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The Quality of Pharmacoeconomic Evaluations of Age-Related Macular Degeneration Therapeutics: A Systematic Review and Quantitative Appraisal of the Evidence

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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 (QHEs) instrument. A systematic search of the English-language literature for economic studies of therapeutic interventions for AMD from 1990 – March 2008 was performed.

Results—A total of 3637 articles were initially identified. Only 24 met eligibility criteria and were rated using the QHEs. 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 vs. 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 vs. studies in which the statistical analyses was 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

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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 analyzed and interpreted the data. WJF and AMI helped to draft the manuscript. WJF and AMI are guarantors.

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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 sub-optimal. There is considerable variation in methodological rigor between the articles, and we have identified several attributes that are predictive of study quality.

Keywords

Quality; Health Economic Study; Age-Related Macular Degeneration; QHES

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 AMD⁸. The incidence, prevalence, and progression of AMD increase with age⁹. Analysis of the data from the Beaver Dam Eye Study¹⁰ found that the fifteen-year cumulative incidence of age-related macular degeneration 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, while 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 United Kingdom (U.K.) where, in 2000, the cost of support services for AMD patients has been estimated at £ 6455 during first year of a diagnosis of blindness and £ 6295 for each year thereafter¹³. 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 Greece¹⁵, and similar estimates were found for Malay populations in Singapore¹⁶. About 88.5 million Americans will reach the age of 65 or older, and about 19 million will reach the age of 85 by 2050¹⁷, and it is projected that by 2050 three out of every ten people in Europe will be over the age of 65¹⁸. The National Coalition on Vision Health in Canada estimates a 111% increase in AMD by 2030¹⁴. Visual impairment and vision loss can lead to a multitude of other problems including increased fall risks and increased dependence on caregivers.^{19–24} AMD is, therefore, of growing socioeconomic 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 United States, treatment with Lucentis[®] or Avastin[®] is currently the most commonly utilized therapy. All of these therapies are targeted toward 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 guidelines⁹ and policy statements^{27,28}. Indeed, there is currently an on-going debate regarding the cost-effectiveness of ranibizumab (Lucentis[®]) vs. bevacizumab (Avastin[®]) in the United States²⁹.

Although there is increasing interest and use of economic analysis in policy-making, few studies have been conducted, that we are aware of, to 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 Figure 2.

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 – March 2008; in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) 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 (i.e. journal and institution), independently reviewed abstracts. The full text of any articles that were flagged 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-minimization 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 (i.e. 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 (i.e. country), the population studied and 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 which cover the essential domains that are 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} (i.e. to ascertain that the scale is representative of the content of the domains being measured). A second panel with expertise in health economics were then surveyed to generate the weighted values assigned to the criteria (i.e. 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 favorably evaluated in comparison to other instruments including the *British Medical Journal* Guidelines³³, the *Journal of the American Medical Association* User's Guide to the Medical Literature^{34,35} and the Canadian guidelines for economic evaluation and pharmaceuticals³⁶ as well as favorably assessed for reliability³⁷. Since its development, the QHES has been reliably applied to evaluate health economic studies in various areas including digestive diseases³⁸, physical therapy³⁹, genetics services⁴⁰, surgical treatment for obesity⁴¹ and the use of drug-eluting stents for cardiovascular disease⁴². QHES scoring proceeds from 0 (worst quality) to 100 (highest quality), with high quality studies considered as those scoring between 75–100 points. As originally developed and validated^{31,32}, the quality categories are as follows: category 1 represents studies of very poor quality (scoring between 0–24); 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 summarize 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 (4 or less vs. 5 or more); type of funding (government vs. private); number of comparator groups (1 vs. >1); study design (controlled clinical trial vs. observational study); study direction (prospective vs. retrospective study); whether statistical analyses (that is 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 3). 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 analyzed 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% confidence intervals: 0.760 – 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 vs. 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 vs. 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 $p = 0.002$.

Discussion

Given the increasing use of pharmacoeconomic analyses to formulate decisions regarding reimbursement policies, both by private insurers, such as in the U.S. healthcare system²⁵, and by governments^{26–28,42,43} including the U.K. National Institute for 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 generalizability 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 generalizability 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 diseases³⁸, physical therapy³⁹, genetics services⁴⁰, surgical treatment for obesity⁴¹ and the use of drug-eluting stents for cardiovascular disease⁴². 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. Secondly, 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 to locate. However, given that we used a broad screening strategy, it is unlikely that our data is 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 our data.

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 standardization among health economic studies of AMD therapeutics.

Economic models of pharmaceuticals and other clinical interventions are increasingly important. Given that AMD is a chronic and progressive disease, economic modeling is useful for projecting clinical outcomes and associated long-term costs. By using a useful and easily understandable metric such as cost per QALY 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. Secondly, 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 is 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 modeling 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 modeling 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 modeling 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 sub-optimal. There is considerable variation in methodological rigor 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 modeling 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 quality of economic analysis in ophthalmology.

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

External validity. This section examines generalizability of the study findings. The representativeness or generalizability of an experimental study design is a function of the degree to which the study population is similar to the population of interest. The external validity of an experiment is the quality of its results as evidence for the general population. The external validity of an experiment is the degree to which the results obtained are under the influence of random treatment or exposure.

Internal validity. Internal validity refers to the degree to which the treatment or exposure is the cause of the outcome. The internal validity of an experiment is the degree to which the treatment or exposure is the cause of the outcome. The internal validity of an experiment is the degree to which the treatment or exposure is the cause of the outcome.

Construct validity. Construct validity refers to the degree to which the treatment or exposure is the cause of the outcome. The construct validity of an experiment is the degree to which the treatment or exposure is the cause of the outcome. The construct validity of an experiment is the degree to which the treatment or exposure is the cause of the outcome.

Statistical validity. Statistical validity refers to the degree to which the treatment or exposure is the cause of the outcome. The statistical validity of an experiment is the degree to which the treatment or exposure is the cause of the outcome. The statistical validity of an experiment is the degree to which the treatment or exposure is the cause of the outcome.

Reliability. Reliability refers to the degree to which the treatment or exposure is the cause of the outcome. The reliability of an experiment is the degree to which the treatment or exposure is the cause of the outcome. The reliability of an experiment is the degree to which the treatment or exposure is the cause of the outcome.

Figure 2.
Glossary of Health Economic Analyses and Related Terms.

Figure 3.
Flow diagram summarizing systematic study selection process.

Table 1

Search Strategies.

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

AND Ranibizumab or Lucentis AND bevacizumab or avastin

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 & 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 & 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 & Natal, 2006 ⁵¹	Photodynamic Therapy with Visudyne (Verteporfin)	Cost-effectiveness analysis	Government Societal	CEA analysis	ND	Spain	TAP & 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

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
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	Cost-utility analysis	Third Party Payer	Decision analytic	ND	Australia	Blue Mountains Eye Study	Westmead Millennium and
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.
Sharma et al., 2005 ⁵⁸	Retaane (Anecortave acetate)	Cost-effectiveness analysis	Societal	Decision analytic (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 the elderly 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 Organization; 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 & 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	Pfizer Ltd

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
							≤6/12.	
Brown et al., 2007 ⁶⁴	Laser Photocoagulation, 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 (Lecunetis), Bevacizumab (Avastin)	Cost-effectiveness	ND	Markov	ND	UK	ANCHOR Trial	ND
Meads et al., 2003 ⁶⁶	Photodynamic Therapy with	Cost-effectiveness	Government	Decision Analytic	2001	USA, UK, Netherlands,	ND	NICE/NHS

TAP: Treatment of age-related macular degeneration with photodynamic therapy; VIP: Verteporfin in Photodynamic Therapy; AREDS: Age-Related Eye Disease Study; MPS: Macular Photocoagulation Study; ANCHOR: Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; ND: Not Described.

Table 3

Assessment of quality of pharmacoeconomic studies on AMD 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 (i.e. RCT – Best, Expert Opinion – Worst) (8)	11	47.83
If estimates came from a subgroup analysis, were the groups pre-specified 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 analytic 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

* Criteria and rating scale developed by Chiou et al.³¹

Overall intraclass correlation (α): 0.807 (95% C.I. 0.760–0.966)

Table 4

Independent predictors of study quality.

Variable	Percent (%)	Mean Quality Score	Std Dev
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
Number of Groups – 1 group	34.8	65.0	11.2
Number of Groups compared – >1 group	65.2	66.3	20.2
Number of Authors of Study four or less	52.2	64.2	21.8
Number 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 US	69.6	65.2	20.2
Study conducted in US	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 $\alpha = 0.05$ ($p = 0.002$)

* Significant at $\alpha = 0.05$ ($p = 0.004$)