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Toronto Health Economics and Technology Assessment Collaborative

Cost-effectiveness of Biologic Response Modifiers Compared to Disease Modifying Anti-Rheumatic Drugs for Adults with Rheumatoid Arthritis: Systematic Review of Economic Evaluations

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Executive Summary

Objective
Biologic response modifiers (biologics) have a greater potential to slow the course of rheumatoid arthritis (RA) but cost more than disease-modifying anti-rheumatic drugs (DMARDs). We systematically reviewed the literature to determine the cost-effectiveness of biologics compared to DMARDs for RA in adults.

Methods
Systematic search of MEDLINE, Embase, National Health Services Economic Evaluation Database, OVID HealthStar, Econlit, and Tufts CEA Registry from inception to 2008 for English-language full economic evaluations of biologics compared to DMARDs. The British Medical Journal (1996) and Phillips (2006) checklists were used to critically appraise selected articles. Results were stratified by indications for use in RA patients according to the American College of Rheumatology (2008) recommendations. Two acceptable incremental cost-effectiveness ratio (ICER) thresholds were used to interpret results: CAD 50,000 and CAD 100,000, per quality-adjusted life year (QALY) gain.

Results
Of 918 identified citations, 18 studies were selected for review. Four studies conducted cost-effectiveness analyses and 16 conducted cost-utility analyses of adalimunab, etanercept, and infliximab (monotherapy, combination therapy). Most methodological limitations were associated with data and reporting practices. In DMARD-naïve patients, biologic-DMARD drug sequences were considered cost-effective only at the CAD 100,000/QALY threshold. In patients who failed methotrexate combination therapy or sequentially-administered DMARDs, ICERs were well above the CAD 50,000/QALY cost-effectiveness threshold, while 40% were below the CAD 100,000/QALY threshold. In methotrexate monotherapy-resistant patients, all ICERs were below the high willingness-to-pay threshold and several were below the low willingness-to-pay threshold, which may be due to using response data from an effectiveness trial biased towards the biologic treatment arm.

Conclusions
The cost-effectiveness of biologics for the treatment of RA has not been widely demonstrated at the commonly cited CAD 50,000/QALY threshold; but there is evidence for cost-effectiveness at the CAD 100,000/QALY threshold. Economic evaluations of biologics are limited by lack of long-term response data in patients taking biologics and other important gaps in the literature.

Background

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that affects approximately 1% of the population.[1,2] The course of RA varies, but for a substantial proportion of patients it is characterized by persistent pain and stiffness, progressive joint destruction, functional disability, and premature mortality.[3] RA also presents a serious socioeconomic burden in terms of direct medical costs (associated with resources consumed to research, prevent, detect, and treat RA) and indirect costs (associated with lost productivity, early mortality, and time contributed by care givers).[4-9]

The pharmacological management of RA has been transformed with the introduction of disease-modifying anti-rheumatic drugs (DMARDs), a large class of drugs that includes azathioprine, hydrochloroquine, D-penicillamine, gold, leflunomide, methotrexate, and sulfasalazine. Whereas drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids control symptoms, DMARDs slow the progression of joint damage that leads to loss of function.[10,11] Guidelines therefore advocate treatment with DMARDs as soon as RA is diagnosed, both to control symptoms and delay disease progression.[12] Newly developed biologic response modifiers (biologics) offer even more hope for persons with RA, having a greater potential to suppress disease activity, improve quality-of-life, and inhibit joint destruction.[13-15] But while biologics may have the greatest potential to slow the course of RA, these drugs cost substantially more than DMARDs. Consequently, current guidelines recommend using biologics for patients with inadequate responses to (a) DMARD(s), largely because of higher costs that preclude their widespread early use.[12,16-18]

Thus, at the core of the debate is the degree to which the superior clinical outcomes achieved with biologics are worth their higher costs. Should earlier treatment with biologics (e.g., as first-line treatment in DMARD-naïve patients) be considered, given their potential to slow disease progression and extend a person's productivity, thereby reducing downstream direct costs associated with health care utilization and indirect costs associated with lost productivity? Since the introduction of Cox-2 inhibiting NSAIDs and DMARDs, RA therapeutic drug costs have more than doubled, and now with the recent introduction of biologics, these costs can only be expected to increase.[19] Not surprisingly, many agencies (including the National Institutes of Health in the United States), have identified the cost-effectiveness of biologics as one of the highest priority research topics in the pharmacological treatment of RA. Decision-makers in public and private health-care systems need a synopsis of existing economic evidence upon which to base funding decisions. An understanding of the existing literature is also essential to identify gaps in the current evidence and to inform the development of future economic evaluations. We therefore undertook a review of the literature to identify and critically appraise existing economic evaluations of biologics versus DMARDs for adults with RA and to determine whether the incremental cost-effectiveness is within the range of generally accepted medical interventions.

Methods

Literature Search

We performed an electronic search of Medline (1950 to September Week 4, 2008), Embase (1980 to Week 39, 2008), National Health Services Economic Evaluation Database (NHS EED) (4th Quarter 2008), OVID HealthStar (1966 to October 2008), Econlit (1969 to November 2008) and the Tufts Medical Center CEA Registry (1976 to November 2008) for economic evaluations published in English, using a search strategy developed with a library scientist. Reference lists of identified economic evaluations and systematic reviews were also manually searched.

Selection of Studies

We included full economic evaluations of biologics (including, but not limited to etanercept, infliximab, adalimunab, anakinra, abatacept, rituximab, natalizumab, golimumab, and eflizumab) compared to any DMARD for the therapeutic management of RA in adults. Full economic evaluations were defined as comparisons that considered both costs (resource use) and consequences (outcomes, effects), including cost-effectiveness analyses (CEAs), cost-utility analyses (CUAs), and cost-benefit analyses.[20] We excluded economic evaluations of biologics for other forms of arthritis, juvenile RA, and mixed arthritis populations where RA-specific results could not be extracted, and articles published in languages other than English. Four reviewers independently applied these selection criteria to identified citations during the title and abstract screening and met in pairs for consensus audits to resolve discrepancies. A fifth reviewer was used to settle disagreements.

Data Extraction

Data were extracted according to current recommendations using a standard data collection form.[21] We extracted study characteristics related to: 1) patients (previous exposure to DMARDS, duration and severity of RA), 2) biologic therapy and DMARD comparator (type, dosage, duration, drug sequencing), 3) study design (country, analytic perspective, time horizon, year of analysis, types of costs, currency, discount rates, health effects, quality-of-life weights to calculate quality-adjusted life years [QALYs], funding source), and 4) study outcomes (average and incremental costs and health effects, incremental cost-effectiveness ratios). Reported average and incremental costs were converted to 2009 Canadian dollars using the Bank of Canada currency converter (www.bankofcanada.ca/en/rates/exchform.html) and adjusted for inflation/deflation using the Bank of Canada Core Consumer Price Index (www.bankofcanada.ca/en/cpi.html). Three reviewers independently extracted data; all data entries were then verified in meetings with the three reviewers present.

Critical Appraisal of Selected Studies

Selected economic evaluations were critically appraised with the British Medical Journal (BMJ) checklist and, in economic studies that involved modelling, the Philips checklist.[22,23] These checklists provided a systematic overview of the strengths and limitations of the selected studies. Three reviewers independently appraised the selected studies and met for consensus audits to resolve discrepancies. A fourth reviewer was used to reconcile disagreements. An approach for incorporating study quality into data synthesis was not used, as there is currently no standardized method for doing so for economic evaluation data.[21]

Summarization of Data

Tables and narrative synopses were used to summarize the characteristics and methodological quality of the selected studies. Principal results, including point estimates of incremental costs and consequences, and

incremental cost-effectiveness ratios (ICERs) were stratified by biologic agent and indications for use of biologics in patients with RA as described by the American College of Rheumatology (ACR) 2008 recommendations (i.e., patients with early RA (<6 months); patients with RA (≥6 months) who failed prior methotrexate monotherapy; patients with RA (≥6 months) who failed prior methotrexate combination therapy or after sequential administration of other nonbiologic DMARDs).[12] We also reported results for RA patients with no previous exposure to DMARDs (DMARD-naïve patients) to determine the cost-effectiveness of biologics as first-line treatment for RA. Cost-effectiveness estimates were not statistically pooled as it was not feasible (e.g., measures of precision were mostly unreported) nor valid due to extensive heterogeneity across the selected studies.[24] However, we reported median ICER values in the text, with corresponding minimum and maximum values. Costs were rounded to the nearest whole number in tables and to thousands (K) in the text. Variables identified by sensitivity analyses that reportedly influenced results were also described.

In cost-effectiveness analysis, ICERs are computed as the ratio of the difference in mean costs to the difference in mean health effects of the compared interventions. ICERs represent the additional cost per additional health benefit (e.g., QALY) gained from an intervention. Whether an intervention is considered cost-effective (affordable) depends on the maximum the decision-maker is willing to pay for an extra unit of health effect (the willingness-to-pay threshold). In most jurisdictions around the world, an acceptable cost-effectiveness threshold for a QALY has not been explicitly defined.[25,26] We therefore used two willingness-to-pay thresholds to interpret results: the commonly cited CAD 50K per QALY, as well as CAD 100K per QALY.[25]

Results

We screened 918 non-duplicate citations, of which 861 were excluded by title and abstract screen (Figure 1). Fifty-eight studies were retrieved, of which 35 were excluded during full text screening and five during data extraction.[27-31] Eighteen economic evaluations were thus selected for inclusion.

Description of Selected Studies

The 18 selected studies were published from 2000 to 2007 inclusive; four conducted CEAs[32-35] and 16 conducted CUAs[28,34-48] (Table 1). The number of comparisons conducted by each selected study ranged from one to 20, comprising a total of 116 comparisons. Biologic agents that were evaluated included adalimumab, etanercept, and infliximab, either as monotherapies (etanercept [n=12], adalimumab [n=3]) or combination therapies, (etanercept+methotrexate [n=4], adalimumab+methotrexate [n=3], infliximab+methotrexate [n=10]). One study evaluated biologics as a class (tumour necrosis factor-alpha [TNFα]-antagonists).[38] We did not identify economic evaluations of the interleukin-1 receptor-antagonist anakinra, or newer (second generation) biologics (e.g., abatacept, rituximab).

Biologics were compared to DMARD monotherapies (leflunomide [n=1], methotrexate [n=7], sulfasalazine [n=1]) and combination therapies (cyclosporine+methotrexate [n=1], hydroxychloroquine+sulfasalazine+methotrexate [n=1]), DMARD sequences (n=10), mixed drug treatments that included DMARDs and other drugs (e.g., NSAIDs) (n=1), and methotrexate+placebo (n=1)(Table 1). Biologic treatment duration included: six months,[32,33] 1 year,[34,42,43] 2 years [44] and, depending on response and toxicity, up to five years,[44,48] 10 years,[44,45] or patients' lifetime.[28,35-41,46,47]

There was extensive study characteristic heterogeneity across the selected evaluations. Patient populations were described as persons with early or late RA (n=1), moderate to severe RA (n=2), active, refractory RA (n=4), or simply persons with RA (n=11). Within these populations, there were patients with no previous exposure to DMARDs (methotrexate-naïve, DMARD-naïve) (n=5)[33,35,40,41,46] or patients whose symptoms were not controlled by DMARDs (methotrexate-resistant, ≥1 DMARD failure) (n=13) (Table 1).

Most evaluations were conducted in the United Kingdom (n=7) (37%), followed by the United States (n=4) (21%), Sweden (n=3) (16%), Canada (n=2) (16%), Netherlands (n=1) (5%), and Japan (n=1) (5%). Economic perspectives included societal (n=10) and payer (n=11). Most evaluations were conducted over a lifetime time horizon (n=10). Other time horizons included: six months,[32,33] one year,[43] five years,[35,44,48] and ten years.[42,44,45]

The types of direct and indirect costs considered in the analyses were highly variable. All studies considered direct costs, such those related to drugs (price, administration, monitoring, toxicity, adverse events), patient visits (out/in-patient, emergency) and care (home, nursing, community, ambulatory, palliative), imaging and laboratory tests, and joint replacement. Eleven of the 18 studies considered costs related to productivity loss from illness (work disability/absence, sick leave, early retirement) or premature death.

Seventeen of the 18 selected studies used model-based analytic approaches (Table 1). The empirical economic evaluation used observational data.[43] All modeling studies used trial data for estimating patients' short-term responses to biologics and DMARDs, except one study, which used registry data.[39] Long-term efficacy data were not available; therefore evaluations with longer time horizons modelled trial data with observational data to extrapolate short-term effects over the long-run. Efficacy data from the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy

(ATTRACT)[49,50] published in 1999 and 2000 were used in all studies that evaluated infliximab,[28,34-36,40,42,45,46] except three studies which used registry or other data[37,41,43] (Table 1). Two studies[40,46] also used response data in patients with early RA from the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) published in 2004.[15] Most studies that evaluated etanercept [28,32,35,37,38,40,41,47,48] used response data from two trials published in 1999.[51,52] Other sources of etanercept response data included the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) published in 2004 [53] used by three evaluations,[40,44,46], a trial published in 2000[13] used by two evaluations,[33,40] and a prospective monitoring study[54] published in 2002 used by two evaluations.[28,44] Similarly, all studies that evaluated adalimunab[28,40,46] used data from the Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Patients with Rheumatoid Arthritis (ARMADA)[55] published in 2003 and Safety Trial of Adalimunab in Rheumatoid Arthritis (STAR) published in 2003;[56] two of these[40,46] also used data from the Prospective, Randomised Trial (DE013) Comparing Adalimunab, Methotrexate, and the Combination of Both over Two Years in Patients with Early Rheumatoid Arthritis (PREMIER) published in 2006.[14]

Critical Appraisal of Selected Studies

The methodological limitations that we identified were largely clustered within criteria associated with data and reporting practices. In particular, most authors did not describe their approaches for identifying and selecting data for key parameters, or synthesizing these data. Many authors did not adequately report point estimates and associated measures of precision for parameters used in their models. Many studies lacked a clear description of aspects related to study design (e.g., failing to report the analytic perspective or rationale for alternative(s) considered) and methods (e.g., failing to report drug dosages, model estimates, sensitivity analysis ranges). Results were frequently poorly reported. Mean costs, mean health effects, and incremental analyses were often not reported.

Appendix A presents the appraisal of the economic evaluations using the BMJ criteria. Several studies did not provide a clear research question[34,37,43,46] or sufficient background on the importance of, and rationale for, the evaluation.[28,33,34,37,38,43,46] Most studies did not describe quantities of resource use separately from unit costs (except four,[36,37,40,41]) or approaches for currency conversion and inflation adjustment (except four [38-40,45]). Eleven of 18 (58%) studies reported incremental analyses, and seven of 18 (37%) studies adequately presented disaggregated and aggregated outcomes. Of the 15 studies that discounted costs and effects, five studies (33%) did not justify their discount rate.[34,42,44,46,48] Only three studies satisfactorily reported ranges used for sensitivity analyses.[37,40,41] Two of the 12 (17%) studies that used stochastic data reported details of statistical tests and confidence intervals.[40,45]

Appendix B presents the critical appraisal of the 17 modelling studies, using the Philips criteria. Eleven to 15 of 17 studies (65-88%) did not provide sufficient evidence of using transparent and systematic methods for identifying data, or adequately describe their process for choosing between data sources, selecting key parameters, and identifying data for essential model parameters. Only four of 17 (23.5%) modelling studies assessed the four types of uncertainty (i.e., methodological, structural, and parameter uncertainty, and uncertainty related to heterogeneity) described by Briggs.[57] Six studies did not clearly describe their synthesis methods to derive treatment effects, and six insufficiently described or referenced data inputted into their model. Methodological weaknesses were also clustered in the criteria section *Structure*, particularly sub-sections *Rationale for Structure* (12 studies did not

adequately describe whether competing theories about model structure were considered), *Structural Assumptions* (seven studies were not adequately transparent about or justified their assumptions), and *Strategies/Comparators* (most studies did not evaluate all feasible options or provide a justification for not doing so).

Results of Cost-utility Analyses

The quality-of-life weight most often used by CUAs to calculate QALYs was a score derived from the EQ-5D[35,37,39-45,47,48] followed by scores derived from the HUI-3,[28,45,46] visual analogue scale,[34,36] HUI-2,[45] and SF-6D[45] (Table 1). One study did not identify the quality-of-life weight used.[38] In 10 of the 16 CUAs, quality-of-life weights were derived by transforming Health Assessment Questionnaire (HAQ)[58] scores using linear regression approaches.[28,35,37-41,45-47]

DMARD-naïve Patients: Biologic-DMARD Sequence versus DMARD Sequence

Five evaluations evaluated a DMARD sequence containing (a) biologic agent(s) compared to a DMARD sequence without biologics, in DMARD-naïve RA patients (Table 2).[35,37,40,41,46] From the payer perspective, median incremental costs per incremental QALY for biologics inserted into the first, third, fourth, sixth and last positions were CAD 207K/QALY (range: 84-1,776K/QALY), 134K/QALY (range: 75-382K/QALY), 124K/QALY (range: 106 -150K/QALY), 125K/QALY (range: 109-142K/QALY), and 77K/QALY (range: 62-106K/QALY), respectively. Thus, there were only instances in which biologic-DMARD sequences were only considered cost-effective when willingness-to-pay was CAD 100K/QALY (Table 2). ICER values tended to decrease as biologics were inserted later into a sequence. The overall median was CAD 130K/QALY (range: 62-1,776K/QALY). Evaluations conducted from the societal perspective. All evaluations were conducted over a lifetime time horizon, with the exception of one which used a five-year time horizon.[35]

Patients with Early Rheumatoid Arthritis: Biologic-DMARD Sequence Compared to DMARD Sequence

One study that focused on patients with early RA. DMARD sequences containing biologics (adalimunab, etanercept [as monotherapy or combined with methotrexate], infliximab+methotrexate) were compared to DMARD sequences without biologics (Table 2).[40] ICER values for patients with early RA (range: CAD 75-91K/QALY) were consistently smaller than those with late RA (range: CAD 134-378K/QALY) and cost-effective at a willingness-to-pay threshold of CAD 100K/QALY.

Patients Who Failed Prior Methotrexate Monotherapy: Biologic Combination Therapy versus Methotrexate Monotherapy

Three studies evaluated biologic combination therapy (infliximab+methotrexate) in methotrexate-resistant patients (Table 2).[34,42,45] All these evaluations took the societal perspective, with two studies also taking a payer perspective[34,42]. All used efficacy data from the ATTRACT.[49] ICER values ranged from CAD 7-92K/QALY. Thus all comparisons found biologic combination therapy to be cost-effective at a willingness-to-pay of 100K/QALY for payer and societal perspectives. In contrast, seven of 12 comparisons undertaken from the societal perspective and two of eight comparisons undertaken from the payer perspective found this therapy cost-effective at a willingness-to-pay of CAD 50K/QALY. These results should be considered with caution, since response data were based on patients who had failed prior methotrexate monotherapy, thus biasing results towards infliximab+methotrexate therapy.

Patients Who Failed Prior Methotrexate Combination Therapy or Sequential Administration of DMARDs: Biologic-DMARD Sequence versus DMARD Sequence

Nine evaluations analyzed the cost-utility of inserting a biologic monotherapy or combination therapy into a DMARD sequence compared to a DMARD sequence, in patients who failed ≥2 DMARDs (Table 1, 2).[35-41,48] All analyses were from a payer perspective, with one evaluation also performing analyses from the societal perspective. ICER values across all analyses ranged from CAD 45-612K/QALY. Out of a total of 35 comparisons, biologic-DMARD sequences were cost-effective in one comparison, and in 14 comparisons, at the CAD 50K/QALY, and 100K/QALY willingness-to-pay thresholds, respectively. There were no consistent trends across results of these analyses, most likely because of differences in methodological approaches.

Results of Cost-effectiveness Analyses

CEAs were conducted by four of the 18 selected studies. All used economic modeling approaches (Table 1).[32-35] Measures of health effects used included life expectancy and response categories based on the ACR core set of activity measures (ACR20[20% of response criteria], ACR50[50% of response criteria], and ACR70[70% of response criteria])[59].

Two studies examined the cost-effectiveness of biologics in DMARD-naïve patients.[33,35] Choi (2002) determined the incremental cost-effectiveness ratio per patient achieving an ACR20 and ACR70WR (weighted) response for etanercept monotherapy versus DMARD monotherapies in methotrexate-naïve RA patients (Table 1). ICER values for all analyses that only included direct costs were larger than those that included direct and indirect costs. For comparisons that considered direct costs, ICERs ranged from CAD 70-90K/QALY, and 70-77K/QALY, for ACR20 and ACR70WR, respectively. Comparisons that compared total (direct and indirect) costs ranged from CAD 66-78K/QALY, and 62-74K/QALY, for ACR20 and ACR70WR, respectively. Coyle (2006) compared a biologic-DMARD sequence included biologics (etanercept, infliximab+methotrexate) inserted into third and fourth positions, to the identical sequence without biologics (Table 1). The incremental cost per additional year with an ACR20, ACR50, and ACR70 response ranged from CAD 18-28K/QALY, 23-36K/QALY, and 93-101K/QALY, respectively.

Two studies evaluated biologics in methotrexate-resistant patients (Table 1).[32,34] Choi (2000) compared the cost per patient achieving either an ACR20 or ACR70WR response of etanercept (monotherapy, combined with methotrexate) versus methotrexate continuation and two DMARD combination therapies (Table 1). Not unexpectedly given the patient population, the most favourable ICERs were for etanercept mono- or combination therapy compared to methotrexate; these ranged from CAD 23-35K/QALY depending on whether direct or total (direct+indirect) costs were considered. As observed in their 2002 study, ICER values for analyses that considered only direct costs were larger than those that considered total costs. CEAs based on an ACR20 response produced larger ICER values than those based on ACR70. ICERs for all other comparisons ranged from CAC 47-147K/QALY. Wong (2002) compared the cost-effectiveness of infliximab+methotrexate to methotrexate (Table 1). Cost-effectiveness ratios of cost per life year gained based on a total costs ranged from CAD 34-48K/QALY, and those based on direct costs ranged from CAD 116-118K/QALY (variations in ICER values across these perspectives were the result of discounting or not discounting costs).

Results of Sensitivity Analyses

The economic evaluations considered a wide array of factors for sensitivity analyses. Results were sensitive factors related to rates (disease progression, compliance, effectiveness,

withdrawal, adverse event, general population mortality, survival, discount, etc.), costs (treatment, drug, time-lost, monitoring, toxicity, indirect, etc.), and other factors (time horizon, biologic sequence position, treatment duration, HAQ conversion factor, etc.).

Results were sensitive to type of quality-of-life weight used to calculate QALYs in all studies that examined this factor.[28,39,41,45] Marra et al. (2007) conducted four separate analyses using different quality-of-life weights for each analysis. ICER values were CAD 37K/QALY, 54K/QALY, 62K/QALY, and 81K/QALY for HUI-3, EQ-5D, HUI-2, and SF-6D derived weights, respectively. Other factors that results were consistently sensitive to included HAQ-related disease progression scores,[28,37,37,38,40,44,46] position of biologic in a DMARD sequence,[37,40,41] and biologic drug costs.[32-34,42,44,46]

Discussion

Our systematic literature search identified 18 economic evaluations of biologic monotherapies or combination therapies compared to DMARDs. A direct comparison and statistical pooling of the results was not feasible because of different methodological approaches and decision perspectives used.

Nearly all reported ICERs were above the pre-defined acceptable cost-effectiveness threshold of CAD 50,000 per QALY gain. All ICERS reported for DMARD-naïve patients and patients who failed prior methotrexate combination therapy or sequential administration of DMARDs (except one[38]) were above this threshold. Any ICER that did fall below the threshold was reported in CUAs that evaluated biologics in patients who had failed methotrexate monotherapy. In these CUAs, patient responses to biologics were based on the ATTRACT, which compared infliximab+methotrexate to methotrexate continuation in methotrexate-resistant patients. This produced a bias towards infliximab+methotrexate therapy.

In contrast, several ICERs were below the pre-defined willingness-to-pay threshold of CAD 100,000 per QALY gain. In DMARD- naïve patients, a small proportion of ICERs (23%) were below this threshold. In patients who had failed methotrexate monotherapy, all comparisons found biologic combination therapy to be cost-effective. However, the caveat regarding the use of ATTRACT data described above also applies here. In patients who failed methotrexate combination therapy or sequentially administered DMARDs, 14 of 35 comparisons found a biologic-sequence to be cost-effective.

Our systematic search identified economic evaluations for three biologics – adalimunab, etanercept, and infliximab – that were relevant to our review, yet in North American countries there are at least six biologics approved for RA: TNFα antagonists abatacept (Orencia™, Bristol-Myers Squibb), adalimumab (Humira™, Abbott), etanercept (Enbrel™, Amgen/Wyeth), infliximab (Remicade™, Centocor/Johnson & Johnson/Schering-Plough), and rituximab (Rituxan™, Genentech/Biogen IDEC), and the interleukin-1 receptor antagonist anakinra (Kineret™, Amgen). Absent in the literature, therefore, were economic evaluations of newer biologics compared to DMARDs.

We identified other gaps in the literature which should be addressed. Research should be conducted to determine how to standardize the choice of outcome measures used in CUAs, given that different methods for eliciting quality-of-life weights yield notably different ICERs. Research is also needed to determine the validity of assuming a linear relationship between functional status measures (e.g., HAQ) and utility indices (e.g., EQ-5D). The EQ-5D is not a direct measure of preference-based quality-of-life (utility). Any method that attempts to predict the EQ-5D rather than utility scores directly (e.g., standard gamble, time trade-off) will be prone to error propagation and bias inherent in the EQ-5D. Another important issue is how to validly determine the potential of biologics to reduce downstream costs associated with RA. Biologics may have greater potential to reduce long-term economic and social costs of RA-related disability compared to DMARDs; CEAs should therefore consider long-term time horizons to adequately evaluate long-term costs and consequences. Related to this is the need for prospective data on patients' long-term responses to biologics. Finally, it has been estimated that direct costs only account for 55.1% of the total cost-of-illness of RA.[4] Eleven of the 18 evaluations selected for our review included indirect costs (e.g., time lost from paid work by patients or caretakers, time costs associated with patients' inability to do chores, leisure-time loss, early retirement). Despite the widespread recommendation to exclude indirect costs from economic evaluations,[60] we argue that studies should conduct separate analyses excluding and including indirect costs.[38]

As in previous studies that examined the quality of economic evaluations,[61-63] we identified a high prevalence of methodological problems. But unlike these previous studies,[61,62] we did not find that reporting practices tended to improve over time. Many evaluations did not adhere to recommended reporting practices that have existed since the mid-1990s,[64-66] well before the evaluations were published. Poor reporting practices make it difficult to judge whether results of economic evaluations can be accepted with reasonable confidence. Part of this problem could be resolved by making materials available on journal Web sites, such that assumptions and data can be reviewed in detail.

This review was conducted according to current recommendations for conducting systematic reviews of economic evaluations in health-care.[21,67] It was not tractable to blind our reviewers to journals and authors because even if journal and author names were concealed, reviewers could identify them by formatting style, references in a study to previous work, or expertise with the literature. Lack of blinding may have influenced the quality appraisal results in favourably or unfavourably. Likewise, pairs of reviewers might have judged differently whether studies fulfilled quality criteria included in the checklists.

Conclusions

Based on a commonly cited acceptable cost-effectiveness threshold (CAD 50,000 per QALY), the results of CUAs of biologics compared to DMARDs for the treatment of RA in adults suggest that biologics are not cost-effective. There is evidence that of cost-effectiveness in selected populations for a willingness-to-pay of CAD 100,000 per QALY. However, economic evaluations in this area have been hindered by large gaps in the literature, including the lack of data on long-term responses in patients taking biologics and the long-term effects of biologic therapy on downstream health utilization and productivity associated with slowing the progression of RA.

Tables

Table 1. Economic Evaluations of Biologics Compared to DMARDs for Rheumatoid Arthritis

First Author Year	Biologic	Comparator	Analysis	Perspective Country	Currency Year	Time Horizon	Discount Rate
DMARD-naïve Patients							
Choi 2002	ETA	SSZ, MTX, LEF	CEA	Societal, United States	USD 1999	6 months	N/A
Jobanputra 2002	ETA, INF+MTX (3rd position)	DMARD sequence	CUA	Societal, United States	GBP 2000	Lifetime	Costs 6%, QALYs 1.5%
Barton 2004	ETA, INF+MTX (3rd, 4th, 6th	DMARD sequences (2)	CUA	Societal, United States	GBP 2000	Lifetime	Costs 6%, QALYs 1.5%
Chen 2006	ADA(+MTX), ETA(+MTX) INF+MTX (1st, 3rd, last position)	DMARD sequences (3)	CUA	Societal, United States	GBP 2004	Lifetime	Costs 6%, QALYs 1.5%
Coyle 2006	ETA, INF+MTX (3rd, 4th position)	DMARD sequence	CEA, CUA	Payer, Canada	CAD N/R	5 years	Costs 5%, QALYs 5%
Spalding 2006	ADA(+MTX), ETA, INF+MTX	DMARD sequence	CUA	Payer, Societal, United States	USD 2005	Lifetime	Costs 3%, QALYs 3%
Patients Who Failed Prior Methotrexate Monotherapy							
Choi 2000	ETA, ETA+MTX	MTX,HCQ+SSZ+ MTX,CyA+MTX	CUA	Societal, United States	USD 1999	6 months	N/A
Wong 2002	INF+MTX	MTX	CEA, CUA	Payer, Societal, United States	USD 1998	Lifetime	Costs 3%, QALYs 3%
Kobelt 2003	INF+MTX	MTX	CUA	Societal, Sweden United Kingdom	EUR, GBP SEK N/R	10 years	N/R
Marra 2007	INF, INF+MTX	MTX	CUA	Societal, Canada	CAD 2002	10 years	Costs 3%, QALYs 3%
Patients Who Failed Prior Methotrexate Combination Therapy or Sequential Administration of DMARDs							
Brennan 2004	ETA (1st position)	DMARD sequence	CUA	Payer, United Kingdom	GBP 2000	Lifetime	Costs 6%, QALYs 1.5%
Kobelt 2004	ETA and/or INF(+/- DMARD(s)	Mixed DMARDs, NSAID, analgesic	CUA	Societal, Sweden	EUR 2002	1 year	N/A
Welsing 2004	ETA (1st, 2nd position)	DMARD sequences (2)	CUA	Payer, Societal, the Netherlands	EUR N/R	5 years	Costs 4%, QALYs 4%
Bansback 2005	ETA, ADA(+MTX), INF+MTX (1st position)	DMARD sequence	CUA	Payer, Sweden	EUR 2001	Lifetime	Costs 3%, QALYs 3%
Barbieri 2005	INF+MTX > DMARDs	DMARD sequence	CUA	Payer, United Kingdom	GBP 2000	Lifetime	Costs 6%, QALYs 1.5%
Kobelt 2005	ETA(+MTX)	MTX	CUA	Societal, Sweden	EUR 2004	5,10 years	Costs 3%, QALYs 3%
Tanno 2006	ETA (1st position)	DMARD sequence	CUA	Societal, Japan	JPY 2003	Lifetime	Costs 6%, QALYs 1.5%
Brennan 2007	Anti-TNFs (1st position)	DMARD sequence	CUA	Payer, United Kingdom	GBP 2004	Lifetime	Costs 6%, QALYs 1.5%

Table 1. Economic Evaluations of Biologics Compared to DMARDs for Rheumatoid Arthritis (continued)

First Author Year	Quality-of-life Weight	Model Type	Costs	Health Effects	Funding	Efficacy Sources
DMARD-naïve Patients						
Choi 2002	N/A	Decision tree	Direct, indirect	ACR20/70WR	N/R	Bathon 2000
Jobanputra 2002	HAQ>EQ-5D	Discrete event simulation	Direct, indirect	QALY	NHS	Moreland 1999; Weinblatt 1999; EEIG 2000
Barton 2004	HAQ>EQ-5D	Discrete event simulation	Direct, indirect	QALY	NHS	Moreland 1997; 1999; Ericson 1999
Chen 2006	HAQ>EQ-5D	Discrete event simulation	Direct	QALY	NHS	Maini 1999, Moreland 1999; Weinblatt 1999, 2003; Bathon 2000; Codreanu 2003; Breedveld 2004; Keystone 2004; Klareskog 2004; St Clair 2004; van de Putte 2004;
Coyle 2006	HAQ>EQ-5D	Markov	Direct	ACR20/50/70 QALY	Health Canada	Maini 1999; Moreland 1999; Lipsky 2000
Spalding 2006	HAQ>HUI-3	Markov	Direct	QALY	USC	Lipsky 2000; Genovese 2002; Weinblatt 2003; Klareskog 2004; St Clair 2004; Breedveld 2005; van de Putte 2005;
Patients Who Failed Prior Methotrexate Monotherapy						
Choi 2000	N/A	Decision tree	Direct, indirect	ACR20/70WR	N/R	Weinblatt 1996; Moreland 1999
Wong 2002	VAS	Markov	Direct, indirect	Life Expectancy QALY	Schering-Plough, Centocor, NIH	Maini 1999; Lipsky 2000,
Kobelt 2003	EQ-5D	Markov	Direct, indirect	QALY	Schering-Plough	Maini 1999; Lipsky 2000
Marra 2007	HAQ>HUI-2/3 SF-6D, EQ-5D	Markov	Direct, indirect	QALY	CIHR, CAN	Maini 1999
Patients Who Failed Prior Methotrexate Combination Therapy or Sequential Administration of DMARDs						
Brennan 2004	HAQ>'Utility'	Discrete event simulation	Direct	QALY	N/R	Moreland 1999
Kobelt 2004	EQ-5D	N/A	Direct, indirect	QALY	Österlund & Kock Foundations	Geborek 2002
Welsing 2004	EQ-5D	Markov	Direct, indirect	QALY	N/R	Moreland 1999; Weinblatt 1999
Bansback 2005	HAQ>HUI-3	Markov	Direct	QALY	Abbott Laboratories	Maini 1999; Moreland 1999; Weinblatt 1999, 2003; Crnkic 2001; Geborek 2002; Keystone 2004; van de Putte 2004
Barbieri 2005	VAS	Markov	Direct	QALY	Schering-Plough, Centocor	Maini 1999; Wong 2001
Kobelt 2005	EQ-5D	Markov	Direct, indirect	QALY	Wyeth Research	Klareskog 2004
Tanno 2006	HAQ>EQ-5D	Markov	Direct, indirect	QALY	Health Ministry	Moreland 1999
Brennan 2007	HAQ>EQ-5D	Discrete event simulation	Direct	QALY	BSR	BSR Biologics Registry

ACR=American College of Rheumatology, ADA=Adalimunab, AZA=Azathioprine, BSR=British Society for Rheumatology, CAD=Canadian Dollar, CAN=Canadian Arthritis Network, CEA=Cost-Effectiveness Analysis, CIHR=Canadian Institutes of Health Research, CUA=Cost-Utility Analysis, CyA=Cyclosporin, DMARD=Disease Modifying Anti-Rheumatic Drug, EEIG=European Etanercept Investigators Group, ETA= Etanercept, EUR=Euro, HCQ=Hydroxychloroquine, INF=Infliximab, GBP=British Pound, JPY=Japanese Yen, LEF=Lefludomide, MTX=Methotrexate, N/A=Not Applicable, NHS=National Health Services, NIH=National Institutes for Health, N/R=Not Reported, PEN=Penicillamine, QALYs=Quality-Adjusted Life Years, SEK=Swedish Kronor, SSZ=Sulfasalazine, TNFs=Tumour Necrosis Factor, USC=University of Southern California, USD=United States Dollar.
> = transformed to

Table 2. Results of Cost-utility Analyses of Biologics versus DMARDs in Adults with Rheumatoid Arthritis

Perspective	Biologic Position	Biologic	Incremental Cost*	Incremental QALY	ICER	First Author, Year	Miscellaneous Detail(s)
DMARD-naïve Patients							
Payer	**First Position**	Adalimumab	89,989	0.65	138,445	Chen, 2006 11	
			79,979	N/R	84,267	Spalding, 2006 2	
		Etanercept	127,751	0.98	130,358	Chen, 2006 12	
			84,114	N/R	118,629	Spalding, 2006 1	
		Adalimumab + MTX	90,284	0.20	451,420	Chen, 2006 13	
			46,606	N/R	257,139	Spalding, 2006 4	
		Etanercept + MTX	128,242	0.62	206,842	Chen, 2006 14	
		Infliximab + MTX	88,782	0.05	1,775,640	Chen, 2006 15	
			45,334	N/R	541,163	Spalding, 2006 3	
	Third Position	Adalimumab	83,578	0.92	90,846	Chen, 2006 6	Early RA
			84,007	0.22	381,850	Chen, 2006 1	Late RA
		Etanercept	37,924	0.21	180,590	Jobanputra, 2002 2	
			70,093	0.56	125,166	Barton, 2004 2	
			117,941	0.92	128,197	Chen, 2006 2	
			41,995	0.27	155,537	Coyle, 2006 1	
		Adalimumab + MTX	84,293	1.06	79,522	Chen, 2006 8	Early RA
			85,378	0.49	174,241	Chen, 2006 3	Late RA
		Etanercept + MTX	117,752	1.57	75,001	Chen, 2006 9	Early RA
			117,909	0.88	133,988	Chen, 2006 4	Late RA
		Infliximab + MTX	28,485	0.12	237,375	Jobanputra, 2002 1	
			52,476	0.31	169,277	Barton, 2004 1	
			83,339	1.04	80,134	Chen, 2006 10	Early RA
			83,576	0.22	379,891	Chen, 2006 5	Late RA
			30,746	0.25	122,984	Coyle, 2006 2	
	Fourth Position	Etanercept	69,814	0.63	110,816	Barton, 2004 4	
			34,282	0.25	137,128	Coyle 2006 3	
		Infliximab + MTX	52,386	0.35	149,674	Barton, 2004 3	
			23,247	0.22	105,668	Coyle 2006 4	
	Sixth Position	Etanercept	71,669	0.66	108,589	Barton, 2004 8	
		Infliximab + MTX	53,809	0.38	141,603	Barton, 2004 7	
	Last Position	Adalimumab	87,653	0.83	105,606	Chen, 2006 16	
		Etanercept	121,937	1.96	62,213	Chen, 2006 17	
		Adalimumab + MTX	88,295	1.14	77,452	Chen, 2006 18	
		Etanercept + MTX	122,416	1.95	62,777	Chen, 2006 19	
		Infliximab + MTX	88,322	0.88	100,366	Chen, 2006 20	
Patients Who Failed Prior Methotrexate Monotherapy							
Societal		Infliximab + MTX	4,751	0.34	13,972	Wong, 2002 3	Discount: costs 3% QALYs 0%
			5,299	0.34	15,584	Wong, 2002 4	No discounting
			4,751	0.29	16,381	Wong, 2002 7	Discount: costs 3% QALYs 3%
			5,299	0.29	18,271	Wong, 2002 8	Discount: costs 0% QALYs 3%
			1,599.90	0.25	6,451	Kobelt, 2003	1-year, Swedish analysis
			8,929.26	0.30	29,864	Kobelt, 2003	2-year, Swedish analysis
			16,924.90	0.30	56,795	Kobelt, 2003	1-year, British analysis
			31,379.40	0.40	78,449	Kobelt, 2003	2-year, British analysis
			72,558	1.17	62,015	Marra, 2007 1	Quality-of-life weight=HUI-2
			72,558	1.95	37,209	Marra, 2007 2	Quality-of-life weight=HUI-3
			72,558	0.90	80,620	Marra, 2007 3	Quality-of-life weight=SF-6D
			72,558	1.34	54,148	Marra, 2007 4	Quality-of-life weight=EQ-5D

Table 2. Results of Cost-utility Analyses of Biologics versus DMARDs in Adults with Rheumatoid Arthritis (Continued)

Perspective	Biologic Position	Biologic	Incremental Cost*	Incremental QALY	ICER	First Author, Year	Miscellaneous Detail(s)
Patients Who Failed Prior Methotrexate Monotherapy (Continued)							
Payer		Infliximab + MTX	16,261	0.34	47,828	Wong, 2002 1	Discount: costs 3% QALYs 0%
			16,444	0.34	48,365	Wong, 2002 2	No discounting
			16,261	0.29	56,074	Wong, 2002 5	Discount: costs 3% QALYs 3%
			16,444	0.29	56,704	Wong, 2002 6	Discount: costs 0% QALYs 3%
			13,142.08	0.25	52,992	Kobelt, 2003	1-year, Swedish analysis
			24,685.25	0.30	82,559	Kobelt, 2003	2-year, Swedish analysis
			20,133.80	0.30	67,563	Kobelt, 2003	1-year, British analysis
			36,593.53	0.40	91,484	Kobelt, 2003	2-year, British analysis
Patients Who Failed Prior Methotrexate Combination Therapy or Sequential Administration of DMARDs.							
Societal	**First Position**	Etanercept	80,492	0.08	545,049	Welsing, 2004 6	
	Second Position	Etanercept	37,675	0.06	299,510	Welsing, 2004 5	
Payer	**First Position**	Adalimunab	33,901	0.47	71,628	Bansback, 2005 5	
			83,578	0.92	90,964	Chen, 2006 6	Early RA
			84,007	0.22	382,546	Chen, 2006 1	Late RA
		Adalimunab + MTX	55,537	0.92	60,190	Bansback, 2005 2	
			84,293	1.06	79,388	Chen, 2006 8	Early RA
			85,378	0.49	174,811	Chen, 2006 3	Late RA
		Etanercept	73,783	1.65	44,501	Brennan, 2004 1	
			39,536	0.06	611,953	Welsing, 2004 1	
			55,208	0.87	63,641	Bansback, 2005 6	
			37,924	0.21	177,214	Jobanputra, 2002 2	
			70,093	0.56	126,293	Barton, 2004 2	
			117,941	0.92	127,559	Chen, 2006 2	
			41,995	0.27	155,537	Coyle, 2006 1	
		Etanercept + MTX	56,428	0.92	71,627	Bansback, 2005 3	
			117,752	1.57	74,906	Chen, 2006 9	Early RA
			117,909	0.88	133,912	Chen, 2006 4	Late RA
		Infliximab + MTX	54,653	0.66	83,300	Bansback, 2005 4	
			23,424	0.26	90,090	Barbieri, 2005 1	
			28,485	0.12	245,556	Jobanputra, 2002 1	
			52,476	0.31	169,823	Barton, 2004 1	
			83,339	1.04	80,057	Chen, 2006 10	Early RA
			83,576	0.22	377,999	Chen, 2006 5	Late RA
			30,746	0.25	122,985	Coyle, 2006 2	
	Second Position	Etanercept	83,442	0.08	324,216	Welsing, 2004 3	
			69,814	0.63	111,524	Barton, 2004 4	
			34,282	0.25	137,127	Coyle, 2006 3	
		Infliximab + MTX	52,386	0.35	150,103	Barton, 2004 3	
			23,247	0.22	105,669	Coyle, 2006 4	
	Third Position	Etanercept	71,669	0.66	108,098	Barton, 2004 8	
		Infliximab + MTX	53,809	0.38	143,491	Barton, 2004 7	
	Last Position	Adalimumab	87,653	0.83	63,340	Chen, 2006 16	
		Adalimumab + MTX	88,295	1.14	77,588	Chen, 2006 18	
		Etanercept	121,937	1.96	62,340	Chen, 2006 17	

***Costs converted and adjusted to 2009 Canadian dollars (rounded to zero decimal points). DMARD = Disease Modifying Anti-Rheumatic Drug, EQ-5D = EuroQOL-5D, HUI = Health Utilities Index, ICER = Incremental Cost-effectiveness Ratio, MTX = Methotrexate, N/R = Not Reported, QALY = Quality-Adjusted Life Year, RA = Rheumatoid Arthritis, SF-6D = Short Form-6D.**

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Appendix A. Results of Quality Appraisal of Economic Evaluations of Biologics: BMJ Criteria (Drummond 1996)

	Choi 2000	Choi 2002	Jobanputra 2002	Wong 2002	Kobelt 2003	Barton 2004	Brennan 2004	Kobelt 2004	Welsing 2004	Bansback 2005	Barbieri 2005	Kobelt 2005	Chen 2006	Coyle 2006	Spalding 2006	Tanno 2006	Brennan 2007	Marra 2007
Study Design:																		
1	Y	Y	Y	S	Y	S	Y	S	Y	Y	Y	Y	Y	Y	S	Y	Y	Y
2	Y	S	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	S	S	Y	Y	Y
3	Y	Y	Y	N	NC	Y	S	N	Y	S	Y	Y	Y	Y	Y	NC	Y	Y
4	N	S	Y	S	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	S
5	S	Y	Y	S	Y	Y	S	Y	Y	Y	Y	Y	Y	Y	S	Y	Y	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	Y	Y	Y	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Data Collection:																		
8	Y	Y	Y	Y	Y	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	NA	NA	NA	Y	Y	NA	NA	Y	NA	NA	Y	Y	NA	Y	N	NA	Y	Y
10	Y	Y	Y	NA	NA	Y	Y	NA	S	NC	NA	NA	Y	Y	N	N	NA	NA
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Y	NA	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	NC	Y	Y	Y	Y
13	NA	NA	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	N	Y	Y	N
14	Y	Y	N	N	Y	NA	S	Y	S	NA	NA	Y	NA	NA	N	N	NA	Y
15	Y	Y	N	Y	Y	NA	Y	Y	S	NA	NA	Y	NA	NA	N	N	Y	N
16	N	N	Y	N	N	Y	N	N	N	N	Y	N	Y	S	N	N	N	N
17	S	S	Y	S	Y	Y	S	Y	S	S	Y	N	Y	Y	S	Y	S	Y
18	Y	Y	Y	Y	S	Y	Y	Y	S	Y	Y	Y	Y	S	S	Y	Y	Y
19	N	N	NC	S	N	N	Y	NA	S	N	N	S	Y	N	N	N	Y	Y
20	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	S	Y
21	Y	Y	Y	S	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	S	Y
Analysis and Interpretation of Results:																		
22	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
23	NA	NA	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
24	NA	NA	Y	N	N	Y	Y	NA	N	Y	Y	N	Y	Y	N	Y	Y	Y
25	NA	NA	NA	NA	N	NA	NA	N	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
26	S	S	NA	NA	NA	N	N	NA	N	N	N	NA	Y	S	NA	NA	S	Y
27	Y	Y	Y	S	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
28	Y	Y	Y	S	Y	Y	Y	NA	Y	N	Y	N	Y	Y	Y	N	Y	Y
29	S	S	Y	N	N	Y	S	NA	N	N	N	S	Y	S	N	N	S	S
30	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
31	S	S	Y	S	Y	Y	Y	S	S	Y	Y	Y	Y	Y	S	Y	Y	S
32	S	S	S	S	S	N	Y	Y	S	Y	Y	S	S	Y	N	N	N	Y
33	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
34	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
35	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

N = no, NA = not applicable, NC = not clear, S = substandard, Y = yes

BMJ Criteria (Drummond 1996)

	Study Design:
1	The research question is stated.
2	The economic importance of the research question is stated.
3	The viewpoint(s) of the analysis is (are) clearly stated and justified.
4	The rationale for choosing alternative programmes or interventions compared is stated.
5	The alternatives being compared are clearly described.
6	The form of the economic evaluation used is stated.
7	The choice of form of economic evaluation is justified in relation to the questions addressed.
	Data Collection:
8	The source(s) of effectiveness estimates used is(are) stated.
9	Details of the design and results of effectiveness study are given (if based on a single study).
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)
11	The primary outcome measures(s) for the economic evaluation are clearly stated.
12	Methods to value benefits are stated.
13	Details of the subjects from whom valuations were obtained were given.
14	Productivity changes (if included) are reported separately.
15	The relevance of productivity changes to the study question is discussed.
16	Quantities of resource use are reported separately from their unit costs.
17	Methods for the estimation of quantities and unit costs are described.
18	Currency and price data are recorded.
19	Details of currency of price adjustments for inflation or currency conversion are given.
20	Details of any model used are given.
21	The choice of model used and the key parameters on which it is based are justified.
	Analysis and Interpretation of Results:
22	Time horizon of costs and benefits is stated.
23	The discount rate(s) is (are) justified.
24	The choice of discount rate(s) is (are) justified.
25	An explanation is given if costs ad benefits are not discounted.
26	Details of statistical tests and confidence intervals are given for stochastic data.
27	The approach to sensitivity analysis is given.
28	The choice of variables for sensitivity analysis is justified.
29	The ranges over which the variables are varied are justified.
30	Relevant alternatives are compared.
31	Incremental analysis is reported.
32	Major outcomes are presented in a disaggregated as well as aggregated form.
33	The answer to the study question is given.
34	Conclusions follow from the data reported.
35	Conclusions are accompanied by the appropriate caveats.

Appendix B. Results of Quality Appraisal of Economic Evaluations of Biologics: Philips Criteria (2006)

	Choi 2000	Choi 2002	Jobanputra 2002	Wong 2002	Kobelt 2003	Barton 2004	Brennan 2004	Welsing 2004	Bansback 2005	Barbieri 2005	Kobelt 2005	Chen 2006	Coyle 2006	Spalding 2006	Tanno 2006	Brennan 2007	Marra 2007
Structure (S)																	
S1a	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
S1b	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
S1c	Y	Y	Y	N	N	N	Y	Y	Y	Y	S	Y	Y	S	N	Y	N
S2a	Y	Y	Y	N	N	Y	S	Y	S	Y	Y	Y	Y	Y	N	Y	Y
S2b	Y	Y	Y	N	NC	Y	NC	Y	Y	Y	Y	Y	Y	Y	NC	Y	Y
S2c	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
S2d	Y	Y	Y	S	Y	Y	NC	Y	Y	Y	Y	Y	Y	S	NC	Y	Y
S3a	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	S	N	Y	Y
S3b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	S	N	Y	Y
S3c	N	N	Y	N	Y	Y	NC	N	NC	NC	S	Y	NC	N	N	N	N
S3d	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	S	Y	Y	Y
S3e	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	S	Y	Y	N	S	Y	Y
S4a	Y	Y	Y	S	Y	Y	Y	S	Y	NC	S	Y	Y	N	N	NC	Y
S4b	Y	Y	Y	S	S	Y	Y	S	Y	NC	S	Y	Y	Y	Y	NC	Y
S5a	S	Y	Y	S	Y	Y	S	NC	Y	Y	Y	Y	Y	S	Y	Y	Y
S5b	NC	NC	S	NC	Y	Y	NC	Y	Y	NC	Y	Y	Y	NC	N	Y	NC
S5c	NC	NC	S	N	S	Y	Y	Y	NA	NC	S	Y	Y	N	N	Y	N
S6a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
S7a	S	S	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	S	Y	Y	Y	Y
S7b	Y	Y	S	S	Y	NA	Y	Y	Y	Y	Y	Y	S	Y	Y	Y	Y
S7c	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
S8a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	S	Y	Y	S	N	Y	Y
S9a	NA	NA	Y	Y	Y	NA	Y	Y	NA	Y	Y	NA	Y	Y	Y	Y	NA
Consistency (C)																	
C1a	N	N	S	N	N	NC	NC	N	N	N	N	Y	NC	N	N	N	NC
C2a	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
C2b	Y	Y	Y	N	Y	Y	Y	S	NA	Y	Y	Y	NA	N	NA	Y	Y
C3c	NA	NA	NA	NA	N	NA	NA	NA	NA	NA	NA	NC	NA	N	NA	Y	NA
C3d	NA	N	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y

Appendix B. Results of Quality Appraisal of Economic Evaluations of Biologics: Philips Criteria (2006) (Continued)

	Choi 2000	Choi 2002	Johannputra 2002	Wong 2002	Kobelt 2003	Barton 2004	Brennan 2004	Welsing 2004	Bansback 2005	Barbieri 2005	Kobelt 2005	Chen 2006	Coyle 2006	Spalding 2006	Tanno 2006	Brennan 2007	Marra 2007
Data (D)																	
D1a	S	NC	Y	S	N	Y	NC	S	NC	NC	S	Y	Y	S	S	NC	NC
D1b	N	NC	NC	NC	N	NC	NC	S	NC	NC	NC	Y	NC	NC	N	NC	NC
D1c	NC	NC	Y	NC	NC	Y	NC	NC	NC	NC	NC	Y	Y	NC	NC	NC	NC
D1d	NC	NC	Y	NC	N	NC	NC	NC	NC	NC	NC	Y	Y	S	N	NC	NC
D1e	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	N	Y	Y	N	N	NC	NC
D1f	NA	NA	NA	NA	NA	NA	Y	NA	Y	NA	NA	Y	Y	NA	NA	NA	NA
D2a	Y	Y	Y	NC	Y	Y	NC	NC	Y	NC	NC	Y	Y	NC	S	Y	Y
D2Aa	Y	Y	Y	Y	Y	Y	Y	Y	Y	S	Y	Y	Y	S	Y	Y	Y
D2Ab	Y	Y	Y	NC	Y	Y	NC	NC	NC	NC	NC	Y	NC	NC	NC	Y	Y
D2Ac	NC	NC	N	NC	NC	NA	NC	NC	NC	NC	NC	NC	NC	N	N	NC	NC
D2Ad	NC	NC	N	NC	NC	NA	NC	N	NC	NC	NC	NC	NC	N	N	NC	NC
D2Ba	Y	Y	Y	NC	Y	Y	Y	NC	Y	NC	NC	NA	Y	NC	NC	NA	NA
D2Bb	NA	NA	Y	Y	Y	Y	Y	S	S	Y	Y	Y	Y	Y	S	Y	Y
D2Bc	NA	NA	Y	S	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	S	Y	Y
D2Bd	NA	NA	Y	Y	Y	Y	Y	S	Y	Y	Y	Y	Y	Y	N	Y	Y
D2Be	NA	NA	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N
D2Ca	NA	NA	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
D2Cb	NA	NA	Y	S	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
D2Cc	NA	NA	Y	S	Y	Y	Y	N	Y	NA	S	Y	Y	Y	Y	Y	Y
D3a	Y	Y	Y	S	Y	Y	Y	S	S	Y	S	Y	Y	S	S	S	Y
D3b	NC	NC	Y	S	Y	NC	NC	S	NC	NC	S	Y	NC	S	NC	NC	NC
D3c	Y	Y	Y	S	NC	Y	Y	S	Y	Y	S	Y	Y	N	S	S	Y
D3d	NA	NA	NA	NA	NA	Y	NA	N	S	NA	NA	Y	Y	NA	NA	S	Y
D3e	NA	NA	NA	NA	NA	Y	NA	N	Y	NA	NA	Y	N	NA	NA	Y	Y
D4a	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	Y
D4b	NA	NA	N	N	N	NA	NA	N	N	NA	N	NA	N	N	N	N	NA
D4Aa	Y	Y	Y	N	Y	Y	Y	N	N	Y	N	Y	S	S	N	Y	Y
D4Ba	Y	Y	Y	N	Y	Y	Y	N	N	Y	S	Y	N	N	N	Y	N
D4Ca	N	N	S	Y	N	Y	N	N	Y	N	N	Y	N	N	N	Y	N
D4Da	S	S	Y	S	Y	Y	Y	Y	Y	Y	S	Y	Y	S	S	Y	Y
D4Db	NA	NA	Y	N	N	NA	Y	Y	Y	N	N	N	Y	N	N	Y	Y
D4Dc	S	S	Y	Y	N	NC	S	NA	S	N	N	S	NA	N	N	N	N

* N = No, NA = Not Applicable, NC = Not Clear, S = Substandard, Y = Yes

Philips Criteria (2006)

Structure (S)			
S1 Rationale for structure		S4 Structural assumptions	S7 Time horizon
S2 Statement of scope/ The perspective		S5 Strategies/ comparators	S8 Disease states / pathways
S3 Statement of decision problem/objective		S6 Model type	S9 Cycle length
S1a	Is there a clear statement of the decision problem?		
S1b	Is the objective of the evaluation and model specified and consistent with the stated decision?		
S1c	Is the primary decision maker specified?		
S2a	Is the perspective of the model stated clearly?		
S2b	Are the model inputs consistent with the stated perspective?		
S2c	Has the scope of the model been stated and justified?		
S2d	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?		
S3a	Has the evidence regarding the model structure been described?		
S3b	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?		
S3c	Have any competing theories regarding model structure been considered?		
S3d	Are the sources of data used to develop the model specified?		
S3e	Are the causal relationships described by the model structure justified appropriately?		
S4a	Are the structural assumptions transparent and justified?		
S4b	Are the structural assumptions reasonable given overall objective, perspective and scope of the model?		
S5a	Is there a clear definition of the options under evaluation?		
S5b	Have all feasible and practical options been evaluated?		
S5c	Is there justification for the exclusion of feasible options?		
S6a	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?		
S7a	Is the time horizon of the model sufficient to reflect all important differences between options?		
S7b	Is the time horizon of the model, and the duration of treatment and treatment effect described and justified?		
S7c	Has a lifetime horizon been used? If not, has a shorter time horizon been justified?		
S8a	Do disease states (state transition model) or pathways (decision tree model) reflect underlying biological process of disease and impact of interventions?		
S9a	Is the cycle length defined and justified in terms of the natural history of disease?		
Consistency (C)			
C1 Internal consistency		C2 External consistency	
C1a	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?		
C2a	Are the conclusions valid given the data presented?		
C2b	Are any counterintuitive results from the model explained and justified?		
C3c	If the model has been calibrated against independent data, have any differences been explained and justified?		
C3d	Have the results of the model been compared with those of previous models and any differences in results explained?		

Philips Criteria (2006) (Continued)

Data (D)			
D1 Data identification	D2B Treatment effects	D4 Assessment of uncertainty	D4C Heterogeneity
D2 Pre-model data analysis	D2C Quality-of-life weights (utilities)	D4A Methodological	D4D Parameter
D2A Baseline data	D3 Data incorporation	D4B Structural	

D1a	Are the data identification methods transparent and appropriate given the objectives of the model?
D1b	Where choices have been made between data sources, are these justified appropriately?
D1c	Has particular attention been paid to identifying data for the important parameters in the model?
D1d	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?
D1e	Has the quality of the data been assessed appropriately?
D1f	Where expert opinion has been used, are the described and justified?
D2a	Are the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?
D2Aa	Is the choice of baseline data described and justified?
D2Ab	Are transition probabilities calculated appropriately?
D2Ac	Has a half cycle correction been applied to both cost and outcome?
D2Ad	If not, has this omission been justified?
D2Ba	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?
D2Bb	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?
D2Bc	Have alternative assumptions been explored through sensitivity analysis?
D2Bd	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?
D2Be	Have alternative assumptions been explored through sensitivity analysis?
D2Ca	Are the utilities incorporated into the model appropriate?
D2Cb	Is the source for the utility weights referenced?
D2Cc	Are the methods of derivation for the utility weights justified?
D3a	Have all data incorporated into the model been described and referenced in sufficient detail?
D3b	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?
D3c	Is the process of data incorporation transparent?
D3d	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?
D3e	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?
D4a	Have the four principal types of uncertainty been addressed?
D4b	If not, has the omission of particular forms of uncertainty been justified?
D4Aa	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?
D4Ba	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?
D4Ca	Has heterogeneity been dealt with by running the model separately for different sub-groups?
D4Da	Are the methods of assessment of parameter uncertainty appropriate?
D4Db	Has probabilistic sensitivity analysis been done, if not has this been justified?
D4Dc	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?

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