The quality of pharmacoeconomic evaluations of age-related macular degeneration therapeutics: a systematic review and quantitative appraisal of the evidence

William J Foster, Waqas Tufail and Amalia M Issa

Br J Ophthalmol 2010 94: 1118-1126
doi: 10.1136/bjo.2009.170282

The quality of pharmacoeconomic evaluations of age-related macular degeneration therapeutics: a systematic review and quantitative appraisal of the evidence

William J Foster,[1,2,3] Waqas Tufail,[4] Amalia M Issa[3,4]

See Editorial, p 1116

[1]Ophthalmic Research and Nanotechnology Group, Department of Physics, University of Houston, Houston, Texas, USA
[2]Department of Ophthalmology, Weill-Cornell Medical College at The Methodist Hospital, Houston, Texas, USA
[3]The Methodist Hospital Research Institute, Houston, Texas, USA
[4]Program in Personalized Medicine and Targeted Therapeutics, Department of Clinical Sciences and Administration, College of Pharmacy, University of Houston, Houston, Texas, USA

Correspondence to
Dr Amalia M Issa, Program in Personalized Medicine & Targeted Therapeutics, Department of Clinical Sciences and Administration, College of Pharmacy, University of Houston, 1441 Moursund Street, Houston, TX 77030, USA; aissa@uh.edu

Accepted 30 April 2010

ABSTRACT

Aim To appraise the quality of published pharmacoeconomic studies of therapeutic interventions for age-related macular degeneration (AMD).

Methods Systematic review of the literature and evaluation of study quality using the Quality of Health Economic Studies instrument. A systematic search of the English-language literature for economic studies of therapeutic interventions for AMD from 1990 to March 2008 was performed.

Results A total of 3637 articles were initially identified. Only 24 met eligibility criteria and were rated using the Quality of Health Economic Studies. The mean quality overall rating was 61.6, with quality scores ranging from 18 to 92. There was a higher mean quality score in the studies designed as clinical trials versus observational type designed studies (mean=74.7(11.4), 52.6 (16.5) respectively, p=0.002) and studies in which the statistical analyses were clearly presented versus studies in which the statistical analyses were not so clear (mean=74.3 (12.3), 53.1 (16.1) respectively, p=0.004). Interestingly, government funded studies exhibited a similar mean quality score to studies that were funded by industry (mean=71.0 (15.1), 61.7 (18.5) respectively, p=0.25). A general linear model was fitted using those independent variables which were significantly associated with quality score. The variables 'study design' and 'statistics presented clearly' were found to be jointly significant and explained nearly 70% of the variation in the dependent variable (R^2=0.68).

Conclusions Our analysis reveals that the methodological quality of the health economic analysis of AMD therapeutic interventions in the literature is suboptimal. There is considerable variation in methodological rigour between the articles, and we have identified several attributes that are predictive of study quality.

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of vision loss in most developed countries,[1–7] and the exudative form of AMD may be responsible for 90% of severe vision loss from AMD.[8] The incidence, prevalence and progression of AMD increase with age.[9] Analysis of the data from the Beaver Dam Eye Study[10] found that the 15-year cumulative incidence of AMD was 14.3% for early AMD and 3.1% for late AMD. In particular, the 15-year incidence of exudative AMD was 4.4% for participants over 75 years of age but only 0.4% for participants in the 43–54 age range, a statistically significant difference. The Blue Mountains Eye Study demonstrated that over 23 000 older Australians are blind from AMD, and more than 90 000 have bilateral visual impairment due to AMD.[11 12] The incidence of AMD is similarly high in the UK where, in 2000, the cost of support services for AMD patients has been estimated at £6455 during the first year of a diagnosis of blindness and £6295 for each year thereafter.[13] AMD affects over 2.5 million Canadians.[14] Data from the Thessaloniki Eye Study revealed estimates of AMD comparable with other Western nations with a prevalence of 2.5% in Greece,[15] and similar estimates were found for Malay populations in Singapore.[16] About 88.5 million Americans will reach the age of 65 or older, and about 19 million will reach the age of 85 by 2050,[17] and it is projected that by 2050, three out of every 10 people in Europe will be over the age of 65.[18] The National Coalition on Vision Health in Canada estimates an 111% increase in AMD by 2030.[14] Visual impairment and vision loss can lead to a multitude of other problems including increased fall risks and increased dependence on care givers.[19–24] AMD is, therefore, of growing socio-economic and public health concern.

The therapeutic options available to treat AMD have grown considerably over the last two decades (figure 1). Current treatment modalities for exudative macular degeneration include periodic intravitreal injections of anti-VEGF medications (Lucentis, Avastin or Macugen), photodynamic therapy with Visudyne and (rarely) thermal ablation of the neovascular membrane with an argon or solid-state laser. In the USA, treatment with Lucentis or Avastin is currently the most commonly utilised therapy. All of these therapies are targeted towards the treatment of exudative macular degeneration.

This increase in therapeutic options has also given rise to health economic analyses of AMD therapeutic interventions in the ophthalmic literature.Such economic analyses are often cited in formulating reimbursement decisions,[25 26] consensus guidelines[9] and policy statements.[27 28] Indeed, there is currently an ongoing debate regarding the cost-effectiveness of ranibizumab (Lucentis) versus bevacizumab (Avastin) in the USA.[29]

Although there is increasing interest and use of economic analysis in policy-making, few studies have been conducted, that we are aware of, to

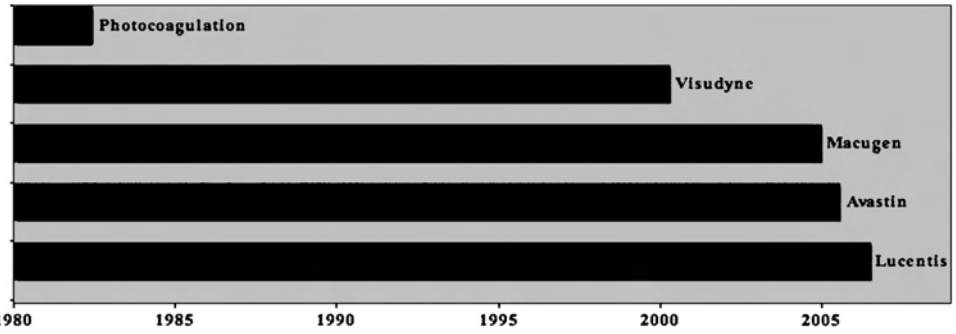

Figure 1 Therapeutic interventions for age-related macular degeneration by year of approval by the United States Food and Drug Administration.

systematically review and assess the quality of the economic evaluations of AMD therapeutics. It is clearly important to critically appraise this body of literature that, increasingly, policy makers are relying on to make decisions that could potentially affect thousands of patients.

Given the growing importance of pharmacoeconomic evaluations of AMD therapeutics, we systematically reviewed the literature to identify and critically appraise the published economic analyses of AMD therapeutics. A glossary of relevant common terms used in economic analyses is shown in box 1.

Our objective was to determine whether sufficient quality evidence exists regarding economic evaluations of therapeutics for AMD. Our specific aims were to appraise the quality of health economic studies of AMD therapeutics using a validated instrument, and to identify predictors of study quality.

METHODS

Study identification and selection

We conducted a systematic search of the literature, for economic studies of AMD therapeutics published between January 1990 and March 2008; in accordance with the meta-analysis of observational studies in epidemiology guidelines.[30] The main search strategies are delineated in table 1. We performed database searches using PubMed, the National Institute of Clinical Excellence, EconLit, Health STAR, Cochrane, the Tufts CEA Registry, and the Canadian Council of Technology Assessment in Health Care. The reference lists of identified studies were also searched for potentially relevant articles.

Two investigators, who were blinded to author and source information (ie, journal and institution), independently reviewed abstracts. The full text of any articles that were flagged

Box 1 Glossary of health economic analyses and related terms

Internal validity: the study conclusions represent within the study
External validity: the representativeness of generalisability of an experimental study
Quality of Health Economic Studies (QHES): a validated instrument (test) that evaluates the quality of studies in health economics
Dependent variable: the variable or outcome measure that the researcher believes is under the influence of some treatment or exposure
Independent variable: a variable that is presumed to influence the outcome measure or dependent vairable
Cost benefit analysis (CBA): an evaluative technique of making economic decisions by weighing the value of all resources consumed (expected total costs) in implementing a programme or intervention against the value of outcome (expected total benefits) in order to choose the best option; both the costs and benefits are expressed in monetary terms
Cost-effectiveness analysis (CEA): a form of economic evaluation to make economic decisions by comparing the relative costs and outcomes (effects); the outcomes can be expressed using measures such as disability-adjusted life years and quality-adjusted life years
Cost minimisation analysis: a relatively easy approach for making pharmacoeconomic decisions by comparing the costs of two or more drugs which have similar or identical outcomes or effectiveness rates such as equal efficacy and tolerability
Cost utility (CU): a special case of CEA where the outcomes are the benefit of the health-related intervention produced in terms of the number of years lived in full health by the beneficiaries such as Quality-Adjusted Life Years
Disability-Adjusted Life Year (DALY): a measure of both morbidity and mortality due to disease; includes the number of 'healthy' years of life lost to premature death as well as disability
Quality-Adjusted Life Year (QALY): the number of years of life that will be added by an intervention, modified by the quality of the additional years (ie, reduced for disabilities such as blindness and need to utilise a wheelchair)
Incidence: the frequency at which a finding (for example, a disease) appears in the studied population; for example, the incidence of exudative ARMD in the USA in 1990 would be the number of newly diagnosed US patients in the year 1990
Cumulative incidence: the frequency at which a finding (for example, a disease) appears in the study population, over a given period of time divided by the size of the population initially at risk
Type of economic evaluation: economic evaluations involve the identification, measurement, and valuation, and then comparison of the costs and outcomes of two or more alternative interventions
Perspective or economic model perspective: the viewpoint chosen for the analysis—that is, does the model take the perspective of the payer, society, or a policy maker?
Dichotomous criteria: fall into one of two different states (ie, yes or no; male or female)
Joint association: two or more independent vairables have an effect on the dependent vairable together, where the independent variables cannot be interpreted separately
Jointly significant: two or more independent vairables have an effect on the dependent variable together where the findings occurring by chance alone in below a certain percentage (ie, 5%)

Table 1 Search strategies

Age-related macular degeneration OR macular degeneration	AND cost-effectiveness
	AND cost–utility
	AND cost–benefit
	AND cost-minimisation
	AND economic
Avastin OR Bevacizumab	AND cost
	AND economic
	AND cost-effectiveness
	AND cost–utility
	AND cost–benefit
	AND cost-minimisation
Macugen OR pegaptanib sodium	AND cost
	AND economic
	AND cost-effectiveness
	AND cost–utility
	AND cost–benefit
	AND cost-minimisation
Lucentis OR pegaptanib	AND cost
	AND economic
	AND cost-effectiveness
	AND cost–utility
	AND cost–benefit
	AND cost-minimisation
(Visudyne OR verteporfin) AND photodynamic therapy	AND cost
	AND economic
	AND cost-effectiveness
	AND cost–utility
	AND cost–benefit
	AND cost-minimisation
Photocoagulation	AND cost
	AND economic
	AND cost-effectiveness
	AND cost–utility
	AND cost–benefit
	AND cost-minimisation
Reimbursement	AND age-related macular degeneration
	AND Macugen or Pegaptanib
	AND Ranibizumab or Lucentis
	AND bevacizumab or avastin

as relevant by either of the reviewers was obtained for further review. We also retrieved the full text of any articles for which it was not possible to determine relevance from the abstract. At this initial screening stage, our objective was to identify any and all articles that described health economic analyses for any AMD therapeutic intervention. Studies were limited to English language publications and were only excluded at this stage if they lacked relevance to AMD or did not deal with human populations.

Two reviewers independently reviewed any articles that passed our initial screening criteria in order to determine whether they should be accepted for further review. Reviewers were not blinded to journal or authors at this second stage. Studies were excluded for either of the following reasons: (1) studies that were not a true economic evaluation (including cost-effectiveness analysis, cost–utility analysis, cost–benefit analysis or cost-minimisation analysis) and (2) studies that were descriptive or reviews only. The two reviewers independently abstracted detailed data onto a structured form, including information on the type of economic evaluation, the type of economic model, the economic model perspective (ie, payer, societal, policy maker), the specific therapeutic product for AMD that was assessed or products compared, the year of analysis if applicable, the study location (ie, country), the population studied and the type of funding source.

Evaluating the quality of the studies

We used a validated quality-scoring instrument designed to measure the quality of economic analyses.[31 32] This instrument, the Quality of Health Economic Studies (QHES), consists of 16 dichotomous criteria, with each criterion weighted. To develop the QHES, an international panel of expert health economists originally selected the 16 criteria that cover the essential domains typically used to evaluate the reliability of an economic analysis. Thus, content validity, an important criterion for the adoption of a rating instrument as scientifically sound, was established[31 32] (ie, to ascertain that the scale is representative of the content of the domains being measured). A second panel with expertise in health economics was then surveyed to generate the weighted values assigned to the criteria (ie, criterion validity was established). A prospective study was conducted to validate the QHES with a third panel of health economists.[31 32] Furthermore, QHES has been favourably evaluated in comparison with other instruments including the *BMJ* Guidelines,[33] the *Journal of the American Medical Association* User's Guide to the Medical Literature[34 35] and the Canadian guidelines for economic evaluation and drugs[36] as well as favourably assessed for reliability.[37] Since its development, the QHES has been reliably applied to evaluate health economic studies in various areas including digestive diseases,[38] physical therapy,[39] genetics services,[40] surgical treatment for obesity[41] and the use of drug-eluting stents for cardiovascular disease.[42] QHES scoring proceeds from 0 (worst quality) to 100 (highest quality), with high-quality studies considered as those scoring between 75 and 100 points. As originally developed and validated,[31 32] the quality categories are as follows: category 1 represents studies of very poor quality (scoring between 0 and 24); studies of poor quality (25–49) fall into category 2; category 3 encompasses those studies of moderate quality (scoring 50–74 points); and those studies in category 4 are considered of high quality (scoring 75–100). Both reviewers independently rated each article using the QHES. We agreed on the interpretations of the criteria contained in the QHES instrument prior to scoring any articles, to avoid different interpretation due to ambiguities.

Statistical analyses

Descriptive statistics were used to summarise quality scores. To determine predictive variables of study quality, we used the QHES as the dependent or outcome variable. We examined the following independent variables: type of economic analysis; years since publication (<3 or ≥ 3 years); number of study authors (four or less vs five or more); type of funding (government vs private); number of comparator groups (one vs more than one); study design (controlled clinical trial vs observational study); study direction (prospective vs retrospective study); whether statistical analyses (ie, whether the statistical tests and the way that the analyses were conducted using standard methods) in each study were presented clearly; whether the length of follow-up was presented; and whether sample size was explicitly stated. General linear models including analysis of variance (ANOVA) and linear regression were used to assess univariate associations of each independent variable on quality score. The F test statistic from these linear models was used to determine statistical significance, with p values <0.05 considered as an indication of statistical significance. Based on the univariate results, a parsimonious

multivariate model was employed to assess the joint association of these independent variables with QHES score.

RESULTS

Our initial search of the literature yielded a total of 3637 articles (figure 2). Of these, 97 titles and abstracts met inclusion criteria for initial screening, and only 24 articles were included in the final analysis.

The characteristics of the studies that were analysed are described in table 2. The mean quality score overall was 61.6, with QHES scores ranging from 18 to 92. Of the quality criteria assessed, the most commonly missing were not displaying the components or scope of the economic model clearly or transparently (73.91%); not using or not justifying the use of health outcome measures or scales (73.91%); failing to explicitly discuss the direction of bias (60.87%); and not disclosing the perspective of the analysis (60.87%) (table 3). Overall, the intraclass correlation between the two raters was 0.807 (95% CI 0.760 to 0.966).

Our analysis of variables to identify predictors of study quality revealed that there was a higher mean quality score in the studies designed as clinical trials versus observational type designed studies (mean=74.7 (11.4), 52.6 (16.5), respectively; p=0.002) (table 4). Studies in which the statistical analyses were clearly presented had a higher mean quality score than papers in which the statistical analyses were not clearly presented (mean=74.3 (12.3), 53.1 (16.1), respectively; p=0.004). There was an indication of a somewhat higher mean quality score for studies designed prospectively versus retrospectively, falling just short of statistical significance (mean=71.3 (13.5), 59.2 (19.7), respectively; p=0.10). Government-funded studies exhibited a similar mean quality score to studies that were funded by industry (mean=71.0 (15.1), 61.7 (18.5), respectively; p=0.25). A general linear model was fitted using those independent variables which were significantly associated with quality score. The variables 'study design' and 'statistics presented clearly' were found to be jointly significant in the model and explained nearly 70% of the variation in the dependent variable (R^2=0.68). The variable 'study design' was significant at p=0.0009, and the variable 'statistics presented clearly' was significant at p=0.002.

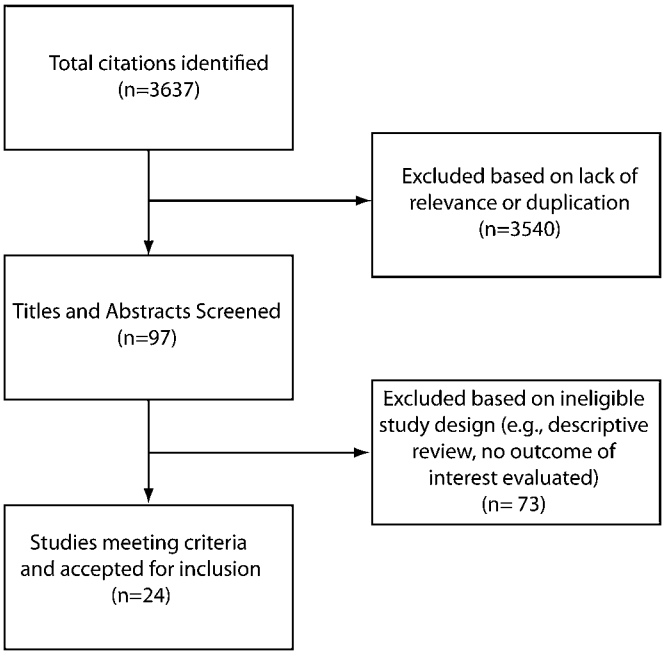

Figure 2 Flow diagram summarising systematic study selection process.

DISCUSSION

Given the increasing use of pharmacoeconomic analyses to formulate decisions regarding reimbursement policies, both by private insurers, such as in the US healthcare system[25], and by governments,[26–28 42 43] including the UK National Institute for Health and Clinical Excellence and the Canadian Agency for Drugs and Technologies in Health, we sought to systematically review and rate the quality of published economic evaluations of AMD therapeutics. Our analysis revealed that less than one-quarter of AMD therapeutic economic studies meet criteria for high quality, as assessed by a validated instrument. The mean quality rating overall was 61.6, with quality scores ranging from 18 to 92. The studies we evaluated generally fell below the threshold of 75 points on the QHES scale, below which, it has been suggested, is indicative of modest quality.[32] We found that quality appears to depend on study design and clear presentation of statistical analysis. Indeed, some 52% of studies did not appear to explicitly use sensitivity analysis to ascertain that a wide range of underlying assumptions were adequately addressed; a finding that others[31 37] have interpreted in different contexts as suggesting a lack of generalisability of the given model to relevant populations. We found that many of the studies evaluated did not clearly display the study methods and analysis of the economic model. Given that health economic studies are intended to be used in clinical decision-making and are increasingly being incorporated into practice guidelines, it is surprising that over 70% of the evaluated studies do not provide details regarding the components of the economic model. It is therefore not possible to adequately judge the validity of the model as presented. Furthermore, some 61% of studies failed to discuss the duration of bias and did not disclose the perspective of the analysis explicitly. Addressing potential biases in economic model assumptions is an important and well-accepted standard of performing health economic analysis,[31 32] particularly since variations in model assumptions can affect the overall result. Failure to explicitly discuss the direction and magnitude of potential biases may lead to overstatement of model results.

Our systematic review of the literature regarding economic analysis of AMD therapeutic interventions and quantitative assessment of study quality using the QHES is limited by several factors. One limitation lies in the use of QHES as a measure of quality. Despite being a validated measure of quality, the QHES mainly reliably measures internal validity of economic studies rather than external validity. Thus, for any given study, it may be difficult to ascertain generalisability and applicability in a particular clinical population of the pharmacoeconomic analysis. Nevertheless, the QHES remains a well-validated instrument for measuring the quality of economic studies, and is useful in shedding light on the utility of the body of economic studies for AMD therapeutic interventions. Indeed, as previously mentioned, the QHES has been reliably applied to evaluate health economic studies in various areas including digestive diseases,[38] physical therapy,[39] genetics services,[40] surgical treatment for obesity[41] and the use of drug-eluting stents for cardiovascular disease.[42] The QHES summary scores for these studies ranged from 63 to 87.1, thereby suggesting wide variation in the quality of published health economic analyses across different disease states. Second, it is possible that additional data (such as that found in the grey literature), which would have added to our study, is available in analyses that we were unable

Table 2 Characteristics of pharmacoeconomic studies evaluated

Study	Therapeutic intervention	Economic evaluation type	Economic model perspective	Economic model type	Year of analysis	Location of data/study	Type of population studied	Funding source
Medical Services Advisory Committee (MSAC), 2001[44]	Photodynamic therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	Policy Maker	ND	ND	Australia	Community nursing, permanent nursing home residency	Government
Donati, 2007[45]	Photodynamic therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	Societal	Markov	ND	Switzerland	Perspective clinical trial	ND
Lees *et al*, 2003[46]	Photodynamic therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	Societal	CEA	ND	Australia	Nursing home, home and community care, accidental falls, disability pension.	ND
Hopley *et al*, 2004[47]	Photodynamic therapy with Visudyne (verteporfin)	Cost—utility analysis	Payer	Decision analytic	ND	Australia	TAP Study	Westmead Millennium Institute, University of Sydney
Bansback *et al*, 2006[48]	Photodynamic Therapy with Visudyne (Verteporfin)	Cost-effectiveness analysis	Societal	Markov	ND	UK	AMD patients from TAP Study	Novartis
NICE, 2003[49]	Photodynamic therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	Societal	CUA	ND	UK	TAP and VIP Studies	Government (National Institute of Clinical Excellence)
Sharma *et al*, 2001[50]	Photodynamic therapy with Visudyne (verteporfin)	Cost—utility analysis	Payer	Markov	ND	Canada	TAP Study	The Principals Research Initiative Fund, Queen's University; The Jeanne Mance Foundation; The E.A. Baker Foundation; The JP Bickell Foundation; The Retina Research Foundation; Wills Eye Hospital
Muslera and Natal, 2006[51]	Photodynamic therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	Government Societal	CEA analysis	ND	Spain	TAP and VIP Studies	ND
Rein *et al*, 2007[52]	AREDS, vitamin therapy	Cost-effectiveness analysis	ND	CEA	2003—2007	USA	AREDS Study data	Division of Diabetes Translation; Centers for Disease Control and Prevention
Trevithick *et al*, 2004[53]	AREDS antioxidant supplementation	Cost-effectiveness analysis	Government	CBA	2001	Canada	Beaver Dam AREDS studies	ND
Smith *et al*, 2002[54]	Photodynamic therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	ND	Markov	ND	UK	Patients with wet AMD (presenting subfoveal CNV lesions)	Novartis Ophthalmic
Earnshaw *et al*, 2005[55]	Pegaptanib	Cost—utility analysis	Societal	Markov	ND	USA	Based on US 2000 census data	Pfizer and Eyetech Pharmaceuticals
Smith *et al*, 2004[56]	Photodynamic therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	Government	Markov	ND	UK	Predominantly classic choroidal neovascular AMD patients	Novartis AG, Switzerland
Hopley *et al*, 2004[57]	Photodynamic therapy with Visudyne (verteporfin)	Cost—utility analysis	Third Party Payer	Decision analytic	ND	Australia	Blue Mountains Eye Study	Westmead Millennium and Save Sight Institutes, University of Sydney

Continued

Table 2 Continued

Study	Therapeutic intervention	Economic evaluation type	Economic model perspective	Economic model type	Year of analysis	Location of data/study	Type of population studied	Funding source
Sharma *et al*, 2005[58]	Retaane (Anecortave acetate)	Cost-effectiveness analysis	Societal	Decision analytical (time trade off)	ND	USA	Phase III clinical trial	ND
Busbee *et al*, 2003[59]	Argon laser therapy (macular photo-coagulation)	Cost—utility analysis	Policy maker	Markov	ND	USA	MPS Studies	Retina Research and Development Fund; The Premier's Award for Excellence; Principal's Initiative Research Fund, Queen's University
Greiner, 2001[60]	Photodynamic therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	Societal	Markov	1998	Switzerland	Homes of older people or blind	ND
Brown *et al*, 2005[61]	Photodynamic therapy with Visudyne (verteporfin)	Cost—utility analysis	Third party payer	Time trade off utility analysis	ND	USA	AMD with subfoveal CNV patients	Non-Profit Organisation; Eye Research Institute
Earnshaw *et al*, 2005[62]	Photodynamic therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	Societal	Markov	ND	USA	US 2000 census	Pfizer and Eyetech Pharmaceuticals
Meads and Moore, 2001[63]	Photodynamic therapy with Visudyne (verteporfin), Argon laser therapy (macular photo-coagulation)	Cost-effectiveness analysis, cost—utility analysis	Government perspective (Regional Evaluation Panel)	Decision analytic; CUA	1993—2000	USA, UK	TAP study	ND
Wolowacz *et al*, 2007[13]	Pegaptanib	Cost-effectiveness	Government	Markov	ND	UK	1000 patients with a best-corrected VA in their better-seeing eye of $\leq$6/12	Pfizer
Brown *et al*, 2007[64]	Laser photo-coagulation, Intravitreal pegaptanib therapy, photodynamic Therapy	Cost—utility	ND	Time trade-off utility analysis	ND	USA	Participants in the macular photocoagulation study, pegaptanib for neovascular age-related macular degeneration study, treatment of age-related macular generation with photodynamic therapy study	ND
Raftery *et al*, 2007[65]	Ranibizumab (Lecuntis), Bevacizumab (Avastin)	Cost-effectiveness	ND	Markov	ND	UK	ANCHOR trial	ND
Meads *et al*, 2003[66]	Photodynamic Therapy with Visudyne (verteporfin)	Cost-effectiveness analysis	Government	Decision analytic	2001	USA, UK, Netherlands, Australia, Denmark	ND	NICE/NHS

ANCHOR, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; AREDS, Age-Related Eye Disease Study; MPS, Macular Photocoagulation Study; ND, not described; TAP, treatment of age-related macular degeneration with photodynamic therapy; VIP, verteporfin in photodynamic therapy.

Table 3 Assessment of quality of pharmacoeconomic studies on age-related macular degeneration therapeutics

QHES criteria* (weight)	Studies missing criteria (N)	Studies missing criteria (%)
Was the study objective presented in a clear, specific and measurable manner? (7)	4	17.39
Were the perspective of the analysis (societal, third party payer, etc) and reasons for its selection stated? (4)	14	60.87
Were variable estimates used in the analysis from the best available source (ie, RCT—Best, Expert Opinion—Worst) (8)	11	47.83
If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? (1)	11	47.83
Was uncertainty handled by: (1) statistical analysis to address random events; (2) sensitivity analysis to cover a range of assumptions? (9)	12	52.17
Was incremental analysis performed between alternatives between resources and costs? (6)	10	43.47
Was the methodology for data abstraction (including value health states and other benefits) stated? (5)	8	34.78
Did the analytical horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3—5%) and justification given for the discount rate? (7)	12	52.17
Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8)	4	17.39
Were the primary outcome measure(s) for the economic evaluation clearly stated and were the major short term, long term and negative outcomes included? (6)	13	56.52
Were the health outcome measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used? (7)	17	73.91
Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear and transparent manner? (8)	17	73.91
Were the choice of economic model, main assumptions and limitations of the study stated and justified? (7)	10	43.47
Did the author(s) explicitly discuss direction and magnitude of potential biases? (6)	14	60.87
Were the conclusions/recommendations of the study justified and based on the study results? (8)	2	8.69
Was there a statement disclosing the source of funding for the study? (3)	9	39.13

Overall intraclass correlation (α): 0.807 (95% CI 0.760 to 0.966).
*Criteria and rating scale developed by Chiou *et al*.[31]

to locate. However, given that we used a broad screening strategy, it is unlikely that these data are incomplete. Third, since the reviewers were not blinded to journal or author at the second stage of review, this may be a source of bias. Fourth, it should be noted that our study is limited by our inclusion of any and all types of therapeutic interventions of AMD, as well as by differences in the characteristics of the populations and study designs in the economic analysis evaluated. Since the QHES is primarily an instrument for measuring internal validity of a given economic analysis, these differences in population characteristics and variation in study design or type of therapeutic intervention should not have a significant effect on these data.

Table 4 Independent predictors of study quality

Variable	Percentage	Mean quality score	SD
Study type was clinical trial*	60.8	74.7	11.4
Study type was observational study*	39.1	52.6	16.5
Statistics clearly presented†	58.9	74.3	12.3
Statistics not clearly presented†	42.1	53.1	16.2
Prospective study design	56.5	71.3	13.5
Retrospective study design	43.5	59.2	19.7
Use of Decision Analysis Software package	86.9	65.9	17.3
Study supported by government funding	44.0	70.9	15.1
Study supported by industry funding	56.5	61.7	18.5
No of groups: 1 group	34.8	65.0	11.2
No of groups compared: >1 group	65.2	66.3	20.2
No of authors of study four or less	52.2	64.2	21.8
No of authors of study five or more	47.8	67.5	12.1
Study author(s) have advanced training in health economics	73.9	69.4	13.4
Study conducted in countries other than the USA	69.6	65.2	20.2
Study conducted in the USA	30.4	67.0	11.2
Sample size not stated	40	61.6	22.3
Sample size explicitly stated	60	68.7	13.2
Length of follow-up specified	60.8	59.9	22.0
Length of follow-up not specified	39.1	69.8	12.7

*Significant at α=0.05 (p=0.002).
†Significant at α=0.05 (p=0.004).

A significant strength of our study is our use of a well-validated instrument, the QHES, to evaluate the quality of the pharmacoeconomic literature on AMD therapeutic interventions. As far as we know, this quality instrument has not been used in any previous studies of AMD therapeutics interventions. Our analysis reveals a lack of standardisation among health economic studies of AMD therapeutics.

Economic models of drugs and other clinical interventions are increasingly important. Given that AMD is a chronic and progressive disease, economic modelling is useful for projecting clinical outcomes and associated long-term costs. By using a useful and easily understandable metric such as cost per quality-adjusted life year gained, for example, pharmacoeconomic models can be used for the purpose of comparing different therapeutic options.

Since such considerations are important for policy makers applying the results of models to the payer's population, it is essential that the methodology of health economic models conform to high quality standards. The use of the QHES instrument to report quantitative ratings can be helpful to decision-makers looking for a useful approach to distinguish between economic analyses. Indeed, in a survey of various individuals who regularly evaluated published health economic studies, 76% of those who did not consider themselves experts in health economics found the QHES to be a useful tool.[38]

We offer several recommendations that we suggest would be helpful in improving the quality of future studies, First, we believe that the QHES criteria can be used as a starting template prior to conducting a pharmacoeconomic study to aid researchers as an a priori type of checklist for deciding what components to include in their analysis. Second, given that health economic evaluations attempt to provide hypothetical depictions of clinical reality, it is imperative that more studies provide appropriately detailed information regarding the methods used to obtain the base-case probability estimates, so

that readers can judge whether they reflect valid data that are representative of clinical situations. Third, it should be noted that consensus recommendations regarding the development of economic models and reporting of results have been developed. We suggest that those engaged in conducting economic analyses and modelling should follow these guidelines. Fourth, ideally, it would be a major step forward for the field of health economics analyses, if collaborative networks of scientists engaged in economic modelling in any given area could be formed to better identify sources of variation between studies and work to improve the quality of studies. Thus, for example, a 'pharmacoeconomic AMD therapeutics collaborative network' could engage in dialogue and work collaboratively to improve modelling data and analyses. Finally, we also suggest that clinicians, decision-makers, policy-makers, journal editors and readers of health economic evaluations become familiar with and apply published guidelines for systematic reviews of economic analyses, such as the BMJ's *Guideline's for Authors and Peer-Reviewers of Economic Submissions*.[33]

In conclusion, our study reveals that the methodological quality of the health economic analysis of AMD therapeutic interventions in the literature is suboptimal. There is considerable variation in methodological rigour between articles, and we have identified several attributes that are predictive of study quality. We have also identified several factors and shortcomings that can be addressed to improve the quality of economic analysis and modelling in this field. This study may be useful for clinicians, health economists, decision and policy-makers in considering health economic analysis of AMD therapeutic interventions and working to improve the quality of economic analysis in ophthalmology.

Funding WJF acknowledges funding from the National Eye Institute of the National Institutes of Health, EY017112.

Competing interests None.

Contributors All authors contributed to the design and conception of the study, reviewed the article critically for important intellectual content and provided approval for the final version. WJF, WT and AMI analysed and interpreted the data. WJF and AMI helped to draft the manuscript. WJF and AMI are guarantors.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Holz FG,** Wolfensberger TJ, Piguet B, *et al*. Bilateral macular drusen in age-related macular degeneration: prognosis and risk factors. *Ophthalmology* 1994;**101**:1522—8.
2. **Macular Photocoagulation Study Group.** Five-year follow-up of fellow eyes of patients with age-related macular degeneration and unilateral extrafoveal choroidal neovascularization. *Arch Ophthalmol* 1993;**111**:1189—99.
3. **Macular Photocoagulation Study Group.** Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Arch Ophthalmol* 1997;**115**:741—7.
4. **Bressler NM,** Munoz B, Maguire MG, *et al*. Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities: Waterman Study. *Arch Ophthalmol* 1995;**113**:301—8.
5. **Klein R,** Klein BE, Jensen SC, *et al*. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 1997;**104**:7—21.
6. **Klaver CC,** Assink JJ, van Leeuwen R, *et al*. Incidence and progression rates of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci* 2001;**42**:2237—41.
7. **Klein R,** Klein BE, Tomany SC, *et al*. Ten-year incidence and progression rates of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 2002;**109**:1767—79.
8. **Ferris FL 3rd,** Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984;**102**:1640—2.
9. **American Academy of Ophthalmology.** *Age-related macular degeneration, preferred practice pattern*. San Francisco: American Academy of Ophthalmology, 2006. http://www.aao.org/ppp (accessed 30 Oct 2009).
10. **Klein R,** Klein BEK, Knudtson MD, *et al*. Fifteen-year cumulative incidence of age-related macular degeneration. *Ophthalmology* 2007;**114**:253—62.
11. **Wang JJ,** Foran S, Mitchell P. Age-specific prevalence and causes of bilateral and unilateral visual impairment in older Australians: the Blue Mountains Eye Study. *Clin Experiment Ophthalmol* 2000;**28**;268—73.
12. **Mitchell P,** Wang JJ, Smith W, *et al*. Smoking and the 5-year incidence of age-related maculopathy: the Blue Mountains Eye Study. *Arch Ophthalmol* 2002;**120**:1357—63.
13. **Wolowacz SE,** Roskell N, Kelly S, *et al*. Cost effectiveness of pegaptanib for the treatment of age-related macular degeneration in the UK. *Pharmacoeconomics* 2007;**25**:863—79.
14. **Buhrmann R,** Hodge WG, Gold D. *Forecasting the vision loss epidemic in Canada: current and projected estimates of age-related eye disease: Interim summary tables prepared for the National Coalition on Vision Health* 2006.
15. **Topouzis F,** Coleman AL, Harris A, *et al*. Prevalence of age-related macular degeneration in Greece: The Thessaloniki Eye Study. *Am J Ophthalmol* 2006;**142**:1076—9.
16. **Kawasaki R,** Wang JJ, Aung T, *et al*. Prevalence of age-related macular degeneration in a Malay population. *Ophthalmology* 2008;**115**:1735—41.
17. **US Census Bureau.** National population projections, 2008. http://www.census.gov/population/www/projections/2008projections.html (accessed 30 Oct 2009).
18. **European Central Bank.** Demographic change in the Euro area: projections and consequences. *ECB Monthly Bulletin* Oct 2006. http://www.ecb.int/pub/pdf/other/pp4964_mb200610en.pdf?d86d6b3376eac6e04a2b65ba00851e73 (accessed 3 Mar 2010).
19. **Coleman AL,** Stone K, Ewing SK, *et al*. Higher risk of multiple falls among elderly women who lose visual acuity. *Ophthalmology* 2004;**111**:857—62.
20. **Lord SR,** Dayhew J. Visual risk factors for falls in older people. *J Am Geriatr Soc* 2001;**49**:508—15.
21. **Klein BE,** Moss SE, Klein R, *et al*. Associations of visual function with physical outcomes and limitations 5 years later in an older population: the Beaver Dam Eye Study. *Ophthalmology* 2003;**110**:644—50.
22. **Ivers RQ,** Cumming RG, Mitchell P, *et al*. Visual impairment and falls in older adults: the Blue Mountains Eye Study. *J Am Geriatr Soc* 1998;**46**:58—64.
23. **Ivers RQ,** Norton R, Cumming RG, *et al*. Visual impairment and risk of hip fracture. *Am J Epidemiol* 2000;**152**:633—9.
24. **Buckley JG,** Elliott DB. Ophthalmic interventions to help prevent falls. *Geriatrics & Aging* 2006;**9**:276—80.
25. **BlueCross BlueShield Association (BCBSA).** Technology Evaluation Center (TEC). Special report: Current and evolving strategies in the treatment of age-related macular degeneration. *TEC Assessment Program* **Vol. 20**, No 11, Dec 2005. http://blueweb.bcbs.com/global_assets/special_content/tec_assessments/vol20/20_11.pdf (accessed 30 Oct 2009).
26. **Department of Health & Human Services (DHHS).** Center for Medicare & Medicaid Services (CMS). *CMS manual system. Medicare national coverage determinations*. Pub 100.03, Transmittal 9, 2004. http://www.cms.hhs.gov/transmittals/Downloads/R9NCD.pdf (accessed 30 October 2009).
27. **National Institute for Clinical Excellence (NICE).** *Guidance on the use of photodynamic therapy for age-related macular degeneration*. London: National Institute for Clinical Excellence (NICE), 2003 Sep 26 (Technology appraisal; no. 68).
28. **National Institute for Health and Clinical Excellence.** *Final appraisal determination—ranibizumab and pegaptanib for age-related macular degeneration*. UK: National Institute for Health and Clinical Excellence, 2008.
29. **Packo KH.** Compounding pharmacies and the law: How did we get into this anti-VEGF pickle? *Retina Times* 2008;**26**:18—22.
30. **Stroup DF,** Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;**283**:2008—12.
31. **Chiou CF,** Hay JW, Wallace JF, *et al*. Development and validation of a grading system for the quality of cost-effectiveness studies. *Med Care* 2003;**41**:32—44.
32. **Ofman JJ,** Sullivan SD, Neuman PJ, *et al*. Examining the value and quality of health economic analysis: implications of utilizing the QHES. *J Manag Care Pharm* 2003;**9**:53—61.
33. **Drummond MF,** Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275—83.
34. **Drummond MF,** Richardson WS, O'Brien BJ, *et al*. User's guide to the medical literature. XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1997;**277**:1552—7.
35. **O'Brien B,** Heyland D, Richardson WS, *et al*. User's guide to the medical literature. XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients? *JAMA* 1997;**277**:1802—6.
36. **Torrance GW,** Blaker D, Detsky A, *et al*. Canadian guidelines for economic evaluation of pharmaceuticals. Canadian Collaborative Workshop for Pharmacoeconomics. *Pharmacoeconomics* 1996;**9**:535—59.
37. **Au F,** Prahardhi S, Shiell A. Reliability of two instruments for critical assessment of economic evaluations. *Value Health* 2008;**11**:435—9.
38. **Spiegel BMR,** Targownik LE, Kanwal F, *et al*. The quality of published health economic analysis in digestive diseases: A systematic review and quantitative appraisal. *Gastroenterology* 2004;**127**:403—11.
39. **Peterson LE,** Goodman C, Karnes EK, *et al*. Assessment of the quality of cost analysis literature in physical therapy. *Phys Ther* 2009;**89**:733—55.
40. **Carlson JJ,** Henrikson NB, Veenstra DL, *et al*. Economic analyses of human genetics services: A systematic review. *Genet Med* 2005;**7**:519—23.

41. **Gerkens S,** Crott R, Cleemput I, *et al*. Comparison of three instruments assessing the quality of economic evaluations: a practical exercise on economic evaluations of the surgical treatment of obesity. *Int J Technol Assess Health Care* 2008;**24**:318—25.
42. **Ligthart S,** Vlemmix F, Dendukuri N, *et al*. The cost-effectiveness of drug-eluting stents: a systematic review. *CMAJ* 2007;**176**:199—205.
43. **Brown A,** Hodge W, Kymes S, *et al*. *Management of neovascular age-related macular degeneration: systematic drug class review and economic evaluation* (technology overview number 43). Ottawa: Canadian Agency for Drugs and Technologies in Health, 2008.
44. **Medical Services Advisory Committee (MSAC).** *Photodynamic therapy with verteporfin (PDT-V) for age-related macular degeneration*, Assessment report. Canberra, Australia: Commonwealth Department of Health and Ageing, 2001.
45. **Donati G.** Cost-Effectiveness of photodynamic therapy with verteporfin for choroidal neovascularization in age-related macular degeneration in routine clinical practice in Switzerland. *J Fr Ophthalmol* 2007;**30**:837—41.
46. **Lees M,** Davey P, Price N, *et al*. Economic evaluation of photodynamic therapy with verteporfin for small subfoveal CNV lesions: the case for Australia. *Value in Health* 2003;**6**:239.
47. **Hopley C,** Salkeld G, Mitchell P. Cost utility of photodynamic therapy for predominantly classic neovascular age related macular degeneration. *Br J Ophthalmol* 2004;**88**:982—7.
48. **Bansback N,** Davis S, Brazier J. Using contrast sensitivity to estimate the cost-effectiveness of verteporfin in patients with predominantly classic age-related macular degeneration. *Eye* 2006;**21**:1455—63.
49. **National Institute for Clinical Excellence.** *Final appraisal determination—photodynamic therapy for age-related macular degeneration*. London: National Institute for Clinical Excellence, 2003.
50. **Sharma S,** Brown GC, Brown MM, *et al*. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to Age-related macular degeneration. *Ophthalmology* 2001;**108**:2051—9.
51. **Muslera E,** Natal C. Cost-effectiveness of photodynamic therapy in age-related macular degeneration. *Arch Soc Esp Oftalmol* 2006;**81**:199—204.
52. **Rein DB,** Saaddine JB, Wittenborn JS, *et al*. Cost-effectiveness of vitamin therapy for age-related macular degeneration. *Ophthalmology* 2007;**114**:1319—26.
53. **Trevithick JR,** Massel D, Robertson JM, *et al*. Model study of AREDS antioxidant supplementation of AMD compared to Visudyne: A dominant strategy? *Ophthalmic Epidemiol* 2004;**11**:337—46.
54. **Smith DH,** Drummond M, Fenn P. *Modelling the long-term benefit of photodynamic therapy (PDT) with verteporfin for age-related macular degeneration (AMD)*. The University of York Center for health economics, Discussion paper 187, 2002.
55. **Earnshaw SR,** Javitt JC, Zlateva GP, *et al*. Cost-effectiveness model for age-related macular degeneration: comparing early and late macugen treatment. *ISPOR 8th Annual European Congress* Florence, Italy, 6—8 Nov 2005. http://www.rtihs.org/request/index.cfm?fuseaction=displayPID=561 (accessed 30 October 2009).
56. **Smith DH,** Fenn P, Drummond M. Cost-effectiveness of photodynamic therapy with verteporfin for age related macular degeneration: the UK case. *Br J Ophthalmol* 2004;**88**:1107—12.
57. **Hopley C,** Salkeld G, Wang JJ, *et al*. Cost utility of screening and treatment for early age related macular degeneration with zinc and antioxidants. *Br J Ophthalmol* 2004;**88**:450—4.
58. **Sharma S,** Bakal J, Sharma SM, *et al*. Drug pricing for a novel treatment for wet macular degeneration: using incremental cost-effectiveness to ensure societal value. *Can J Ophthalmol* 2005;**40**:369—77.
59. **Busbee BG,** Brown MM, Brown GC, *et al*. CME review: a cost—utility analysis of laser photocoagulation for extrafoveal choroidal neovascularization. *Retina* 2003;**23**:279—87.
60. **Greiner RA.** Cost of care for patients with age-related macular degeneration in Switzerland and cost-effectiveness of treatment with verteporfin therapy. *Semin Ophthalmol* 2001;**16**:218—22.
61. **Brown GC,** Brown MM, Campanella J, *et al*. The cost—utility of photodynamic therapy in eyes with neovascular macular degeneration—A value-based reappraisal with 5-year data. *Am J Ophthalmol* 2005;**140**:679—87.
62. **Earnshaw SR,** Javitt JC, Zlateva GP, *et al*. Cost-effectiveness model for age-related macular degeneration: comparing Macugen to Visudyne. *ISPOR 8th Annual European Congress*, Florence, Italy. 6—8 Nov 2005. http://www.rtihs.org/request/index.cfm?fuseaction=displayPID=5612 (accessed 30 Oct 2009).
63. **Meads C,** Moore D. *The clinical effectiveness and cost utility of photodynamic therapy for age-related macular degeneration. WMHTAC, Department of Public Health & Epidemiology* University of Birmingham. Report number 24, 2001.
64. **Brown GC,** Brown MM, Brown HC, *et al*. A value-based medicine comparison of interventions for subfoveal neovascular macular degeneration. *Ophthalmology* 2007;**114**:1170—8.
65. **Raftery J,** Clegg A, Jones J, *et al*. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modeling cost effectiveness. *Br J Ophthalmol* 2007;**91**:1244—6.
66. **Meads C,** Sales C, Roberts T, *et al*. Clinical effectiveness and cost—utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2003;**7**:1—98.