VALUE-BASED MEDICINE ANALYSIS: OPHTHALMIC COST-UTILITY ANALYSES

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It is the philosophy of *Evidence-Based Ophthalmology* that the best evidence-based medicine should provide the foundation for knowledge, which will allow practitioners to provide the highest quality of medicine for our patients. Although the knowledge of a numerical or statistical change is critical, this information must be taken to another level to ascertain the true *value* of evidence-based discoveries to patients and society. As an example, it was shown in the Branch Retinal Vein Occlusion Study[1] that laser treatment of macular edema occurring secondary to retinal vein obstruction yields a long-term mean visual acuity of 20/40-20/50, as compared with a mean visual acuity of 20/70 in the untreated group. But equally as important is the question, "What does this mean for the quality of life for my patient?"

Value from an interventional therapy occurs when it positively affects: (1) quality of life and/or (2) length of life. Therapies that do not accomplish at least one of these goals have a questionable role in the armamentarium in the fight against disease.

The length-of-life component can often be extracted from evidence-based medical information in the literature. Quality-of-life information, however, is not so readily available. Why? Because many mechanisms for measuring quality have been nonstandardized, inapplicable across diverse medical specialties, and far from uniformly accepted.

In 1968, Klarman and associates[2] first used the quality-adjusted life-year (QALY). The QALY measures the value conferred by an intervention. In 1977, Weinstein and Stasson[3] reported a methodology for ascertaining the cost-effectiveness of interventional medical therapies. On the basis of utility theory, it has been modified to incorporate: (1) evidence-based medicine, (2) patient-based preferences, (3) decision analysis, and (4) economic modeling with discounting to account for the time value of money.[4,5] A brief explanation of each of these components follows below:

Evidence-based Medicine

Incorporates the highest quality of medical information available. Because of the high standards and confidence in the methods, the information obtained is typically reproducible, thus giving clinicians conviction in the therapies they provide for patients.

Patient-based Preferences (Utility Analysis)

Utility analysis is a methodology to assess the quality of life associated with a health (disease) state. By convention, a utility value of 1.0 is associated with perfect health and a utility value of 0.0 is associated with death. The closer a value to 1.0, the better the quality of life associated with a health state, whereas the closer to 0.0, the poorer the associated quality of life.

Utility values have been obtained from physicians, administrators, researchers, and the general public, but increasing numbers of researchers[5–7] believe those obtained from patients are the most valuable. Above all, it is the patients who have the actual disease who can best appreciate the effect it has on quality of life.

A number of methodologies are available to measure utility values, including the standard gamble technique, the willingness-to-pay technique and the time tradeoff technique. The latter seems to be the most reproducible and valid.[5]

With the time tradeoff technique, a patient is asked how many years he or she believes they will live. The patient is then presented with the scenario that he or she could trade an amount of the remaining time of life in return for being rid of a disease entity. The proportion of time traded subtracted from 1.0 yields the utility value.

As an example, the average patient with counting fingers vision in the better eye is typically willing to trade approximately 50% of his or her remaining life in return for perfect vision in both eyes. Thus, such a patient with a 20-year life expectancy is generally willing to trade 10 years. The resultant utility value is **0.50** (1.0–20/10). If a patient is willing to trade 2 of 10 remaining years, the utility value is **0.80** (1.0–2/10).

Utility values are not necessarily static, and improvement of visual acuity by an interventional therapy often yields an improvement in utility value. For example, a patient with counting fingers vision in the better seeing eye from a cataract who achieves 20/40 vision after cataract extraction typically improves from a utility value of 0.50 to 0.80. Thus, there is a gain of 0.3 utility points from the surgery.

In addition to improvement gained from an interventional therapy, the duration of improvement also contributes to the value conferred by the therapy. The duration can be taken into account by using the QALY, which is derived by multiplying (the utility value gain obtained from an interventional therapy) and (the years of duration of the therapy). The cataract patient who improves from a utility value of 0.50 before surgery to 0.80 after surgery, and who experiences the benefit for the remaining 20 years of life, would thus gain a total of **6.0** (0.3×20) QALYs from the surgery.

Although this is not typically the case in ophthalmology, a therapy that improves the length of life will also yield more QALYs as duration of the benefit effect is in the equation used to derive the number of QALYs gained.

It should be noted that vehicles other than utility analysis are available for measuring quality of life. Most, such as the VF-14[8] and MOS short form-36[9] are scaling systems that ask a number of set questions that are particularly task oriented. While valuable in their own right, these vehicles are often not applicable across all specialties in medicine. Additionally, because of the specific number of set questions, they may miss variables related to the quality of life associated with a health state that are of unique importance to a patient. Utility analysis, in contrast is believed to be more all encompassing because it incorporates aspects, including those that are task-specific, psychosocial, economic, etc (The name of this section has been changed from cost-utility analysis to value-based medicine analysis to reflect the specifics of value-based medicine, which incorporates cost-utility analysis principles with patient values and perceptions. Specifics are described in Value-Based Medicine section in the following).[10]

Decision Analysis

Decision analysis allows the determination of the most probably outcome, given the confounding variables that go into an equation. When various treatment options are available, decision analysis allows one to determine the optimal treatment strategy, based on the maximization of utility values. Decision analysis can be combined with Markov modeling,[11] which takes into account recurrent risk, such as the yearly chance of developing choroidal neovascularization in a second eye in a patient with unilateral neovascular macular degeneration.

Decision analysis is necessary because many variables contribute to an outcome. In the case of cataract surgery, the treatment can be complicated by macular edema, endophthalmitis, retinal detachment, and other adverse variables. These all have an effect upon the final, mean visual acuity (and thus the utility value) obtained after surgery. When the utility value associated with a visual acuity is used in a decision analysis tree, the mean difference in utility points gained from a therapy can be ascertained.

Cost-utility (Cost-effectiveness)

Amalgamating the costs associated with an interventional therapy with the number of QALYs gained from the therapy yields the cost per QALY ($/QALY). Using the cataract example in which the patient gains 6.0 QALYs, and assuming the total cost is $6000 for the treatment, the resultant $/QALY is $1000.

Discounting: It should be noted that the costs associated with an interventional therapy must be discounted to account for the time values of money. This occurs because money has a changing value.[12] A million dollars invested today is worth more than a million dollars invested in 5 years because that million dollars invested today has the ability to generate a return over the next 5 years. In healthcare, a year of life gained today and paid for today is a better bargain than a year of life gained in 10 years, but paid for today. Thus outcomes, or QALYs gained, are also discounted to maintain the integrity of the discounting of money at the same time.[4] Alternatively, the discounting of QALYs can be rationalized by considering that fact that good health now can be used to earn resources that will increase in monetary value over time.

Discounting rate: The rate of discounting is variable, but those with an interest in cost-effectiveness suggest that a 3% rate for healthcare is probably most appropriate.[4,13] The rationale for 3% is that it represents the amount that dollars can earn in a safe investment (eg, a government bond at 5%) minus the level of annual inflation (2% recently).

Cost-utility standards: Cost-utility parameters are in their infancy at the present time. Nevertheless, it has been suggested that interventional therapies costing less than $50,000/QALY gained are cost-effective,[14] whereas those costing more than $100,000/QALY gained should not be considered cost-effective.[15] The criteria for cost-effectiveness are highly dependent on the resources a given society is willing to devote toward medical care. Thus, a cost-effective intervention in a wealthy country might not be considered cost-effective in a country with substantially less wealth.

In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE),[16] which also uses time tradeoff utility analysis, performs a cost-utility analysis on interventions to decide whether they should be recommended to the National Health System for funding. At the current time, a number of other European countries are following NICE, which generally has an upper limit for cost-effectiveness of £20,000/QALY (US $40,000/QALY), with a higher limit of £30,000/QALY (US $60,000/QALY) for select interventions.

A Source of Confusion

One source of potential confusion in the healthcare economic arena should be clarified for the readership. Healthcare economists from the Panel for Cost-Effectiveness in Health and Medicine,[3] a group organized by the Public Health Service in the mid-90s, refer to the analysis described herein as a *cost-effectiveness analysis*. Other researchers[17–21] refer to an analysis using the outcome of $/QALY as a *cost-utility analysis*, whereas analyses using other outcomes, such as cost per life-year, cost per vision-year, or cost per disability-free year are referred to as cost-effectiveness analyses. The editors herein believe that cost-utility analysis is the preferred term for an analysis using the QALY in the outcome, as there is little uncertainty as to the type of analysis. Despite the term cost-utility of cost-effectiveness, the result is referred to as more or less cost-effective, rather than more or less utilitarian.

Value-based Medicine[20]

Value-based medicine uses the concepts employed in cost-utility analysis, but incorporates the following important refinements:

1. The practice of medicine is based on the value (improvement in patient quality of life and length of life) conferred by interventions.
2. Patients should have access to the healthcare interventions that confer the greatest value.

3. If the value of interventions is the same, then the preferred intervention is the one that is least expensive.
4. The utility values employed are only those obtained from patients who live or have lived in the health state under study.
5. Until another form of utility value analysis is demonstrated to unequivocally be preferable, time tradeoff utility values are used.
6. The input standards should be standardized to allow a comparison of all analyses.

The input standards are as shown below:

i. **Utility values:** time tradeoff
ii. **Utility respondents:** patients who have lived in a health state under study
iii. **Analysis perspective:** reference (average) case
    1. This is used so that interventions will be comparable across all specialties.
iv. **Cost perspective:** third party insurer (direct healthcare costs).
    1. This perspective includes all cost bore by the insurer and outcomes in QALYs.
    2. Although the societal cost perspective (included all related costs: direct healthcare, direct nonhealthcare such as caregiver costs, and indirect costs such as disability costs) will be preferable at some point, there is no agreement as to the exact costs and what cost basis should be incorporated.
v. **Costs:**
    1. Average Medicare costs for physicians and other providers, acute hospitalization, ambulatory surgical centers, durable equipment, rehabilitation, home healthcare, and skilled nursing facilities.
    2. Average Medicaid cost for nursing home care.
    3. AWP (Average Wholesale Price) for pharmaceuticals. This is likely to be replaced by the Average Sales Price (ASP), as required by Part D of Medicare, in the near future.
vi. **Discounting:** 3% annually
vii. **Sensitivity analyses:** 1-way sensitivity analyses should be performed on all variables on which uncertainty exists. Two-way and 3-way sensitivity analyses are indicated if there are several variables about which there is a considerable degree of uncertainty.

The outcomes used in value-based medicine analyses include:

i. QALY gain
ii. Total costs
iii. Percent gain in value
iv. $/QALY

A value-based medicine analysis follows, adapted from the text *Evidence-Based Medicine to Value-Based Medicine*. Chicago: AMA Press; 1–324.

Cost-Utility Analyses for Ophthalmic Interventions

In this issue, we are including the outcomes of comparable cost-utility analyses performed on ophthalmic interventions. The value gain, associated direct medical costs and the cost-utility of each intervention, from the reference case perspective, are shown in the Table 1.

Ophthalmic Interventions and Value-based Medicine Principles

The value gain, cost and cost-utility associated with a number of ophthalmic and other interventions are shown in the Table 1, with an emphasis on interventions for neovascular macular degeneration. The underlying evidence-based data for each interventional cost-utility analysis fulfill ***Value-Based Medicine Principle I***. *Value-based medicine analyses should use the highest level of evidence-based data, preferably from randomized clinical trials and/or meta-analyses.*

The cost for each is calculated over the years of interventional benefit for the reference case. For example, the reference case timeline is 12 years for neovascular

Table 1. Conferred Value (Improvement in Quality of life), Cost, and Average Cost-utility Associated With Ophthalmic and Other Interventions (Discounted at 3% Annually)

Intervention	Value Gain*	Costs	$/QALY
Vitreoretinal interventions			
Laser, subfoveal choroidal neovascularization[18,22]	4.4%	$2012	$8179
Photodynamic therapy for occult subfoveal choroidal neovascular-neovascularization ≤4 disease areas in size[23]‡	5.8%	$16,348	$47,799
Pegaptanib therapy (intravitreal) for all types of subfoveal choroidal neovascularization[24]	5.9%	$25,589	$66,978
Laser for macular edema with branch retinal vein occlusion[1,25]	6.1%	$960	$21,333
Laser, classic, extrafoveal choroidal neovascularization[26]	8.1%	$1722	$28,700
Photodynamic therapy for classic subfoveal choroidal neovascularization[22,27]	8.1%	$16,348	$31,544
Ranibizumab therapy (intravitreal) for occult/minimally classic choroidal neovascularization[28]†	15%	$50,000	Pending
Nonvitreoretinal ophthalmic interventions			
Cataract surgery, initial eye[29]	20.8%	$2525	$2020
Cataract surgery, second eye[30]	12.7%	$2507	$2727
Statins HMG-CoA reductase inhibitors) for hyperlipidemia‡	3.9%	$36535	$70,700
β-adrenergic blocker for systemic arterial hypertension‡	8.3%	$8246	$3640

*Recalculated from utilities obtained on a cohort of 1000 patients with ocular diseases.
†Approximate ranges.
‡Data on file at the Center for Value-Based Medicine, Flourtown, PA; photodynamic therapy = photodynamic therapy with verteporfin (Visudyne).

macular degeneration therapies,[18,22] 12 years for cataract surgery,[28,29] 23 years for hypertension therapy, and 19 years for statin therapy. Each of the analyses herein is comparable because all adhere to ***Value-Based Medicine Principle II***. *Value-based medicine, cost-utility analyses should use standardized inputs (time tradeoff utilities, patient utility respondents, direct medical costs and the Medicare Fee Schedule and reference case perspective) and standardized outcomes (value gain in percent, QALY gain, and $/QALY) to allow the comparability of all analyses across all of medicine.*

Cataract surgery in the initial eye confers the greatest interventional value among the interventions shown, whereas intravitreal ranibizumab confers the greatest value for the treatment of neovascular macular degeneration. Of note is the fact that each of the interventions for the treatment of neovascular macular degeneration confers greater value than the treatment of hyperlipidemia with statins, the latter which is among the most common interventions in the medicine.

According to the data shown in the Table 1, intravitreal ranibizumab therapy is the intervention of choice for the treatment of occult and minimally classic subfoveal choroidal neovascularization. Despite the fact that its cost of treatment is the highest among comparators, ranibizumab therapy confers the greatest value of the neovascular macular degeneration therapies. It therefore fulfills ***Value-Based Medicine Principle III***. Every patient should want, *and should deserve, the intervention for their condition, which confers the greatest value.*

If ranibizumab is unavailable and the treatment of subfoveal occult choroidal neovascular lesions ≤4 disc areas is under consideration, both intravitreal pegaptanib therapy and photodynamic therapy statistically confer the same value. This comparison illustrates ***Value-Based Medicine Principle IV***. *The costs associated with an intervention become relevant only when the value conferred by comparator interventions is similar, in which instance the less expensive intervention becomes the preferred intervention.* In this case, photodynamic therapy is the preferred intervention as it is less costly than pegaptanib therapy.

Benefits of Value-based Medicine Analyses

The value-based medicine analysis methodology described herein has the following advantages over evidence-based data alone when assessing the value of an interventional therapy[19–21]:

1. It measures the *value* conferred by all interventions using the same outcome (QALY) and allows this value to be compared with that conferred by other interventions across all specialties, no matter how disparate.
2. The value conferred by an intervention includes all benefits in regard to improvement in length of life and/or quality of life.
3. All benefits and all adverse effects are included in calculating the value.
4. It takes into account the best *evidence-based medicine*, which is most reproducible and reliable from randomized clinical trials.
5. It incorporates *patient-based preferences* into the value component, a critical, basic principle of value-based medicine.[19,21]
6. It allows a comparison of *cost-utility* across all medical specialties using the common denominator of cost/QALY ($/QALY).
7. It highlights therapies of great value and also points out those that have negligible value, no value, or that may be harmful, so they can be improved or discarded.
8. It identifies interventions of equal value, thus allowing healthcare stakeholders to give preference to those, which are less costly.
9. It allows a comparison of patient value across international borders.

It is the intention of *Evidence-based Ophthalmology* to have a feature in each issue that highlights the value and/or cost-utility of an ocular intervention. It is our philosophy that knowledge and understanding of value are far better parameters than guesswork and anecdotes that guide us in certain of our therapies. We believe this is the path of the future, and that it is critical for physicians and other healthcare professionals to take the lead in establishing cost-utility (cost-effectiveness) analyses. Their knowledge and voice are critical for the best long-term interests of the most important people in the healthcare system—the patients.

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