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Can we reduce disease burden from osteoarthritis?

An article in the recent Bone and Joint Disorders Supplement presented a measure for translating trial outcomes into a quality-of-life (utility) scale and comparing the cost effectiveness of current interventions. Both the measure and the cost-effectiveness analysis raised questions.

(Med J Aust 2004; 180 (5 Suppl): S11-S17)

Use of the TTU is questionable

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TO THE EDITOR: Segal et al propose a new method — "transfer to utility" (TTU) — to convert clinical and quality-of-life (QOL) trial-based outcome measures to a common metric — quality-adjusted life-years (QALYs) — to compare the cost-effectiveness of different interventions.[1] TTU uses regression to map clinical and QOL instruments to a "utility-equivalent scale" that aims to measure strength of preference for health outcomes. In their example, several instruments were administered to osteoarthritis patients. Australian Assessment of Quality of Life (AQoL) scores were regressed on SF-36 subscale scores and QALYs were generated from published SF-36 results by means of a conversion algorithm based on these parameter estimates. The approach is novel, but we question its validity.

Utility and health-related quality of life (HRQOL) are fundamentally different concepts. HRQOL is a standardised multidimensional, ordinal measure of the individual's perception of how disease and treatment affect physical, social and emotional functioning. Measuring utility requires a critical next step: capturing strength of preference for outcomes in a unidimensional interval scale. HRQOL and utility scales have very different interpretations. Any appearance of similarity is superficial. The algebra of scale conversion is easy, but conceptually problematic.

TTU involves a complex trail of estimation and prediction. Ordinal SF-36 subscale scores are used as arguments in regression, imposing interval properties. Statistically valid interpretation of the resulting parameters requires dummy coding. The dependent variable is the AQoL score generated by applying the AQoL algorithm, developed in previous research using a different population[2] to respondents' surveys. The new algorithm from the TTU regression parameters is used to convert published trial-based average SF-36 subscale scores to AQoL scores. Misspecification errors are built into the predicted AQoL scores. Information about variability in outcomes and preferences in intermediate measures, and hence uncertainty around point estimates of predicted AQoL scores, is suppressed.

How plausible are these results? Segal et al report an estimated "utility gain" 12 months after hip surgery of 0.304 (from 0.464 before surgery to 0.767 at 12 months).[1] The interpretation is that an average patient undergoing hip surgery for osteoarthritis would be willing to forgo about 40% of their remaining life span for the quality-of-life improvement the surgery would provide.

Apparently, sophisticated quantitative approaches cannot add information about factors not measured in trials. The validity of the approach stands or falls on appropriate statistical methods, data quality and interpretable results. TTU potentially introduces bias, suppresses information relevant to decision-making and may lead decision-makers to place undue trust in point estimates based on heroic assumptions.

1 Segal L, Day SE, Chapman AB, Osborne RH. Can we reduce disease burden from osteoarthritis? An evidence-based priority-setting model. *Med J Aust* 2004; 180 (5 Suppl): S11-S17.
2 Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. *Qual Life Res* 1999; 8): 209-224. ❑

TTU is valuable for comparing disparate management options

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IN REPLY: The "transfer to utility" TTU technique was devised to compare disparate interventions, using published clinical trial literature, where utility data are not reported. While collection of utility data in clinical trials would be preferable, until this occurs routinely a means to translate reported quality-of-life scores into utility scores is highly useful. Other groups are also grappling with this.[1]

In developing the TTU weights, various sophisticated statistical techniques were explored. However, added complexity did not improve the estimates. Contrary to the suggestion by Viney and colleagues, the TTU estimates are highly plausible and were vetted by our reference panel of clinical experts. Taking the example Viney and colleagues cite, a 0.304 increase in utility score for hip replacement indicates a patient would, on average, be willing to forgo 30.4% of remaining life-years to obtain the benefits of surgery

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There should be no more than 5 references. The reference list should not include anything that has not been published or accepted for publication. Reference details must be complete, including: names and initials for up to 4 authors, or 3 authors et al if there are more than 4 (see mja.com.au/public/information/uniform.html#refs for how to cite references other than journal articles).

— not 40% as incorrectly stated by Viney et al. This is consistent with the large increase in well-being observed following hip replacement (in the seminal trial, SF-36 mean scores increased from 26.9 to 66.6 for physical function, 14.6 to 58.7 for role physical, and 32.9 to 72.8 for bodily pain).

Whether the TTU introduces bias (a characteristic of other summative approaches to estimating health, such as the popular DALYs) is a matter for future research. Undoubtedly, all population-wide approaches suppress specific information, but the purpose of the priority-setting model supported by the TTU is not to provide information on individuals, but to compare management options to give clinicians and policymakers another way of understanding the comparative performance of disparate interventions.

1 Andrews G, Issakidis C, Sanderson K, et al. Utilising survey data to inform public policy: comparison of the cost-effectiveness of treatment of ten mental disorders. *Br J Psychiatry* 2004; 184: 526-533. ❑

Cost-effectiveness findings not based on available evidence

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TO THE EDITOR: At Pfizer, we are very concerned about major conclusions drawn with regard to cost-effectiveness of COX-2-specific inhibitors (CSI) in the article by Segal and colleagues;[1] these conclusions are based on an entirely inadequate and inappropriate database.

The CSI cost-effectiveness analysis is based on two publications described by Segal et al as "seminal",[2,3] and on a *British Medical Journal* editorial described as "a report by the US FDA [United States Food and Drug Administration]".[4] The first of the two "seminal" publications was a pivotal study for registration purposes;[2] the second was neither pivotal nor "seminal".[3] The purported "report by the FDA" presents the authors' opinion of a single study[5] which does not reflect the overall body of gastrointestinal (GI) safety data for either CSI or non-steroidal anti-inflammatory drugs. The issues with this study and the inaccuracies in the editorial have been reported.[6]

Segal et al[1] have apparently ignored at least 20 other publications (references available on request) comparing the safety and efficacy of celecoxib with NSAIDs; we would consider these relevant to any valid analysis of cost-effectiveness. There are probably a similar number of relevant publications for the second CSI, rofecoxib, which should also be considered if an analysis of the CSI class is to be rigorous.

The body of evidence (previously summarised[7]) shows that CSIs are associated with a 50% or lower incidence of serious GI complications than non-specific NSAIDs, which results in lower mortality. Any cost-effectiveness analysis that ignores this GI safety advantage of CSIs over NSAIDs is incomplete. Therefore, the conclusions by Segal et al that "Non-specific NSAIDs and COX-2 NSAIDs were found to perform similarly in terms of outcomes and side effects . . ." and " . . . In most scenarios, COX-2 NSAIDs are dominated by non-specific NSAIDs"[1] are not true reflections of either the trial data nor real-world clinical practice, and may mislead the medical community as to the relative safety of these agents.

It is important to note that the full body of celecoxib data has been submitted by Pfizer as a cost-effectiveness analysis to the Pharmaceutical Benefits Advisory Committee (PBAC). Contrary to the conclusions of Segal et al, in every scenario in the PBAC submission celecoxib was more cost-effective than non-specific NSAIDs. Celecoxib is currently listed on the Pharmaceutical Benefits Scheme and this indicates that it was considered cost-effective. An abstract has been published regarding the cost-effectiveness of celecoxib in the Australian setting.[8]

We consider that every statement made in the article by Segal et al with regard to the cost-effectiveness of COX-2-specific inhibitors[1] is inaccurate and misleading, as it is not based on the available evidence. We request a retraction statement from the authors.

1 Segal L, Day SE, Chapman AB, Osborne RH. Can we reduce disease burden from osteoarthritis? An evidence-based priority-setting model. *Med J Aust* 2004; 180 (5 Suppl): S11-S17.
2 Bensen WG, Fiechtner JJ, McMillen JI, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999; 74: 1095-1105.
3 Williams GW, Hubbard RC, Yu SS, et al. Comparison of once-daily and twice-daily administration of celecoxib for the treatment of OA of the knee. *Clin Ther* 2001; 23: 213-227.
4 Juni P, Rutjes AW, Dieppe PA. Are selective COX2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? [editorial]. *BMJ* 2002; 324: 1287-1288.
5 Silverstein FE, Faich G, Goldstein JL. Gastrointestinal toxicity with celecoxib versus non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. *JAMA* 2000; 284: 1247-1255.
6 Silverstein F, Simon L, Faich G. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib [letter]. *JAMA* 2001; 286 (19): 2399-2400.
7 Yeomars ND. Impact of cyclooxygenase-2 inhibitors: Are they fulfilling their promise [editorial]. *Intern Med J* 2004; 34: 145-147.
8 Grobler M, Schaffer D, Burke TA, Morant S. The cost-effectiveness of celecoxib compared with conventional NSAIDS in the treatment of arthritis. *Intern Med J* 2003; 33 Suppl: A84. ❑

Making all data publicly available would be welcome

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IN REPLY: Our economic analysis of COX-2-specific inhibitors (CSIs) was part of a research program on priority setting. The application to osteoarthritis (OA) involved cost–utility analyses of 19 interventions (written up in a 195-page research report[1]), and was subject to peer review by an advisory panel including senior clinicians. The research drew on over 200 references, 23 on CSI, but a limit of 50 references for articles in the *Medical Journal of Australia* meant that full referencing was not possible.

Evidence of efficacy in OA and adverse events (gastrointestinal and cardiac) are incorporated in our QALY estimates, the latter based primarily on the seminal CLASS trial (Celecoxib Long-term Arthritis Safety Study), and the United States Federal Drug Administration (FDA) analysis[2-4] of this trial (summarised previously[5]). The FDA report concludes that for the primary endpoint specified in the study protocol — clinically significant upper gastrointestinal event (CSUGIE) — for the entire study period there was no significant difference in adverse events between the celecoxib arm and the combined diclofenac/ibuprofen arms

($P = 0.45$).[2] Using the broader definition — combined CSUGIE and gastroduodenal ulcer (CSUGIE/GUD) — a significant difference is reported between combined non-specific non-steroidal anti-inflammatory drugs (NSAIDs) and celecoxib ($P = 0.040$), but not with diclofenac ($P = 0.295$).[2] The FDA concluded that "celecoxib was not able to demonstrate it was statistically superior to diclofenac in terms of the clinically important UGI [upper gastrointestinal] endpoints and conditions defined in this study. The same is not true when comparisons are made to ibuprofen."[2] The dominance of non-specific NSAIDs reflects celecoxib priced at $32.13/month (for 200 mg/day) and diclofenac at $13.42/month (for 75 mg/day)[6] and evidence of equivalence in management of OA and GI side effect profile. We agree this does not support a conclusion about class dominance. All NSAIDs and all CSIs are not the same.

Celecoxib is listed on the Pharmaceutical Benefits Schedule, but, as submissions by companies to the Pharmaceutical Benefits Advisory Committee (PBAC) are confidential, the research team may not have had access to all relevant evidence. We would welcome access to such information from which to prepare revised estimates. Placing all submissions to the PBAC in the public domain, as now occurs with reports of the PBAC, would allow a more informed public debate on these matters and would be most welcome.

1 Segal L, Day S, Chapman A, Osborne R. Priority setting in osteoarthritis. Melbourne: Health Economics Unit, Monash University, April 2003.
2 FDA Medical officers report. Available at: (accessed Aug 2004).
3 FDA. Statistical Review Briefing Document for the Advisory Committee. Available at: www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_04_stats.pdf (accessed Aug 2004).
4 FDA Medical Officer's Gastroenterology Advisory Committee Briefing Document. Available at: www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_05_gi.pdf (accessed Aug 2004).
5 Juni P, Rutjes AW, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? [editorial]. *BMJ* 2002; 324: 1287-1288.
6 Australian Government Department of Health and Ageing. Schedule of pharmaceutical benefits, May 2004. Canberra: DHA, 2004. ❑