doses of cytarabine and anthracyclines are important in specific subsets of patients. A meta-analysis of trials comparing high-dose with standard-dose cytarabine during induction has shown an improved relapse-free and 4-year overall survival for patients younger than 60 years with *de novo* AML who receive high-dose cytarabine as a part of their induction regimen.[1] This finding was further corroborated by a recent randomized trial demonstrating a higher response rate and improved overall survival in patients younger than 46 years who received high-dose cytarabine induction compared with those receiving the standard cytarabine dose (6-year overall survival 52% versus 43%; $P = 0.009$).[2] Other data have suggested that further escalation of the cytarabine dose beyond levels that saturate intracellular arabinofuranosylcytosine triphosphate is not beneficial.[3]

Cytarabine dose is particularly important in the treatment of patients with the core-binding factor leukaemias, which have a more-favourable risk profile; the administration of several courses of high-dose cytarabine as consolidation therapy improves the survival of these patients.[4] In addition, a higher dose of the anthracycline daunorubicin (90 mg/m^2 versus 45 mg/m^2) benefits patients younger than 60 years, with the exception of those with adverse cytogenetics and molecular aberrations (such as *FLT3* internal tandem duplication).[5]

Clearly, escalation of chemotherapy dose seems to benefit patients with more-favourable risk disease including young patients and those with more-favourable cellular biology determined by cytogenetics or molecular abnormalities. It is tempting to speculate that the leukaemic cells in these patients are more susceptible to the effects of cytotoxic chemotherapy because of as yet unidentified mechanisms. Therefore, the limiting factor in such patients will be the limits of tolerability of the escalated dose of chemotherapy. Other agents with novel mechanisms of action and with