

Determining the Cost-Effectiveness of Neovascular AMD Treatments

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BY MELISSA M. BROWN, MD, MN, MBA

STATEMENT OF NEED

Retina specialists now have several approved therapies at their disposal for the treatment of age-related macular degeneration, in addition to some off-label treatments as well. It is important that we have a mechanism that allows us to compare the relative benefits and outcomes among different treatments, based on clinical trial results, and factor in adverse events. When we have a method whereby this can be accomplished, we can then also factor in the costs of treatments and come up with a way of determining value.

TARGET AUDIENCE

This activity is designed for retinal specialists and other ophthalmologists.

LEARNING OBJECTIVES

Upon successful completion of this learning program, the participant should be able to:

- Identify the treatment options that retina physicians currently have in their armamentarium and the clinical trials that accompany these treatments.

- Cite the components of a value-based analysis.
- Cite the evidence that value-based decisions are based on
- Discuss how visual outcomes are correlated with utilities.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions. This test is available exclusively online, at www.CMEToday.net. Once you register and log in, you can take the test, get real-time results, and print out your certificate. Please e-mail ckoury@bmctoday.com or call 484-581-1821 if you have any questions or technical problems with the Web site.

Upon completing the activity and achieving a passing score of $\geq 70\%$ on the self-assessment test, participants can print out a CME credit letter awarding *AMA/PRA Category 1 Credit*.™ The estimated time to complete this activity is 1 hour.

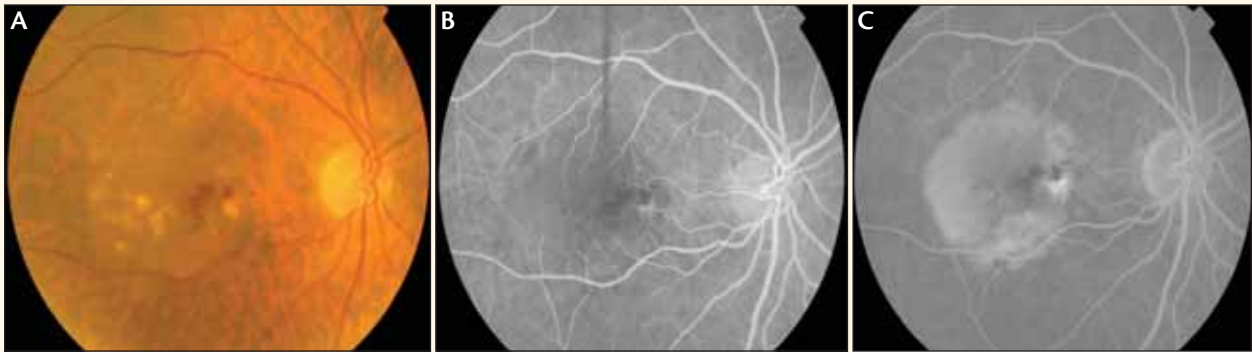


Figure 1. Neovascular age-related macular degeneration in a patients with 20/100 visual acuity.

ACCREDITATION

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FACULTY CREDENTIALS

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FACULTY DISCLOSURE DECLARATIONS

Dr. Brown disclosed that she is a consultant for Allergan, Cochrane Collaboration, EMMES, ERI, Eyetech, Genaera, Genentech, Merck, Novartis, Pfizer, and the National Institute on Aging.

INTRODUCTION

One of the most important questions facing retina specialists today is what treatment to use for patients with age-related macular degeneration (AMD)?¹ Now, when we see a patient with neovascular AMD, a visual acuity of 20/100, a decrease in vision after 1 week, and a fundus photo like this (Figure 1) our stomachs do not necessarily have to fall right to the floor.

After performing the appropriate tests, we consider the current treatment options available to us, including laser photocoagulation, photodynamic therapy (PDT), pegaptanib sodium (Macugen; OSI/Eyetech and Pfizer, New York, NY), and ranibizumab (Lucentis; Genentech, San Francisco), as well as the off-label choices of PDT plus intravitreal triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, New York, NY), and bevacizumab (Avastin; Genentech, San Francisco).

COMPARING BENEFITS ACROSS CLINICAL TRIALS

How do we compare benefits of the various inter-

TABLE 1. CLASSIC NEOVASCULAR AMD

Study	Start	Treatment	Control
TAP	20/100-2	20/160+1	20/320+1
VEGF IS	20/80	20/126-1	20/200+1

ventions based on the outcomes of varied clinical trials? Different trials have different baseline visual acuities, different treatment endpoints, and different control groups (Table 1). We also have to factor in the adverse effects associated with various treatments. Some of the adverse effects associated with AMD treatments include endophthalmitis, stroke, back pain, phototoxicity, and glaucoma. To compare treatments while taking these factors into consideration, I suggest that we use a value-based approach. We first look at value from the perspective of a change in the quality of life (QOL), and then a gain in the length of life (LOL). We measure these two factors in terms of quality-adjusted life years (QALYs), and we also take into account costs to determine cost-utility.

Interestingly, these data are unaffected by gender, ethnicity, age, education, income or nationality—which was a surprise to us.

Let me be very clear that when we compare treatments, we first look at value. When we talk about value, we are not talking about dollars, we are talking about increased QOL and LOL. In particular, with regard to AMD, we are talking about QOL.

START WITH THE EVIDENCE

This formula is not smoke and mirrors—it is good economic analyses. We start out with the best evidence-based clinical data that we have, so we strive to use randomized clinical trials. Our value analyses is only as good as the clinical data that we use, so we take our very best evidence-based data and we convert that data to value form. We factor in the effects of the benefits as well as the adverse events, and then we can compare the values among treatments. This allows us to compare the treatments that offer the same types of outcomes and the same kind of value—and then we can look at the actual costs.²

TABLE 2. NON-CLASSIC CNVM WITH AMD

Study	Start VA	Treatment	Control
VIP <4 DA	20/100-2	20/100+1	20/160
VEGF IS	20/80	20/126	20/200
MARINA	20/80-1	20/63+2	20/160-2

TABLE 3. OCULAR UTILITIES CORRELATE WITH BETTER EYE VISION

Better Eye	Utility
20/20 OU	1.00
20/40	0.80
20/100	0.67
20/400	0.54
NLP OU	0.26

We start with the evidence (Table 2), and then we can determine value with a utility analysis. Utility analysis is a method to quantify the QOL associated with all health states. Interestingly, these data are unaffected by gender, ethnicity, age, education, income or nationality—which was big a surprise to us.³

We can then correlate visual outcomes with these utilities. At our center, we use a large QOL Valuation Database that consists of time trade-off methodology and more than 40,000 utility value data points. The database enables us to cross-reference with many other QOL health classifications across most health fields (Karnofsky Performance Status Scale, ECOG/WHO scale, Likert Scale, ACR, AHA Classifications, Rankin Scale, etc.), in addition to visual acuity.

An intervention is considered very cost-effective if it is <\$50,000 per QALY, and not cost-effective if it is >\$100,000 per QALY.

We have learned that the ocular utilities correlate with the better seeing eye. Using this information, we can now look at, for instance, the typical patients with AMD (Table 3).⁴ We can take a partic-

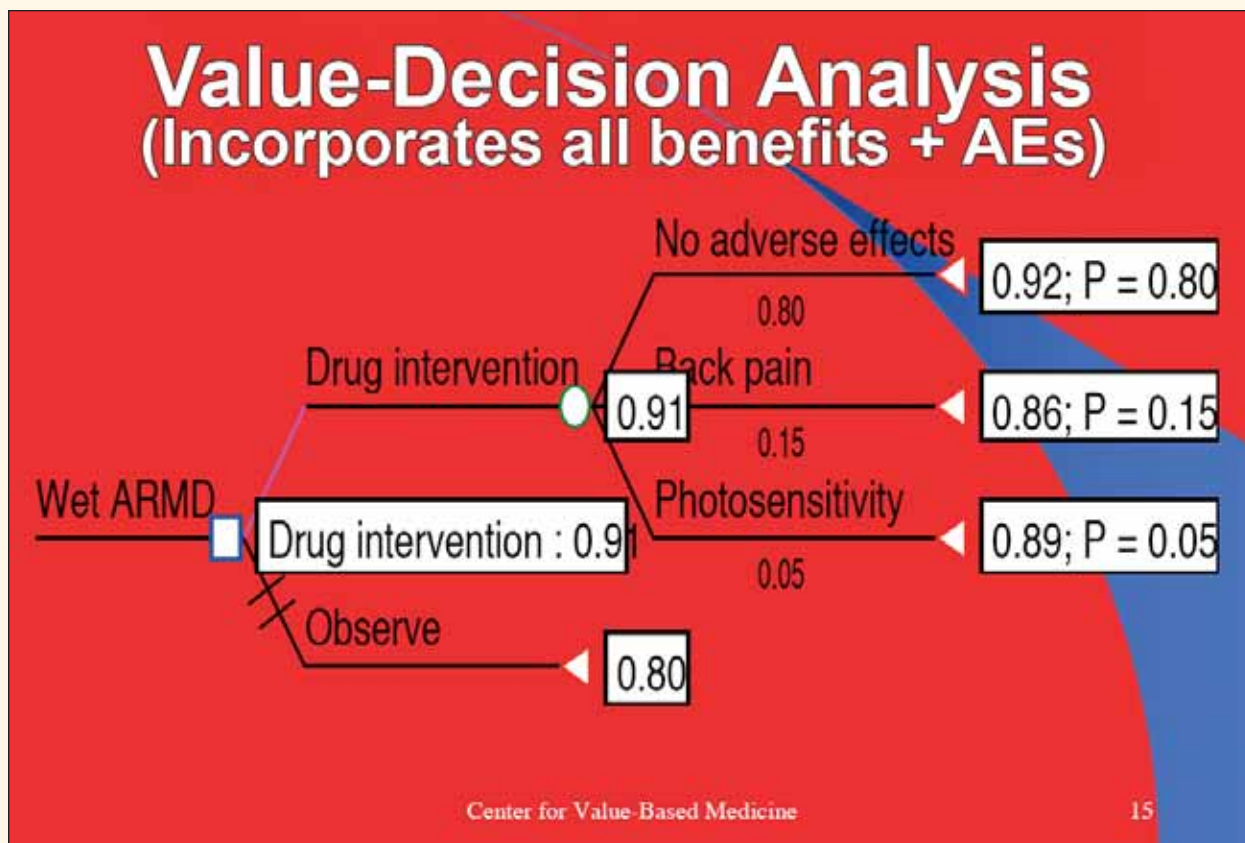


Figure 2. We can take a particular drug, look at the clinical trial data, and apply the basic utility to come out with what the improvement is with this drug, a value-decision analysis.

ular drug, (Figure 2) and look at the clinical trial data, and the prevalence of adverse effects are seen and how often there are no adverse effects, apply the basic utility or the effect from a patient standpoint on their QOL and determine what the improvement is with this drug.

EVALUATE QOL FOR MACULAR DISEASE

In patients with macular disease, we are evaluating the QOL, less so the LOL. We take that total improvement in utility value and multiply it by the duration of how long that person will have the benefit from treatment, in years (in these models we use 12 years as the reference case for AMD) and we get a total QALY gain.

We can also talk about conferred improvement in terms of percent value gained. For example, the use of statins is associated with a 3.8% value gain, according to our data from the Center for Value-

Ranibizumab is within the commonly accepted parameters for cost-effectiveness.

Based Medicine. We have calculated the value gain data in terms of treatments for classic subfoveal choroidal neovascularization (CNV) (Table 4), all according to Level 1 evidence from large clinical trials. The value gain associated with laser treatment, based on evidence from the Macular Photocoagulation Study (MPS),⁵ is 4.4%. The value gain for pegaptanib is 5.9%, based on data from VEGF Inhibition Study,⁶ the value gain associated with PDT, based on TAP (Treatment of Age-related Macular Degeneration with Photodynamic Therapy),⁷ is 8.1%, and for ranibizumab it is 17.0%,

HOW ARE NATIONAL COVERAGE DECISIONS MADE?

BY ROSS J BRECHNER, MD, MS (Stat), MPH

An introduction to Medicare's National Coverage Determination (NCD) is an important topic for ophthalmologists. My job at the Centers for Medicare and Medicaid Services (CMS) is to look at all of the literature out there and put together solid coverage.¹ I am the only ophthalmologist at CMS, and I am certainly pro-ophthalmology.

An NCD has a high likelihood of happening now, surrounding the new treatments available for managing age-related macular degeneration and the new data related to these new outcomes.

WHAT IS A NATIONAL COVERAGE DETERMINATION?

Medicare makes NCDs when a request is made regarding specific medical service and treatments for Medicare beneficiaries (Table 1). When a request for an NCD comes in, the medical services or treatments may or may not be currently covered by Medicare, and the medical services or treatments may or may not be approved by the US Food and Drug Administration (FDA). CMS does not always follow the FDA, as the data it uses is not always as rigorous as what we would like.

Who can request an NCD? Any person satisfying the requirements as listed in the *Federal Register*² and amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003. So, the request can come from any ophthalmologist externally—and occasionally, if we see a lot of things happening in a field and there hasn't been one and we think it could solve a lot of issues—a request will come from inside CMS.

What prompts NCDs? An external request is most commonly generated when there is a current national noncoverage policy or there is substantial variation in Local Coverage Determination (LCD) policy that is being questioned. Internally generated NCDs happen when new technology shows a potential to have a major clinical or economic impact on the program, or there are concerns about inappropriate use or nonuse.

WHAT ARE THE STEPS?

The major steps to an NCD include a benefit category determination (BCD), a coverage analysis, and the effective date and implementation date (Figure 1). In performing a coverage analysis, we are very careful to look at all of the available literature, doing complete searches—

TABLE 1. NATIONAL COVERAGE DECISIONS

- What is an NCD?
- Who can Request an NCD?
- What is required?
- What are the Timelines?
- Effective Date versus Implementation
- Reconsideration
- Local Coverage Decisions versus National Coverage Decisions

in ophthalmology, I do this part. Once the CMS publishes a final decision, it becomes effective that moment.

The authority for the BCD comes from the Social Security Act or Title XVIII. An example of a BCD that makes sense to us as ophthalmologists is *physician service*.

EVIDENCE-BASED MEDICINE APPROACH

We take an evidence-based medicine approach to making coverage determinations, in terms of that which is "reasonable and necessary." In the statute, is a medical treatment or service reasonable or necessary, there is no strict definition of reasonable or necessary. This can be both fortunate and unfortunate.

The evidence-based medicine approach with regard to reasonable and necessary include the following components:

- Standard evidence-based medicine. Takes into account study design (minimize bias), study execution, appropriateness of outcomes studied, appropriate analysis, and generalizability (beneficiaries, setting).
- Technology must produce clinical benefit. Diagnostic accuracy data necessary but not sufficient, and improvement in health outcome.
- Supported by strong research evidence.
- Assessment question. Is there adequate evidence to conclude that the service improves net health outcomes of Medicare beneficiaries?

When we look at the evidence we have, we apply the standard gauges of quality to the evidence. We investigate and grade all studies, and then we put them all together. The evidence includes:

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TABLE 4. CLASSIC SUBFOVEAL CNV

Level 1 Evidence, large clinical trials	
Therapy	Value Gain
Laser (MPS)	4.4%
Macugen (VEGF IS)	5.9%
PDT (TAP)	8.1%
Lucentis (ANCHOR)	17.0%

TABLE 5. OCCULT SUBFOVEAL CNV

Level 1 Evidence except *	
Therapy	Value Gain
Macugen (≤ 12 DA) VEGF IS	5.9%
PDT (≤ 4 DA) TAP	6.3%
Lucentis (≤ 12 DA) MARINA	15.7%
PDT/IVK (all) European Study 06	11.2%*

*level 4

based on the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) 1-year data.⁸

What about for occult subfoveal CNV (Table 5)? For pegaptanib the value gain is 5.9%, for PDT it is 6.3%, for ranibizumab it is 15.7%, and for PDT plus intravitreal triamcinolone, it is 11.2%. Please note this last value gain is based on Level 4 evidence. The discounted 12-year costs of treatment based on their use in clinical trials are \$15,277 for PDT; \$24,313 for pegaptanib; and \$52,652 for ranibizumab.⁹ In the United States, we talk about cost utility in terms of cost divided by QALY. An intervention is considered very cost-effective if it is <\$50,000 per QALY and not cost-effective if it is >\$100,000 per QALY.

Clinically gathered data to date show promising QOL improvements with bevacizumab and PDT plus triamcinolone. This data is very early.

COST-UTILITY FOR TREATMENTS

If we look at the discounted cost-utility, in terms of US dollars per QALY, we see that pegaptanib, in all types of AMD, is \$66,978; for PDT, occult <4 disc areas (DA), \$33,078; and for ranibizumab, nonclassic disease, it is \$50,691 per QALY. For the sake of comparison, the cost-utility of statins is \$69,300 per QALY and hypertension is \$11,500, based on Center for Value-Based Medicine data.

Value-based assessments compare the value of all AMD interventions and allow us to incorporate the

benefits, adverse effects and the costs into our analysis. We can maximize patient quality of care by knowing what treatment is the best to use; this is an excellent scientific basis for treatment decisions.

For AMD treatment, the clinical trial evidence today indicate ranibizumab to be a clear leader in value, improvement in quality of life assessed by visual outcome utility, and those of adverse effects. Treatment with ranibizumab is, at this point, within the that commonly accepted parameters for cost-effectiveness. We are currently using 12 injections per year in our analyses based on current evidence, however, it is more than likely that over time that number will go down.

Of course another important question is what about bevacizumab? Clinically gathered data to date show promising QOL improvements not only with bevacizumab, but with PDT plus intravitreal triamcinolone. This data is, however, very early. ■

1. Brown M. Cost-effectiveness of AMD Treatment. Presented at Retina 2006: Emerging New Concepts. Nov. 10-11, 2007. Las Vegas.

2. Brown M, Brown G, Sharma S. Evidence-based to value-based medicine. AMA Press. 2005.

3. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol*. 2000;118:47-51

4. Brown MM, Brown GC, Sharma S, et al. Health care economic analyses and value-based medicine. *Surv Ophthalmol*. 2003; 48:204-222.

5. Macular Photocoagulation Study Group. Visual outcome after laser photocoagulation for subfoveal neovascularization secondary to age-related macular degeneration. The influence of initial lesion size and initial visual acuity. *Arch Ophthalmol*. 1994;112:480-488.

6. Gragoudas ES, Adamis AP, Cunningham ET, et al for the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for Neovascular Age-Related Macular Degeneration. *N Engl J Med*. 2004;351:2805-2816.

7. Brown GC, Brown MM, Campanella J, Beauchamp GR. 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.e1-679.e10.

8. Brown DM, Kaiser PK, Michels M, et al for the ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432-1244.

9. Brown G. *Ophthalmology*: in press.

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- prospective vs. retrospective studies,
- randomized vs. nonrandomized,
- concurrent vs. hx comparisons,
- large vs. small studies,
- blinded vs. unblinded observers, and
- functional vs. technical outcomes.

TIMELINE

The timeline for coverage decisions, before the Medicare Modernization Act, used to be whenever Medicare decided to make a decision. Now, it takes 6 months for the final decisions. During the first 30 days, the decision is posted and we gather comments. We spend the next 5 months working up a decision, taking 3 months to put it together, and then after 2 months of beauracracy, we can post it. We have another 30-day comment period 2 months later, after the decision is effective. Decisions can be made effective sooner—this is a 9-month process.

looked at in its entirety. Also at the time of a final decision, people may feel that there has been a misinterpretation of the literature and they present that to CMS for us to reconsider as well.

LOCAL COVERAGE DECISIONS

Most coverage decisions are local (LCDs), and national decisions are few in number. The local coverage decisions allow for gradual diffusion and regional variation in policy, with responsiveness to the local care community. Sometimes the regional variations are beneficial, sometimes they are not. A recent example of an LCD that became an NCD is bariatric surgery for weight loss. We had different coverage arrangements going on all over the country and it was a big problem. So we wrote a powerful NCD decision and it took care of all of the problems for the patients and physicians. There are some people who are not happy with it, but overall we have gotten good feedback.

If you are thinking about a NCD, you are welcome to call me. We have a committee that is available to discuss

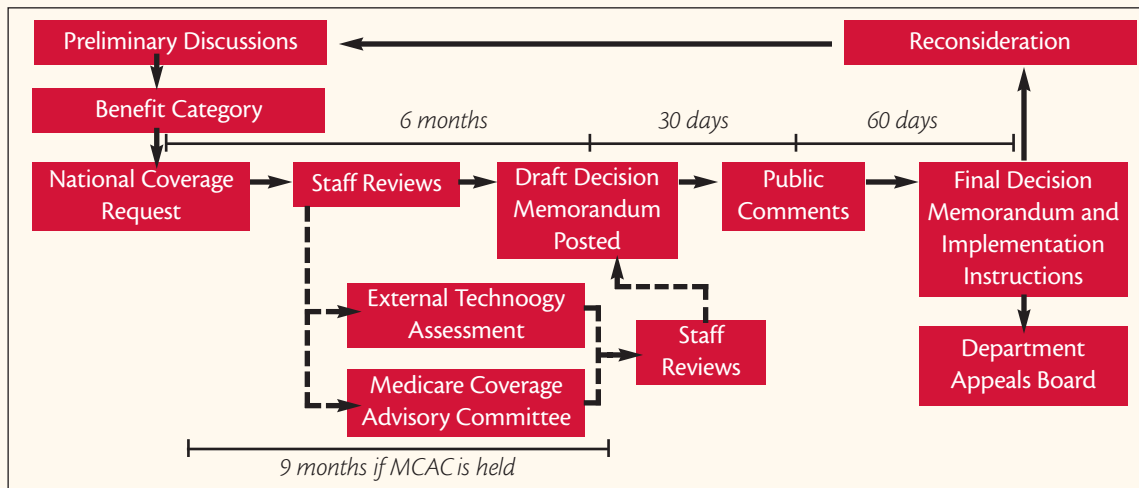


Figure 1. Medicare national coverage process.

This period can be extended if we have a Medicare Coverage Advisory Committee meeting. That is simply if the profession, outside agencies, and the public want to get together and voice opinions and they can also present their own data.

After a decision becomes effective, sometimes people are unhappy with it or new data comes up. For example, there could be additional medical and scientific information, results from new clinical trials, new scientific or medical publications, or studies supporting the reconsideration. The decision is once again opened up and

these decisions. We can help you with the request, tell you what you need, and even what is missing when you send in a request. The key to a positive NCD lies in bringing together solid data. You must be able to articulate with sufficient good quality evidence how Medicare approval of this technology will improve the health status of Medicare beneficiaries.

1. Brechner RJ. National coverage decisions. Presented at Retina 2006: Emerging New Concepts, held in conjunction with the American Academy of Ophthalmology annual meeting. Nov. 10-11, 2006. Las Vegas.
 2. Federal Register Vol. 64, No. 80/Tuesday, April 27, 1999 and Federal Register/Vol. 68, No. 187/Friday, September 26, 2003.

CME QUESTIONS

To answer these questions online and receive real-time results, you must visit www.CMEToday.net.
 CME credit is now available EXCLUSIVELY via www.CMEToday.net.
 E-mail ckoury@bmctoday.com if you have any problems accessing the site or taking the test online.

1. Which of the following is not an adverse effect associated with AMD treatment, discussed in the activity?
 - a. endophthalmitis
 - b. back pain
 - c. headaches
 - d. glaucoma
2. The best-evidence based data comes from randomized clinical trials.
 - a. true
 - b. false
3. Which of the following statements is true with regard to the QOL Valuation Database discussed?
 - a. it uses time trade-off methodology
 - b. it allows the use of more than 40,000 utility value data points.
 - c. it can cross-reference with other QOL health classifications
 - d. all of the above
4. Utility analyses are greatly affected by things like gender, ethnicity, and education level.
 - a. true
 - b. false
5. Quality of life (QOL) as a measurement is more important than length of life (LOL) when it comes to a discussion of AMD patients.
 - a. true
 - b. false
6. Which of the following interventions are associated with the highest percentage value gain, according to the activity?
 - a. pegaptanib
 - b. PDT
 - c. ranibizumab
 - d. PDT plus intravitreal triamcinolone
6. Which of the following interventions is associated with the highest 12-year costs, based on their usage in clinical trials?
 - a. pegaptanib
 - b. PDT
 - c. ranibizumab
6. Which of the following interventions is associated with the highest cost in terms of discounted cost-utility, US dollars per QALY.
 - a. pegaptanib
 - b. PDT
 - c. ranibizumab
9. According to the activity, if an intervention is associated with a cost utility <\$50,000 per QALY it is not cost-effective.
 - a. true
 - b. false
10. With regard to the sidebar on Medicare Coverage Decisions, is it true that evidence-based medicine principles apply to the CMS' decision-making process?
 - a. yes
 - b. no