Trends-in-Medicine

December 2005
by D. Woods

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

MEDICARE COVERAGE ADVISORY COMMITTEE (MCAC) MEETING ON AGE-RELATED MACULAR DEGENERATION (AMD)

Baltimore, MD
November 29, 2005

The MCAC meeting seemed to be focused on how to design better trials of treatments for AMD, the leading cause of blindness in people 65 years old or older, with an estimated 165,000 new cases each year. However, it was obvious early on that panel members were confused about many things, including definitions, experimental treatments, and even the questions posed to the panel.

The panel was asked to vote on which measures currently used are best for primary/intermediate endpoints, and the discussion focused on definitions of visual acuity and function, rather than on individual therapies. MCAC chair Dr. Alan Garber commented, "The voting questions are about established technologies for the treatment of AMD…The issues are about the measures and evidence both in support of measures that have been used and in support of established technologies for the treatment of AMD."

The panel finally agreed that:

- Visual acuity and VFQ-25 are valid visual outcomes, and both of those plus Amsler grid, glare recovery, contrast sensitivity, and visual fields are valid health outcomes.
- Short-term studies should be at least three months long, and longer-term studies should be at least one year.
- There is sufficient evidence to assess the benefits of laser photocoagulation and intravitreal steroid injections, but the panel was divided on the value of oral vitamins and antioxidants and experimental therapies such as Genentech's Lucentis (ranibizumab) and Avastin (bevacizumab) and Alcon's Retaane (anecortave).
- There are many areas where there are large gaps in the data for AMD therapies.
- Randomized clinical trials (RCTs) are critical.

BACKGROUND

The FDA has approved several therapies to treat AMD:

- Photodynamic therapy (PDT) with QLT's Visudyne (verteporfin). This is approved for predominantly classic AMD-related subfoveal choroidal neovascularization (CNV). Use in occult AMD with no classic or minimally classic CNV is an off-label use.
- Anti-angiogenesis therapy: Eyetech's Macugen (pegaptanib).
- Intravitreal steroids: Bristol-Myers Squibb's Kenalog (triamcinolone acetonide).

- Laser photocoagulation, though this can cause thermal damage to the retina.
- Vitamins and other treatments.

Medicare covers PDT, but there is no national coverage for the other therapies; rather, coverage for those is at the contractor's discretion. Several newer treatments are not yet approved and, again, the coverage is up to each Medicare contractor. Investigational agents mentioned at the meeting included:

- Genentech's Lucentis (ranibizumab)
- Genentech's Avastin (bevacizumab)
- Sirna Therapeutics' siRNA
- GenVec's adenoviral PEDF (AdPEDF)
- Oxigene's combrestatin
- Genaera's squalamine
- Alcon's Retaane (anecortave)

CMS Perspective

A CMS official said his agency wants to know a lot more about how these AMD treatments are affecting patients, "We need to know how they are being measured (in terms of effect), and we need to see if we can standardize these measurements…Medicare will be approached to pay for these things, and we need to be careful."

He said a review of the literature pertaining to AMD treatment from 1976-2005 found 83 pages relevant to the agency's objectives, "Of those 83 there are a significant number that talked about a new measurement for macular degeneration but didn't have a lot of data to support the measurement." For instance, he explained:

- **Visual function.** "In terms of visual function, I found a paucity of strict validation data, definition, and standardization on what is visual function. We have an intuitive thing about it in ophthalmology, but when I read the literature, I didn't find a lot defining standardizing of visual function."
- **CNV lesions.** He said he didn't find any studies that validated using size, type, and number of CNV lesions as a measure of need for treatment or for tracking progress.
- **Fundus photos.** "Any grading is complex, very expensive, and time consuming."
- **Automated visual field testing.** He said that this testing is widely used, but in the literature there was very little information about whether it is a valid way to judge AMD. "There is a paucity of validity data on use in AMD…OCT (ocular coherence tomography) might be useful in monitoring CNV before and after laser photocoagulation, but the data strength is weak."
- **Other.** He said other measures such as reading speed, scanning laser ophthalmoscope (SLO), face recognition and expression, macular mapping test scores, macular computerized psychophysical tests (MCPTs), and glare recovery (photostress) also are not validated.

The CMS official was critical of past AMD trials: "I have some observations. They are harsh, but I keep coming back to them. In almost all the trials, there was very little agreement in all the different studies over what the cutoff points were. People used visual acuity a lot, but what was the cutoff point? Some patients had improvement in 15 letters, some had status quo, some had eight letters of decrease, some had less than 15 letters, some had less than 30 letters…The conditions of measurement were very often not mentioned or detailed…We also found that the inclusion and exclusion criteria varied widely in trials re (with respect to) treatment and measurement of AMD. There didn't appear to be any standardization or consistency across trials, even when they were measuring the same outcomes with a similar treatment effect."

He recommended:

- Further evaluation of AMD treatments as new data are accumulated.
- Standardization of inclusion and exclusion criteria for RCTs on AMD, where possible.
- Standardization of cutoff points and methods of measuring outcomes in AMD.
- Clinical trials should be designed with attention to CMS evidentiary needs.
- Studies to fill in the gaps in knowledge need to be conducted, including combination studies of new drugs coming out and with those already proven to have benefit in AMD. Combinations may be more effective than any single drug treatment alone. Panel members agreed that combination therapy is increasing in use and problems associated with it need to be addressed.

Expert Witness Presentations

Two representatives from the Duke Center for Clinical Health Policy Research discussed quality of life issues. One said, "The reality is that AMD really impacts these patients and we aren't able to measure it objectively." They agreed that NEI-VFQ and VF-14 "have appropriate psychometric properties for use in AMD and other diseases affecting central vision."

The key issues for the Duke team were:

- The status of current methods of measuring quality of life in AMD patients.
- The factors that may influence responses using these methods.
- How these methods are related to traditional outcome measures (i.e., visual acuity, contrast, and severity).

MCAC panelist Dr. Ron Klein of the University of Wisconsin-Madison Medical School gave a presentation on photography protocols. He concluded, "Grading fundus photographs using standard protocols offers an objective, reliable approach to detecting early and late AMD over time."

Dr. George Williams, representing the American Academy of Ophthalmology, and Dr. Neil Bressler of Johns Hopkins University Hospital discussed visual acuity on an eye chart compared to visual function. Dr. Bressler said, "It isn't an exact 1:1 correlation, and yet the primary outcome in CNV clinical trials has been the proportion of people who avoid a loss of ≥15 letters from baseline to one year. We believe it is a clinically relevant difference." He discussed Lucentis which is expected to be approved by the FDA next year, and its impact on quality of life: "Ranibizumab compared with sham was highly effective for avoiding ≥15 letter visual acuity loss and increased the chance of improved visual acuity by ≥15 letters in AMD subjects…Assuming FDA approval, ranibizumab outcomes are rapid."

A Genentech official said that his company plans to file a BLA in December 2005 and is requesting priority review status for Lucentis. He said that Lucentis "demonstrates improvement in mean visual acuity across all subtypes and superiority to PDT in a head-to-head trial…Ranibizumab has demonstrated the ability to significantly improve visual function and vision-specific quality of life outcomes in AMD patients."

A Novartis speaker described a proposed enhanced InSight CNV registry, a disease-based registry aimed at evaluating long-term outcomes with all AMD treatment options over at least two years. He said that the enhanced registry will be disease focused, rather than product specific, and will include patients on all treatments, including patients who may not be candidates for randomized trials.

An Eyetech speaker described Macugen therapy for wet AMD, saying that safety data for the drug "have been excellent. The most severe side effects are related to the injection procedure itself and not the drug." He called Macugen the "Swiss army knife of vaso-active factors."

Dr. Peter Kaiser, speaking for QLT, made the case for combination therapy. He said, "We need to do better than 95% moderate vision loss, so some of the other outcomes could include mean improvement in vision, significant visual gain (i.e., ≥3 lines), and we want to see anatomic changes, for example, a decrease in retinal thickness."

Dr. Jonathan Davit of the Potomac Institute for Policy Studies and Wilmer Ophthalmological Institute described the latest advances in combining intravitreal steroids (intravitreal triamcinolone or IVTA) with PDT to treat AMD. He said, "The conventional wisdom is that steroids 'dry up' the lesion. Anecdotally, however, glaucoma and cataract specialists are reporting an uptick of patients presenting…As we race for the cure, we really have to keep our eye on safety as well." He warned of the risks of PDT plus steroids, saying, "At the very least, a confirmation study ought to be undertaken with a real eye on safety before there is increased proliferation of intravitreal steroid injections."

A co-inventor of OCT, Dr. Carmen Puliafito of Bascom Palmer Eye Institute said, "OCT is rapid, noninvasive, pain-free, and risk free. OCT, when used for monitoring AMD patients, identifies fluid in the macula, shows response to therapy, shows when treatment effect is wearing off, and decreases the overall number of treatments by allowing the physician to treat only when needed…The greatest value of OCT is in demonstrating a treatment effect and then following patients and withholding therapy until needed."

Dr. Timothy Stout of Prevent Blindness America said that he did a phone survey of 21 physicians on the West Coast to get opinions on various methods for evaluating AMD. He said that they were:

- **Very confident** about visual acuity, VFQ, extent of CNV, drusen extent/progression, and fluorescein angiography.
- **Somewhat confident** about the Amsler grid and contrast measurements.
- **Minimally confident** about glare recovery.

Dr. Jason Slakter, representing Vitreous-Retina-Macula Consultants of New York, told the panel, "Monotherapy for CNV has limited potential for improved visual acuity. The rationale exists for the use of combinations of various pharmacological agents and other therapies such as PDT. Efficacy results suggest improved visual acuity outcomes and a reduction in the need for treatment at follow-up."

Question and Answer Session

A doctor in the audience asked the panel to consider safety above efficacy, warning that the use of intravenous Avastin off-label has an undesirable and suspect safety profile. He said, "I'm concerned with the use of anti-angiogenic agents that haven't been studied enough."

The panel's consumer advocate asked the CMS presenter why the session focused on wet AMD disease when 90% of AMD patients have the dry kind. He said, "We've actually heard nothing about the dry type…Do you proceed through dry to get to wet?" The CMS official answered, "Yes, you do go through dry to get to wet." A panel member added, "I think we use the terms dry and wet more as a way of referring to patients, but in terms of affecting visual acuity itself, it's advanced stages of macular degeneration that we should be concentrating on."

A panel member asked the CMS official about various measures of visual outcome, and the CMS official responded, "The direct ones include visual acuity, glare recovery, and contrast sensitivity…Visual acuity has the most oomph."

Several panel members questioned the quality of life data for AMD drugs. One panel member said, "If you try to validate a tool and use visual acuity, and then you present a study like the Macugen study, where you show an impact on a primary endpoint, say visual acuity, and then you say you feel more confident about the data, aren't you going kind of in a circle? Is there not a hole in the logic?...My question is the validation of these quality of life studies because part of our decision is going to be what types of endpoints are important in studies coming up." Another expert said, "The quality of life instruments are complementary tools. It's easy to say they are a shortcut, but they really are a complementary tool to visual acuity that may be more specific to patient needs and to real life situations. There is some circularity, but you want some assurance that there is a correlation. But, again, in the end, you're looking at an individual patient, and that's why quality of life measures are complementary. You're asking the patient if he is impacted by the disease." Another expert added, "Really the starting point here is that we're asking the question that patients care about, which is, 'What do you do with your vision that you care about but that you can't do now?'"

Asked about VF-14, one of the Duke physicians said, "I'm one of the developers of VF-14, and it would be a mistake to think that either of these instruments was developed to measure visual acuity. These instruments correlate rather imperfectly with visual acuity. Patients come in telling you that they see terribly, yet when you measure them on an eye chart, you refract them down to 20/30. So when these instruments were developed, large groups of patients were taken into a room, asked about their lives and what parts of vision were most important to them." A panel member said, "Patients' perceptions play a large role in assessment. That said, I'm interested in the instruments because that will play a large role in this whole process. First, how do you determine which patients will receive a particular therapy? Which instrument are you going to use?...It seems the instruments may vary with the kind of effect that you're looking for. Some may take a long time to occur, and some may happen very quickly. Then, do you use functional or anatomic tests to determine the outcome? And, finally, how do you determine whether additional treatment is needed? Do you wait to see if there is a decline over six months?"

A Duke physician said, "I think the quality of life measures are pretty good, with the acknowledgement that there is an overlay. Cranky people are cranky, and they're not going to be happy, whatever you do."

Although OCT wasn't included in many of the studies referred to at the meeting, a speaker said that it is very new and will be included in future trials and used as a determinate factor. The panel chair said, "The ideal study would use OCT to monitor in one group and not the other, and you'd use critical criteria to decide when the next treatment would be. Then you'd want to know if the OCT group did better by some well-validated measure. Presumably this doesn't exist, but there might be other studies to get there." A Duke physician said, "It might be better in a mass trial, but you will have patients where the OCT looks better and you're not seeing loss of vision, but at the same time you'd have people where the OCT looks worse, yet they're seeing better, for some reason. An OCT that looks good doesn't always correlate with function."

Continuing the discussion about measurement, the CMS representative said, "Maybe we need a conference on finding visual function. That might be naïve, but we need some place to start. The base is getting lost because there's too much confusion about all these different measures. There are a lot of measures, but not all of them have been validated, and everything takes money and time."

PANEL QUESTIONS FOR PRESENTERS

Combination therapy. The panel chair asked, "What is the evidence that modifying therapy based on results with any combination improves outcomes compared to just monitoring therapy with indications like vision loss?" A Johns Hopkins physician said, "There is no evidence so far. We're too early in the process. We learned that some of these treatments work just a few months ago. The trials were designed to say: Does the therapy…give me a better outcome compared to my control? The answer is yes. Now we want to go beyond that. We need designed studies to help us to confidently predict (when to stop therapy)…We don't have that information yet."

Outcome measures. A non-voting panel member asked, "Do I take it that there's no risk from these outcome measures? Patient risk hasn't been discussed today. Are adverse events not an issue?" A CMS official said, "I didn't see a lot of information in most of the material…With photocoagulation, does something else happen aside from photocoagulation of the retina? I didn't get the impression that there was a safety issue with any of these things, including taking antioxidants. I wasn't impressed with any issues."

Safety. Asked about safety concerns with steroids, a CMS official said, "The only steroid that had a blood-pressure elevating effect was anecortave…I didn't find a lot of super good data on that problem. But we know that putting steroids in the eye carries an extra risk." The panel chair said, "We are not concerned today whether steroids cause glaucoma…You can imagine side effects not picked up by angiography...Are the measures we're using capable of detecting serious side effects? Are they adequately measured in the same measures we're using re (with respect to) effectiveness in AMD." Another panel member said, "We were asked to comment on the adequacy of the existing data for treatments. It seemed that if (steroids) are part of the combination therapy, we should know more about it." An expert warned the panel, "When you face the rapid proliferation of off-label use of medications in the absence of FDA-monitored safety studies, there can be huge safety signals out there that are going unrecognized."

Population studies. A panel member asked, "Is there anyone here who has tried to put this all together for a population base? For example, anyone from the VA?" A Duke expert said, "I work for the VA, and this has been a very difficult topic. Part of the issue is that you have different entities and different interests. There is no answer."

Biology. A non-voting panel member asked, "Do we really understand the biology of this disease? The answer is no, we don't. My question is, how will practicing ophthalmologists gauge when the next round of therapy will be done? Should CMS request or require that the next round be based more on functional assessment or an anatomical assessment?" Dr. Bressler responded, "We're assessing all this now. We're analyzing the trials. I'm assuming it will be both anatomic and functional. I assume the physician will assess physical measurements, looking at OTC and angiography as well because they give different information."

OCT. An official from the National Retina Institute said, "There are three studies I've seen comparing OCT to the previous gold standard regarding the thickening of the retina...It seems clear that OCT is in fact more sensitive in clinical evaluation...We still don't have studies that provide us with the next important piece of evidence, and that is how well OCT correlates to clinical outcomes. But there is an increase in consensus that OCT is a very valuable imaging technology …Personally, if I had my choice for only one test, I'd opt for OCT. So, increasingly OCT is becoming essential for managing these patients." An official from the American Academy of Ophthalmology said, "It will be five or 10 years before we have another technology."

Quality of life. The CMS non-voting panel member said, "I have another quality of life question…Relatively few people receive what is in the protocol. That has implications for the companies and for this body. In order to try to address that issue, it's important when we see impressive percentage numbers, to keep in mind that a great number of people treated or non-treated will do okay. And, therefore, we are going to treat a number of people – 2, 3, 6 – to help one. So, what is most valuable, if it exists, is to pare down these measurements to see if we can collapse that number needed to treat, and we can predict better which patients will benefit. I do not think that those necessarily exist, but as we do these studies, it is a good idea to ask for that information – the number needed to treat. Secondly, when we are presenting these studies to our patients and our examiners, we have to be able to explain to them that you may not see a benefit from this treatment, but you should go through the course. That has more to do with quality of life – a categorical variable. What am I going to get out of it? The patients are going to be asked to expend sometimes money, sometimes time, and sometimes pain, and they need to know the quality of life." Dr. Bressler added, "It will influence your recommendation to the patient so that they understand what their expectations are...I think the number needed to treat is important."

Trial entry criteria. A patient advocate on the panel asked, "Why don't we have standardized inclusion and exclusion criteria, and why don't we have agreements?...Why don't we have standardized outcomes? It's very peculiar. We're often asked to compare apples and oranges. Why is it that the outcomes are always different in these studies? Blame it on the manufacturers, blame it on ego." A speaker said that there is some standardization from the FDA: "It used to be with laser coagulation that you lost a lot of vision – six lines or more. As we got more sophisticated, we got a three-line loss. And there's an argument in the community whether two or three lines is a clinically relevant outcome...Now it looks as if the three-line loss may be a primary outcome in future trials. What we're trying to define right now is what should be a primary outcome."

PANEL DISCUSSION AND VOTES

The committee spent the afternoon wrestling with the unclear and messy questions on AMD treatment. Panel members often didn't understand the questions, language had to be explained, votes had to be retaken, and motions were repeatedly made to revise the questions. While discussing the question about which other currently available outcome/intermediate measures should be considered, one panel member said, "I think this question might be moved to Question 5, which is, 'Where are the gaps in our knowledge?'" This remark seemed to sum up the panel's uncertainty and general lack of knowledge.

Although discussion was allowed for each question, the votes were unorganized and rushed. At one point, a panel member asked, "Is our goal to make recommendations to the world? Or is this the last time we're going to address the issue?"

Question #1a

Each of the following has been reported as measures of disease activity or outcome in AMD. Some are direct measures of visual outcome, unambiguously representing a patient's well-being. Others are intermediate endpoints, meaning that they are intended to predict visual outcomes, even if they are not outcomes themselves. For each of the measures below, how confident are you that it is a valid endpoint?

The panel voted visual acuity, VFQ-25, Amsler grid, glare recovery, visual fields, and contrast sensitivity are all valid final AMD health outcomes. Visual acuity and VFQ-25 were voted as definitely valid and the remaining measures were voted "unsure."

The panel first decided to vote whether each point would be a valid final or intermediate endpoint, or neither. After the vote, during which visual fields was voted as an intermediate endpoint, discussion ensued about its connection with visual acuity. One panel member said, "If you put visual acuity in as

a final endpoint, why not put in the others, such as the Amsler grid, glare recovery, and visual fields? All these strike me as being in the same category." The panel asked an FDA representative to define several terms.

Panel Opinion of Possible Outcome Measures

Endpoint	Valid health outcome	Valid visual outcome
Visual acuity	Yes	Yes
VFQ-25	Yes	Yes
Extent of CNV	---	Unsure
Amsler grid	Yes	Unsure
Drusen extent/progression intermediate	---	Unsure
Geographic atrophy	---	Unsure
Glare recovery	Yes	Unsure
Contrast sensitivity	Yes	Unsure
Fluorescein angiography	---	Unsure
Visual fields	Yes	Unsure
Ocular coherence tomography	---	Unsure

Question #1b

Which other currently available intermediate measures should be considered? Revised to: Which other currently available outcome/intermediate measures discussed at this meeting should be considered by CMS?

No measures were nominated, and the panel voted "none."

One panelist mentioned that reading speed had been discussed earlier in the day, and the panel's non-voting CMS member said it could be incorporated. Another member mentioned multi-focal ERG, microperimetry, and autofluorescence as three promising measures. A third panel member said, "It wasn't directly relevant, but where do we talk about negatives? If I were CMS, I'd want to monitor negatives as well as the positives." The panel chair responded, "Those absolutely need to be included, but shouldn't be discussed today. That's really not on the agenda for today but absolutely should be included one way or another." Another physician on the panel said that he had read something about cytokines, asking, "Is that something easily measurable or measured?"

The panel chair said, "This is actually a voting question… We're not asking you to vote on whether something is valid, but whether something should be considered." The physician with three suggestions read them again, and when the first measure came to a vote, he was the only one voting. After a short silence, a panel member said, "We just don't know. We have no idea." Another said, "We just need more information." A CMS official said, "The focus should be on things we've discussed today. I think c-reactive protein (CRP) was discussed, and I think high-speed angiography was, too."

The CMS non-voting member suggested that the panel could discuss and vote on what criteria could be used for future technologies, but was met with resistance. One panel member groaned, "That is just too huge. It would take the whole day." Another CMS official said, "Say Company A shows up in our office and says, 'We have a new gizmo or drug that we think will be great in treating AMD. We want you to tell us the outcome needed for that trial for you to say you'll pay for it.' That's the scenario. Are there any outcomes other than (those listed to the left) that you want CMS to tell Company A?"

A panel member asked the FDA representative if there are any other tests for AMD in addition to those listed in the chart to the left, and the answer was no. He said, "Nothing other than what you already discussed, unless they were looking for a specific claim or target, or asking for an additional function. We have a set of parameters that we accept or don't accept. We separate those two things."

Question #1c

What are the appropriate chronological criteria for short-term and long-term outcomes for AMD treatments?

The panel voted for a three-month minimum for the short-term studies, and a one-year minimum for long-term studies.

The panel discussed the definitions of short term and long term, and there was some confusion about whether the question was aimed at trial design, not coverage decisions. A CMS official said that the question was a trial design question, and the panel chair said, "That intent was not clear to me." The FDA representative, asked for input, said, "For AMD, we wanted at least one-year data, recognizing that these patients were older, and one year was a reasonable portion of the rest of their lives on which to base efficacy. So, it was minimum one-year data, and we wanted that to be in at least two-year trials. We have encouraged follow-up after that." The CMS official said, "In looking at the literature, most people were between (age) 75 and 80 in one trial. Most of the other studies involving CNV involved one- to two-year follow-ups. But the new treatments looked at shorter periods of time. Some of the data shows some of these effects last for a period of time until another injection. We talked about when to re-treat. So it's hard for us to tell. Most of us are in trials for a couple of years, and it wouldn't be unreasonable to follow that…The short-term outcome: Is that the first point in time at which you will do a measurement and find a clinically significant change – or not?"

Question #2a

At present, usual and approved care for AMD includes photodynamic therapy with verteporfin, laser photocoagulation, intravitreal injection of pegaptanib, and vitamins. How confident are you that there is sufficient evidence to

assess the health benefit of the modalities compared to watchful waiting only?

The panel voted *highly confident* for laser photocoagulation, intravitreal injection, but split on oral vitamins and antioxidants.

Question #2b

How confident are you that there are modalities other than laser photocoagulation, intravitreal injection of pegaptanib, and vitamins that provide a health benefit when compared to watchful waiting?

- Lucentis – 2 members highly confident, 6 unsure
- Retaane – 4 members unsure, 1 not valid, 3 not voting
- Avastin – 2 members highly confident, 3 unsure, 2 not valid, 1 not voting
- IVTA – 6 members unsure, 2 not voting

Question #3

Based on the evidence reviewed, how confident are you that the treatments such as photodynamic therapy with verteporfin, laser photocoagulation, intravitreal injection of pegaptanib, and oral vitamins, antioxidants, and zinc will positively affect the outcomes listed in Question 1a?

- Visudyne **– unanimous: highly confident**
- Laser photocoagulation **– unanimous: highly confident**
- Macugen **– 4 highly confident, and 4 unsure**
- Vitamins plus zinc **– 3 highly confident, and 5 unsure**

Question #4

Based on evidence reviewed, how confident are you that the approved treatment modalities reviewed in Question 1, used singly or in combination, produce clinically significant net health benefits in the treatment of AMD?

CMS asked for this question to be deleted.

Question #5

What are the knowledge gaps in current evidence pertaining to the usual care and outcome measurements of AMD?

The panel came up with a variety of suggestions, including:

- Real practice outside a trial or treatment algorithms.
- Diagnostics for progression.
- Outcome measurements.
- AMD patient subgroup responses to specific therapies.
- Adverse side effects and economic data.
- Cost of care indications.
- Genomic/cell biology/stem cells.
- Simple quantification of angiographic analysis.

Question #6

What trial designs will support the development of sufficient evidence to determine the appropriate treatment of AMD?

The panel essentially agreed that RCTs are critical.

The panel chair asked, "We're not going to resolve the question of what you do, but do you want to foreclose the possibility of anything other than a randomized trial?...We've heard some doctors are using Avastin who want it, but it needs a randomized clinical trial. We have to be clear about what we're doing." A CMS official said, "It's a broad definition of designs. We have a new drug on the market, a new procedure – verteporfin. There is no RCT, but should we stop collecting data on it?...Macugen has finished its two RCTs. What's next for it, and how should it be followed? What should be the next time of evaluation? And co-enzyme A – I pulled that one out of the air – we're going to inject orally to see if we can use it in AMD. What's the trial that we use to see if it works? There are various levels of treatments out there. One of those different kinds of evidence collecting tools includes RCT versus comparative trials versus registry versus claims databases."

A panel member said, "If you restrict the design to RCTs, you might do a disservice to people using other drugs out there. There may not be sponsors for those RCTs, and if we're talking about some drugs that are promising, if RCTs are a requirement, they might not be allowed to show their efficacy even if practitioners think they're efficacious." Other panel members offered these comments:

- "I'll take a little exception to that…They don't do trials because the clinician says it works."
- "I was specifically talking about a RCT."
- "I think in this day and age we have to have verified actual evidence, and an RCT is evidence."
- "It's not a fatal disease. For the purpose of this disease, given what we know about available treatments, the presumption should be RCT first. And if the sponsor has a really strong, compelling reason why something other than an RCT would suffice, let that sponsor make his or her case."
- "RCT can be used for analysis, safety, and efficacy – anything you need to know…It's a very fertile ground. But who's going to pay for it?"

There were also some specific comments about Avastin, including:

- *Panel member #1:* "I have no conflicts. There's a drug called Avastin, which is probably as good as Lucentis. And I want to know who's going to sponsor an RCT to check the clinical efficacy of Avastin. From what I hear, no one will, and that drug won't be tested rigorously."
- *Panel member #2:* "Maybe that's where NIH should get in. If there's no sponsor, someone else has to step in."

- *Panel member #3:* "Not having a sponsor is not cause not to do a trial."
- *Panel member #4:* "There's a company that owns that. If they make a decision to sponsor they do, and if they don't, they don't. Isn't it the same company that owns Lucentis and isn't there a reason for them not to do that based on financial reality? I'm just putting that out on the table."
- *Genentech:* "Genentech is developing Lucentis and does manufacture Avastin for cancer therapy."
- *Panel member #1:* "Are you saying that Genentech would be interested in investing in a trial?"
- *Genentech:* "Genentech is not developing Avastin. It's not intended for that use (AMD). We'd have to reformulate it, and it would take another five to seven years, so the short answer is no."
- *Panel member #5:* "I believe in the RCT theory, and I understand the limit we have and maybe this is another gap in our knowledge, which is what is the difference between these two medications?"

Question #7

Based on the scientific evidence presented, how likely is it that utilizing valid treatment outcomes in studying patients with AMD will result in conclusions that can be generalized to the Medicare population?

The panel generally agreed with the principle of the question.

After the meeting, a panel member was asked why his colleagues didn't back him up on the Avastin issue. He shrugged his shoulders and speculated that his colleagues might not know about it. Another panel member said that he didn't know about Avastin until he started reading material for this meeting. A third doctor said he thinks that if an enhanced registry is implemented, doctors using Avastin for AMD would be able to show its efficacy in that registry.

♦