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CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Coverage Advisory Committee

November 29, 2005

Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

Panelists

Chairperson
Alan M. Garber, M.D., Ph.D.

Vice Chairperson
Alexander H. Krist, M.D.

Voting Members
Michael Abecassis, M.D.
Harry B. Burke, M.D., Ph.D.
Mark Fendrick, M.D.
Clifford Goodman, M.D.
Bryan R. Luce, Ph.D.
James E. Puklin, M.D.
Jonathan P. Weiner, Ph.D.

HCFA Liaison
Steve Phurrough, M.D., M.P.A.

Consumer Representative
Morgan Downey, J.D.

Industry Representative
William R. Clarke, M.D., M.Sc.

Panelists (Continued)

Guest Expert Panelists
Leon B. Ellwein, Ph.D.
Ronald Klein, M.D., M.P.H.
Patrick Price, M.D.

Executive Secretary
Michelle Atkinson

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PANEL PROCEEDINGS

(The meeting was called to order at 7:59 a.m., Tuesday, November 29, 2005.)

MS. ATKINSON: Good morning and welcome, committee chairperson, members and guests. I am Michelle Atkinson. I am the executive secretary for the Medicare Coverage Advisory Committee. The committee is here today to discuss the evidence, hear presentations and public comments, and make recommendations regarding the treatment for age-related macular degeneration.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statute prohibits special government employees participating in matters that could affect their or their employers' financial interest. Each member will be asked to disclose any financial conflicts of interest during their introduction. We ask in the interest of fairness that all persons making statements or presentations also disclose any current or previous financial involvement in any ophthalmic device company. This includes direct financial

investment, consulting fees, and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside this room.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda, and therefore, cannot allow extra time.

There is a timer at the podium you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair in front of the stage for the next speaker, and proceed to the chair when it's your turn.

For the record, voting members present for today's meeting are Alex Krist, Michael Abecassis, Harry Burke, Mark Fendrick, Cliff Goodman, Bryan Luce, James Puklin, and Jonathan Weiner. A quorum is present and no one has been recused because of any conflicts of interest. The entire panel including the non-voting members will participate in the voting.

Anyone requiring transportation following the meeting should sign in at the registration desk during the breaks.

I ask that all panel members please speak directly into the mikes. You may have to move the mikes since we have to share. And lastly, everyone, please remember to discard your trash in the trash cans located outside this room. And now I would like to turn it over to Dr. Phurrough.

DR. PHURROUGH: Good morning. I'm Steve Phurrough, director of the coverage group here. Thank you for your attendance, and a special thank you to the panel members for their willingness to help us with this process. I want to introduce our new chairman and vice chairman. Alan Garber, a previous member of the MCAC, was on the MCAC for a period of time and due to rules had to leave, is back now as chairman. And Alex Krist, who is now our vice chairman. Thanks to them for agreeing to participate a bit extra in the MCAC. This continues our more recent MCACs where we are looking at particular technologies, procedures, services that are of interest to our beneficiary population, issues that we know we will be addressing, we suspect fairly soon, and we want to have an opportunity for the public to

understand based upon MCAC's recommendations what we think about the current evidence and what we think some of the evidence developed needs to be in the near future as these technologies come to us. We think these are good forums and we appreciate your participation.

I would like the panel to introduce themselves now and then we'll turn it over to Dr. Garber, and if the panelists, we'll start at the far end, will introduce themselves and any disclosures they might have.

DR. PRICE: My name is Pat Price. I'm a Medicare medical director and I have no disclosures.

DR. KLEIN: Ron Klein, epidemiologist, ophthalmologist. I have consulted for Eye Tech, Genentech and Novartis.

DR. ELLWEIN: Leon Ellwein, National Eye Institute, associate director. No conflicts of interest.

MR. DOWNEY: I'm Morgan Downey, executive director of the American Obesity Association. I'm here as the consumer representative and I have no conflicts of interest.

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MR. CLARKE: Bill Clarke, chief technology officer, GE Healthcare, and I have no conflicts.

DR. WEINER: I'm Jonathan Weiner, deputy director at the Johns Hopkins School of Public Health, and I have no conflicts of interest.

DR. PUKLIN: I'm James Puklin, an ophthalmologist at Kresge Eye Institute at Wayne State University in Detroit and I have no conflicts.

DR. LUCE: I'm Bryan Luce, director of clinical policy at MEDTAP International. My company continues to consult with most of the companies involved with this.

DR. GOODMAN: I am Cliff Goodman, vice president of the Lewin Group. My parent company does ongoing consultation with some of the companies of interest, but I have no personal financial interests.

DR. FENDRICK: I am Mark Fendrick, University of Michigan, no conflicts.

DR. BURKE: Harry Burke, internist, George Washington University, no conflicts.

DR. ABECASSIS: Mike Abecassis,

transplant surgeon from Chicago, no conflicts.
DR. KRIST: Alex Krist, family physician, Virginia Commonwealth University, no conflicts.
DR. GARBER: Alan Garber, internist with the Department of Veterans Affairs and Stanford University. I have no conflicts to disclose.
DR. PHURROUGH: Alan, I turn it over to you.
DR. GARBER: First of all, I want to welcome everyone for coming here nice and early the first Tuesday after Thanksgiving, and I'd especially like to thank the panelists for coming here.
Just a few very brief comments about how we will proceed today. First of all, I want to emphasize that in order to ensure that everyone who wants to speak has an opportunity to speak, we will adhere very strictly to the time guidelines. The speaker will have a little flashing green, yellow and red light available to them. When the red light goes on, you will be cut off right where you are. And I'm sorry, it may sound a little bit strict or even a little bit rude, but that's what

we've found is necessary to ensure that the meeting proceeds according to schedule and that the people who wish to speak can do so, so we will be very strict about that, and the people who have been scheduled speakers, I think have already been told about that.

Second, I would like to urge anyone who is speaking before the panel today to tailor their comments very closely to the questions that we will be voting on. If the past is any indication, there is a temptation to discuss several issues that may be of interest to all of us but don't have a lot to do with the voting questions. And the voting questions today are principally about the measures that we can use to look at vision-related outcomes. And in addition, there are voting questions about established technologies for the treatment of AMD. Those are the two main issues.

This is not a meeting that is principally about the importance of AMD, I think we all believe very strongly that it is a very important condition, and furthermore, that any treatment that makes a difference in this disease is worthy of very serious consideration. But

those are not the issues today. The issues today really are about the measures and about the evidence both in support of various outcome measures that have been used and in support of established technologies for the treatment of AMD, and we'll hear a lot more about those questions very soon.
So I would like to ask speakers to address those voting questions, not necessarily any specific treatment unless that specific treatment is part of the voting question, and not really about the importance of AMD or the benefits of treating it successfully. We can accept that as a starting premise for today, that an effective treatment is indeed a good thing for Medicare beneficiaries, and I doubt that there would be any disagreement about that point.
So, we have a number of presentations that will be dedicated directly to these voting questions and before we start with the scheduled speakers, let me just ask if any of the panelists have any questions.
Okay. We will proceed with the CMS presentation of Stuart Caplan.
MR. CAPLAN: Good morning and thank

you, Chairman Garber, panelists, invited guests, members of the public. On behalf of the Medicare and Medicare Services, I welcome you to the Medicare Coverage Advisory Committee today to discuss age-related macular degeneration, or AMD. The CMS staff present today includes presentations from Dr. Ross Brechner as the medical officer, myself, Stuart Caplan as the analyst, the MCAC executive secretaries, Michelle Atkinson and Kimberly Long, Dr. Louis Jacques, who is director, Division of Items and Devices, and Dr. Steve Phurrough, director of the Coverage and Analysis Group. I would also like to thank my CMS colleagues who worked hard with me to prepare today's presentation.

Today's presentation includes information on AMD treatments and outcome measures along with a review and data analysis of those measures, the history of Medicare coverage related to those treatments, along with MCAC panel questions. We will also hear presentations by Dr. Ross Brechner who will discuss the AMD disease process and evidence summary, Dr. Ron Klein who is presenting information on AMD clinical outcomes, Dr. David Matcher who will present the technology

assessment, and Dr. George Williams, from the American Academy of Ophthalmology.

The panel has received the following materials, all of which are publicly available. The draft technology assessment provided by the Agency for Healthcare Research and Quality, copies of the articles reviewed, the written testimony of scheduled presenters, a summary of evidence provided by CMS, and questions for the panel. A complete set of these materials is also available on the desk outside of this room.

Age-related macular degeneration is the leading cause of legal blindness in Americans over the age of 65. The National Eye Institute estimates that there are 165,000 new cases of AMD each year for all populations. Of those 165,000, 90 percent or about 150,000 are diagnosed with dry or non-exudative AMD. 10 percent of cases, or 16 to 17,000 have the wet or exudative form of AMD. The exudative form of AMD causes more rapid and severe vision loss. The estimated prevalence for AMD in Americans over the age of 65 is 7.1 percent, or approximately 1.2 million individuals. There is no cure for AMD. There are, however, a number of available treatments. Ocular

photodynamic therapy with verteporfin, known as OPT or PDT, is the most widely used treatment and there is quite a bit of evidence for it. Anti-angiogenesis therapy is aimed at specific drugs related to the growth of abnormal blood vessels in the retina. Anti-angiogenesis therapy which is currently approved consists of pegaptanib sodium or Macugen, which is administered by intravitreal injection. Laser photocoagulation provides relief, but it causes burn damage to the retina, so with the attendant risk present, this treatment may have less appeal. Vitamin therapy and other treatments are also available and various therapies are currently undergoing FDA trials. Except for ocular photodynamic therapy with verteporfin, Medicare has not issued national coverage determinations for other AMD therapies. The FDA has approved clinical use of verteporfin for predominantly classic AMD-related subfoveal choroidal neovascularization or CNV. However, treatment for occult or minimally classic AMD is an off-label use. However, in January of 2004, CMS extended their coverage of verteporfin

for broader indications than the FDA label when certain clinical criteria are met. Dr. Brechner will explain the nature of these various types of AMD lesions in his presentation.

The national coverage determination on OPT with verteporfin can be found on the CMS coverage web site at the following address.

Pegaptanib sodium or Macugen is a type of drug known as anti-vascular endothelial growth factor or anti-VEGF. Pegaptanib sodium is FDA-approved for all types of AMD-related CNV as determined by fluorescein angiography, and CMS has not issued a national coverage determination for this therapy, coverage is at contractor discretion.

A number of non FDA-approved treatments are in clinical trials and are nationally noncovered by CMS. Anecortave acetate and ranibizumab are administered by intravitreal injection. Both of these drugs inhibit growth of abnormal retinal blood vessels. Other drug therapies are in FDA trials, including Squalamine and other treatment modalities.

Bevacizumab, or Avastin, is an FDA-approved drug for metastatic colon cancer. It

is being used off label by intravitreal injection, and coverage is at local contractor discretion. Triamcinolone acetonide, FDA-approved for a number of indications, and is also being used off label by intravitreal injection to inhibit abnormal vessel growth. CMS is silent on the off-label use and coverage is at contractor discretion. Coverage of laser photocoagulation is also at contractor discretion.

There are ongoing trials involving combination therapies of FDA-approved drugs. CMS is also silent on these combination therapies and once again, coverage is at contractor discretion.

Now I would like to get to the panel questions.

Question number one: Each of the following have been reported as measures of disease activity or outcome in AMD. Some are direct measures of visual outcome, unambiguously representing visual aspects of patient well-being. Others are intermediate endpoints, meaning that they are intended to predict visual outcomes, even if they are not direct measures of outcomes themselves.

For each of the measures below, how

confident are you that it is valid as a measure of visual outcome? If it is not a valid measure of visual outcome, how confident are you that it is a valid intermediate endpoint?

Those measures are: Visual acuity, the VFQ 25, extent of choroidal neovascularization, Amsler grid, Drusen extent/progression, geographic atrophy, glare recovery, contrast sensitivity, fluorescein angiography, visual fields, and ocular coherence tomography.

Question 1B. Which other currently available outcome or intermediate measures should be considered?

1C. As new technologies arise, will new outcome or intermediate measures be needed to demonstrate benefit in the treatment of AMD?

Question 1D. What are the appropriate chronological criteria for short-term and long-term outcomes in AMD?

Panel Question 2. At present, usual and approved care for AMD commonly includes photodynamic therapy with verteporfin, laser photocoagulation, intravitreal injection of pegaptanib, and oral vitamins, antioxidants and zinc.

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2A and B. How confident are you that, A, there is sufficient evidence to assess the health benefit of these modalities compared to watchful waiting? And B, are there therapies other than photodynamic therapy with verteporfin, laser photocoagulation, intravitreal injection of pegaptanib, and vitamins that provide a health benefit when compared to watchful waiting?

Question 3. Based on 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 1?

Question 4A. Based on the evidence reviewed, how confident are you that the improved treatment modalities such as photodynamic therapy with verteporfin, laser photocoagulation, intravitreal injection of pegaptanib, and oral vitamins, antioxidants and zinc used singly or in combination, produce clinically significant net health benefits in the treatment of AMD.

4B. Based on evidence reviewed, how confident are you that the other treatment

modalities, used singly or in combination, produce clinically significant net health benefits in the treatment of AMD?
Panel Question 5. What are the knowledge gaps in current evidence pertaining to the usual care and outcome measurements of AMD?
Question 6. What trial designs will support the development of sufficient evidence to determine the appropriate treatment of AMD?
And finally, Question 7 for the panel. Based on the evidence presented, how likely is it that studies using valid measures of outcomes in treatment of AMD will result in conclusions that can be generalized to the Medicare population?
I would like now to introduce Dr. Ross Brechner, the lead medical officer for this process. Dr. Brechner is a board certified ophthalmologist, and statistician. Ross.
DR. BRECHNER: Good morning. My talk is shorter than these questions. Good morning, Chairman Garber, members of the Medicare Coverage Advisory Committee, members of the public, colleagues, good to see you all. This morning's talk of mine is on the summary of evidence regarding AMD, age-related macular degeneration,

medicines and treatment.
Some of the objectives, we will discuss the MCAC purpose related to age-related macular degeneration. The history of coverage has been well covered by Mr. Caplan. A little about the epidemiology of AMD and how we did our literature search. Then some of the data, and then some conclusions and recommendations.
In terms of the MCAC purpose, one of the real interesting things is that if you could weigh our ability to treat AMD either minimally or moderately successfully back 30 or so years, and then go and you weigh it now, it would be a lot heavier. There is a new revolution in AMD treatment right now and we need to know a lot more about how these treatments are affecting our patients and we need to know how they are being measured, and let's see if we can standardize these measurements, and that way Medicare can judge whether these treatments are reasonable and necessary for their beneficiaries. Of course Medicare only will be approached to pay for these things and we need to be very careful about whether or not we cover these.
Now AMD is a degeneration of the

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central vision, central macula, and it falls into two general categories, dry and wet. In the dry kind, there are what we call Drusen soft where you see AMD positive in the retina. We also see pigmentary and epithelial changes and geographic atrophy. And then the wet kind is categorized by choroidal neovascularization which is exudative, or as Mr. Caplan says, exudative.

The types of AMD and progression of them, this is just a brief chart sliding from no maculopathy to soft Drusen and pigment changes, to geographic atrophy, and the important point in this slide is that geographic atrophy is an advanced form of maculopathy but it is still of the dry type, whereas choroidal neovascularization is of the wet type.

This is a picture of a normal macula, there's none of these hard Drusen or anything else in there. This picture has a small bit of early age-related maculopathy, and you'll see this in all the pictures but however, this schematic is showing the progression, but these are the soft Drusen.

In this picture you can see an atrophic central retina and behind it you can see through

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to the geographic atrophy.
And then finally, along with the schematic showing progression to the exudative AMD, you can see a picture of what CNV looks like to the eye in the retina with some bleeding, some elevation of edema, some small bit of exudation.
An important description of AMD, AMD subtypes is going angiographically, progressing angiographically.
Now a classic form of, a classic neovascularization is described by a lacy pattern on fluorescein angiography and if the percent of the entire lesion that the lacy pattern or CNV covers is greater than 50 percent of the total area of the lesion, it's called predominantly classic, less than 50 percent is minimally classic, and then if there's no classic, it's called purely occult.
For those that don't have a concept of what it might be like to have a visual loss from AMD, here's one example of what it might look like. You have some blurring in early AMD and some central vision loss in late AMD.
With regards to the epidemiology and prevalence, there are approximately eight million

persons in the United States right now who have some form of AMD, and 85 to 90 percent of it is dry. 1.75 million have advanced AMD, which includes geographic atrophy, and generally the prevalence is zero percent below the age of 50 to 55. And the prevalence of AMD in persons 75 years or older, it's approximately 7.1 percent, and the exudative type overall is 1.2 percent of those persons who are in that age group.

In terms of the incidence of early AMD, the Klein and Beaver Dam study, and Dr. Klein is with us today on the panel, showed that there was a 12.1 percent cumulative incidence of early macular degeneration in this population over ten years, and 2.1 percent incidence in that same population over ten years of the late kind.

In terms of risk factors, there were two major categories for AMD, one is the modifiable type and the other is the non-modifiable type. Of the modifiable type, the most important is considered to be smoking. With regard to the non-modifiable types, as age increases, the chance or the risk factor for getting AMD increases, females have more of a chance of developing AMD than males, having family

history increases your chances, and being white compared to nonwhite increases your chances. Now when we started drawing data, we were looking at two major areas of questions today. One was how about current treatments that are out there as compared to observation or watchful waiting, even as a group, do they give us the impression that there is something out there that helps us in terms of a net health benefit? And the second set of questions was, let's look at the AMD outcomes out there and see how they measure and see whether we have valid reliable measurements even though a lot of us intuitively accept these measurements axiomatically, because we were kind of raised with it in the training. This, we won't read through this slide, but out of all the papers that we found, and I wanted to be widely inclusive because I was looking for some information on this, we included 110 papers that were relevant to our MCAC objectives, and they ran from 1976 to 2005. Of 110 papers, there were 83 that we found acceptable compared to 27 that weren't. But of those 83, there were a significant number that talked about a new measurement for macular degeneration but

didn't have a lot of data to support the measurement, but for completeness to see what was out there, I included some of that.

With regard to visual acuity, up to 1976, Snellen charts were in very common use and in 1976, Bailey and Lovie developed a chart that is right here that had letters of equal legibility, fixed ratio between rows on the base ten, the same number of letters in each row, and uniform between-letter and between-row spacing, so that the rows, the visual acuity angle doubles.

Now, Ferris et al. in 1982 supported its use in trials when it was used at four meters, and in 1988 the original paper was once again verified in some studies as valid and reliable. In 1993, Reeve measured a set of patients four weeks apart with this chart to check and see if visual acuity stayed the same and found out it was reliable.

There was generally fair support for the use of VA with certain caveats.

The question of quality of life will be addressed by the Duke people today who did a TA for AHRQ and they will present that data.

In terms of visual function, during my whole reading, I found that there was a paucity of

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strict validation data, definition, standardization of this topic of what's visual function. We all have an intuitive feeling for it in ophthalmology and I thought maybe it was just my own intuition that was floating around, but when I read all the literature, I didn't find a lot defining it or standardizing it.

In a 1988 study, Pelli developed a new letter chart and on each line increased the contrast of the letters by one over the root of two from group to group. He devised it to be used at three meters and this is very often used in studies. In 1988, Greeves et al. also had a study showing that the 20 decibel chart was a good screening device for macular disease, as long as it was used with another test of some kind. Lennerstrand in 1989 demonstrated that optotype charts were better than electronic tests for measuring contrast sensitivity. And in 2004, Mones did a review and claimed that there was good evidence for use of contrast sensitivity in CNV due to AMD as part of the overall visual function, which was, once again, not defined. Now, the evidence from good trials in respect to validation of contrast sensitivity and its use for measuring

AMD is really sparse.
The Amsler grid is an old favorite.
This is what it looks like on paper. This is what it might look like to a patient who has central vision change in the macula, some distortion.
Studies have indicated that the Amsler grid test has poor validity, and actually its sensitivity is not that good either, and it has poor specificity with regard to AMD. Once again, good data are sparse.
We found that with regard to size, type and number of lesions, many studies used this as a measure for need of treatment and the tracking of progression of AMD. Intuitively it makes sense, but we didn't find any studies that validated this use because axiomatically, the profession considers this to make sense and so they just do it.
With regard to fundus photos, in 1991 Klein et al. detailed a precise method for grading AMD. Although it was varying, there was good reliability and validity, it was not doable by all, and as any of us with any relations to these centers know, is complex and very expensive and time-consuming. Dr. Klein will describe this

method in an upcoming talk this morning. In 1995, Bird et al. published a paper describing methods for taking and grading transparencies, but there were no validation methods discussed in that particular paper. In 1993, Scholl et al. said there was good reproducibility with a revised version of the grading system that he established, and the grading system was that that was promulgated by the International AMD Epidemiological Study Group. Van Leeuwen et al. reported that digital images were as good as transparencies. So there is generally good data on grading and staging if you take into account all of the evidence. Visual field automated testing is widely used, but in the literature there was very little information about whether or not this was a valid way to judge AMD. One paper that I just mentioned recently by Nazemi concluded that 3-D computer automated threshold Amsler grid tests could correlate with fluorescein angiography and that perhaps monitoring scotomas in patients with AMD was a potential for tracking down and following AMD, but the paucity of data or validity of data is just not enough to really satisfy us.

With respect to OCT, optical coherence tomography, Hee et al. in 1996 took 90 patients with untreated exudative AMD, compared the measurement of that by OCT to fluorescein angiography for identification and classification, and concluded that it might be useful in monitoring CNV before and after laser photocoagulation.

In 2005, Salinas et al. did a prospective observational case series of OCT in patients both before and after PDT, but there is 62 eyes that they looked at, and they had high sensitivity for detecting CNV activity whether or not the diagnosis was made before or after treatment. Specificity was modest, 50 to 60 percent. The authors concluded that OCT might be useful for indicating CNV activity. Similar results were found in a consecutive case series by Sandhu in 2005. Once again, though, the data strength is weak and there were no RCTs found.

Seddon, as part of the AREDS trial, a multicenter trial which I will talk about briefly later, took patients from that and measured their C-reactive protein and found that over a period of six-plus years of follow-up, elevated CRP level

was an independent risk factor for developing AMD. Reading speed has been in a couple of good trials but once again, when I looked around, there wasn't anything that validated what kind of reading speed, et cetera, et cetera. This is an example where Elliott tested 15 persons with AMD and tested 15 persons with normal eyes in 2001 on the Bailey-Lovie chart, and people who had AMD were, surprise, slower in reading, and he said it might be a way of monitoring progress. But once again, there is a paucity of data.

With regard to the scanning laser ophthalmoscope, Fuji et al. in 2003 found that using that technique and looking at increased disease duration, they found it was associated with a worse fixation pattern and retinal sensitivity deterioration, and thought that maybe they could use this instrument following the progression of AMD. Again, very weak data.

Now, I've got four more of these. The following measures have currently little or no good data to support them and I mention them for completeness. Face recognition, facial expression discrimination. Macular mapping test score, from Bartlett et al., is a software program on a

computer that gets targets. Macular computerized psychophysical test, a test that identifies white dots on a black screen. Glare recovery or macular photostress, very sensitive but not specific.

Now I'm going to move on to the second part about the overall question, what do we have out there and as a group, does it help us? The macular photocoagulation study, an RCT multicenter study from the 1980s, conducted over a number of years, which some say had a great role to play. And in that one the argon and krypton studies were halted early because of reduced visual acuity loss in the treated groups.

In the submacular surgery trial, also an RCT, there were 454 patients randomized to either simply observed or surgery, and the groups had essentially an equal or nonstatistical difference at the end with regard to the improvement or decrease of vision. So, they determined that submacular surgery is not helpful to many commonly found lesions in AMD eyes. Interestingly, there were some positive results on the NEI-VFQ test they gave these people, surgery was better than observation in terms of quality of life.

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In the treatment of age-related macular degeneration with photodynamic therapy study, there was an RCT multicenter study in the U.S. and Europe with 609 patients, 402 were randomized to PDT and 207 to observation, followed for a period of two years. The significant finding in this study was that of those who had dominant classic CNV, 59 percent lost less than 15 letters at 24 months, as compared to 31 percent in the observation group. One of the major conclusions is that PDT prevents visual acuity loss in certain cases of subfoveal CNV.

In the Radiation Therapy for AMD Study, the RADS study, also a randomized controlled trial, 205 patients with CNV randomized to a treatment group of 101 patients, a control group, and each group was given eight fractions of two Grays and/or sham respectively. There was no effect of the treatment on the treatment group versus the observed group as measured by a mean reduction in visual acuity.

Now the first of the anti-VEGF agents to be approved was Macugen or pegaptanib. In the study published last December in the New England Journal of Medicine, they combined the two studies

and had approximately 1,200 patients and they were randomized to four groups, observation, 0.30 milligrams, 1.0, or 3.0 milligrams of intravitreal injection of Macugen every six weeks for one year. The endpoint was the loss of less than 15 letters of VA. At least 25 percent of the patients, or not at least, but approximately 25 percent had some PDT treatment prior to, at the beginning of or during the study. Taking that into account and looking at all three groups, there was a 70 percent with Macugen, all three groups who had received Macugen, there was 70 percent of the group who had lost less than 15 letters at one year, versus 55 percent of the observed group. With regard to anecortave acetate, a randomized controlled trial was done by D'Amico et al. in 2003. The patients were broken into four groups, 3, 15 and 30 milligrams, versus the control. There was juxtascleral deposition on anecortave acetate, and at 12 months the 15-milligram group, which was administered at six-month intervals, was shown to be statistically superior to placebo on mean change, visual acuity, stabilization of vision, and prevention of severe vision loss at the time of the trial.

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Now some other agents that are currently out there just for mention, and Mr. Caplan covered these, ranibizumab, Triamcinolone, Squalamine and others, in my summary of evidence that has been posted, there is a list of trials.

Now what's been approved is verteporfin, pegaptanib, and anecortave acetate, as you may all know, is gaining approval letters.

What's next? Well, there are some guesses but no one is sure.

AREDS, the age-related eye disease study, 5,000 participants aged 55 to 80 in 11 clinical centers nationwide. They were being given one of four treatments, zinc alone, antioxidants alone, a combo, or a placebo. And after six-plus years, it was determined that high levels of antioxidants and zinc significantly reduced the odd for development of advanced AMD and associated vision loss in comparison with the placebo.

Now, some observations. These are a little bit strong, but they are my observations and I keep coming back to them. In almost all of the trials, in everything that I read, there was

very little agreement in all of the different studies for what cutoff points, what outcome measures -- I mean, people used visual acuity a lot but what was the cutoff point? Some had improvement of 15 letters, some had status quo, some had mean visual acuity, some had eight letters of decrease, some had less than 15, some had less than 30. I looked at each one and thought okay, that's what they said, fine, but in order to compare all this data, I found it difficult to look across them on that basis alone and to compare, and this was true for a lot of the different measurements that we went through. Also, the conditions of measurements were very often not mentioned with detail and in some cases where they were mentioned, due to time constraints and other things, I wasn't sure, it wasn't spoken about that they were followed correctly. For example, visual acuity again, what were the lumens in the room, how were they handled, was it standardized, how far from the chart were they. Sometimes they were one meter from the chart, two meters, four meters, and a patient with macular degeneration is liable to lean forward a little bit. So there are all kinds

of things out there to compare, but nobody is doing something to validate these measurements. Now, I also found that the inclusion and exclusion criteria varied widely in the trials with regard to treatment and measurement of AMD. You know, each time they made some sense, they didn't include somebody here, but it was difficult to compare or cross all the trials because they were different in all the trials, which meant that the base from which they came was different.

Okay, conclusions. I will repeat some of the observations. There is a general paucity of data that clearly validate the standard measurement testing modalities in and of themselves with the exception of some VA measures, fundus photos and QOL, and I don't have the slides for QOL at this point, Duke is going to present that.

The literature does make reference to a lot of different ways to measure outcomes of AMD, yes, that's for sure. I haven't even gotten them all in here. There are different RCTs and other AMD studies that all used different and widely diverse inclusion and exclusion criteria, as I mentioned. They used different or undefined

conditions for measuring various outcome measures, as I mentioned. Follow-up in clinical trials range from months to over six years or more, with most ranging from one to three years, but that's partially understandable because this is new, it's hard to get, but the question is how long should we be following it, one of the questions we have here today.

The data with regard to laser, intravitreal injection and vitamins may be sufficient at present to assess the health benefit of these modalities when compared to observation. Other modalities may be on the verge of or close to showing a health benefit when compared to watchful waiting. There is sufficient evidence in the literature to determine whether or not treatments such as PDT or photocoagulation can positively affect some of the outcome measures submitted before this MCAC.

Recommendations. Further evaluation of AMD treatments, well, that's a given. Standardization of inclusion and exclusion criteria for RCTs on AMD where possible, and I say where possible because this isn't a frictionless surface and it's not perfect, but we need to see

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if we can't get these standardized. Standardization of cutoff points and methods of measuring outcomes for AMD. Clinical trials should be designed with attention to CMS evidentiary needs, so be thinking about us, not devoting all your attention, but be thinking about us if you're planning for your product to come through us.

And then, studies to fill in the gaps of our knowledge need to be developed. And I have an asterisk next to the first one, well designed validation studies for outcome measures. And then, combination studies of the new drugs coming out, and this is already happening, but as they are happening, they all need to keep this stuff in mind so before it gets too far down the pike and some stuff is developed, we need to look at whether combinations are more effective than any single drug treatment alone, unless we find a treatment that takes care of 100 percent of the patients.

And this little thing, this is the end of my talk, this is from a temple in Katmandu, I took a picture when I was passing through there out of Tibet. Thank you very much.

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(Applause.)
DR. GARBER: Thank you, Ross. David Matcher, from Duke.
DR. MATCHER: Good morning, thank you for the invitation to talk today. I'm representing a group from the Duke University evidence-based practice center. I am an internist and more of a methodologist. Some of the people who are, in addition to being methodologists, are also ophthalmologists. Today Dr. Suner and I are going to be giving this presentation as a tag team. First of all, as Dr. Brechner presented just a moment ago some issues of measures, objective measures of deficits from age-related macular degeneration to another set of issues about the measure of age-related macular degeneration, namely quality of life measures. In a sense, what I carried out of this last talk, Ross's last talk was that certainly objective measures have been used to a certain extent but very inconsistently and the question really remains, what do they really mean from a clinical experience and patient experience, and I do think they are necessary to show it's something worth having, something worth covering.

So what we're going to talk now about is the quality of life measures in AMD and we're going to be focusing to a certain extent on the technical aspects of these measures. You should be aware that there is a web site that has our full report and all of the evidence tables and each of these various studies that we looked at. This presentation is not an opportunity for us to go over that document, but rather, to quickly go over what is contained in the document, some of the conclusions of the document, and to focus as much as possible on the issue of, are the visual quality of life measures a contribution to our understanding of the impact of AMD and treatment for AMD? And the really crucial question of what response do these clinically mean? The questions I will be addressing, you will see hopefully now, were the questions that were raised earlier in the morning. I'm going to now turn this over to Dr. Suner, who is going to talk now about the technical issues.

DR. SUNER: Thank you, David. It is an honor and a pleasure to stand before this distinguished panel, colleagues and other interested parties in this very important subject.

As Dr. Brechner already mentioned, AMD is a significant problem that affects central vision of the retina, and is the leading cause of irreversible vision loss in this country. It does affect many people in this country, and particularly relevant to this panel, it affects significant populations of the Medicare recipients.

The key questions that the MCAC tasked the Duke team with are presented here. The first key question was as to the status of quality of life measures in AMD, specifically what quality of life measurements have been used to evaluate patients with AMD, whether these particular instruments have also been applied to other eye conditions with similar central vision loss impact, and the psychometric properties of these particular instruments.

The second key question is, what were the factors that may influence the response of these particular instruments to quality of life?

And the third question was, how do these measures relate to traditional outcome measures that you already heard about from Dr. Brechner, namely visual acuity, reading speed,

contrast sensitivity, and clinical severity of AMD.

Vision-specific quality of life is important. The reality is that this really impacts many patients and we have to get these measures many times. Specifically, a person with 20/40 visual acuity with AMD, that may have a very different impact, whether this quality of vision of 20/40 is good for them or not. The person who is reading the stock market report may be severely impacted as opposed to someone who's out in nature and walking in the outdoors. It's also a condition that affects both eyes, asymmetrically at times; however, your better seeing eye may one day become the most impacted or most severely impacted eye in the future. And finally, as alluded to before, patients have different needs and preferences. A patient who lives alone in a big city with poor public transportation will be impacted differently than the patient that has a very strong family network at home with them and can get around with that family member.

So as Dr. Matcher indicated, all the assessments and fine detail is available on the CMS web site under this particular MCAC, and that

contains all the evidence tables and methodologies that we'll summarize in the interest of time at this point.

With key question one in terms of quality of life measures used in AMD, early on, general health measures such as an SF-36, for example, were used, and these measures were found to be insensitive to the impact of visual acuity and other objective measures and general visual quality of life.

More specific measures in task performance, and this has not been very well studied, there's one large study in the literature, the Salisbury eye evaluation. However, this is categorized to AMD all that well, but that is a very useful way to look at this particular instrument. However, there are difficulties in that it's a very time-intensive and difficult to standardize measure.

Now getting to the crux of the matter, there have been five instruments that have been fairly well studied. One of them, the VF-14, I'm happy that Jonathan Javitt, one of the pioneers in developing this instrument is here. And also, the NEI-VFQ, the activities of daily vision scale, and

the Vision Care Module 1, which again, in this particular case applies to more of anger, loneliness, fear, as opposed to specific vision-related functional aspects. The DLTV is a U.K.-based measure developed actually for AMD specifically.

And again, we'll talk about some of these, and this is a snapshot of what some of these instruments measure. As you can see, there is some commonality in some of these instruments. As you can see, there is some commonality to some of these instruments. As you can see on the far right, the VCM1, however, focuses more on other aspects rather than functionality; specifically, they focus on loneliness, anger, fear of loss of vision, fear of losing more vision, but the other ones are fairly focused on some of these tasks. Some of these include driving and some focus more on subtleties in driving such as driving at night or difficult conditions or whatnot, where the other ones have more general impact.

You'll see also some of these focus on some tasks of caring for themselves, such as reading medicine bottles, seeing television, walking up and down stairs. And finally, again,

some more of the activity of daily life and you can see that some of these instruments have more common elements or common features in the question sets.

In terms of the psychometrics, we looked at reliability, stability and responsiveness initially, and this table focuses basically whether there was varying degrees of evidence in favor of these psychometric properties. NA means it was not evaluated, a zero means no strong evidence for the psychometric property was found to evaluate in this particular trial, a plus means there was moderate evidence in favor of this property, and two pluses means there was strong evidence. As you can see, the ones that were most widely studied in the context of AMD, the VF-14 and VFQ do have some desirable psychometric properties for the evaluation of AMD. Other ones, the DLTV showed promise but did not have enough details or with enough patients to make that determination.

In terms of key Question 2, what factors influence responses to these instruments, you can see here some of these are very logical, such as emotional distress and fear, some of them

are rather interesting as in this particular case, this type of fear was sometimes greater in patients who lost vision in one eye and had vision loss in the other, as opposed to one who has lost vision in both eyes. Depression was also a conflicting factor with influenced response in the context both of people with pre-condition depression and ones that developed depression after the diagnosis or impact of AMD.

In terms of key Question 3 and how these instruments relate to traditional measures in terms of visual acuity, what I want you to focus in on this particular table is that for both of the instruments that have been widely studied, the VF-4 and VFQ, there was some correlation of a score, again, the higher the score the better the functional, so there was some association on the score with the level of visual acuity. However, I want to also point out that there was quite a bit of spread within these scores, and that goes again to the point of determining what's important to the patient, someone with 20/40 vision. Again, these are measures from a dark room with high contrast, which is not the world that we live in and that's the world that we have to deal with

every day, especially when looking at these comparisons. So there is correlation, however, there is some spread.

In terms of responsiveness, I also want to point out three particular studies or findings. One is, Dr. Brechner referred to before, the submacular clinical trial where there was not found to be a benefit in visual acuity of the macular surgery. However, there was an impact in terms of the VFQ in this case, and again, we have to look at is that a real effect and again, an impact that we can detect in measuring visual acuity in a very controlled setting, as opposed to one of the real old questions and how we're dealing functionally with their vision.

The second one I wanted to mention for responsiveness is the AREDS trial, and in that one there was responsiveness in terms of loss of visual acuity and worsening in clinical severity with a corresponding dropoff. So again, these patients had progression of their AMD with a corresponding worsening of their VFQ score, and usually eight to ten points. Dr. Matcher will quote to that point and tell you what point loss means and how that can be quantified more

specifically.
And the final point I wanted to mention in terms of responsiveness is the study looking at surgery in AMD where you had a very radical procedure for this condition. However, in that particular study, there was a strong correlation of visual acuity improvement, VFQ improvement, with a significant eight to ten-point improvement in the VFQ overall score and also improvement in subscales as well. So having said that, I will turn it back to Dr. Matcher, who will present another perspective with the nuts and bolts of the particular instruments and how these apply to AMD.
DR. MATCHER: Thanks, Ivan. Now what I'm going to turn to is an issue that was given to us in the MCAC protocol, or the CMS protocol from AHRQ, and that is, what do these differences mean and can we put some clinical personal meaning on these definitions? So I'm going to focus on this concept of the clinical meaningful difference at the forefront of this concept.
There are two general approaches that were taken in defining what might be a clinical meaningful difference. One approach is called the distribution-based approach where we look at the

changed scores in longitudinal designs or differences between group means, which are cross-sectional designs, and compare against statistically-derived benchmarks. When you think about this, some of the earlier psychological literature talks about the differences that you might expect to see, or how much difference can you distinguish between children of different ages, say between 15 and 16 years old, can you distinguish between heights and then you look at the variation of heights and you look at the standard deviation units of that and say, well, if you can make that decision, if you're able to see that, that is a perceptible and meaningful difference, then the amount of standard deviation in those 15 or 16-year-olds represents a benchmark. So it's really in some sense about psychological perceptions.

The alternative approach would be an anchor-based approach which compares observational changes in a longitudinal design, or comparing between-group differences in a cross-sectional design. So if someone says well, I got a five point difference, and you all say yes and walk away at nearly the same time, does this make a

difference to you, do you feel that you've improved or do you feel that you have worsened it. So let's first talk about distribution-based approaches to looking at meaningful differences in these quality of life measures. There are two measures that floated to the surface in our evaluation, the VF-14 and the VFQ, both primarily because they had been the best studied and also clinically both had generalists and ophthalmologists in the group as making sense, so those were the ones I'm going to focus on right now.

So if we look at this concept of the number of standard deviation units that you get results from benchmark estimates are that if you have a measured difference of .2 standard deviation units, that would be small; moderate, that would be .5, and .8 or more would be a large difference. So if you can focus in on how much noise there might be being measured, you can look at the difference between means given that noise that's there. So being able to distinguish a difference of .2 for the VF-14 is 4, with a score differential in the VFQ of 3, and then 10 and 7 for moderate, and then 16 and 11. Now, we may not

have said anything with 4 points, but on both the VF-14 and VFQ scales we're talking about somewhere 4 and 16 units, or 3 and 16 units on a 100-point scale, and you notice that the VF-14 has a slightly higher variance.

Let's move to another measurement. A couple of ways, or actually three ways we're going to approach describing what may be a clinically important difference, first looking at cataract surgery, which is an intervention that is generally agreed to have a vivid improvement, quality of life measures improve by an order of one standard deviation, this sometimes is called effect size, typically called effect size. What that tells you is the clinical meaning of that difference is certainly below that value and that is a big difference, so a difference of 14 to 20 points is, whatever, we're interested in something smaller than that, so at least it brackets it.

Now this again is a slide that Ivan just showed you a moment ago, but I'm showing to you for a different reason, namely that you can see that going from 20/20 to 20/40 vision, on the VF-14 or VFQ you're talking about a 50-point change, so that's certainly something that you

would all care about, and that difference is on the order of 10 to 15 (inaudible). For those of us who wear glasses, perhaps we have a more vivid image than that, but if you take your glasses off, you know what I'm talking about.

Now, another way to look at this is to actually just get down and dirty and look at the scale, let's just look at the different elements of the scale and ask yourselves, what point do we begin to see changes in responses and does that make sense, and there are three issues that are raised in these fields. There is an impact of vision on activity, there is the perception of life impact of visual change, and there is impact on the frequency of performance. So I'm going to go through the questions in each of these domains, not all the questions, but just illustrator to give you like, if you like to think four or eight or ten points is meaningful based on these questions, then you've got your answer. Okay.

How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house or using hand tools? Now, response possibilities ranged from no difficulty

at all to stopped doing this because of your eyesight. So think about this, you've gone from I don't have any difficulty cooking on the stove, fixing things around the house, blah, blah, blah, or I don't do them at all because I can't see, because of my vision, okay? Now, how many points is that? Four, okay.

Now, if I ask the same question but I was talking about driving and talking about going from I'm driving to I'm not driving because of eyesight, so think about what driving means to you, your mother, grandmother or a patient, driving to not driving because of eyesight, four points.

Perception on life, again, this is the VFQ but this is pretty much fairly general, and I will comment in a minute about the VF-14. I worry about doing things that will embarrass myself or others because of my eyesight. Now, I have a little problem with my vision and occasionally I will trip over steps and I sometimes get embarrassed. Now it doesn't keep me from going out, so I'm probably closer to definitely false, but if I were to say that it was definitely true, that would be another four-point change.

Frequency of performance, are you limited in how long you can work or do other activities because of your vision? None of the time to some of the time, for these things that require vision, that would be two points. If I go from none of the time to all of the time, that's four points.

Q. And now, just to give you an example from the VF-14, which has a different scoring system, which is not exactly, it's more of an approximation, do you have any difficulty even with glasses, writing checks or filling out forms? This is an activity many of us engage in, checks or filling out forms. No to yes, with a great deal of difficulty. So if you say no, I have no difficulty, and then you go to great difficulty, that's about a five-point change.

So let me summarize by saying first of all that there are certain validated and clinically responsive vision-specific instruments for measuring health-related quality of life in individuals with AMD, including the NEI-VFQ and the VF-14 questionnaires.

These vision-specific quality of life measures have been successfully applied to other

eye conditions affecting central vision, particularly cataracts, corneal diseases and macular edema.

In terms of psychometric properties and having looked at other measures and other conditions, I would say that these have been appropriately measured in many contexts and for many patients. Have they been as well as they possibly could, no, but they certainly rise to a relatively high level in terms of quality of life measures that are out there. We do believe that there are other instruments that are promising and that require further evaluation, and some of the instruments being developed looking at task performance are very promising, are not too time-consuming and may be standardized.

The VFQ and VF-14 correlate moderately well with traditional measures but they are not the same measures, okay? So on the one hand we're not talking about saying these are related measures but really, they are complementary measures.

The VFQ has been found to have excellent responsiveness where visual improvement has occurred. I'm going to skip this slide.

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Well, I'm just going to close on that slide and just point out, again, that we believe at this point that the, that the measures have approached prime time and are appropriate to use. They do complement the objective measures, they do correlate and add something to the objective measures, and a difference in the order of five to ten points, we believe represents a clinically important condition.

DR. GARBER: Thank you, David.

DR. KLEIN: I wanted to thank the organizers of this meeting for the invitation to speak today and I will be speaking about grading of age-related macular degeneration, a subject which is near and dear to my heart, and I have been involved with for the past 30 years.

I would like to begin by discussing some basics of epidemiological studies and begin with some photography protocols. Almost all of the studies of grading start with the use of a fundus camera or fundus cameras with various settings, defining the magnification, the number of fields taken, establish a baseline and frequency of follow-up, the photographer's training which involves orientation and

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certification by the central reading center, and a central review of the photographs along with feedback.

This is an old photograph taken from the study showing how the camera was mounted and used, it used film, the photographer is taking a photograph of a dilated pupil, and this camera is still active now 25 years after the first set of photographs were taken using the same protocols and methodologies. Newer cameras now involve digital technologies.

Fundus photography is not an easy business, it is subject to a lot of artifacts and some of these are seen here. It's out of focus, this is a normal fundus photograph of the right eye and you lost of some of the field, subjects occasionally blink, the subject to camera distance will vary, and there are a lot of artifacts that result from dust and dirt on the lens and alignment problems. And all of these contribute to the fundus photo and possible artifact that you're viewing. With the advent of digital photography, some of these a minimized in the system, the photographer can see what they're grading, what they're photographing.

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This is an example in one of the studies we're discussing where we sent back monthly feedback to the photographers in the center for evaluation of various types of artifacts for actual gradability and other information, so there is a constant feedback to the study centers to maintain high quality fundus photography.

This is one methodology that was worked out for the five or six large multicenter studies around the world which involved, and clinical trials which involved taking free-standing fundus photographs, one centered on the (inaudible) area, into field three, which, this is taken (inaudible). This is from a film-based camera and the film comes back, we began with Kodachrome and we changed, we now use Ektachrome and are finding a close likeness to Kodachrome.

And this person actually places a grid centered on the phobia, which is here, this which defines the macular area, inspects the macular area to grade in various locations. The grader taking this film images, grades them using a light box, for various lesions. In the digital age, with digital cameras, they basically come up on

the computer and using various software the same grader can be seen doing it, and it is now also done on the computer as well.

The grading of early AMD has evolved since the '60s and '70s by various groups, and some meetings in Baltimore in the mid 1980s, which involved trying to standardize some of these lesions that would be acceptable in terms of how they were grading them. Lesions that have been graded by the Drusen, the size of the Drusen, the type of Drusen, area and location of the Drusen, and whether there were pigmentary abnormalities such as increased pigmentation, RPE depigmentation, and the location of the pigmentation.

This is just the fundus photograph of the left eye showing abnormalities and this is one of the standardized grades that evolved during the work on age-related maculopathy, and as a result of these meetings was then standardized in the international classification scheme, which shows various size circles, circles with various diameters, less than 63, 125, 150, various sizes, and they were the size of intrusion in the area involving the abnormality.

This is just an example of area demonstrating area size, areas, and the amount of Drusen, and what they found is if they counted the number of areas and the number of Drusen in a certain area, and it's somewhat easier. This is an illustration of a grid on a left eye with an area of concern that's about 50 microns in diameter and many of the epidemiological studies that have been done show that larger areas than this are particularly prone to advanced stages of AMD.

This is a series of photographs from one of the studies of the population at the time, and it illustrates that one individual here was followed over a 15-year period. And starting on the left, there are very few Drusen here, and over the 15 years, what we found over the 15-year period is that a different atherosclerosis will be found, and some individuals over five years will go this fast, and some individuals start here and go back this way and the Drusen will disappear without any treatment, and also come back again later as you see here, so this just sort of illustrates one course.

The grading of late AMD, as shown on

these photographs, you see neovascularization with rising AMD, PRE detachment, subretinal hemorrhaging, scarring of the macular area, and geographic atrophy. You sometimes find the neovascular in one eye and the other eye might have geographic, and in rare instances the geographic will become wet after a long course of this, it will disappear, leaving atrophy. This is from the AREDS that other people spoke about, and this has just been published in the November issues of the Archives of Ophthalmology, and it describes a more detailed severity scale. In took over about 20 years of work to define the natural history of it and this is a fairly sensitive scale based on the grading of progression of the disease. This actually took a long time to evolve, about three-and-a-half years and a lot of statistical work looking at each area and thinking about increasing the risk of more severe stages. These are neovascular, but this severity scale is, can really only be done by grading clinically, it's fairly easy to do, but it does offer some good reliability and actually reproducibility.

And in the same issue of the November

Archives this year is a scale that's based on large (inaudible) and is a simple clinical scale based on presence of Drusen, progression, and stage of the disease. We're still working on the severity scale which can be used, and this is one example that might be, it's not being used yet, but we're looking at this and look at the right and left eyes and looking at progression of the scale two or three steps which are clinically meaningful.

I did want to make one point, that the earliest incidents, although you define it by large scale fusion where this really begins, we're finding from some of the population-based data in Beaver and elsewhere that having multiple small lesions do increase your risk over a 15-year period, so it may actually begin earlier than is currently viewed and we may need to look at these multiple small abnormalities as a stage of early AMD.

In conclusion, I think grading fundus photographs using standardized protocols offers an objective reliable approach to detecting early and late AMD over time. I have not spoken about fluorescein angiography and things that you have

heard others speak about, but I think a severity scale that came out of the (inaudible) trial, will provide a sensitive measure of clinically meaningful change at early stages of AMD, and it's important that we have such a scale. Thank you.
(Applause.)
DR. GARBER: Thank you, Ron. George Williams, from the American Academy of Ophthalmology.
DR. WILLIAMS: Thank you. The American Academy of Ophthalmology wishes to thank CMS for the opportunity to present to this MCAC. My name is George Williams, I'm an ophthalmologist and a member of the Medical Center of Ophthalmology, and I represent the American Academy of Ophthalmology here today. I served as a researcher in many of the technologies and treatments that you've heard of today and I have been both a paid and nonpaid consultant to several of the companies that provide these technologies.
This will be a two-fold presentation. First, Dr. Neil Bressler from the Johns Hopkins University will present, and then I will close.
DR. BRESSLER: Thank you, George. Good morning, Dr. Garber and others. I am Neil

Bressler, I am an ophthalmologist and a member of the American Academy of Ophthalmology and am appearing on their behalf today. I'm also a retinal specialist, I'm chief of our retina division at Johns Hopkins University, and have a clinical interest in clinical trials. I chaired the submacular surgery trials that you heard about earlier where we began to look into quality of life outcomes for macular degeneration. I serve as chair of a monitoring committee for the National Eye Institute's intramural research program and work in a variety of trials, both in macular degeneration and diabetic retinopathy. I have no direct conflicts of interest but my university, the Johns Hopkins University receives a variety of grants from most of the corporations that are here today, for research on my behalf. My wife is a paid consultant to Genentech, Susan Bressler, and serves on their committees as a retina specialist.

I would like to discuss briefly where we are with treating neovascular AMD because it has been a very fast-moving field in the last two years. And because of the nature of the talk this morning, I want to touch on the quality of life

measurements and what we have seen and how they relate to macular degeneration. Dr. Matcher and his colleague very well described visual acuity and eye charts, compared with how we read or how we recognize people's faces; it is not an exact one-to-one correlation. And yet, the primary outcome for evaluating potential problems with neovascularization has been the proportion of people who avoid 15 or more letter loss from baseline to one year on these charts. These charts, as you've heard, have five letters per line, so a 15 or more letter loss would be going to three lines where the size of the letters actually double in size, and every three lines they double again, and that was judged to be a clinically relevant difference and we believe it is.

However, there are other important secondary outcomes that recently have been looked at in clinical trials. This includes the proportion net gain. 15 or more letters decline in one year after macular degeneration does not cause complete irreversible loss if caught at a certain time, and some people following treatment actually can gain three or more lines of vision.

So by concentrating on these one-year changes in vision target quality of life, using the National Eye Institute visual function questionnaire, these outcomes as reported by study subjects, because visual acuity, as has been pointed out, may not fully describe the influence of choroidal neovascularization on patient-reported visual functions. Quality of life outcomes are critical to patients and therefore to physicians when we are making treatment decisions.

Now this is mentioned briefly in the full report and the responsiveness of the NEI-VFT changes over a period of time. This was done by the NIH-sponsored AREDS group and is reported in Number 14 of the Archives of Ophthalmology in 2005 where they showed that changes in the overall NEI-VFT score and the subscale scores of ten points or more were associated with a clinically significant change in vision, that is, a 15 or more letter change. So it was mentioned that somewhere between five and ten letters is probably a relative change, but at least ten or more points is a definite change, correlating with a 15 or more letter change.

And it also correlated with people who

progressed to the advanced stage of macular degeneration who had started with the intermediate stage, a term that we use to describe it as Drusen, no geographic atrophy in the center of the retina and no choroidal neovascularization. I want to discuss the use of ranibizumab, which is pending FDA approval, and it does have an impact on quality of life, because ranibizumab compared with the sham treatment was highly effective for avoiding 15 or more letter loss. It also increased the chance of increasing visual acuity by 15 or more letters, but this was in very specific subjects, those who had had an initial visual loss when they walked in of between 20/40 and 20/220, but that's generally what you see when patients walk in when they're symptomatic. Now there were some patients with lesion characteristics seen on fluorescein angiography without any clinical evidence. Why was this? This is because it can just stand still, they may be seen with excellent vision for years. So often those cases on angiography that were minimally classic or occult with no classic that had evidence of previous disease progression weren't enrolled in these trials, and we're not

sure they should be extrapolated to those without this.

They also didn't enroll patients in another trial that had predominantly classic AMD who did not have evidence of recent disease progressive correction, because we've seen in general that these cases often deteriorate rapidly and we would not want them to wait three months to see if there is progression.

We see (inaudible) observation, not mainly scarred or blood, and neovascularization is under the center of the retina. And despite the results shown at the top of this slide, the question was, did ranibizumab have similar beneficial effects on patient-reported quality of life changes due to vision function as noted for the visual acuity changes, because these were the visual acuity changes.

That is the sham, 62 percent of the people avoided 15 or more letter loss, so not everybody lost vision assigned to the sham. It was much better with the two doses of ranibizumab, where 95 percent avoided 15 or more letter loss in one of these trials, the MARINA trial, looking at minimally classic or occult with no classic

lesions along with disease progression. Also important as a secondary outcome was that only five percent of the sham people improved by 15 or more letters, compared with the two different doses of ranibizumab, where 25 to 44 percent improved by 15 or more letters, three or more lines of vision, where they could see letters now half the size on the chart where they walked in at baseline to one year. So in trying to discuss if this has an impact on the NEI visual function questionnaire, MARINA also looked at those. Now baseline, the score for having this choroidal neovascularization in the sham was at 71 and in the ranibizumab group, 58. What is that? Well, that's like a test score. If you got a 58 on a math test, I don't think you'd be so happy, and these patients unfortunately with choroidal neovascularization start with quite low visual function questionnaire overall scores. Now in order to look at a definite gain, this is not to say the minimum relevant gain, but a definite gain of ten or more points of the composite score, we see that even in the sham, ten percent had a definite gain of ten or more

points. How could that be? Well, because some of them perhaps blood went away, fluid went away, their vision actually improved doing nothing, and so their function capacity improved as well, or they perceived that their function was improving a bit more. But this is in contrast to ranibizumab, where we see that 33 percent improved by ten or more points on the visual function composite scoring, and this is reflected in the individual subscales that make up this score.

So for near activities, you can see that's 44 percent improved by ten or more points; for distant activities, 40 percent improved by ten or more points, whereas dependency on others because of your vision, 30 to 33 percent improved by ten or more points. Social functioning and mental functioning, and role difficulties, just look at how difficult is it to do certain roles because of your vision. This was seen for general vision but it wasn't seen for color vision. We don't expect that this has an impact on changes in color vision like we saw for peripheral vision, and that makes sense as well, lending validity to the tests that were done.

It had no impact on general health.

This is a generalized health questionnaire so it's done in some macular surgery trials, like the SF-36. You probably won't see any changes in the outcomes. And for super-ocular changes, although with driving there was an impact, some people had a change where they probably went from not being able to drive or very fearful of driving to now being able to drive because of the improvement in vision.

We see that these changes, if we look at the average change, for example the near activity score, being able to do near activities over time, occurred mainly over three months but there still was some slight improvement between three and 12 months, and the ranibizumab group is shown in the colored lines, compared to the sham group shown in white. This is true for distance activities as well. And if you look at the differences at 12 months, these were the mean changes, and you can see that the mean change for the ranibizumab group was plus six, and on average is about ten points difference, the averages are a ten-point difference with a minus four and minus five for the sham group.

So the conclusions from this MARINA

trial looking at the impact of ranibizumab on patient-reported vision function show that they were more likely to report increases of at least ten points, a level that we judged to be a very clinically relevant improvement in function for the NEI-VFT overall score and also all the subscales that are involved in central vision activities. These results are consistent and supported.

And what do they do to ophthalmologists who are deciding to consider this treatment? They increase our confidence of the visual acuity outcomes that already were reported, where we indicated that 95 percent had a 15 or more letter loss and 25 or 35 percent improved 15 or more letters. So what's this impact? Well, when we evaluate ranibizumab-treated subjects, not only are they more likely to read an eye chart that has very high contrast better than sham-treated subjects at one year after entry, but also are more likely to report clinically relevant improvement in their vision specific quality of life outcomes. These results have increased our confidence regarding decisions of recommending it for a patient similar to those enrolled in MARINA,

and then increased our confidence in why we think it would be a good outcome for Medicare to consider when they're deciding on coverage. I now want to close with how this is relevant to other diseases that Medicare has to cover in this population. We've already learned that this problem, unfortunately, is likely to double in its incidence over the next 20 years. What does that mean? Well, in another preference study report that was also reported in the Archives of Ophthalmology 2005, we used a series of questions rather than a standard method where you need a lot of visual acuity. We asked questions orally so it doesn't affect patients that are having problems with vision, but we have a preference value scale. Like a thermometer, zero to 100, where 100 is perfect health and perfect vision. And when we do this, subtotals for neovascularization is about a 65. Now, preference value is probably a tricky word to use when we speak to the lay public, because we don't prefer to have neovascularization, we don't prefer to have death. But by using this to compare to other preference values that were obtained in the literature, this is an area that there is a big

interest in at Hopkins, and just as heart failure has about a 75. Symptomatic AIDS has about a 58. Chronic liver failure on home dialysis has about a 55.

Macular subchoroidal neovascularization is actually involving both eyes, and we show these scores here. In 792 subjects actually consisting of people with both one or both eyes involved, a minor stroke between 50 and 70, and complete blindness, around 30 to 40. That means that patients value their vision and do not value having this choroidal neovascularization. And when we do cost effectiveness studies using these preference values as a utility measurement, it suggests that unfortunately, even these costly therapies likely wouldn't be chosen by these patients to be able to preserve their vision or improve their vision.

So in summary, in terms of visual acuity outcome, changes in ten or more points on the NEI-VFT really do represent clinical relevant endpoints in our recent clinical trials that would warrant consideration of treatment. And assuming FDA approval, we don't know if it will be approved, but assuming FDA approval, ranibizumab

and other agents are warranted for coverage for evaluations, diagnostics and conjunctive treatment that could lead to decreased numbers of patients. Anything that will reduce the cost of this would be very helpful. And, the products warrant investigations that will determine if other treatments are non-inferior, or even superior to the new treatments that are being developed. Thank you very much.

DR. WILLIAMS: As a service to its members and the public, the American Academy of Ophthalmology developed a series of guidelines called preferred practice patterns concerning characteristics and components of quality eye care. The preferred practice patterns are based on best available scientific data, assisted by panels of knowledgeable healthcare professionals. In some instances, such as the result of carefully conducted clinical trials, the data are particularly well developed and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

Preferred practice patterns provide guidance for the practice, not for the care of a

particular individual. While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients, and the goal of these practice patterns is not to expect a successful outcome in every situation. These practice patterns should not be deemed conclusive of all proper methods of care, not exclusive of other methods of care reasonably directed at obtaining the best possible results. A physician may address every patient's needs in different ways. The physician must make the ultimate judgment about the propriety of care for a particular patient in light of all the circumstances presented by that patient. Preferred practice patterns are not medical standards to be adhered to in all individual situations.

Preferred practice patterns provide treatment recommendations. These treatment recommendations are designed to provide three primary sources of information. Each preferred practice pattern should be clinically relevant and specific enough to provide useful information to practitioners. Each recommendation that's made is given an explicit rating that shows its importance

to the clinical care process, and this should be evidence based. The recommendations are rated according to the importance of care as level A, this is deemed most important, level B, moderately important, or level C, which is relevant but not critical.

The panel also rates each recommendation on the strength of the evidence and the available literature to support the recommendation made. The ratings of strength of evidence are also divided into three levels. Level A would include such things as randomized controlled clinical trials, level two would include controlled trials without randomization, cohorts, case control studies, and level three would consist of studies, case reports, and expert opinion.

The evidence that is cited is that which supports the evaluated recommendation as something that should be performed to improve the quality of care. The panel believes that it's important to make available the strength of the evidence underlying the recommendation, but again, the preferred practice standards are not medical standards to be adhered to in all situations and

they do not supersede treatments that are deemed by the treating physician to be in the best interest of each individual patient. Furthermore, they should not impede traditional diagnostic and therapeutic technologies.

The age-related macular degeneration preferred practice pattern is revised by American Academy of Ophthalmology on a regular basis whenever new treatments or technologies occur that change treatment patterns. The last revision of the PPP for age-related macular degeneration was just approved by the board of trustees of the Academy on September 17, 2005 and is available on the Academy website. Thank you.

(Applause.)

DR. GARBER: Thank you. It is now time for our break. We are a little bit ahead of schedule, but we will resume at ten o'clock on the hour, at 10:00 a.m. we will resume.

(Recess.)

DR. GARBER: Okay. The first speaker will be Charles Semba, from Genentech.

DR. SEMBA: Thank you for the opportunity today. I am Charles Semba, director of vascular and ophthalmic medicine at Genentech.

Because of the time constraints, I will be happy to provide more details in the Q&A session. My objectives today are essentially three-fold. First, to highlight key clinical trial endpoints for patients with wet AMD; secondly, provide a brief summary of the Lucentis clinical development program, and last, remarks on how Lucentis may set a new standard for the treatment of wet AMD.

Current approved therapies for wet AMD merely slow the rate of vision loss, and there remains an unmet clinical need for therapies that will restore and improve vision. The traditional FDA benchmark for approval of new AMD treatments has been to stabilize VA at one year using a calibrated eye chart. With emerging new therapies, a potentially higher bar could be established to help revolutionize treatments to restore and improve vision. These include better ways of characterizing gains in VA, assessing vision-related quality of life, or even assess improvements in anatomic outcomes using newer imaging technology.

Ranibizumab is a protein that is engineered for intraocular use which binds

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specifically to VEGF-A. VEGF plays a major role in regulating abnormal blood vessel growth in a variety of vascular disorders of the eye, including wet AMD. Ranibizumab binds to VEGF and prevents its attachment to receptors on blood vessels, thus inhibiting vascular overgrowth and the disease process.

Our clinical program studies all subtypes of wet AMD. We will be filing our BLA in December and requesting priority review status with the FDA. Our two Phase III pivotal trials are MARINA and ANCHOR. Since the submission of these slides, I'm happy to announce that the ANCHOR trial met its primary study endpoint, as did our other trials thus far. Overall, the clinical program for ranibizumab has demonstrated improvement in mean visual acuity across all lesion subtypes in wet AMD and superiority to PDT in a head-to-head trial.

MARINA evaluated MC/O lesions which represent approximately 75 percent of patients with wet AMD, and met its primary endpoint of less than 15 letters lost on the standard eye chart. But, more importantly, MARINA also met all other key clinical endpoints including clinically

meaningful gains in vision, overall gain in vision versus a decline for the control, and restoration of 20/40 vision, the threshold that allows most patients to drive a car again. Improvement in VA was also supported by clinically significant changes in near and far activities, activities which allow patients to write a letter, read street signs, and function in a visually independent manner.

This slide summarizes the FOCUS results. However, since the submission of the presentation, we announced our ANCHOR results and I wish to briefly review ANCHOR instead. ANCHOR met its primary endpoint and, similar to FOCUS, demonstrated an overall gain in mean visual acuity. ANCHOR and FOCUS both studied the PC population. However, ANCHOR was a head-to-head monotherapy trial that demonstrated superiority to PDT, whereas FOCUS studied the combination of ranibizumab plus PDT against PDT alone.

We are aware that physicians are interested in exploring the off-label use of Avastin. Avastin and Lucentis are different molecules designed for vastly different indicators and routes of administration. Lucentis has been

specifically manufactured and evaluated through a large and robust clinical program over the past several years. We are committed to filing the BLA and getting Lucentis approved and to patients as soon as possible.

Our clinical program involves approximately 1,400 patients followed for up to three years with close monitoring and surveillance. Overall, ranibizumab in MARINA and ANCHOR was safe and well tolerated; the overall benefits outweigh any potential risks. I will be happy to discuss any specific questions about the safety profile during the Q&A session.

In summary, there remains an unmet need for novel therapies that improve and restore vision in patients with wet AMD, not merely slow the rate of decline. Ranibizumab is the first therapy to demonstrate clinically meaningful gains in vision overall in a large Phase III program across a broad wet AMD population. Ranibizumab meets the outcome evaluations as outlined in the MCAC questionnaire and may set a new standard for AMD treatment. I thank the committee for its attention.

DR. GARBER: Thank you. The next

speaker is Robert Vitti, from Novartis.
DR. VITTI: Thank you. I would like to thank the committee for inviting me, and I will be addressing data collection as it relates to wet AMD and patient registries.
A summary of key points, as you have heard from others, the clinical management of AMD is undergoing a revolutionary change with the emergence of new drugs and treatment strategies, as well as transition from merely the prevention of vision loss to gain in visual acuity as the ultimate treatment goal. The perceived need to address these changing trends has inspired the creation of the InSight CNV registry, which is a disease-based registry for evaluating long-term outcomes in all treatment options. The registry purports to address the knowledge gaps in the recurring care, outcomes data on combination therapy in particular, and ostensibly will assist retinal specialists in making informed treatment decisions for their patients. CMS supports expanded collection of clinical data through its CED process.
The goals of data collection are to document real-world experience with no patient

exclusion criteria and no mandated treatment schedules. It's hoped that a large robust population will be enrolled and followed in the long term to ensure clinically meaningful analysis, and the results that we generate will be helpful in generating future clinical trials and will provide a focus on combination therapy. By way of background on InSight, the initial registry was launched at an AAO meeting in 2001. It was open to patients with CNV treated with verteporfin, and while available at the time, it was a wet-based database sponsored by Novartis. The next two slides are just examples of the type of data that we accumulated. This is a summary of enrollees. You see we have 2,500 patients over 112 physician sites. As we look at the subset of patients treated with the combination therapy, we can see that this is a significant proportion of patients over time. These next slides are sort of an example of the type of data that can be obtained from such set of patient registry. Now, the registry is disease-focused rather than product-specific; therefore, it purports to capture the use of all treatment options for CNV/AMD, again,

providing long-term outcome management of the disease and ostensibly locations that might be able to enroll candidates for good randomized controlled clinical trials. Importantly, it is governed by an independent oversight committee. This is just a graphic of the geographic distribution of the participating sites over the 48 states.

Now in conclusion, I don't think it's arguable that treatment options for AMD will continue to increase in the near future. Clinical practice is moving towards combination therapy to treat this disorder and clinicians in the real world will need information to help guide their treatment decisions. Clinical data registries can accomplish this by combining this data, and also, some questions can be raised that need to be answered in a better context with respect to clinical trials. Thank you.

DR. GARBER: Thank you. I would like to remind all speakers to please state your disclosures before you begin speaking. Our next speaker will be Tony Adamis.

DR. ADAMIS: Good morning. Thank you for the opportunity to speak before you. I am

Tony Adamis, chief scientific officer at Eyetech, and therefore have a conflict. My purpose today is to address certain questions that were posed to us, number one, the level of evidence that's required to accept the therapy as being clinically relevant, and secondly, what is the time frame under which these patients should be followed. Macugen received FDA approval in 2004, and it does two important things. One, it inhibits abnormal blood vessel growth, and two, leads to an improvement in visual outcome. Our program initially was small but has grown now to over 1,200 patients at 117 sites. As a result of our Phase I and II studies, it seemed to have promise, was safe and effective, and therefore, we proceeded to two rigorously controlled randomized clinical trials, double masked, which served as a basis for our approval. We entered all patients with wet AMD with these lesion sizes and subtypes, and the endpoint was visual acuity where losing three lines was highly significant. As you can see here, there was approximately a 50 percent benefit to using Macugen, with no variation among the subtypes, and it preserved visual function with approximately 35 percent fewer patients

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progressing to legal blindness when receiving Macugen. Through two years these effects stabilized, and there appears to be a continued benefit of Macugen compared to control. There were subsets of patients who gained visual function. Shown at two years here, 35 percent of patients lost not even a letter, 22 percent gained one line, 17 percent gained two lines, and 10 percent gained three or more lines out to two years. It appears that there is continued benefit for continuing the treatment for two years, at the end of which the results have been excellent.

Of the side effects that have been seen, the most severe is the injection procedure itself and not the drug, as you can see here. And in the second year, the safety profile is quite similar. Further, safety risks are modifiable. With education, with sterile techniques being applied, the risk for cataract has dropped and most importantly, retinal detachment dropped dramatically and statistically was zero at the end.

The most rigorous data, those required by the FDA and European authorities are visual

acuity, which is highly validated, and the data that we've presented and others have presented for the endpoint established a two-year safe and effective treatment for this disease. Thank you for your attention.

DR. GARBER: Thank you. Next speaker, Peter Kaiser, from QLT.

DR. KAISER: Thank you. I am Peter Kaiser, a retinal specialist with the Cole Eye Institute, and am appearing today on behalf of QLT. I as well as my institute receive grants from QLT, as well as all the companies that are presenting today.

CNV progresses from oxidative stress or hypoxia, which causes release of inflammatory mediators and proangiogenic cytokines, leading to inappropriate vascular growth, progressing to exudation, hemorrhage, and then the final aspect of discoid scar formation which typically causes permanent loss of vision.

So what do we have that can stop this? The ideal treatment would be to block this neovascular stimulus; it would prevent the growth of abnormal blood vessels, eliminate the edema and finally, eliminate the retinal scarring that

occurs.
Do we have an ideal treatment? Well, we have treatments that target angiogenesis, and some of the others we've heard about already. We have steroids, which also target inflammation and fibrosis. And finally, we have PDT, which may damage the vasculature and leads to thrombosis of the vessels.
Hence, we believe the ideal treatment may be a combination therapy, for instance, using PDT to block the vascularization and Macugen to prevent angiogenesis, leakage and fibrosis. In ophthalmology and throughout medicine, including HIV and, more importantly, in cancer, combination therapies are being administered with good outcomes, and with the Lucentis results, the bar has been raised. We need to be better than 95 percent moderate vision loss. We need to be better than 95 percent in other visual outcomes.
Some of those who preceded me have indicated that a significant outcome would be a mean improvement in vision. No other studies beside the (inaudible) significant visual gain, three to four line gain in vision. This is very important to us and our patients, but we also want

to see anatomic changes, the lesions decrease in size, we want to see the retinal scarring repaired. And finally, taking cost into account, we need to worry about how many treatments need to be given to patients.

In a Macugen Phase I/II study, vision increased using combination of Macugen with verteporfin. This was a small study at an early time point, and then Augustin, a larger study which has been alluded to already. The Focus study, this was the study design, and the treated patients had the course that we see, with all the patients showing a net loss of visual acuity at 12 months. But the combination treatment, and this is the first clinical trial that actually showed this, had a net improvement, a difference of 13 letters, and this was an area that we want too, improvement in visual acuity, a net improvement over time.

But also, the study indicated that with combination treatment, there were a fewer number of treatments required. From baseline, there were 1.3 treatments, versus 3.4 for the verteporfin alone.

There are also studies now looking at

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the use of combination treatments using steroids. There have been published trials and they generally found combination patients overall had less than a three-line loss of vision, similar to the results we were seeing in the Focus study, and importantly, also seeing improvement in vision with 18 percent having a significant improvement in vision. And again, the number of treatments were dramatically less than the 3.4 we saw for verteporfin alone.

There are also case series looking at steroid monotherapy, and a study looking at a sustained release steroid implant.

In conclusion, we have a pharmacological rationale to use combination treatment, PDT and antigenesis drugs in treating neovascular AMD. The evidence does not support steroid monotherapy at this time. Photodynamic therapy and antigenesis as combination therapy has improved visual acuity outcomes and reduced the need for treatment, but these results were in small studies, and we will need randomized clinical trials to verify these results. Thank you.

DR. GARBER: Thank you. The next

speaker is Jonathan Javitt, who has multiple affiliations.

DR. JAVITT: Thank you for inviting me today. Over the years I have consulted for just about every organization in the room, including CMS back when it was HCFA.

As you just heard, one of the latest trends among retinal specialists is to combine intravitreal steroids with PDT to treat AMD. Ocular steroids are well known to cause glaucoma, and Kenalog contains a black box warning against its ophthalmic use. Conventional wisdom tells us that steroids dry up the lesion and certainly OCT and FA's look better. Anecdotally, glaucoma and cataract specialists are reporting an uptick of patients presenting with glaucoma and cataract subsequent to receiving intravitreal steroids. No clinical trials have ever shown the safety and/or efficacy of this practice and there has been no long-term follow-up series reported yet.

There are various techniques for how one uses it for analytic purposes, but how we did it is all in the slides. Basically we set up three study cohorts and one controlled cohort, a cohort of those who received PDT and no

intravitreal steroid injection, those who received neither PDT nor steroids, those who received steroids only, and those who received steroids plus PDT. And what you can see is a substantial difference in the likelihood of onset of glaucoma among those who received intravitreal steroids and those who received intravitreal steroids plus PDT compared to those who received neither steroids nor PDT over the course of 1,250 days of observation. This is a survival curve showing there is a glaucoma-free interval.

So if you do that as a Cox proportional hazards model and look for the risks, intravitreal steroid injection alone places a 4.2-fold increased risk of the whole onset compared to no steroid injections, and Visudyne plus intravitreal steroid injection is associated with a 5.8-fold increase in risk of glaucoma in these patients compared with no steroid injection or PDT alone. There was no appreciable risk for cataracts, by way of contrast.

So where are we? Well, the use of intravitreal steroids, not surprisingly, seems to be associated at least in those Medicare beneficiaries who receive the therapy, presenting

a higher risk for subsequent glaucoma than having no therapy or PDT alone. Steroids plus PDT are associated with an even greater risk. And there is no detectable increased risk of cataracts. So, I guess my point to you today, and I'm speaking specifically to Question 4B and Question 5 before the panel, is as we race for the cure, as we search for efficacy, we really have to keep our eye on safety as well.

The Secretary's office of services identified drug safety as a key component of this 500-day plan, and the safety risk that's identified associated with the use of PDT or steroids is not widely appreciated or talked about in the retinal community today, but what the risk of glaucoma is, it's increasingly talked about and the warning on the steroid box is, you know, clearly there. 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 injection, and as we continue the off-label use of new medications even absent FDA-monitored clinical trials and in the absence of FDA premarket approval, it is critical that we make a real effort to monitor ocular and systemic

safety issues. This is particularly true in medications with documented risks of severe adverse events such as stroke. Thank you for inviting me here.
DR. GARBER: Thank you. Next speaker, Carmen Puliafito, of the Bascom Palmer Eye Institute.
DR. PULIAFITO: Thank you very much. I am a consultant for Valcon, Eyetech, Genentech, and Zyte, and as co-inventor of OCT, I participated in international property agreements with my former employer, the Mass Eye Ear Infirmary. I would like to speak to the use of OCT in making clinical decisions in retinal pharmacotherapy.
OCT is a technology which takes multiple scans of the retina and gives us transverse information about the retinal structure. We receive information about fluid and blood, traditionally we used angiography, but we know now that there are structural elements to vision loss, macular edema, fluid under the retina, PED, and OCT sees that.
What are the advantages of OCT? It's rapid, non-invasive, pain and risk-free, and it

provides qualitative cross-sectional imaging and ultimately provides quantitative data. What do we use it for? It identifies fluid in the macula, it shows response to therapy, it shows when a treatment effect is wearing off, and it decreases the overall number of treatments by allowing the physician to treat only when needed. So we believe that this technology is broadly applicable for all anti-VEGF treatments, and have found it useful in using Macugen, ranibizumab and other agents.

At Bascom Palmer, Dr. Philip Rosenfeld is dong a prospective study in which OCT is used to evaluate eyes in a very aggressive way following initial therapy and then we are going to evaluate its usefulness in making clinical decisions. This is an eye treated with ranibizumab and you can see over the first seven days a restructuring, remodeling of the retina correlating with visual improvement. So we view this as valuable to clinicians going forward and as we look further out, here's 30, 60 and 90 days after initial treatment, we could monitor retinal structure and subsequently make decisions.

There is a correlation between central

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retinal thickness and visual acuity in patients treated with anti-VEGF agents. Here you see a decrease in retinal thickness over the first three months of therapy with ranibizumab, correlated with changes in visual acuity.

Fluorescein angiography, which has been the gold standard to date, does have a slight risk of anaphylaxis, which does require the injection of fluorescein, and it is a more expensive test. And here is that same patient examined with fluorescein angiography. What you will see if you're not an ophthalmologist is that this is a qualitative change and we get lots of structural information.

So I would agree with Dr. Bressler, we need to do more studies looking at the clinical decision-making process around the use of anti-VEGF agents because we know that they are going to be widely employed, and the greatest value of OCT is probably the demonstrated treatment effect, and then following patients and withholding therapy until needed. Thank you very much.

DR. GARBER: Thank you. Our next speaker, Timothy Stout, from Prevent Blindness

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America.
DR. STOUT: Hi. Thank you for asking me to present today. My conflicts of interest include being a consultant to Pfizer, and my institution receives grants from many of the companies that are here presenting.
I was specifically tasked today to present to you questions about point one and modified point five. As you know, it's been mentioned before that age-related macular degeneration is a significant problem, it's estimated that in the next 15 years the number of people severely affected will move from 1.7 million to nearly three million people.
How do we currently follow these people? Question 1 in the form was, which of the following tests are reasonable ways of following patients who have age-related macular degeneration? We performed a 23-physician telephone survey to ask that question. Half of the people that we surveyed were in academic centers, half the people were in private practice, all of the physicians were retinal-only practices, and two-thirds of them did surveys off medical records.

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The question was posed on a one to four scale, and these are the results. People felt that visual acuity, that they were highly confident that was an important question to ask in assessing how pervasive AMD was. The VFQ 25, highly confident. The Amsler grid, that was somewhat confident. Glare recovery was minimally confident. Contrast sensitivity, somewhat confident. Fluorescein angiography, highly confident. Visual fields, somewhat confident. Ocular coherence tomography, highly confident. So that's the results of a poll, and all these retinal physicians were on the west coast. They felt that the gold standards, visual acuity, fluorescein angiography and ocular coherence tomography defined, were best employed as short-term evaluations over three months. Obviously over a longer period of time, visual acuity, fluorescein angiography and VQF 25 are used as well.

I will skip over our current treatments.

The last thing I was asked to do was briefly mention what are our current tasks in our knowledge regarding macular degeneration and what

kinds of questions should be answered, and as you know, there is quite a bit of information on locally delivered therapy. Some of these specifically target vascular endothelial growth factor, some of these include the neuroprotective and anti-antigen factors, (inaudible) steroids, which are certainly interactive, and other drugs that interact with proteins.

In discussing the current gaps of knowledge with these retinal specialists, these were questions that came up over and over. One was the genomics and proteomics of disease susceptibility and progression. The cell biology of the dry form of macular degeneration, how the retinal cells die, what's the process of that, what is actually taking place. What is the potential and practicality of stem cells for either neural activity or endothelial derivation, how can they be manipulated and how can they be put into good clinical use. People felt that there were a number of questions about vascular permeability, and although we have heard a lot about anti-VEGF growth factors, certainly that's not the only factor involved. And then a final comment that we heard repeatedly, what's the role

of the immune system, specifically complement factors in age-related macular degeneration. So those are the some five points that repeatedly came up over these phone interviews that people shared, and we feel these are current gaps in our knowledge and deserve attention. Thank you very much.

DR. GARBER: Thank you. I think this is a dual presentation, T. Mark Johnson and Bert Glaser, from the National Retina Institute.

DR. JOHNSON: Thank you. My name is Mark Johnson, I'm a practicing vitreal retinal surgeon. I've been an investigator in all the trials that we've discussed this morning but I have no direct financial interests.

The points that we would like to bring forth this morning are three. One is that improvements in traditional imaging techniques will offer improved both outcome measures as well as methods of understanding the pathophysiology of macular degeneration. Secondly, as has been alluded to, the combination of traditional techniques including laser with new pharmacological techniques will offer improved opportunities for visual outcomes. And thirdly,

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combining these two points and improving our understanding of macular degeneration will allow us to develop individualized treatment directed at specific subtypes of macular degeneration. This list is familiar from this morning's discussions. New technologies in terms of imaging such as dynamic or ICG imaging, OCT and possibly macular microphoto imaging. Current therapy approaches including laser treatments as well as pharmacologic treatments are now at the point where we can begin to combine treatments. Angiography continues to improve and provide important information on vascular physiology. The advent of dynamic imaging allows us to better understand not only the pathophysiology of what macular degeneration is, but also begins to identify subtypes of macular degeneration that may differ from a biologic and treatment perspective, including primary intraretinal angiomatous proliferation or RAP lesions, as well as polypoidal neovascularization. This is a high speed ICG of a patient, and you can see that the high speed ICG actually allows us to identify and characterize these lesions, particularly isolating intraretinal from

the subretinal components of these vascularizations, thus allowing us to apply directed therapy.

Laser treatment does continue to offer certain advantages, including the ability to provide limited therapy with a limited number of treatments, obtaining rapid and stable results, as well as the opportunity to be combined with pharmacologic therapy.

In this case, using a high speed ICT, treatment is applied to a very isolated area of the lesion and when combined with a single injection of intravitreal medication, provides both objective and subjective conclusory responses which sustain at least six months out in our experience to date.

I'm now going to allow Bert to conclude our presentation.

DR. GLASER: My name is Bert Glaser, and I am a practicing retina specialist and I have been involved in many of the clinical trials that have been discussed today, but I have no financial interest in any of the pharmacologic companies.

We talked about the use of high speed ICG angiography and that addresses one of the

questions which talks about, 1B, which other currently available outcome/intermediate measures should be considered? And we want to emphasize to you, the use of dynamic high speed ICG angiography provides much more detailed views of the neovascular process.

In this case here, this is of course an angiogram showing the extensive lesion. Unfortunately, the movie didn't play before, but the movie shows how you can identify each individual vessel within this and identify vessels that are actually forming the feeder, like a stem on a leaf, that you could then isolate and treat in a very localized fashion, and this is another approach to refine those treatments.

Here you see a patient where it shows the fluid under the retina and then three days later after treating the feeder vessel, you were able to collapse it and improve vision. In addition, in this series, and this is a series that's going to be presented very soon at a national meeting, you combine this with the intravitreal (inaudible). And normally when you see these feeder vessels, you're not going to retreat several times in the first three months

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and then retreat subsequently over the year. However, in this series of patients, we were able to combine it with individual treatment, and we reduced the need for retreatment substantially, and only one patient out of 17 needed to be retreated within a six-month period. It was a small group, but at least some data starting to get at the multiple different types of treatment that we can use and looking at parameters including visual acuity, but also the number of treatments necessary. Intravitreal injections once a month or once every six weeks are rather daunting for a patient. Laser should not be discounted and it should be kept in the mix, we believe, because it is a relatively low cost reproducible method. Also, improvement in imaging techniques is going to be very important, and combination treatments, again, are likely to play an increasing role, as you have heard a lot this morning. Future trials are going to be important. A lot of small pilot studies may be necessary to help sort this out because the number of patients with macular degeneration, while large, is not infinite, and that's going to be one

of our big challenges, how do we get enough data, enough patients to be able to assess all these permutations that we need to and want to look at, and that is a true challenge. Quality of life analysis and also a cost analysis is going to be very important, not only cost analysis from the provider standpoint, but a cost analysis from the patient standpoint in terms of time out of work, time out of other productive activities, since all of us who are older and healthier are working longer, so I think that needs to be put into play. So in summary, we want to emphasize the importance of new imaging techniques to be combined with existing techniques. We want to also emphasize and join the people who were talking about the importance of combined treatment and broaden the number of permutations that we can include and the way we measure success of these combined treatments. And the ultimate goal is to remember that AMD is a complex varied disease and we really need to have the goal of being able to individualize treatment so we can improve outcomes for each individual patient at their particular stage and type of disease. Thank you very much.

DR. GARBER: Thank you. Our final

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scheduled speaker is Jason Slakter.
DR. SLAKTER: Thank you very much.
Jason Slakter, practicing retinal physician in New York City. Transportation for this meeting was provided by Alcon Laboratories. I have had consulting and working relationships with I think all of the companies involved in AMD treatment today, but I'm really here to discuss what I think is important from a patient point of view.
If we can skip directly to slide 18, you have already heard about some of the monotherapy approaches, including the use of Macugen, Lucentis, Retaane and other treatments. We've heard already over and over again about the use of combination therapy and I think as a group we're going to have to deal with it because if you haven't figured it out already, you will certainly have to deal with it in the future.
Monotherapy for CNV has certainly given us some remarkable results. We went from acute to moderate vision loss and more recently to a state where we can often offer the patient the opportunity for improvement in visual function.
The problem is, some people say look at the data. We now have 95 percent of the patients who have

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less than three-line vision loss, we have the ability to take 30 percent of our patients and give them three lines of vision gain, look how far we've come. I strongly urge asking, what have you done lately? 30 percent is great, give me 50, 70 or 90. When I walk out of my office with every patient 20/20, I'm satisfied.

So I think we need to look forward. We need to start with a combination of therapies to make better vision outcomes, decrease the growth of CNV, which I think will translate into better visual function. And reduce the risk of vision disturbances both from an anatomic point of view and quality of life point of view.

We all know that there are many steps involved in the angiogenic cascade of a downfall in vision, and the nice part of the complex system is that we have multiple points at which we can attack the process, and we can inhibit or reduce the growth of neovascularization. We've heard already about the angiogenic growth factors such as VEGF, there are inflammatory mediators, there are cytokines involved in the process, and obviously many of them are already in development in fibromacular tissue and certain growth factors

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associated with those. We do have experience to date, although in a limited fashion, with verteporfin therapy or PDT plus a number of other agents, and I will quickly review a couple of them. We've already heard from Peter Kaiser about the Spaide trial for steroids, this was the first published trial, a small number of patients given both photodynamic therapy and steroid, and that was the first study that we showed the improvement in visual acuity rather than simply the stabilization or less loss of vision that we were used to. Most importantly, again, this from our point of view will be very critical to look at, the number of treatments was reduced, and that is very important from a quality of life point of view, from a cost point of view and, as we've heard already, from a safety point of view. Fewer treatments and better visual outcome means a better life for our patients. The larger study by Augustin in Europe looked at 199 patients with PDT and triamcinolone, he saw an average of about 1.25 treatments, he did see some problems but visual acuity was improved, so he said we have to look at safety, but also outcomes. There are a number of clinical trials

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currently under way to answer the question in a statistical manner whether or not combinations of PDT and steroid will in fact improve visual outcomes.

We've already heard the combination of Lucentis with photodynamic therapy had better vision outcomes than we would normally have expected, PDT alone 68 percent, versus 91 percent with a combination treatment, with reduction in vision loss, improvement in visual acuity, better with combination therapy and again, fewer treatments of PDT in the combined treatment group than in the treatment with verteporfin therapy alone.

Anecortave acetate, the final trial, as discussed earlier, is a treatment delivered outside the eye on a six-month basis, and compared it to combination therapy or with sham treatment groups, and what was found was that although visual acuity was declining in this small study, the treated with PDT alone didn't work and the combined treatments did better. What was interesting was that the use of anecortave with PDT, again, reduced the need for verteporfin treatments and in small groups receiving both

showed improvement in visual outcome, suggesting that less may in fact be more in the long term. What can we conclude from these studies? Monotherapy, while exciting for CNV and raising the bar as far as treatment of visual function, does have limitations for our patients. 30 percent is great, 50 percent would be better, and 100 percent would be ideal as far as visual improvement. Certainly there is a clinical and preclinical rationale for the use of combination treatments such as PDT and other agents for treating neovascular AMD. And we want to look at some of these combination therapies that improve visual outcomes, reduce the need for treatment at follow-up, and the results from the trials that are ongoing now hopefully will establish a magnitude of benefit.

I just want to conclude with one addition. We've heard about the VFQ study and we all know about the visual function 14 questionnaire. I noticed that in this discussion that something is missing. We looked at the impact of the disease on vision, we looked at the impact of the disease on quality of life. We have to start looking at the treatment on quality of

life, let's look at the treatment and decide if the treatment had an impact on our patients, and that's going to be important as we assess these treatments in the future. Thank you very much.

DR. GARBER: Thank you. Thank you to all of the scheduled speakers for some very informative presentations, and I hope you will all be able to stick around for the session where we will be, have additional questions for you.

We now enter the period of open public comments. There are nine people who signed up. I would like you to line up by the microphone up here in the front of the room, not on the podium. Please state your name, your affiliations and disclosures, please. You will have two minutes each. Two minutes. These are the people who signed up as open public speakers.

MS. EARNSHAW: I'm Stephanie Earnshaw. My travel here was funded by Eyetech and Pfizer, and I do consultations for Eyetech and Pfizer. When we considered cost analyses becoming more and more important, these data have been supplemented with health economics perspectives. Visual severity and visual acuity have been key in performing economic valuations of cost expected

analyses and cost unit analyses when evaluating treatment for AMD, and this is all due to availability of the data that is out there. So I just wanted to bring that out, that visual acuity is important when looking at cost.

DR. GARBER: Thank you. We have eight other people signed up here as open public speakers. Okay.

DR. FRIBERG: I'm Tom Friberg, from the University of Pittsburgh. I was one of the principal investors in the AREDS trial and I've been involved in almost all these trials that have been discussed. My way was paid by Pfizer today. I'm here primarily as an advocate for my patients today and that is, with CMS and MCAC, your position is really more influential than ever, and many of us and many of our patients make the assumption that if something is Medicare-approved, that it is both effective and safe. I have more problems with safety rather than efficacy. If we try it and it doesn't work, sometimes these diseases are difficult, but with respect to safety, I think we have a higher barrier.

I am particularly concerned about the

use of anti-VEGF agents that have not been carefully studied and I am afraid or I'm worried about the low event rate that occurs with some of these safety issues requiring actually large numbers of patients to be evaluated. And I really do hope that we don't become where a treatment that is improved, at least by MCAC or CMS, turns out to be another Vioxx. Thank you.

DR. GARBER: Thank you.

DR. GRAGOUDOS: I am Evan Gragoudos and I am from Los Angeles and am a retinal specialist and director of a retinal service there. I would just like to make only two comments.

One is that you have quite a lot of studies that now are at different stages, and I would like to emphasize as far as clinical trials, I was involved in a trial concerning the dry type of the disease, and we had two studies that were randomized to show benefit, and although the numbers were small, we did a big study, and the feeling of the group, it was not good for microgeneration and also the side effects of the disease. So you have to look at randomized trials because A and B is a very important decision and could be easily deceived.

The other issue is, I think we have to insist on visual acuity as the primary endpoint. All of the other endpoints such as individual acuity, quality of life, et cetera, et cetera, are important, but by far, I think the visual acuity is the most important point for judging these results.

DR. GARBER: Thank you.

DR. SANDERS: I am Reginald Sanders, a practicing retinal specialist in the D.C. area and I also represent the American Society of Retinal Specialists. I briefly would first like to thank you for the opportunity to speak and I'd like to admire the presentations done today.

I would just like to say that as a practicing retinal specialist, if clinical trials are done for a certain medication, that's then a starting point for us, but our clinical experience in the field as we find out what really works, and certain drugs that show clinical benefits in a study, we find out and the point has been made about the outcomes for treatment and their efficacy don't always bear out. So I would like to plead to the panel and CMS to allow us as practicing retinal specialists, to have, as best

we can, unfettered access to the different treatments so we can decide for ourselves and see for ourselves what works and doesn't work for our patients.

DR. GARBER: Thank you. Any other public comments? Then we will -- we're a bit ahead of schedule, but the next agenda item is for questions to presenters. So this is for the MCAC panel members to ask questions of the presenters. Your questions of course should be directed toward information that will help us to answer the voting questions, so let's open it up to the panelists. James.

DR. PUKLIN: I would like to ask Dr. Brechner if he would care to elaborate on some of these long-term potential complications that smaller studies for a shorter period of time may not reveal. Do you have anything in mind?

DR. BRECHNER: For instance, the use of intravenous Avastin on label for colon cancer has a safety profile that's not so good, and I think the product has a black box warning, although the disease is very serious, and assuming the risk of taking IV Avastin might be okay for them. But for us to make the assumption that because we are

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putting such a small amount of drug inside the eye when we're using intravitreal Avastin, that there is no way that this could cause any serious side effect, I think this might be very misleading. I mean, we have other agents that we use in ophthalmology where we can put one drop of let's say Asimilol on a person's eye and they can have a cardiovascular side effect or event.

So these drugs we use are potent. I'm not saying that Avastin might not be a breakthrough with respect to its treatment efficacy, but I do want to make sure that it's safe, and I don't believe that the safety issues have been well worked out, and I don't think it's really correct to have our Medicare recipients be the ones doing that safety trial.

DR. GARBER: Mark Fendrick.

DR. FENDRICK: Thank you, Alan. I actually have a question for both Dr. Brechner and the Duke team. One of Mr. Caplan's first comments was that 90 percent of the people who have macular degeneration have the dry type, which we've actually heard nothing about. And I was concerned by the semantics when Dr. Brechner said, which I'm not sure is correct, that you can either go to dry

or wet, and you don't proceed through dry to get to wet. So if you could just inform us a little bit more about the natural history of someone who is diagnosed with age-related macular degeneration which is dry, which is far more common to the wet. And then to the Duke team, what do we know about the quality of life study specifically in the 10 percent or less of people who actually have the wet lesions which all of the treatments have focused on? I guess I'm trying to help get to Dr. Brechner's point, that we've heard nothing about the substantial majority of the people, how we diagnose them, how we monitor them before they get to these fine specialists who provide care to them. Is there anything we can do or anything we can just think about doing for restoring these people's dry lesions before they go onto wet?

DR. BRECHNER: Within CMS, it is felt that the geographic atrophy is more serious than just the early type where you just get bruising. The schematic was attempting to show that even though it was classified as late stage maculopathy, it was a result of neovascularization.

DR. FENDRICK: And does it affect most

people?
DR. BRECHNER: Yes. It's not essential that we see it, but it may pop up a little.
DR. FENDRICK: Are the predictors of dry to wet understood, or not understood?
DR. BRECHNER: Yes, they are understood. I mean, things we talked about are predictors for progression of AMD, and we don't know exactly why some people progress and some people don't. With respect to the dry AMD, the question that you asked, the one study that I did not put in was the study of people who had not progressed to wet disease and that was, that predominantly people who had dry macular degeneration or no macular degeneration at all, and they were randomized to the different kinds of, you know, vitamin treatments, et cetera. So that study was significant in terms of what we have to offer, it was a combination of antioxidants and zinc.
DR. FENDRICK: So, do people with dry lesions have severe vision problems as well? I'm trying to figure out, if such a small percentage, or if 90 percent have this, these people with dry

lesions that actually present to us in primary care than this small percent of wet lesions.
DR. BRECHNER: There is a whole spectrum. You can have signs of macular degeneration without the symptoms, but one of the slides that I showed showed the kind of things that can happen with early macular degeneration where there is a little bit of blurring in central vision, but that's just one person. So there is that whole gamut, the whole spectrum of effects on vision.
DR. GARBER: Ron, did you want to make a point on that question?
DR. KLEIN: I think we use the terms dry and wet more as a way of referring to patients what type of macular degeneration they may have, but in terms of affecting visual acuity itself, the advanced stage of macular degeneration that we would be concentrating on, and they are the geographic atrophy and the neovascular AMD that has severe effects on visual acuity, not the Drusen themselves and the Drusen pigmentary changes. And if you look at the prevalence of both those lesions, in non-Hispanic whites in America, they are about equal, the global

neovascular AMD and geographic causing visual loss in the present populations. But as you look at the long-term incidence in the younger people over 15 years, it's the neovascular that's more frequent, more than the geographic. But if you look at patients 85, it's seven times greater geographic than neovascular. So after 85, if you're 85 and have escaped the late changes, you are more likely to develop the geographic atrophy causing loss of vision, and there is a need for drugs or approaches that will reduce the progression of the Drusen to the advanced stages of the geographic atrophy, but that's not really the subject of this meeting.

DR. GARBER: Bill, is it on this point?

MR. CLARKE: Yes. On an epidemiological level, are they even the same disease?

DR. KLEIN: Good question. There is a lot of good work out there looking at the factors that lead people to develop Drusen in the first place and why some people go on to neovascular stages versus atrophic stages, and we are slowly working this out. We have found various genetic factors that neovascular takes, and there is less

information about the atrophic process, why that occurred, but I think there are different stages of macular disease where reasonable steps such as smoking will progress to neovascular.

MR. CLARKE: Just to clarify, the atrophic disease, that appears to be a different process from the dry or from the wet, and I just wonder, is that always the end stage of CNV?

DR. KLEIN: The end stage of CNV would be the fibrotic destruction of the retina which occurs usually acutely and there are drugs to prevent that. In some cases the natural progression is that fibrosis may lead to an atrophic stage and the geographic atrophy is actually slowed. The Drusen generally aggregate together and then some of them begin the retinal destruction when certain photoreceptors die. So it's possibly and probably a different process that occurs from different factors, both environmental, genetic, and there's probably many different genotypes being lumped together in the event of AMD and geographic atrophy.

DR. GARBER: Ivan, I think you were ready with your response.

DR. SUNER: Ivan Suner, from the Duke

team. Alluding to Mark's previous question, I think it's a very salient and pertinent question. I think we are focusing on limited therapies for the wet AMD and that's where we see a significant impact. I think we are all taking a step back and looking at the dry AMD, basically because that is a bigger pool of patients, and if you can somehow prevent them from becoming wet, I think that's where the holy grail will be.

And I think what we're going to see over the next few years is again, as Dr. Klein was alluding to, we're trying to look for pre-lesion conditions, and I think as we're learning more, these are genetic factors, we've already seen on various studies and it has been confirmed now, that it may be that a complement factor or chromosome one account for about 42 percent of AMD patients. A second mutation of chromosome ten now confers a 50-fold increase for the risk of AMD. So we believe genetic factors are important in this sort of matrix when we put together genetic factors, biologic factors, inflammatory markers, and other dispositions like smoking.

So I think in the end as we go along, we will come up with a matrix and tell the patient

with a very early form of AMD, you will not progress to wet AMD, you're okay, and maybe with dietary considerations you will be okay, versus a patient that we know will progress to wet AMD. Hopefully in early stages we will recognize that with this matrix and be able to intervene with pharmacologic, dietary, or other forms of intervention to prevent that progression. So again, I agree that we are focusing on the wet AMD which may be a smaller pool, albeit the higher impact pool, but I think in the future as we go forward with more trials, looking at other imaging technology, other forms of angiography and OCT, and the other cast of biomarkers and serum, we may be able to have a matrix to have predictive value and hopefully tailor therapy to prevent this disease.

DR. FENDRICK: Can you answer specifically a question? The sophisticated analysis that you and Dr. Matcher presented about the sensitivity and the interactivity of the quality of life measures across the board of AMD, have you looked at those specifically in the wet patients, the CNV patients, because these patients have had bad eyesight for a long period of time

and as we know from other diseases, the applicability to certain conditions really will throw off the quality of life measures over a period of time.

DR. SUNER: That's a great point.

Again, part of the difficulty is that many of these studies look at a very heterogeneous pool of patients, so some of them reflect a population with 10 or 15 percent that have wet versus the ones that are normally seen. The ones that are more clean, the ones that look ar a particular intervention in a very defined patient population, which includes the submacular Drusen trial, or you can assert a patient population that has bilateral wet disease, or unilateral wet disease, and so you're looking for a study with a staging characteristic for dry AMD. And in those you are able to tease apart some benefit on the quality of life evaluation in the NEI-VFQ. And again, that's particularly the SFT, the AREDS, but these have to be very well-defined patient populations where you have similar risks of progression and similar clinical phenotypes of the disease process.

DR. GARBER: All right. Cliff Goodman and then Michael Abecassis.

DR. GOODMAN: The first question that we need to answer seeks to distinguish among measures, direct and intermediate. I think I know which six of those are direct measures of visual outcome and I think I know which five of those are intermediate endpoints and I was hoping you could confirm that for us. I think that will help us in our subsequent discussions of the 11. Ross, do you want to give it a try or do you want me to give it a try?

DR. BRECHNER: Go ahead. I'll grade you.

DR. GOODMAN: Well, I think that the direct ones are visual acuity, VFQ 25, extent of CNV, glare recovery, contrast sensitivity, and visual fields. So those would be the direct measures of visual outcome, and the others would be intermediate, which are more kind of biologic markers, extent of CNV, Drusen extent, geographic atrophy, fluorescein angiography, and OCT. Am I about right on those, that the latter five would be the intermediate endpoints?

DR. BRECHNER: Yes, five would be intermediate endpoints.

DR. GOODMAN: So we have six direct and

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five intermediate.
DR. BRECHNER: Yeah, and of the ones that are direct, visual acuity has the most --
DR. GOODMAN: I'm not into that just yet, but that's a breakdown of the six and the five?
DR. BRECHNER: Yes.
DR. GOODMAN: Next question. Judging from the Duke team's presentation, though, it seems as though they also discern that the VF 14 might accompany the VFQ 25 as another valid measure of psychometric and other problems.
DR. BRECHNER: Yes, they did say that.
DR. GOODMAN: Would you agree to include the VF 14 with that?
DR. BRECHNER: Well, quality of life, yes, but that's up to them. But I would, yes, I would be inclined to think that based on their conclusions, so we may want to say quality of life instruments, VFQ and VF.
DR. GOODMAN: Okay. And then finally, did your evidence analysis look at the association between these indirect endpoints and the direct measures of visual outcome, did you look at the association or correlation?

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DR. BRECHNER: Yes. I mean, I looked at everything I could find. There's very little data on that, associations in general quality of life instruments and some of these other measures. There are occasionally, like I mentioned one where they looked at fluorescein angiography and OCT to see whether or not there was a visual field finding, and fluorescein angiography was looking at it in between, but there was very little hard validated reliable data on those.

DR. GOODMAN: Hard reliable data on the association between the intermediates and the directs, is that what you're saying?

DR. BRECHNER: Yes.

DR. GOODMAN: That's what I thought.

DR. BRECHNER: Yes. I mean in general, although visual acuity is widely used, there is a paucity of real validation, standardization of reliability.

DR. GOODMAN: You're talking about within measures of validity for that standard, but I was asking about the association or correlation between the intermediates and the directs.

DR. BRECHNER: There is almost no data.

DR. GOODMAN: That's very helpful,

thank you.
DR. GARBER: Cliff, I think this was a very appropriate question, but we will also undoubtedly want to explore these in more detail during the panel deliberations, because you've really gone to the heart of some of the voting questions with your questions to Ross.
DR. GOODMAN: Absolutely. I just wanted to make sure I understood what they presented to us.
DR. GARBER: That's perfectly appropriate, but we will go into this in more detail later. Next is Michael and then Harry.
DR. ABECASSIS: I have a general question about these quality of life studies and I guess I would direct it to the group from Duke. And maybe I'm just applying something or maybe I'm just not very smart, but I think if you are trying to validate a tool and you use something like visual acuity to validate the tool, and then you use some of the other quality of life tools to validate a specific quality of life tool, and then you present a study like the Macugen study where you show an impact on a primary endpoint, visual acuity let's say. And then you say that you feel

more confident about the data because you have juts demonstrated that you see a similar impact on quality of life which used the primary endpoint as validation, are you not going in kind of a circle? Is there not a hole in the logic? I'm not an epidemiologist, but it would seem to me that there is a hole in that logic. So my question has to do with the validation of these quality of life studies, because I think part of our decision is going to be what types of endpoints are important in studies that are coming up. If I'm just stupid, just tell me.

DR. SUNER: I think we're all in the same sort of haze. I guess from my clinician standpoint, part of these quality of life instruments help explain why a patient may lose two lines of vision with treatment and be very happy, and then you have a patient who gained two lines of treatment be very upset at you, and it's a complementary tool. I don't think, it's easy to take the shortcut, but I would disagree with that gross statement, saying I think it's a complementary tool to visual acuity that is more specific to patient needs, more specific to real life situations.

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In our report we also talked about performing task instruments, which may be a better test, because you're watching somebody put string through a needle or whatever, tasking them and defining some steps, and that may be a better standard than a visual quality of life instrument. However, again, it's tough to reproduce, they are difficult to carry out in a large trial. So again, I think that there is some similarity. I have some reassurances that there is a correlate with an objective measure, be it visual acuity, be it reading speed, be it driving a car. But again, I think that in the end you're looking at the patient individually and trying to assess their visual needs, and my point is that these quality of life measures are complementary as opposed to stand-alone or a surrogate to pure visual acuity. Again, it's a very circular argument to be made, but when you look at an individual patient, I think it's very helpful. Again, 80 percent of the patients, how are you being impacted by what you have, be it dry disease, wet disease, treatment, how are you impacted really? And this is different than visual acuity which is just a sheet, as opposed to

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talking to the patient to see how they are impacted in their day-to-day activities in a social situation.

DR. ABECASSIS: So the day-to-day data is more of an epidemiologic point of view?

DR. MATCHER: My only goal here was to talk directly to the personal values. Really, the whole point is we're asking a question about this whole notion of validity, and really the starting point here is that we're asking a question that patients care about, what is it that you do with your vision that you care about that you can't do now that you could do before, or that you can do now that you couldn't do before. So, there is this notion of face validity or content validity saying we have questions that as human beings we all acknowledge make sense, we have questions that we care about.

But then you get into the issue of, well, does it have psychometric properties, that's the whole range of properties a measure should have, and that's something that's worth using in the context of a study, you know. So you want to know, for example, if this measurement says, if you're going to say that they have better visual

function, would it make much sense that that measure also corresponded to worse visual acuity, and that would not make any sense. So it's not that you're using it to validate it, but you're using, directing the question to a measurement that you thought was face valid, does it make sense in some subgroup that you would get responses that you hoped for, or would you get responses you felt were not appropriate.

DR. ABECASSIS: But if it's efficacy that we are trying to define, then shouldn't you be looking at a solid primary endpoint?

DR. MATCHER: Which might be what?

DR. ABECASSIS: Which might be visual acuity.

DR. MATCHER: But the point is that visual acuity doesn't necessarily correspond to what people can do nor what people perceive those capabilities. So the point is, what people really care about are these quality of life questions. The issue is, how do we ask them in a way that we can then use them in a larger environment, clinical research and ultimately clinical practice.

DR. GARBER: I think Jonathan Javitt

may have something to add there.
DR. JAVITT: Well, I'm one of the people who wrote the VF 14 and validated it to begin with, and to the extent there are questions about the VFQ, its grandfather is here in the room also, Dr. Ellwein. But it would be a great mistake to state that either of these instruments were developed in order to find another way to measure visual acuity.
They were developed with the recognition that visual acuity as perceived by a patient in a dark room looking at a brightly lit eye chart is one small piece of the question of how that patient sees. And one of the things these instruments teach you is that they correlate relatively perfectly about an R square .3 to .4 with visual acuity. If a patient is coming in and telling you that they see terribly, they can't do anything, and yet when you measure them on an eye chart, you refract them down to 20/30. Correspondingly, a patient may have 20/50 on an eye chart, but they get around and do what they need to do in their lives.
So when these instruments were developed, large groups of patients in focus

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groups were asked about their lives, asked about the dimensions of vision that are most important to them, and that's how the questionnaires were developed. It's only as a secondary validation test so we could say okay, now that we've developed these from a psychometrically appropriate perspective and measured the patient's concerns, how do they happen to correlate to other measures, including visual acuity, including contrast sensitivity, including things like the SF-36 which measures general health status. So it would be a mistake to think that the visual acuity drove the validation, which leads to a circle. While I have the microphone for a second, as a non-retinal specialist, to go back to Dr. Fendrick's question, macular degeneration is very simple if you're a non-retinal specialist. It is the progressive death of retinal epithelial cells with their overlying photoreceptors. Dr. Klein has spent his life studying macular disease and I don't think he will disagree with that. Now if you get to the point where all the retinal pigment epithelial cells have died, you've got geographic atrophy and it's very likely that those people will blast off into the wet phase of

macular degeneration. But if along that path of degenerative disease, you get a very (inaudible) membrane, you are almost certain to blast off into the neovascular phase, which can then lead to acute vision loss.

And the question what can you do as an internist is to do good patient reporting, get them wearing hats, get them wearing sunglasses, get them to think about not smoking and taking vitamins.

DR. FENDRICK: As a follow-up to my first question, and those of us who've done a lot of MCACs have heard about surrogate markers in 25 different diseases in response to a very simple question, tell us how the surrogate marker links to the clinical outcome that matters. And I'm happy to use the Duke scale or your scale, or anything where the patient says this is impacting my life, my vision is impacting my life. Why don't we know more about how these objective measures that we hear and see, whether it's fluorescein or other types of imaging, why don't we know about how these things relate to vision changes?

DR. JAVITT: Macular degeneration, you

get people who were stable for years and then people who go into blast crisis, okay? The neovascularization is a blast crisis, that's the blinding of your eye. And most of these surrogate markers that you're hearing about are markers for identifying an acute phase of the disease for which we suddenly have new therapies and can keep people from going blind overnight. We don't yet have therapies that can deal with that chronic stage of the disease that leads to geographic atrophy other than hats and sunglasses, and you're the guy who prescribes those to your patients.

DR. GARBER: Next is Harry Burke, and then Bryan Luce.

DR. BURKE: This is a very interesting discussion. Just as an aside we look with suspicion at quality of life and measures associated with it, usually because a patient's prior perception plays a large role in the current quality of life assessment and it's very difficult to control a patient's prior perception in trying to validate this instrument.

That said, so yes, I'm interested in the instruments, because I think that's going to play a large role in this whole process, what

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instruments you use. So if we have therapies that are effective on some people and not on all people, then of course the first question is how do you determine which patients are going to receive the particular therapy, what instrument are you going to use to determine which patients are going to receive which therapy?
And then I think a second related point is, you have an effective therapy and a couple things could happen. You could have visual improvement or no improvement, you could have stabilization, or you could have a reduced decline. It seems to me that the instrument you use may vary depending on what you're looking for, because some of these may take a long time to occur, some may happen very quickly, and whereas reduced decline may take a long time, and then you need to determine whether to use a functional test or anatomic test to determine what the outcome is.
And then finally, I think an important point is how do you determine whether additional treatment is needed? In other words, if you are predicting it's going to be effective, do you wait to see a continued visual decline over six months, do you do an anatomic test in two weeks, because

you want to intervene as soon as possible if the first therapy wasn't effective. So I would just ask some of our panelists, how do we determine what the test is for each of these situations?

DR. MATCHER: I'm going to start by saying I can't answer your question.

(Laughter.)

DR. MATCHER: It is a philosophical question on some level, and that's what I was referring to.

DR. BURKE: Well, let's get to the practical question, how do you determine which anatomic or functional test?

DR. MATCHER: Ultimately the question goes to what you're trying to accomplish in the medical enterprise, and what you're looking for to accomplish in that enterprise is to make everyone happy and then that defines what kind of measure you might be looking for. If what you're saying is that the enterprise that you're interested in is allowing people the opportunity to be happy through having really good vision, then I think that the optimal measure just speaking to them is something like how well you can read, you care about driving, these are some of the tasks

involved in driving, so it's specifically task-oriented. As an alternative, I think the quality of life measures which really do capture those things are pretty good, with the acknowledgment that there is this overlay of well, cranky people are cranky and they're not going to be happy no matter what the heck you do for them.

DR. BURKE: Right, but I'm also looking more at visual acuity versus the VQT and I'm asking the question, well, do you use visual acuity even if you have a treatment which you expect to have a radical improvement when you do the test, do you do an anatomic test? In other words, you know, what's the standard for what test you use?

DR. SUNER: I think the problem is that all the anatomic tests are surrogates, and we don't know how the retinal cells are dying or why they're dying. Now you measure by OCT and look at a patient that has a very swollen retina, subretinal fluid and intraretinal fluid on OCT, a leaking angiograph, but the anatomic technology they look to says it looks anatomically okay, so you know, they may be objective measures but they're not effective in looking at what is

causing visual loss in this disease and that's the main issue. So again, these are all surrogate measures that are not getting at the crux of why people are losing vision or why they're cranky or why they're unhappy.

DR. GARBER: I think I understand what Harry is asking and can sort of answer it, but the direct question I think is, in what respect have these been validated as tests to predict progression and response to treatment? In other words, the ideal study would be something like the following: You do OCT to monitor in one group and in another group you don't and you use clinical criteria or something to decide when to do the next treatment or add combination treatment, or somehow change the management. And then you'd like to know, did the OCT group do better by some well delegated measure. Presumably that study doesn't exist, and in Ross's review I don't think there was a single such study, but there may be other kinds of studies to get at that question, so I think Harry's question is, what kind of evidence is there of that kind?

DR. SUNER: That could be done in a mass trial, but having said that -- we have the

ability to go to a reading center as an observer. Having said that, though, you will have to realize that the OCT and the fluorescein look better if they're not seen, they're glossy. At the same point, you have people that the OCT and fluorescein look worse, yet they are seeing better for some reason, and I think you can't explain exact data. If you see an OCT that looks good, if you see an angio that looks good, at least you think you've done what we can do, but it doesn't always correlate with function.

DR. GLASER: I think you touched on a very difficult point, and that's how difficult it is to assess some of these measures. The reality is that OCT is a relatively new technology, and most of the studies that you heard about today, those deal with a non-OCT part of the protocol, and it's only been in the past two or three years where we started to better understand the implications of OCT. That said, there have been some preliminary efforts toward comparing OCT with visual function. We might find out, for example, an individual could have a normal retinal thickness and still have very poor vision due to poor macular perfusion, or there could be another

reason for decreased vision such as optic nerve damage. So, although it does give us a time shot of the biologic activity, is does not correlate with the visual function.

Another example would be patients that have visual loss and geographic atrophy that have relatively standard or statistically normal retinal thicknesses, but they actually be atrophic. So we're at the present time unable to use OCT as a surrogate for visual function. What we can use it for, though, and increasingly I think most retinal specialists will agree with this, is as a surrogate for response to therapy. So we use this as just one aspect of our decision-making process, somewhat analogous to perhaps in internal medicine where if a chest x-ray is getting better, that's good, if the fever's going down, is the patient breathing better, and that's I think the way we look at these newer technologies.

DR. BURKE: What about the angiography, do you use that as a measure of response to treatment or are there other measures?

DR. GLASER: Personally we have looked at most of the trials, and some of the

characteristics that we've looked at have been the lesion size, progression of the lesion, whether or not various forms of revascularization are present over time, conversion from one form to another, and increasingly we're finding that fluorescein angiography is not an optimal tool for correlating with visual acuity. We can now see patients that have very poor results from angiogram, yet have relatively good vision with therapy, so I would say that fluorescein angiography has poor correlation ability with visual function, as is ICG.

DR. BURKE: Thank you.

DR. GLASER: I would like to expand a little bit on what was just said, and I want to do that by stepping back a little bit and reminding everybody that macular degeneration is a complex process and we shouldn't view this as a bureaucrat, trying to find out directly going from dry to wet, that in and of itself is difficult. But just sort of take the cases with wet macular degeneration, and you start to get neovascularization from the choroid running up into this subretinal space and sometimes into the retina. And then you have leaks of fluid, and

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then you have blood that leaks up there, and sometimes some inflammatory process going on. And if you're interested in one single test to be able to be predictive in this complex disease and all of its various stages, it's going to be very tough. And I think that one of the things that we're seeing is that you can't take OCT alone and say OCT is going to predict AMD, or you can't take fluorescein angiography. We talked about high speed dynamic therapy which can show more about the anatomy. None of those can you take as one single test. There's a lot going on, and we may find all the tools we need, but I think it's really going to require a spectrum of tests that will help us get at, is there neovascularization, are they leaking a lot, have they been around enough to cause damage, at what stage is the damage to the retina from the leakage? Therefore, is there some belated recovery? These are complicated and I think it's trying to take one test and pin everything to one test, and it's just not going to happen at this stage of the technology. So I think it's going to require the whole spectrum of tests, and I just didn't want someone to get the idea that we were

talking about that everyone wants one measure and throw out the rest, and I think that would be a dangerous thing to do at this stage in our development, and in fact I think we need more tests to be able to really get at this complex disease.

DR. BRECHNER: Just about as Dr. Glaser started talking, I was thinking about one of the points that I raised in the talk, which was the definition of visual function, because indirectly, this is an area you might be referring to, how you define visual function and measure it. And I mean, I would like to say that we could take all of these different measurements in a trial and put them in a nice little multiple regression thing and pluck out the ones that are less important, but I think that's down the road.

What you're up against is a quandary, we don't have the ability in my opinion to do all that, we haven't studied that way yet and it needs to be. Maybe we need to have a conference on defining visual function, because you need someplace to start, because what everybody is doing is kind of doing what they know how to do and the base is getting lost because there is too

much confusion with all these different methods. And there are a lot of outcome measurements out there, but none of them have been validated, and everything takes money and time, there is that problem. But that question of visual function, that definition of it is what I think you're getting at.

DR. GARBER: Let me interject a quick time check question. I would like to wrap this up, but I understand our lunch was strategically placed at 11:30, presumably to beat the crowds in the cafeteria, and we're a little bit late for that, so I want to get the sense of the panel. We could continue with this, I thought we would be done with this by now, but it sounds like a question that merits more discussion. I have a long list of people who have questions to ask. Would the panel feel comfortable if we went down, got lunch, brought it back here, and then continued?

I heard noises of disagreement. The reason that we're not allowed to eat here is because past groups have left their de troitus behind, so if we're going to be able to eat here in the future, we have to all make sure we take

care of the garbage and leave the room clean, and everybody takes responsibility for that, panelists, audience, members, everyone.

So we will resume here at noon.

(Luncheon recess.)

DR. GARBER: Welcome back, everyone.

We're going to resume now, and Jonathan Javitt was just about to answer Harry's question before we broke for lunch.

DR. JAVITT: Mostly I was going to point out to Harry that when the world looks for, since we are unable to talk to John Eisenberg on a regular basis, when the world looks for answers on how does one distinguish measures of therapeutic efficacy or clinical effectiveness, usually people talk to either Alan Garber or to Mark Fendrick or to Bryan Luce, and you see all the expertise is on that side of the table. And to get to the specific question you're asking, if you want to know whether you've dried out the retina, then you need to do a clinical test that tells you, and that could be a fluorescein, it could be an OCT, it could be something that we don't yet know about. But you also want to know whether drying out the retina matters at all in how the patient

is going to see today, tomorrow or next year, then you need to be doing a quality of life instrument as well as the visual acuity, but the measures exist for very different reasons.

DR. BURKE: The thrust of my question was how do we measure when we do a treatment, how do we measure the overall conclusion, and how do we measure the intermediate outcomes to determine whether an initial treatment was effective and maybe needs to be followed up with combination therapies, you know, so you know, how do we measure it? Is visual acuity the gold standard here? It's a highly subjective test, and is that the --

DR. JAVITT: Visual acuity is the result.

DR. BURKE: Do we measure that as the endpoint?

DR. JAVITT: After the treatment if you want to know if the patient's retina is better or worse, did you dry out the retina with whatever you did, then you use something like the OCT or fluorescein to find out, did you dry out the retina. Now, did that have an effect on the patient's vision is a separate question, and a

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longer term question, quality of life, as the people at Duke have looked at, does all the money we spent on this therapy have a quality of life impact on a patient that matches the money that we might have spent to treat diabetes?

DR. BURKE: A separate question, because driving out the retina as an end to itself would not be an outcome either. It is only relevant to the extent that it will either stop the progression of the disease or improve the vision, right?

DR. JAVITT: Right. If I go to Carmen Puliafito with a leaking neovascular membrane, I want him to treat me so the membrane stops leaking and my retina dries out, and I don't want him to be measuring my quality of life. On the other hand, if someone is bringing out a new therapy and wants to convince a regulator why that new therapy ought to be paid for, and has to demonstrate how that new therapy benefits patients compared to other therapies for other illnesses, quality of life is one of the ways we can compare across societal obstacles for treatment.

DR. BURKE: Right, but I --

DR. JAVITT: And in fact there are any

number of people, regulators and others, published in the literature, that it's almost immoral to think of using quality of life measurements to make a decision about an individual patient, but we're treating their disease as best we can.

DR. GARBER: Jonathan, I wanted to kind of come back to a question, and you all can feel free to also add your thoughts. A couple of people have mentioned and you just mentioned the idea of using some of these tests, angiography, OCT, et cetera, to monitor disease progress, but I have a really simple question. What is the evidence that alternate treatment based on any combination of those tests alters outcomes compared to, say, just waiting until there is visual deterioration or some other clinical measure of change in disease status?

DR. JAVITT: Well, again, you're asking the non-retinal ophthalmology guy, so I'm going to be fascinated to hear how Neil answers this, but from my perspective, all of the pivotal trials that the manufacturers have submitted for FDA approval and in the approved products and in the soon-to-be-approved products, suggest without a shadow of a doubt that choroidal

neovascularization is bad for you, that when choroidal neovascularization happens, you get swelling of the macula, ultimately you get a hemorrhage of the macula, and you irrevocably lose vision. So you don't have to wait for bad things to happen or not to happen in order to determine whether your treatment is showing any signs of efficacy.

Along the way you can be doing other noninvasive measures on that neovascular membrane to see whether it's shrinking or not shrinking, or whether it's getting bigger. The minute you leave the pivotal study and change the protocol as you go along because you will never get FDA approval for the world of clinical practice, you're in a world where you either treat or give placebo and then you see if the patient goes blind or doesn't, and tailoring the treatments along the way to see, did that neovascularization resolve, are the blast cells going down or not. If it's no, you know, are the platelets coming up or not, you know, the patient will live or die. But Neil will do better.

DR. BRESSLER: Why don't you repeat it?

DR. GARBER: The question was, what is

the evidence that modifying therapy, and I think in more of a monitoring situation than initial therapy question, what is the evidence that modifying therapy based on the results of any combination of the tests that we discussed improve outcomes, compared to just modifying therapy based on clinical indicators like vision loss?

DR. BRESSLER: There is no evidence so far, it's too early in the process. We've learned that some of these treatments worked just a few months ago, but those treatments did not include in their protocol okay, if I stop based on a certain OCT level or if I continue based on a certain fluorescein angiographic outcome, do I know I'll have a better overall outcome than if I didn't do that. The trials are designed to study the therapy that is initiated at baseline and continued for a certain amount of time to see if there were better outcomes compared with my control, and the answer was yes.

Now we would like to go beyond that, but we don't have evidence so far to tell us should I continue to treat someone at month six, seven, eight or nine based on their OCT, visual acuity, fluorescein angiography or anything else.

We need to design studies that will help tell us if we can confidently predict in the future that we should stop the therapy when the OCT is flat, the visual acuity hasn't changed, the angiogram hasn't shown any growth, would we get the same outcome than if we continued the therapy without that information. So we don't have that evidence yet, we obviously need it to improve on our therapies, improve the frequency of applying the therapy.

DR. GARBER: Thank you. Now, we are going to resume our list of questioners, and Bryan, you have been waiting for an hour.

DR. LUCE: Thank you. I have four or five questions at this stage. The first question I have has to deal with, goes back to the quality of life measurement issue, and as I think we all understand it, we're talking about people with disease oftentimes in one eye, and yet sometimes in both eyes, and it's been mentioned that the visual acuity instrument picks up pathologies and outcomes associated with one eye, but sometimes we are dealing with a person with two eyes. And the degree to which these studies that have looked at this, as well as the clinical trials, are really

focusing on the bad eye with the good eye compensating. That's the beginning I would like to have maybe the Duke team talk about, maybe others as well.

And then secondly, the degree to which a patient preference utility helps with that, and the role that utility plays. I realize that the evidence base is not very strong right now, but is this something that's going to lead to the efficacy of treatments and their utility in relieving this disease?

DR. MATCHER: Let me answer the second question first. We specifically avoided talking about utility measures, in part because the volume of evidence supporting them is much smaller, and in some cases it was unclear which patients, new patients or old patients, but basically there were two groups that used utility measures in the context of visual loss.

When you're talking in terms of general information, utility measures are distinct from reference to quality of life measures in that utility measures strictly speaking are asking for an individual to assess a health state in terms of their willingness to accept some sort of risk or

willingness to give something up to avoid that. So if the patient says I have this visual (inaudible) whatever it is, or you can take a painless pill which has these effects, but if you don't die, you know, you will have perfectly normal vision. But then if you tell the patient there is a one in a hundred chance, a one in a thousand chance, a one in 50 chance that pain is going to kill you, (inaudible) and that's where utility measure is.

Now having said that, there were earlier discussions pointing out that that's kind of a weird question to ask, and a lot of people perceive it as something they don't want to do in the context of research, practice or anything. And indeed, about 20 percent of subjects will find that a difficult question to answer. So utility strictly speaking is a hard thing to do. It's different than quality of life, which says what is your willingness to make trade-offs. And someone might say with a particular health situation, I don't like it. That's a lousy answer, so you have to ask them in terms of their willingness to accept risks, and if they say I'm not willing to accept the risks, it justifies it, as opposed to a

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utility question.
So, why don't I like utility? It's for that reason, and the other reason is that (inaudible) the measure that is recommended by economists, although I would be willing to be proven wrong by the economists in the room, but it is measured outcomes that are preferred in assessing the relative value in terms of allocating health resources, so from a policy perspective, utility is exactly the measure you want to have, okay?
So utility may be a preferred measure, but it's a hard measure to get, a lot of people find it difficult to answer that.
DR. LUCE: Do you think it would be sensitive? The SF-36 doesn't appear to be sensitive enough to pick up changes in general health assessments like are you willing to accept the risk.
DR. MATCHER: Your first question -- utility measures tend to be very insensitive, I measure treatment A is better than treatment B, okay, and --
DR. LUCE: Uh-huh.
DR. MATCHER: And to answer your first

question --
(Inaudible colloquy.)
DR. MATCHER: Utility tends to be a high variance measure, I won't respond, or can't respond, or I can't deal with the condition, so there is a problems with the measurement even for people who do understand it and are willing to play the game.
Now, to go back to your first question about utility assessment --
DR. LUCE: Let me clear it up, the relationship on the risk of the second eye.
DR. MATCHER: Again, ideal quality of life, but utility measures, utility is much more corroborated with the vision in the better eye, okay, than vision in the worse eye.
DR. LUCE: Which is what one would expect.
DR. MATCHER: Right.
DR. SUNER: The first question, I believe was in the SFC and also in AREDS. There was felt to be a benefit in the second eye, in the worse eye, in the quality of life measures with therapy, or just overall quality of life measures.
Back to the utility point, again, it's

a great thing conceptually, because without the validity, utility mostly is hanging on a different visual acuity being attributed to arguments of where are they in this A and B continuum or progression stage, and basically visual acuity as a utility is not disease state or the quality of life measurements.

DR. MATCHER: Actually, let me clarify that a little bit. The two groups that I am familiar with, they did do utility assessment, and they did look at those relative to visual acuity and then tried to create a map between visual acuity and utility, and my inference from that is what they were looking for was looking for an opportunity to perform an outcome analysis that hinged on visual acuity, that is, just taking the visual acuity outcomes and just hanging a utility value to that visual acuity.

DR. BRESSLER: There is some in the literature and there is more coming out on it. Even having this neovascular form affect one eye has an effect on a person's visual function questionnaire, presumably on their perception of their quality of life, so it was different than what people expected because they have people that

have lost an eye their whole life who continue to function just fine, and clearly a spatial perception of how they're functioning, how they're sewing, how they're seeing for distances, et cetera, was affected even when only one eye was affected.

Now, there is a strong correlation with it going down even further once the second eye is affected, but it clarified for us that you probably want to take care of that first eye as well, and possibly you should do that because it has an impact on not only their visual acuity of the first eye but their perception of their quality of life as a person, so that's very important.

We also treat the first eye because we never know how that second eye is going to do and unfortunately, if you develop this neovascularization in the first eye, half of those people will develop this in their second eye as well, and you don't know which is going to end up being the better functioning eye. And to our surprise, there is an impact on even the first eye on somebody.

DR. BRECHNER: (Inaudible.)

DR. BRESSLER: We did look at that, and that did not have an impact on that, so there weren't many people who had depression as defined by that scale, it was only about five percent of the people, but even adjusting for a variety of factors in the regression analysis, still, the first eye being affected has an impact when these people walked in on their quality of life.
DR. BURKE: Was it significant?
DR. BRESSLER: Yes.
DR. GARBER: You presented a slide that showed, I think, a visual analog scale utility for people with AMD.
DR. BRESSLER: The preference value scale, yes.
DR. GARBER: It looked like it was a vision analog scale.
DR. BRESSLER: Yes.
DR. GARBER: So the question is, was that rating their overall well being, how was that question phrased?
DR. BRESSLER: The question is phrased and it's referenced in the Archives of Ophthalmology. The questions were three questions, so that the person first rated their

assessment of their vision from perfect vision in both eyes to total blindness in both eyes. Then they rated their state of health. If they had perfect vision, or they said they had perfect vision, and then they were asked where is your state of health if you are completely blind, and that allowed us to take the two anchor points and get a reference value as a utility value of where their vision was on their state of health.

DR. GARBER: So if you gave a result of .67, I forget the exact number, that's, a one on that scale being perfect vision?

DR. BRESSLER: And perfect health.

DR. GARBER: So that's fairly standard, and obviously it had nothing to do with the presence of AMD, given the numbers.

DR. BRESSLER: Correct. And we have some correlation, it's not perfect, as you had lower and lower levels of vision in the better seeing eye, you can see it going down, but there is a wide correlation, because again, just as the qualities of life don't exactly correspond to 20/50 vision, they are measures of vision perception, so it is true for these utility values that we measure, there is some correlation.

DR. GARBER: Bryan, did you have some more questions?
DR. LUCE: Yes. The initial question has to do with Jonathan Javitt's discussion about the risk of use of steroids. It wasn't picked up by anybody else and I don't quite get a sense of the germaneness to our discussion and whether this is something we should be concerned about in thinking about combination of therapies, and I would like to have any of the presenters who were talking about combination therapy or anybody else to provide a little bit more, or give their opinions as to how that was germane to us.
DR. GARBER: Bill, did you have something on that?
MR. DOWNEY: Yeah. That was getting close to my question. I wanted to ask particularly the CMS review staff, in regards to patient safety, it's mentioned at the AOA meetings, it's a big deal there, but do I take it from this morning's presentations that there are no risks from any of these outcome measures in terms of patient safety?
And secondly in terms of treatment, that if you could characterize if there are

adverse events and their prevalence or whether that's just not an issue, or if the studies were adequately designed to identify any patient risks.

DR. BRECHNER: I'm sure, I'll attempt to answer that, and there are other people that could answer that better, because I did not see a lot of information on it. Most of the material that was used was tested for safety in measurements like talking about in terms of intravitreal injection. I didn't see that much else happened so I'll let some of the other people answer that for their individual studies, but I didn't get the impression that there was a major safety issue with any of these things, including taking antioxidants, although I think there are some known entities with taking too much of it. I was not impressed with any issues with the exception of that, and submacular surgery, that's obviously got some high risks to it, but that trial showed no difference in the treatment. And aside from that, I didn't see any major scares. The other question that Dr. Luce had, what was the first part of that?

DR. LUCE: It had to do with steroids and when they talked about combination therapy, at

least one of the presenters indicated steroids was part of a combination cocktail.

DR. BRECHNER: There was a steroid which didn't have the normal pressure-elevating effects, it was an acetate, and so there was no problem in terms of that. And as to other materials, I didn't find a lot of super good data on that problem. However, if you are injecting steroids into the eye, you can have elevated pressure and you have to watch for that. I don't know that putting steroids in an eye carries an extra risk with it, but I would still defer to these good people here.

DR. PHURROUGH: Let's see if I can perhaps clarify the question. When we put an MCAC together, we address specific issues to the particular MCAC, and part of this is methodological questions around how we can best in the future make some decisions around current, new or old technologies. Our questions are not whether steroids work or don't work. However, when we put the information out that we're going to have at one of these meetings, we are required by law to have the option of public presentations and so people come and present to us. We ask them

to present around the questions, but they present whatever they want to present around. Dr. Stout did a superb job of very clearly focusing on what we asked him to focus on, what do you think about our questions? Some of the others were a little bit broader as to whether certain technologies work or not, and you can feel free to ignore those comments. The issue here is not do the technologies work or not, the issue is what are the methodologies around the studies that will allow us to accurately determine whether they work or not.

DR. GARBER: Can I just take, maybe I interpreted Bryan's question differently. We are not interested today in whether steroids cause glaucoma, that is not our question. But I thought Bryan might be getting at it a little bit differently, and that is when you look at these measures of vision or the anatomic measures and so on, are they capable of detecting side effects as well as benefits? So you can imagine visual side effects that are not picked up by a technique like angiography, like early glaucoma or something like that. So I thought that was the nature of your question, are the measures we're using capable of

determining the vision-related side effects, not if somebody somehow gets an MI and they miss the eye altogether, they get something in a blood vessel somewhere, but for visual-related side effects, are they adequately measured in the same measures which we're using to look at effectiveness in treating the AMD. Is that what you were getting at?

DR. LUCE: That was very good. I'm tempted to say yes. No, that wasn't specifically what I was getting at, but we were asked to comment on the adequacy of the existing data for treatments and for other treatments coming up, and we're getting close to those questions, it seems to me. It wasn't just a measurements issue as I understood the questions, and since this was part of the combination therapy, we should know more about it.

DR. GLASER: First of all, there is not a lot of data on the pressure of the eye other than to know it will go up, but what I wanted to do is make sure we're being accurate in our description of this, and the term that is being used is that these patients get glaucoma. I'm a retinal specialist, but you know, to get really

specialized, I'm a right retinal specialist. But glaucoma is generally thought of as a disease which is associated with high pressure, but also is causing loss of nerve fiber layers, damage to the optic nerve, and there's a whole complex to the disease. What we really talk about when we say glaucoma related to steroid injection, for instance, is that the pressure goes up and it usually goes up transiently in most patients and then goes away. So I think to call it glaucoma is not an accurate statement. It's an elevation of intraocular pressure. Under some cases you might then progress to glaucoma maybe, but I think for accuracy of how we look at this, we are looking at elevating the intraocular pressure but not necessarily causing glaucoma. You can have some patients who have glaucoma, but were not necessarily causing glaucoma.

DR. GARBER: Jonathan.

DR. WEINER: I have one quick question and one that may be a little less quick. The quick question is for Dr. Stout. I agree that that was on target, and I read with interest your mini-survey of specialists. Can you tell us a little bit more about how you identified the

people surveyed for your confidence in their evaluation method?

DR. STOUT: Yeah. This was nonrigorously performed, given the amount of time we had to do it. Basically, I made a series of phone calls to people that I knew who were practicing only retina on the west coast who were eye surgeons.

DR. WEINER: You weren't joking about the west coast?

DR. STOUT: No, I was really serious, for no good scientific reason. The one thing I attempted to do is get a good distribution between academics and nonacademics.

DR. WEINER: How many?

DR. STOUT: 21.

DR. WEINER: On the west coast.

DR. STOUT: Yeah. And what I did, you know, I asked the questions with a zero to four point scale, how important are these, is this a good index, is this a bad index, and I went through many of the questions that were posed to me and I focused on the two of those, gaps of knowledge and how important is that index.

DR. WEINER: That's helpful, thanks.

The other question, having been on an MCAC for a year or two, it's important for Medicare recipients, there are a lot of good people working on this, but I think as usual, it's sometimes clear as mud. There is a lot of complexity, there are a lot of right answers, and by the way, on this particular MCAC, I believe there is lots of evidence and the measures are better than is often the case.

The bad news in my opinion is how do we put this all together and move forward. And so, given that, in our context of Medicare trying as it does to do the right things, people still are all over the place. So I often ask, in an organized system, whether Veterans Affairs, Kaiser Permanente, I'm just wondering what if anything they might do differently on an ongoing basis, not research, but in terms of care provision in Veterans Affairs or military hospitals or Kaiser, a place on a fixed budget, a place with economic considerations, that tries to put this all together for patient populations, what do they do? Can anyone help me with that?

DR. SUNER: I work at the VA, I'm on the executive board for the VA quality group, and

this has been a very difficult topic to deal with as a retinal specialist and a VA ophthalmologist. And part of the issue is that you have different entities, different interests in the VA pharmacy committee that submits to the VA hospital budget, for example, and there is no answer. Basically you try to push these in front of your patients, and good luck to you, which -- how many are in that same boat right now? So, again, I think that's a good question to ask, but I don't think the VA is a good model, it won't answer your question.

DR. WEINER: Are there other models out there, other nations perhaps? I guess the answer is it's important to make the right decision today. Thank you.

DR. GARBER: Bill.

MR. CLARKE: I think this may be a follow-up question to that and my question revolves around something I think I asked earlier which is, do we really understand the biology of the disease, and I think clearly from our definition this afternoon, the answer is no, we don't. So, I understand from the testimony that there is widely varying approaches used, and my

question is, how will practicing ophthalmologists gauge when a next round of therapy should be done? It goes back to this anatomic versus function question.

As I understand it, the criteria of primarily anatomic, does a practicing ophthalmologist, or should CMS request or require that the next round of such therapy be based more on the functional assessment or an anatomic assessment of the disease?

DR. BRESSLER: We are actually assessing all of those now, but having had the results of these trials, and the trials as I said, didn't include assessments of that, assessment by anatomic versus functional, but rather if visual acuity drops regardless of what you see anatomically, something is not going in the right direction. Alternatively, if some of this vision keeps improving from month to month, you're still going in the right direction. And the largest indicator of success, I think will be function by visual acuity, and we suspect that the OCT will tell us something, because if we see that the retina is getting thinner and thinner, that implies to us that we're improving. The

fluorescein angiogram may show something different than the OCT. The fluorescein angiogram shows growth of a lesion with a growth rate that you might not detect on the OCT. So I suspect, I don't know what interval, but we will be seeing the person in follow-up subjectively, how are you doing, and objectively by taking visual acuity and other physical measurements, and looking at least at OCT and fluorescein angiography.

MR. CLARKE: Just a follow-up on that. What's understood between observers about the reliability of fluorescein angiography, how reproducible is that between observers?

DR. BRESSLER: It depends on what question you're asking me. If you're asking me if they're good within an office, there's probably very good inter and intraoffice reliability. If you're asking the more specific question of how large is this lesion, then you get into the area of neovascularization, and the grader might have a different opinion versus three ophthalmologists who got together and all discussed it among themselves. We find that when these are graded in the clinical trials, very often there are two graders who are quite experienced and when both

graders are used, and then both graders are used again, you can see that it is highly reproducible, but for an individual grader or individual physician when we compare the measurements, there is a wide disparity for specific lesions.

MR. CLARKE: Is leakage too late in this disease, angiographic leakage as an absolute indication for additional therapy? As an ophthalmologist, would you say that's just too darned late?

DR. BRESSLER: Not necessarily. The vessels that are there that are just newly formed, they are very susceptible to not having tight junctions and leaking, and that can be seen at a microscopic level, so maybe you could pick up some way earlier that we don't know of, but it's certainly an advantage of the time that you pick up some leakage, yes.

MR. CLARKE: Thank you very much.

DR. GARBER: I think we're, unless there are further questions for the presenters, I think we're ready to move to the next stage. Oh, go ahead, Mike.

DR. ABECASSIS: So, I would like to get

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sort of a determination as to whether the feeling is by practicing ophthalmologists that OCT is quickly, is there evidence that OCT is becoming a better anatomical measurement than fluorescein angiography, because the data that was shown seemed very exciting, but I'd like to get a sense from the general retinal specialists as to whether that's the right perception or not.

SPEAKER: The American Academy of Ophthalmology has a group that looks at new technologies and currently OCT is being evaluated. There have been three studies that I'm aware of that have looked at the ability of OCT to detect retinal thickening or edema in comparison to the previous gold standard, which was clinical examination with a (inaudible), a contact lens. And it seems clear based on these studies that OCT is in fact more sensitive than clinical examination in the texts that we're reading. We still do not have studies that provide us with the next important piece of evidence, and that's how well does OCT correlate different outcomes and that's a lot of what we have been discussing already. But I think there is an increasing consensus that OCT is a very

valuable imaging technology for following retinal disease, and personally if I had my choice of only one test that I could have, I would probably want an OCT, because it gives us a better feeling for the biology of the process at the time. Issues such as leakage or staining tend to be very subjective even among highly trained and certified investigators. If you look at the various clinical trials, we see that the area rate in those trials is anywhere between 10 and 20 percent, and that's among experienced investigators, so I think increasingly OCT is becoming absolutely essential to the management of these patients and we hope that this assessment will be completed and published over the next few months.

DR. GARBER: Yes, James.

DR. PUKLIN: This question is for Dr. Williams or Dr. Puliafito. I understand there is technology which is actually here but may be even more relevant than the conventional OCT, which is an ultrahigh resolution OCT capability, and perhaps one of you would like to comment on that as it may be perhaps an even more reliable technology for assessing macular function of the

disease process.
DR. PULIAFITO: I think it's useful but it's not perhaps relevant at this time because there are already 3,000 OCT-IIIs out there, so it's going to take five years or ten years before we have another technology.
DR. GARBER: Harry.
DR. BURKE: Just a brief follow-up question and yes, you can come up because you're the one who said it. You said that multiple modalities would be used, but you said if the patient was getting better, you would assume, you know, if the vision got better, you would assume that the vision got better you wouldn't have to go in and treat them, their vision is getting better. The alternative is if the vision is getting worse, no matter what the OCT shows, you're going to assume something is going wrong. It's unclear to me how these other modalities would change your management.
DR. BRESSLER: Well, that's at one point in time. So if someone, if their visual acuity is getting worse, for example, but I feel that their OCT is getting better, I might suspect that there is still room for improvement, that

something anatomically happened that might be causative, it isn't always, so you might treat them one more time and see if you're still going in the right direction. Because at one point in time you can't tell that, you might need multiple of these until we have trials to tell us what are the most reliable for them. So we don't have that information, they are measuring different functions, and I believe that's why we're going to have to use a variety of these to try to make a judgment. Even if it saves three treatments and the person remains stable, that's probably worthwhile saving, so that's why we're currently using all three, until we have evidence to say if you have just this information, here's the outcome you get.

And in reference to the OCT and fluorescein, they do measure different things, so we don't have the information yet to say if the OCT showed no change, how often do we see a change on fluorescein angiography. We know it could happen, that is, there could be growth of the edema and we might not pick that up looking at the OCT, since it could happen. So until we know that we're not missing something that would change the

outcome for the patient, many people likely will want the ability to measure both as they're following the patient.

MR. CLARKE: Don't go away, I have a follow-up. Talking about AMD, which is really almost an anatomic description of the disease, I want to make sure I understand. Are there examples or very many examples of macular degeneration that is purely cellular? In other words, do you as a retina specialist see cases with a retinal degeneration that is not defined as AMD?

DR. BRESSLER: We do, and there are other diseases. Retinitis pigmentosa, for example, starts as a loss that we can't image in any way.

MR. CLARKE: I'm sorry, I should have been more clear. Where there is no anatomic report but there's vision loss.

DR. BRESSLER: With macular degeneration, we do not see loss of vision without seeing anatomic changes in the retina.

MR. CLARKE: That's the question.

DR. BRESSLER: So you either see Drusen, there may be tiny pigment in that field, a

tiny atrophy, or the more obvious geographic atrophy through the center of the retina, or full-blown neovascularization.
MR. CLARKE: Thank you.
DR. GARBER: Patrick.
DR. PRICE: I have two questions, and one or the other has to do with the quality of life issue. First of all, I want to put this in a context and that is as a carrier when we track these treatments, and they are commonly practiced, most people do not go through the full therapy for whatever reason, relatively few people receive what is in the protocol, and that has implications for the companies, it has implications for this body. In order to try to address that issue, I think that it's important when we see very impressive percentage numbers to keep in mind the great number of people who whether treated or not treated, will do okay. And therefore, we are going to treat a number of people, say two or three or six, to help one. So that what is most valuable if it exists is to tear down these measurements to see if we can collapse that number needed to treat and we can predict better which patients will benefit. Now, I do not think that

those necessarily exist, but the point I'm trying to make is that as we do these studies, is it a good idea to ask for that information, the number needed to treat. That's number one.

Number two is that when we are presenting these studies to our patients in our exam room, we have to be able to explain to them that you may not see a benefit from this treatment, and yet you should go through the course. Now that has more to do with a quality of life, not a continuous variable of visual acuity but a categorical variable, what am I going to get out of it. Because the patients are going to be asked to expend sometimes money, sometimes time, sometimes pain, and they need to know a quality of life.

So that, I guess Dr. Javitt, is it illogical to say that the quality of life issue has any kind of correlation or condition-temporary measurement to a number that we can use as a continuous variable to best guess the number to treat? You have to have some sort of measure to confirm your comfort level with treating and it also will influence your recommendation to the patient, so that they understand what their

expectations are.
You're absolutely right that because of this disease, previous to the ranibizumab results, our discussion was we're going to reduce your risk of further vision loss. In other words, you have a 30 percent chance of losing vision instead of a 50 percent chance. That means either way you're not going to gain. And this is important, and we recommend treatment, and if we see that the vision gets so bad or the lesion grows so much that it appears there is no value to treatment, then even it that treatment was better than no treatment, after one or two years people may discontinue and that's why we don't see a follow-through with the treatment.
Now we've moved a little step closer because of the ranibizumab that says that 30 percent maybe will improve vision, so the expectation of the patient walking in is I will improve, but you have to temper that by saying a majority won't improve, but their chance of improving is greater if you do this than not, and they need to know that as well. So, I think the number you need to treat is important for that. I believe Jonathan wants to answer the second one.

DR. JAVITT: I think it's important that when you show quality of life, and you talk about quality of life outcomes across populations, you treat patients in terms of efficacy and in terms of clinical outcomes. When we talk about the outcome of AMD it's really binary, you either lost your vision or your vision was preserved. So when you talk about saving, you know, $75,000 to save the quality of someone's life here, that's across a population, any individual person either won or lost.

I'm a little concerned about the question about the steroid. Could you do me a favor and read back Question 4B and Question 5 for the MCAC?

DR. GARBER: 4B, based on evidence reviewed, how confident are you that the other treatment modalities used singly or in combination, produce clinically significant net health benefits in the treatment of AMD?

DR. JAVITT: And what is 5?

DR. GARBER: What are the knowledge gaps in current evidence pertaining to the usual care and outcome measurement of AMD?

DR. JAVITT: And those were

specifically the reasons I brought those slides on the steroid and glaucoma. I'm not going to ask the MCAC to focus on steroids or glaucoma, but to point out that, you know, when you face the rapid proliferation of off-label use of medications in the absence of FDA-monitored safety studies within the Medicare population, there can be huge safety signals out there that are going unrecognized and the population can be put at substantial risk. I'm hopeful that people will follow up on the steroid data, confirm it with Medicare on their database, and take whatever action is appropriate. But I'm also suggesting that to the extent MCAC is interested in combination therapy and to the extent that that combination therapy involves the use of products that are not labeled that do not have FDA-approved labeling for the purposes that it's used in AMD, that there really be a safety surveillance mechanism set up to catch the one in a hundred or one in a thousand complications that could really expose patients to substantial harm.

DR. MATCHER: Going back to the number of patients being treated, when looking at the data from the studies where quality of life

measures are being used, the results are often variable, and the reason for that is statistically we don't have the power to look at it (inaudible), but the question you're raising seems really really important and also very, not typically that difficult to answer if as a panel you believe that it should be, the data should be presented in the following way. That is, what is the probability, what proportion of the people gain a certain level of improvement, that being a five-point or ten-point, whatever the panel deems, rather than just getting what the mean distribution of the group is. That's what's important, because I want to be able to say to my patients that in this study, of ten people who were treated, one person got an improvement of at least 15 points, and however many of ten points or five points. So that's what you're asking for, it's not something that the studies typically provide, but they could.

DR. BRESSLER: I couldn't agree more, that the mean is a great way for us to determine how to proceed further with the treatment, there is something to test. But we do try to give clinically relevant outcomes that are perhaps

sometimes dichotomous, like how many lost three or more lines, what's the percentage that gained ten or more points on the NEI-VFQ, and these are important to help us in translating the results of the trial to the patients and in any number to treat analysis.

DR. PRICE: Can I be real specific about this last point? Is the effect score and the resource score in the VFQ, is that similar to a number needed to treat, is that what we should be looking at to answer these questions? Are these people on an individual basis likely to be helped?

DR. MATCHER: Well, the importance of this question, we're looking for a way of indirectly getting people information about what are they getting for whatever they are investing, whether it's time, money, their hopes, whatever it may be. And what I'm saying is you could take this data and modify it so it will be numbers that say what are the numbers that you need to treat in order to gain a benefit that is a big benefit, so you're likely to, if you say out of five or ten patients, one patient might have this result. People might argue about whether it's an

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appropriate thing to do with a population level or individual level, but that could be done.

DR. GARBER: Alex.

DR. KRIST: Just a couple of questions. I just wanted to clarify about the statement with the American Academy of Ophthalmology technology evaluation on OCT and that being a superior diagnostic test. I just wanted to confirm that on the types of studies those were based on, most of the studies I've seen that were looked at here compared sensitivity and specificity versus angiogram or something like that. Was that the level of evidence that you were making your statements from?

DR. WILLIAMS: Well, it was not compared to fluorescein angiography, which is generally accepted to be a poor indicator for macular edema. The standard technique for detection of macular edema is stereoscopic fundus photography or biomicroscopy, and there was a randomized trial that looked at that correlation, and found some of those. These studies looked primarily at the ability to determine macular edema, thickening of the retina, and found that with OCT we were able to detect increased

thickening of the retina that could not be detected with just biomicroscopy.

DR. GARBER: This is the last question and then we're moving into open deliberations. Mark.

DR. FENDRICK: I saw our esteemed chairman looking at his watch and cutting you off, but some of the panelists who know me well, I have to ask one last question, which goes back to this superb evaluation by the CMS folks, and Alex and Alan, I've asked this of people in numerous specialties when we're conflicted and confused about the issues that are raised in the summary about why we don't have standardized inclusion and exclusion criteria and why we don't have an agreement among all the studies with all the innovations, why we don't have standardized outcomes? It's very peculiar, I think. Why can't you either choose among yourselves or ask for help from the outside, but the fact is, we're often asked to compare apples and oranges. This is not just unique to diagnosis and treatment for age-related macular degeneration, it's something we see over and over again. But there does seem to be a united front

among the major investigators in the field that you feel you could actually pull this off in future studies. I don't think anyone on this panel, as long as we had the outcome measures in particular that covered surrogate outcomes that you all agree upon, whether angiography or the newer things, whatever else, and whether you used the same visual acuity, which you appear to do, and you should probably agree on the quality of life.

So I guess my question is, why is it that we have to read these studies and the outcomes are always different? And they blame it on the manufacturers, blame it on the organizations, but what it comes down to is when we get together for our deliberations, can't we get agreement that in moving forward, that in all these great studies that guys like you have done, they're all over the chart, and yet we have to compare them and it becomes very confusing.

DR. BRESSLER: It wasn't done to confuse you.

DR. FENDRICK: I think there is someone that did that intentionally.

(Laughter.)

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DR. BRESSLER: We have changed some outcomes as the expectation of the treatment has changed, so with much apology, it used to be for laser photocoagulation, you either lost a lot of vision, six lines or more, or you didn't, and that was the outcome. As we got a little more sophisticated treatments, we went for a three-line loss. And there is an argument in the community whether two or three lines is clinically relevant, and so then you see that argument reflected, whether either two or three lines is a clinically relevant outcome.

We do have some vary fairly good standardization from the FDA trials where three lines, 15 letters is the primary outcome, so that's good, and that was for loss. And now that we see that some of these treatments to many people's surprise could actually improve vision, we're finding that a three-line gain may become a primary outcome for future trials.

And finally, you're right, we're at the point where we're just starting with the NEI-VFT and we're trying to define right now what should be a primary outcome. We're pretty much in agreement in the early stage here that there is a

definite change, but trying to establish a minimum clinically relevant change and that is somewhere, as you saw in the Duke presentation, between five and ten, and we don't know what that is. So I think in a nutshell is where we are. It is our goal to be able to compare across trials and to do future trials with similar outcomes without getting stuck to not be able to go forward. We certainly appreciate your critique and agree that the goals should be fairly comparative.

DR. FENDRICK: Is there any structure in place? If there is anything out there now, I'd like to know that.

DR. BRESSLER: Informally.

DR. GARBER: Let me just ask another aspect question. There are two issues about differences between trials, one is they have different measures altogether, and the other is that you're looking at the same measures but these are distributions that shift, like number of lines visual loss or improvement, and you're using different cutoffs. But your raw data enables you to answer the question, what's the chance of going two lines, three lines, et cetera.

I have a really simple question. Would

it be feasible in future meetings for you investigators to present us the entire distributions in some sense so that we can compare apples to apples instead of oranges, one uses two lines, one uses three lines, is that --

DR. BRESSLER: We encourage in the Journal reports to provide the distribution of changes in visual acuity and to provide the distribution of the absolute levels of visual acuity, in addition to whatever the primary dichotomous outcome shows in addition to the means, whether it's sensitive, whether it's not, as to all relevant outcomes. So many of these problems, the tables do have those.

DR. GARBER: Okay, great.

DR. SLAKTER: I just wanted to address the first part of your question, which was your sense that it's a little confusing not only in outcome but in our patient selection. I think to understand the different treatment modalities, we began with a therapy that was a destructive approach, we took lasers, we had to select lesions not under the center. We then moved into an era where we could deliver a spot of light to a particular area which was a well-defined area that

we had to select, and also were able to select the area based on the amount of blood present in the lesion and also the mechanical size of the spot to be delivered. Now we're finding as the results of clinical trials we can apply it to more lesion types, and they can be more spread out.

But you have to understand that even within that kind of realm, there is a different photoactivity or biology of the different drugs. So when selecting a clinical drug, you may have a drug that you believe is appropriate to a type of neovascularization for that type of drug pattern. So unfortunately, while we'd like to standardize outcomes, it may not be so easily standardized across all these trials because of the types of treatment we're using, particularly when we move to combination therapies.

DR. FENDRICK: But very quickly, you're not an expert talking to your peers. Ophthalmologists in the community, do they have the ability to basically know that certain patients should go down certain paths?

DR. SLAKTER: That question is difficult and in the community right now, we're still trying to answer that, so if you're having

difficulty, so are we.

DR. GARBER: Thank you. Now we are going into open deliberation. We have a scheduled break and I want to get the sense of the committee if we can do without the break and continue on our current course. If you have to leave the room momentarily, we will understand, but otherwise, we will continue on.

Let me just ask that if the speakers can stay a little bit longer in case there are further questions, that will be great. We don't always think of all the questions we have for you during the formal question session, so if you could continue to be available for us to draw on you as resources, that would be very helpful.

Stuart, I think you were going to put up the voting questions. While he's putting up the voting questions, particularly for the first question about the different measures, I wanted to ask the committee if they would feel comfortable if we maybe did a straw poll first, a completely nonbinding vote on where we stand on answering the questions for these 11 measures and then we discuss the real vote, would that suit the committee? Okay. Just so we can find out which

areas are likely to be areas of consensus and which ones there is disagreement on.

MR. CAPLAN: I will read these questions one more time.

Panel question number one. Each of the following have been reported as measures of disease activity or outcome in AMD. Some are direct measures of visual outcome, unambiguously representing visual aspects of patient well-being. Others are intermediate endpoints, meaning that they are intended to predict visual outcomes, even if they are not direct measures of outcomes themselves.

For each of the measures below, how confident are you that it is valid as a measure of visual outcome? If it is not a valid measure of visual outcome, how confident are you that it is a valid intermediate endpoint?

Those measures are: Visual acuity, the VFQ 25, extent of choroidal neovascularization, Amsler grid, Drusen extent and progression, geographic atrophy, glare recovery, contrast sensitivity, fluorescein angiography, visual fields, and ocular coherence tomography.

So that's the end of that part of

Question 1, Alan. Would you like to proceed with that section?

DR. GARBER: Yes. So we have a rather complex task here and I think the first part is, can we form a consensus about which of these measures should even be considered final endpoints and which should only be considered intermediate endpoints, and then go one by one over to validity, okay? Mark.

DR. FENDRICK: One clarification. So for the indirect measures that Cliff has alluded to, if you're now suggesting the possibility that we just go in order, 1 through 11, or that we do it by six and five, what if we believe that the surrogate measure actually measures the surrogate measure beautifully but you have no confidence that the surrogate measure has any value in visual outcome, so how would you want us to vote there?

DR. GARBER: Well, for the first stage, it's already been considered as a surrogate outcome, and the answer to that question is yes, and the second stage is is it valid? Now valid surrogate outcome, intermediate outcome is actually the term.

DR. FENDRICK: The way it's written

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is --
DR. GARBER: It says intermediate endpoint, and a valid intermediate endpoint means it has to predict a final outcome.
DR. BURKE: Right. It's only as good as the link.
DR. FENDRICK: Right. But we heard from the world's experts that there are no data to inform us on that point.
DR. GARBER: That dictates how you would vote.
DR. FENDRICK: Okay.
DR. GARBER: Cliff, did you want to say something?
DR. GOODMAN: The question comes back to whether these are direct or indirect measures of visual outcome.
DR. GARBER: Yeah.
DR. GOODMAN: So you could have a real fine surrogate outcome, very precise, but if it isn't correlated with visual outcome, then it is not valid for us today.
DR. GARBER: Then it is not valid, yes, it is not valid in that case. So maybe the way we can proceed is first, if we could just take a vote

on whether each one of these should be considered as a final outcome, that is a measure of patient well-being, or should it be evaluated as an intermediate outcome. And no, you can't vote twice for one measure, it's got to be one or the other, okay? So for the first round we're going to vote, should this be considered a final outcome and evaluated for its AMD uptake, or should it be considered as an intermediate endpoint.

DR. GOODMAN: Does final outcome mean final visual outcome?

DR. GARBER: Final outcome as a measure of well being, vision related, the visual aspects of well being.

DR. BURKE: So it's qualified.

DR. GARBER: So we're going to go one by one. The first vote is should it be considered a final outcome. The second vote, should it be considered as an intermediate outcome. And you only vote one or the other. Okay?

DR. PUKLIN: Can you have an intermediate outcome as a final part of the study?

DR. GARBER: That's what happens sometimes, but that's not what we're voting on. The question is, how should we evaluate it, as a

final outcome or as an intermediate endpoint.
Okay. First, visual acuity, all those
that think it should be considered as a final
outcome, raise their hand.
(Unanimous response.)
DR. GARBER: All those who think it
should be considered an intermediate endpoint.
(No response.)
DR. GARBER: VFQ 25, how many would
treat that as a final outcome?
(Hands raised.)
DR. GARBER: And how many as an
intermediate endpoint?
(Hands raised.)
DR. WEINBERG: Are we going to lump VFQ
and VTF together?
DR. GARBER: Lumping together, yes.
Okay. Extent of CNV, how many think it should be
considered as a final outcome?
(Hands raised.)
DR. GARBER: How many think it should
be considered as an intermediate endpoint?
(Hands raised.)
DR. GARBER: Amsler grid, how many
think it should be considered final outcome?

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(Hands raised.)
DR. GARBER: How many as an intermediate endpoint? Let's do that again. We don't like extensions at this stage.
DR. WEINER: Is there a none of the above?
DR. FENDRICK: No neither.
DR. GARBER: No neither. If you think it has no value, if you think for example its best shot is as an intermediate outcome, you can say that, but that doesn't mean you're going to say it's valid or not. We're only thinking about how to evaluate it.
DR. FENDRICK: Okay.
DR. GARBER: Amsler grid, how many think it should be considered a final endpoint?
(Hands raised.)
DR. GARBER: Okay, three. How many think it should be considered as an intermediate endpoint?
(Hands raised.)
DR. GARBER: Okay. Drusen extent/progression, final outcome?
(Hands raised.)
DR. GARBER: Intermediate endpoint.

(Hands raised.)
DR. GARBER: Geographic atrophy, final outcome.
(Hands raised.)
DR. GARBER: Intermediate endpoint.
(Hands raised.)
DR. GARBER: Glare recovery, final outcome.
(Hands raised.)
DR. GARBER: Intermediate endpoint.
(Hands raised.)
DR. GARBER: Contrast sensitivity, final outcome.
(Hands raised.)
DR. GARBER: Intermediate endpoint.
(Hands raised.)
DR. GARBER: Fluorescein angiography, considered as a final outcome?
(No response.)
DR. GARBER: Intermediate endpoint.
(Unanimous response.)
DR. GARBER: Visual fields, final outcome?
(No response.)
DR. GARBER: Intermediate endpoint.

(Unanimous response.)
DR. FENDRICK: What is it?
DR. BRECHNER: Peripheral vision, a measure of the field.
DR. GARBER: We mean standard vision field tests, right?
DR. BRECHNER: Yeah.
DR. GARBER: Standard visual field tests. Visual tests, should that be considered a final outcome?
(No response.)
DR. GARBER: Or intermediate endpoint.
(Unanimous response.)
DR. GARBER: So that's intermediate. And then finally, OCT, final outcome?
(Hands raised.)
DR. GARBER: How many for intermediate endpoint?
(Hands raised.)
DR. KLEIN: Can I just make a comment? This is dealing with anatomy and function rather than final and intermediate. Final is also confusing.
DR. GARBER: I think the intent of final outcome is what do we think is valid as a

measure of something that patients experience themselves, as opposed to something like a lab test that might give you a final outcome.

DR. ABECASSIS: I agree, I think it's rather confusing because if you're looking for visual acuity tests, it may not be the final state of visual fields, it could be an intermediate test that's taken and it could get worse or better, so I think that there is some confusion about the finality of the word final.

(Laughter.)

DR. PUKLIN: Aren't you really asking about primary endpoints and secondary endpoints?

DR. GARBER: Yeah, that's one way of looking at it, but the question, what we call final outcome in these questions is something that would be a valid measure of outcome. So if you sought improvement in something and in no other measure that we looked at, did you consider that good enough to establish that the treatment made the patient better in the way that they treated the patient. So when you talk about some of these, when there is some ambiguity whether they should be intermediate or final, I think sometimes the issue is it may simply not be that important

as a final outcome even though it could be phrased as such. So that's something to come out in our discussion of whether they are valid. Right now we are only really concerned about where to pigeonhole the discussion.

DR. KLEIN: But with visual acuity and visual field defects, one having been voted for final, the other having been voted to be intermediate, highlights the point I was trying to make. They should be the same whatever we decide.

DR. GARBER: So if you want to revisit the visual fields. Is the head of the FDA ophthalmology branch here, someone who can comment on the visual fields question?

DR. CHAMBERS: Wiley Chambers, FDA. Visual fields measurement is the definition of how well you see not dead center but in different areas. If you're going to take visual acuity as a direct measure, you can only take visual fields also as a direct measure, and the fields is the extent to which you see dead center or you see off to the side, so they can't be different, whether direct or indirect.

DR. BURKE: I think another way of looking at the surrogate outcomes and true

outcomes, the end result is the true outcome. So for example with our cardiac stents, we have Dopplers for MI, and chest pain would be a surrogate outcome. So another way of thinking about it is, is this really a surrogate true outcome later on, all right? So instead of intermediate, the surrogate is used to indicate something later on is going to happen.

DR. GARBER: Yeah. I always thought chest pains were a real outcome, personally.

DR. PUKLIN: Aside from the (inaudible) presenters commented about the usefulness of tests such as OCT but not directly correlatable to whether the disease process is finally under control or in remission, or the patient is getting the maximum benefit from the therapy. The bottom line comes down to the visual acuity, and perhaps all these other things which are descriptive of the anatomy or tests that are unreliable such as the Amsler grid are secondary helpful measures but not the primary, but secondary measures. So I would like to suggest that may help to clarify the concept so we have people expressing an opinion on the concept that we are considering.

DR. ABECASSIS: Can I make a motion? I

don't know if you may want to just consider discussing primary endpoints and secondary endpoints, and then deciding whether or not if they are strong primary endpoints or strong secondary endpoints.

DR. GARBER: Well, primary and secondary endpoints, there is an important distinction here and the nomenclature is used different ways in different contexts, which is one reason for the choice of the term intermediate. The secondary endpoint simply means something that was considered to be important to include as a predefined endpoint in a trial but not important enough to be the number one endpoint to look at, and there are many considerations that go into choice of primary and secondary endpoints. An intermediate endpoint is often a secondary endpoint but not necessarily. Intermediate endpoint means it is not the health outcome that patients value, but it may be a very strong predictor. An example would be blood cholesterol level or blood pressure level, where the patient doesn't experience their cholesterol level, but a physician --

DR. BURKE: Or PSA.

DR. ABECASSIS: Or ROCT.
DR. GARBER: Right. So that's the reason for the term intermediate, and then they are evaluated in terms of whether they actually predict these final health outcomes.
DR. BURKE: So getting back to the FDA position, it just seems that anything the patient is reporting on, visual acuity, the Amsler grid, glare recovery, contrast sensitivity, visual fields, all seem to be in the same bailiwick conceptually, and if we're going to put visual acuity in as a final, then why should these other ones not also be final, right?
DR. WEINER: Harry, the problem is there are two dimensions. That's one. The other is reliability and validity, and you're saying we to put them both in.
DR. BURKE: No, no, I'm just saying we're categorizing into one of two categories. All these struck me as being in the same category, things that the patient is directly reporting on, okay? So if you say that the final visual acuity is a final outcome, then the rest of these things, good or bad, are the same genre.
DR. GARBER: Let me say that what you

say is certainly logical, but there is another reason that you might not want to assign them in the same category. That is, you may think of something that's a very weak final endpoint, like in the Amsler grid, but if there were data showing that performance on the Amsler grid predicted very likely, and it's not, but say something like a measure that everybody accepts, like VFQ 25, then it should be evaluated as an intermediate endpoint. It might be a very strong intermediate endpoint even if this group did not feel good it was a good measure of final visual outcomes.

DR. BURKE: I appreciate that point in that view. You know, everything, I just at first blush, I was just suggesting you take the simplest approach and categorize everything that looks the same in the same category.

DR. GARBER: Let me ask how many people, I understand there's a sentiment to revote on visual fields, especially because not everyone understood exactly what that was intended to measure. Do we want to revote on the other ones too?

DR. BURKE: I already voted that they were final.

DR. ABECASSIS: Can we ask, what were the initial results?
DR. GARBER: Visual acuity was final; VFQ 25, final; extent of CNV was intermediate; Amsler grid, intermediate; Drusen extent/progression was intermediate; geographic atrophy, intermediate; glare recovery, intermediate; contrast sensitivity was final; fluorescein angiography, intermediate; visual fields, intermediate; and OCT, intermediate.
DR. ABECASSIS: So the ones that would be questionable, I think, given our discussion just now would be glare recovery, contrast sensitivity, or the Amsler grid and glare recovery, and visual fields.
DR. BURKE: Exactly.
DR. GARBER: Let's look at the vote on those because there will be some people who might want to change their votes. Amsler grid, how many think it should be treated as a final?
(Hands raised.)
DR. GARBER: And how many as intermediate?
(Hands raised.)
DR. GARBER: So that will be treated as

final. Glare recovery, how many think it should be final?
(Hands raised.)
DR. GARBER: And how many intermediate?
(Hands raised.)
DR. GARBER: Final. Visual fields, how many think it should be treated as final?
(No response.)
DR. GARBER: And how many think it should be intermediate?
(Unanimous response.)
DR. GARBER: Okay, let's move on. Any other desires to change the classifications? Jonathan.
DR. WEINER: Sorry to ask, but if our role here is to make recommendations to the world and the field in what we're suggesting as the measures CMS would like to get back to them, and that will happen by the time we're finished with this, is this the last time we are going to address this issue? I don't see a question for reliability or validity, so that's why I'm asking.
DR. BURKE: It's coming, it's in the questions.
DR. PHURROUGH: You haven't voted on

any of the questions yet. Any voting that you have done thus far has nothing to do with the questions yet.

DR. GARBER: Okay. So Jonathan, my understanding is yes, we are supposed to be doing some guidance to CMS on this matter. Okay. Now, visual acuity, how confident are you that that is valid as a measure of visual outcome?

DR. KLEIN: I think it's unfair to just do it yes or no. Where are our cards?

(Inaudible colloquy.)

DR. GOODMAN: Are you confident is a binary; how is not.

DR. GARBER: Unfortunately, there are a set of guidelines that would help you to answer this which have not been approved yet.

DR. ABECASSIS: How about highly, moderately, not at all?

DR. BURKE: We always had the cards with one through five historically, we just don't have the cards today, but forget the past.

DR. GARBER: Steve, do you want to comment?

DR. PHURROUGH: I think we're probably better served by, without getting to the level of

a one-to-five scale, do you think there is some validity to this particular measure, a binary question, do you have some confidence.

DR. GARBER: Actually, Steve, and I hate to tell you what would serve you best, but I think it would be much better if we had, say, some that are highly confident, some not at all, and then have a gray area where there is some but limited evidence where it's not at all clear-cut.

DR. LUCE: Dr. Stone provided guidance as to highly, somewhat, or minimally.

DR. GARBER: That's three categories. So, are people comfortable with that. The first category means that a trial demonstrates an improvement on the health outcome and clearly demonstrates a patient benefit, okay? The third outcome means it contributes virtually nothing, and the second one we're uncertain about, okay?

DR. WEINER: You said patient benefit, is that different?

DR. BURKE: It's just measuring, is it a valid measure, is what we're asking about, either it is or it isn't, or you have no idea.

DR. GARBER: Okay. So we'll say that one means definitely valid outcomes; two means

we're unsure; and three means that it's not, okay?
Visual acuity, how many ones?
(Unanimous response.)
DR. GARBER: How many twos?
(No response.)
DR. GARBER: How many threes?
(No response.)
DR. GARBER: VFQ 25, and that also
includes the VF 14, how many ones?
(Hands raised.)
DR. GARBER: How many twos?
(Hands raised.)
DR. GARBER: How many threes?
(Hands raised.)
DR. GARBER: Okay, so the ones carry.
(Discussion off the record.)
DR. GARBER: Okay. Extent of CNV --
I'm sorry, that was intermediate, so Amsler grid
was a final. Amsler grid, how many ones?
(No response.)
DR. GARBER: How many twos?
(No response.)
DR. GARBER: How many threes?
(Unanimous response.)
DR. GARBER: Glare recovery, how many

ones?
(No response.)
DR. GARBER: How many twos?
(No response.)
DR. GARBER: How many threes?
(Unanimous response.)
DR. GARBER: Contrast sensitivity?
One?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: And three.
(Hands raised.)
DR. GARBER: Jonathan?
DR. JAVITT: I'm a little concerned because there's been no public discussion of contrast sensitivity as a measure because until a moment ago it wasn't all that relevant. The main difference between contrast sensitivity is it is a measure where you can see a dark black letter against a bright white background, and that letter then starts to become less distinct. And there is a raft of literature that has appeared recently that does not correlate visual acuity very well with slips and falls, with vehicular accidents,

with other disasters that befall elderly Americans, but does correlate contrast sensitivity with all of those adverse outcomes. Anybody, or many people can see a black E on an eye chart in a dark room when they know the letter is an E, but that's very different from can you see a pedestrian who's wearing gray clothes along the side of the curb as the dusk is coming in. One of the most dramatic studies was recently published in the literature looked at a number of traffic intersections around the country the day before and the day after daylight savings time was initiated, so the only difference was one hour more sunlight or one hour more contrast, and there was a four-fold increase in vehicular collisions due to a lower contrast environment. So it could be that after a public argument about whether contrast sensitivity is meaningful and a consideration of the literature around contrast sensitivity, this panel would deem contrast sensitivity not to be significant, but I don't think that that literature has been asked or has been reviewed today.

DR. PHURROUGH: Unless the panel asks for something, we should just keep going.

DR. GARBER: Does the panel want to hear Mark on that subject? Okay. Visual fields?
MR. CLARKE: Are we voting?
DR. GARBER: Yes, we took care of that. Visual fields, how many vote one?
(Hands raised.)
DR. GARBER: Two?
(Hands raised.)
DR. GARBER: And three?
(Hands raised.)
DR. GARBER: Okay. Now we go back to intermediate outcomes and again here, for intermediate endpoints, we'll use the same one, two and three, and this is your confidence that it predicts a final endpoint that's valid, okay? The final endpoint that we believe is meaningful, are you confident that the intermediate endpoint predicts one or more of these final outcomes or some other measure that you find to be valid. So then we have the first intermediate endpoint, extent of CNV, and we can have discussions by the way, I don't mean to rush through the voting, these are real voting questions. So, any discussion on extent of CNV as an intermediate endpoint? Okay. All those who

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rate it one?
(Hands raised.)
DR. GARBER: Two?
(Hands raised.)
DR. GARBER: And three?
(No response.)
DR. GARBER: Drusen extent and progression, discussion? How many rate it one?
(No response.)
DR. GARBER: Two?
(Hands raised.)
DR. GARBER: And three?
(Hands raised.)
DR. GARBER: Geographic atrophy, discussion? One?
(No response.)
DR. GARBER: Two.
(Unanimous response.)
DR. GARBER: Three.
(No response.)
DR. GARBER: Fluorescein angiography, one?
(No response.)
DR. GARBER: Two.
(Hands raised.)

DR. GARBER: Three.
(Hands raised.)
DR. GARBER: And ocular coherence tomography. One?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: Three.
(Hands raised.)
DR. GARBER: Okay. We did pretty good timing-wise, I'm not commenting on how you voted. Okay, B, which other currently available outcomes or intermediate endpoint measures should be considered? We've already added the VF 14.
DR. FENDRICK: Several of the speakers spoke about reading speed; is that something we need to add?
DR. PRICE: That could be implied from the VF 14, although there is a definite measure.
DR. PUKLIN: Do these have to be validated tests at this point?
DR. GARBER: The question is asking should they be considered, I don't think that means it has to be validated; is that correct?
DR. PHURROUGH: Yes.

DR. PUKLIN: Because there are some additional tests that are being used. One is the multifocal ERG, another one is microperiphery, and even a newer one is something called auto fluorescence. These are tests that can be done on the functioning of the retina that might be valid as intermediate endpoints.
DR. GARBER: Would you place them as a two or as a one, or as a three?
DR. PUKLIN: Two.
DR. GARBER: Okay. Bryan.
DR. LUCE: Utility of preference.
DR. GARBER: If I were a voting member, I would second that.
DR. LUCE: But you don't want to.
DR. ABECASSIS: But we heard that those are not very sensitive.
DR. GARBER: But we've seen evidence to the contrary.
DR. WEINER: Will we have time to comment on negative outcomes or ectogenesis, or something that long-term CMS should monitor?
DR. GARBER: Could you expand on that?
DR. WEINER: I mean Dr. Javitt, for example, it was not directly relevant but it is

indirectly relevant. If I were CMS, I would want to monitor not only the positive, but also the negative. Is this a place to raise that or later, is this a good place to raise it or perhaps I should let it go.
DR. GARBER: Maybe I can make one quick suggestion. I think that may absolutely need to be included but I'm not sure that's the case. I think there may be some side effects from therapies that are not eye-related side effects, and do you still want to include them? That's not really on the agenda today for today but it absolutely needs to be included one way or another.
DR. ABECASSIS: I'd like to ask a question of the ophthalmologists on the panel about possibly including, in my reading for preparation of this, there is some evidence that cytokines may be important. Is that something that is easily measurable or measured.
DR. KLEIN: Luken 6 can be measured, C-reactive protein can be measured, the evidence is not a slam dunk, it's more controversial. Some of the case control studies have demonstrated it and population-based studies have not found it, so

I would put it more in the level of two at this point.

DR. GARBER: Okay, these are actually voting questions so we need to vote on the items that should be considered.

DR. LUCE: Just a point, in case it's not picked up, the question just says should be considered, as opposed to should be employed, so even though the measure may, we may be uncertain about whether a measure is really good, the question is should it be considered, so I think that's there's a lower threshold.

DR. KRIST: I think it's going to be kind of hard to vote on these as one, two or three, because we haven't had any opportunity to kind of review these.

DR. GARBER: I'm sorry. The question is not asking you to address whether they're valid. However, I would suggest that if you think it is so utterly speculative that we're going on no data at all, then we should probably say it shouldn't be considered at this time. But absolutely, this is not a vote on whether it's valid or not, it's just on whether it should be considered.

DR. KRIST: Whether we should put it on a list of things.
DR. GARBER: Yes. James, could you restate the three items you mentioned?
DR. PUKLIN: I mentioned multifocal ERG.
DR. GARBER: So how many think it should be added to be considered?
(Hand raised.)
DR. GARBER: How many do not?
(Hand raised.)
DR. GARBER: So we've got one yes vote, one no vote, and a heck of a lot of abstentions.
DR. LUCE: We just need more information.
DR. PUKLIN: I can withdraw the suggestion. I read the question to indicate whether or not there might be other available measures that one might wish to consider in going forward with research in this area.
DR. PHURROUGH: I think the focus should be on things that we have discussed today, had some presentations about today, or you choose to take some time to have some discussion about them, rather than just a list of issues for which

there have not thus far been any discussion. So I'm not sure if I recall this morning, C-reactive protein was listed in one talk, I think high speed angiography was discussed, and I think that's probably it.

MR. CLARKE: Some of this might be as these new technologies arise, I mean, that's a binary question and to that can be added, and this might be the following.

DR. GARBER: That's a good suggestion. I think if I understand Steve's comment, what I'm really hearing is based on the discussion today, were there other things not on this list that maybe we should consider in the future, those that were discussed today so we have some basis for making some judgment about that. And so James, would it be okay if we skipped to that version or do you still want to have the three that you mentioned?

DR. PUKLIN: I will withdraw.

DR. PRICE: Would it be possible to collapse those three into one question, and have that new question be, if new measures are present or in the future available, what criteria should they meet in order to be able to serve as markers,

and that would be like a likelihood ratio.
DR. BURKE: We could spend the rest of the afternoon on that.
DR. GARBER: That's not a simple question. Steve just turned to the panel saying we can't answer this question. If that's what the large number of abstentions meant, you can just say that. James.
DR. PUKLIN: I merely suggested these because these are tests that have been applied to some of these clinical studies and may be applied or utilized in macular degeneration studies going forward, and their role in outcome results have not been I think determined, but I thought it was the objective of the panel to discuss all the options going forward and this seemed appropriate there. If you would like to place it somewhere else or not consider it, that's fine.
DR. KRIST: That might also go under five, where are gaps in our knowledge. You're talking about things that may have advantages to measure in the future. Right now I'm not sure I'd want to see a study of those outcomes, but I think we have a gap in knowledge to say, are they predictive of our final visual outcome that we're

hoping for?
MR. CLARKE: 1C is the binary question, understanding that as new therapies involve, we will probably need new outcomes measures, yes, no. And then 5 is more broad in terms of what might we need in the future broadly, you know. I think it is important to pick up things like ERG because it goes to the structure function, and we may not know how it affects the disease, but I would hate to miss that entirely.
DR. GARBER: So Bill and Alex, are you suggesting that we pause in the discussion and put these issues all under 5?
MR. CLARKE: I think we can certainly treat 1C as a yes, no, and I won't begrudge what the answer will be, and then under 5, yes, we fold these in to show that as thoughts of the panel saying the gaps in our knowledge include understanding retinal function, understanding X, being able to get earlier intervention measures, something like that.
DR. GARBER: And does that take care of what we need for 1B, so we don't need a separate vote on that?
DR. PHURROUGH: Let me see if I can --

it's always simpler to come up with the questions than it is to give an answer. Company A shows up in our office and says we have this new gizmo drug, whatever, that we think is going to be great in treating AMD, and we're putting a trial together right now and we want you to tell us the outcomes that need to be in that trial for you to say we'll pay for it. That's the scenario. Are there any outcomes other than 1 through 11 that have been discussed today that you would have us CMS to tell Company A needs to be in that study based upon what we know today about AMD. So it's not a sort of futuristic question, it's more what do we know today, what should we tell this company, here are the outcomes for AMD, and the answer may be 1 through 11 is appropriate based on your validity votes.

DR. GARBER: All right. So Steve, to answer your question then, I think this would need to be phrased, what other currently available outcomes and intermediate endpoints are valid, because you presumably don't want them to come to you with something where it's purely speculative validity or unknown validity, right?

DR. PHURROUGH: We could in fact, if

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the information isn't sufficient today, you may be telling us, here's something you should look at and determine its validity before you offer that up as a requirement. So because there was not, these were not, anything outside of 1 through 11 was not part of a discussion, they may well be valid, there was not enough information today because we didn't ask them to determine whether they're valid or not, but there's a potential for them to be valid, so it's something we should consider.

DR. GARBER: I have to say, I don't think this panel is prepared to say anything about potential for validity for stuff we haven't done a review of.

DR. PHURROUGH: Agreed, which is fine, I'm not asking you to do that. I'm saying, is there something that was discussed today that we ought to consider.

DR. GARBER: How about this? Of the universe of outcome measures discussed today, are there some that we think might be valid and should therefore be considered, other than 1 through 11? Is everyone comfortable with that?

MR. DOWNEY: I have just a brief

question. Do we know what, or can you tell us what the FDA requires of developers, if it's different, or it's not on the list of 1 through 11?
DR. CHAMBERS: Wiley Chambers, FDA. There are no additional tests that are, we would routinely require of a company for an AMD indicator as we already discussed, unless they were looking for a specific claim or target benefit, or something for some particular function. And we have a set of parameters that we accept and don't accept, but that's in the approval, we separate those two things.
DR. GARBER: Let me reread what I think I understand to be Steve's question. The revised one is, which other currently available outcomes or intermediate measures discussed at today's meeting should be considered by CMS? Are people comfortable with that wording?
(Panelists indicating assent.)
DR. GARBER: So, we now have to have nominations for endpoints.
DR. FENDRICK: I move for none.
DR. BURKE: I second that.
DR. GARBER: Any further discussion?

So, the motion is for a no answer to which other currently available outcome/intermediate measures discussed at today's meeting should be considered by CMS.

DR. WEINER: Hold on. The patient preference, that wasn't my idea, but I hate to see it go completely, and it was discussed briefly.

DR. LUCE: You mean utilities and preference.

DR. WEINER: Utility and preference.

DR. GARBER: Then you should vote no if you believe that should be considered. Okay. Is everybody clear? If you vote yes, it means 1 through 11 cover the whole territory; if you don't believe that, you should vote no to the motion. Okay? All in favor of the motion to say zero is the answer?

(Hands raised.)

DR. GARBER: Five voting members; is that right? All those against the motion, raise your hands.

(Hands raised.)

DR. GARBER: Three. Okay. So we're not adding anything.

So 1C, is there a consensus of the

group that 1C can be rolled into Question 5? All in favor?
(Unanimous response.)
DR. GARBER: Opposed?
(No response.)
DR. GARBER: Okay, D, 1D, what are the appropriate criteria for short-term and long-term outcomes for AMD treatments?
DR. LUCE: I think there would be a benefit for that being explained better.
DR. BURKE: I tried to get at that question earlier today about, you know, if you detect something earlier or wait six months to see if the vision changed, and I really didn't get a very clear answer as to short-term and long-term, but it needs to be clarified.
DR. ABECASSIS: Can I maybe put the FDA on the spot again, because there is some question about long-term and short-term, so maybe the FDA can clarify.
DR. BURKE: Sorry to put you on the spot.
DR. CHAMBERS: Wiley Chambers, FDA. We're put on the spot all the time, it doesn't bother me. We have for AMD for better or worse

decided that we wanted as at least one-year data, recognizing that these patients were older, that one year was a reasonable portion of the rest of their lives upon which to base efficacy, so we have said we want a minimum of one year of data in order to be able to approve it. We have wanted that to be in at least two-year trials, realizing that sometimes the answer at one year is different than the answer at two years, or that some people may choose to make that difference. We have encouraged continued follow-up after that, but recognizing the average age of these patients is older, we will lose follow-up, so we have not to date required anything beyond two years.

DR. BURKE: Would it be fair to say that you wouldn't allow a second intervention in the study in say six weeks if there was refraction from disease? In other words, there was a short-term outcome?

DR. CHAMBERS: Again, our preference is for people to try and go for the first year before there is an intervention in disease. However, we also define particular endpoints, we recognize certain amounts of visual loss as being detrimental to the patient from AMD, and if you

achieve that endpoint, we will not block people from receiving whatever other therapies the physician believes is in the patient's best interests.
DR. BURKE: So, is there a time interval for that, a decline in visual acuity where they may use another intervention within a year?
DR. CHAMBERS: We have not set a time frame.
DR. BURKE: Because customarily there is some time interval.
DR. CHAMBERS: It is unusual to be less than six months, it is very unusual to be less than three months.
DR. BURKE: Thank you.
DR. GARBER: Mark.
DR. FENDRICK: I move to amend this question to appease Harry, to have it read, what are the appropriate criteria for short-term and long-term positive outcomes, or net beneficial outcomes, and then move to adopt the FDA one year for short-term and two years for long-term.
(Inaudible colloquy.)
DR. GARBER: Let me ask, and I don't

know whether this should be directed to Steve or to Ross, but what the intent of the question is. One of the presenters, I forget who it was, showed different outcome measures used at different points in time, but one of the questions is what is the -- short-term in itself, that means if a company comes with their drug and they demonstrate improvement on that outcome, we send them the signal that's okay, even though that might not be valid six months later. Is that the intent of the question?

DR. BURKE: I think outcome is neutral, it can be positive or negative, and to focus on just the positive, if you miss the negative aspects, you can have a negative outcome in three months that may trigger it.

DR. GARBER: Your point is well taken. I'm just trying to find out what the intent was.

DR. BRECHNER: In looking over the literature, one of the studies that I mention did follow people for six years, and I believe the age population was between 65 and 80. So if you follow their reasoning, they didn't think six years was too long a time to follow somebody if they were old. Most of the other studies

involving CNV involved one to two-year follow-ups, but new treatments are looking at effect in a shorter period of time. There are a couple new ones that are coming out and some of the data shows that some of these effects last for a period of time and then they talk about when is the next time, you treat a bunch today, so it's really hard for us to tell. But most of them are in the trials for a couple of years and I think it is reasonable to encourage them to follow them even longer to see what's going on when you treat them, how long does it last, et cetera. However, at current, most of them are one to two years.

DR. BURKE: We're talking about short-term outcomes, not short-term studies. In other words, if you have a long-term study with short-term, intermediate outcomes, we're on the way.

DR. ABECASSIS: Could I ask a question, and this is for the retinal ophthalmologists. If you're treating a patient and you're seeing a response by any one of these 11 measures, especially the anatomical ones, what would be a reasonable amount of time that you would want to see a response, the shortest period of time where

you would want to see a response before you said there was no response? Would it be three months, would it be six months, would it be a week?
DR. BRESSLER: Three months is reasonable to say it looks like there may be no response.
DR. ABECASSIS: So, can I suggest that three months be short-term and a year would be long-term, and if there is disagreement with that, we can revisit it.
DR. BURKE: I think that's what the difficulty is. We're not talking about how long the study should go on, we're saying what kind of outcomes should you be looking at in terms of the patients. You're clearly going to have short-term outcomes. You're not going to wait a year if the patient continues to decline, right?
DR. PHURROUGH: The question wants to know when, it's not concerned about why, but when there are outcomes that should be looked at on the short-term basis and there are outcomes --
DR. BURKE: You said why, how about what?
DR. PHURROUGH: We're not asking the what, we're only asking the when question.

DR. BURKE: Oh, that's easy.
DR. GARBER: I'm not positive that is an easy question, and one of the reasons it's not easy is the need to consider both negative effects as well as positive effects, and when we're talking about intraocular pressure that may not clinically be glaucoma at that point, what if glaucoma does develop but it takes two years or three years to develop? It seems to me that what constitutes long-term follow-up may very well vary with these particular treatments and its expected side effects.
DR. BURKE: I agree, so splitting the time from the treatment and from the task that you use to determine the outcome, I think is difficult. I mean, the simple question of what's short-term and long-term, irrespective of all these other issues, and we don't want to get into the details and kinds of outcomes and kinds of tests, that's another story, but I think the easy answer is just three months and one year.
MR. CLARKE: Is that the intent of the question from CMS?
DR. PHURROUGH: Yes, when is the intent of the question.

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MR. CLARKE: And I have to say, this discussion is around study design versus reimbursing.
DR. LUCE: These are solely coverage decisions.
MR. CLARKE: And when I read this, I took the intent to be, what is the minimal period of time through which outcome data could be presented and a reasonable determination of coverage could be made.
DR. PHURROUGH: No. The question is a trial design question, what is the earliest possible time that you would ever do an outcome measure for which you could see some change that was not insignificant, and what is the longest trial period of time under which you should follow a patient after which there will be no response to treatment.
DR. GARBER: I think that intent was not crystal clear to me from the wording of the yes, so I wonder, Steve, if you could rephrase the question.
DR. PHURROUGH: How short is short-term and how long is long-term.
(Inaudible colloquy.)

DR. PHURROUGH: Short-term outcome is that first point in time in which you will do a measurement, at which time you could find a clinically significant change.
DR. BURKE: Or no change.
DR. PHURROUGH: Or no change, but you would not measure it before then because it would not be clinically significant, whether it was an adverse outcome, or positive outcome, negative outcome, regardless of what the outcome is, what is that first point in time that you're going to measure.
DR. LUCE: So there's an agreement that the first threshold is three months, and the question to me is what's the second threshold.
DR. GARBER: I was trying to write while you were speaking, Steve, so tell me if I got your question right here. What is the minimum amount of time to determine a response to therapy.
DR. PHURROUGH: We want a definition of what is the short-term outcome and short-term being defined as the minimum amount of time to see a clinical change for which you would then perform an outcome measure.
DR. LUCE: So we need to know something

about the efficacy of the treatments and at what point you're confident that you're seeing a change or that you won't see a change, and it sounds like it could be three months in both directions.

DR. ABECASSIS: I think we should just have a short-term which I think has been very well defined and answered by the practitioners as three months. And then we should, I'm still a little confused about the long-term, so I think we should just answer the short-term and then discuss the long-term.

DR. BURKE: I second that.

DR. GARBER: So, it's just what are the appropriate criteria for -- it's not appropriate criteria, it's time frame.

DR. BURKE: What is the definition for short-term.

DR. ABECASSIS: The criteria, three months could be a criterion for short-term. So if that's how you phrase the question, then the answer is whatever time period you used that is effective is the time period for short-term.

DR. PUKLIN: The criteria may actually be different than what's defined by the studies that have been reported, because Dr. Price has

mentioned that he in his capacity at the carrier saw that some patients aren't completing all of their treatments and some of the protocols. So perhaps if you'd like to ask some of the investigators, it would seem to me that the shortest time interval might vary with the study type, so if one studied drug actually caused an outcome over a six-week period or 12-week period, and some may take longer, so perhaps having a uniform cutoff point may be inexact, imprecise.
DR. ABECASSIS: It's the shortest.
DR. BURKE: Right. I mean, when would you begin checking, you know.
DR. PHURROUGH: If you're going to design a study, what is that first measurement of time that you are going to require in your protocol that all physicians follow?
DR. PUKLIN: Is everyone in agreement today that three months was the earliest assessment?
DR. BURKE: Yeah. I make a motion that short-term is defined as three months.
DR. GARBER: What is the question though?
DR. PHURROUGH: Give us the three

months and we'll live with it.
DR. GARBER: Okay, so the answer is three months, that's what we're voting on, the answer is three months.
DR. BURKE: Correct.
DR. GARBER: All in favor.
(Hands raised.)
DR. GARBER: All opposed?
(Hands raised.)
DR. GARBER: All hopelessly confused? Okay, it carries.
Number 2. At present, usual and approved care --
SPEAKER: What about long-term?
DR. GARBER: Steve, what is the question?
DR. PHURROUGH: In designing a trial for treatment of AMD, how long would you follow patients, what would be the term of a long-term outcome in following patients being treated for AMD?
SPEAKER: Is this a minimum?
DR. PHURROUGH: Where you're going to end the trial, the trial is not going to go out forever, it's going to finish. So if someone

comes to us, we're going to have to tell them, if you don't carry this trial to this length of time, we're not going to consider the data.

DR. GARBER: So it's the minimum amount of time.

DR. BURKE: Could it be a range, could it be one to two years?

DR. WEINER: How about at least a year, preferably longer?

DR. PHURROUGH: Give us a number, whole number, number of months.

DR. BURKE: 12.

DR. GARBER: Okay. I think I heard a motion that the minimum is 12 months. Do I have a second?

DR. FENDRICK: Second.

DR. GARBER: Any discussion? All in favor?

(Hands raised.)

DR. GARBER: Opposed?

(Hands raised.)

DR. WEINER: Can we add that we prefer longer?

DR. GARBER: We just voted that minimum means at least 12 months.

DR. BURKE: And longer is better.
DR. GARBER: The sense of the panel is longer is better than 12 months.
Now, number two. At present, usual and approved care for AMD commonly includes photodynamic therapy with verteporfin, laser photocoagulation, intravitreal injection of pegaptanib, and oral vitamins, antioxidants and zinc. A, How confident are you that there is sufficient evidence to assess the health benefit of these modalities compared to watchful waiting only? Are people comfortable using the one, two, three classification? Okay. Any discussion? So, we can take these as a group. I point out -- you want to do them individually? Let's start with verteporfin. Any discussion before voting?
DR. LUCE: Just one piece of discussion here and that is in terms of health benefit, I'm not sure about that particular product, but there's a difference between (inaudible) and visual acuity, which has been really the standard care. And so the terms health outcomes, I presume visual acuity will suffice here?
DR. GARBER: I think that's your call.
DR. KRIST: We could argue that we just

defined this in Number 1, and in Number 1 we said what the outcomes should be and what the time frames should be, so putting this in the context of how it flows, Number 2 would be, which adhere to the guidelines that we just voted on.
DR. GARBER: Okay, verteporfin, all those rating this as a one, meaning that you're highly confident?
(Unanimous response.)
DR. GARBER: Number two?
(No response.)
DR. GARBER: And number three.
(No response.)
DR. GARBER: Laser photocoagulation.
One?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: And three.
(No response.)
DR. GARBER: Intravitreal Macugen.
One?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)

DR. GARBER: Three.
(No response.)
DR. GARBER: And oral vitamins, antioxidants and zinc. One?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: Three.
(No response.)
DR. GARBER: B, how confident are you that there are therapies other than these that were discussed that provide a health benefit when compared to watchful waiting? And I think the intent here was, are there other things that you are confident are effective that we have not discussed today?
DR. LUCE: That is approved?
DR. FENDRICK: Anything on that list that was not discussed today.
DR. GARBER: Not limited to approved. But here I'd suggest -- well, is there anything that you think would merit a one that was not on that list?
DR. FENDRICK: How about the one, it starts with an R, we heard a lot about that.

DR. GARBER: You'd put that as a one?
DR. FENDRICK: No, I'm saying that would be on the list, that would fall in the category of others that were discussed today.
DR. PUKLIN: So would Avastin.
DR. ABECASSIS: Maybe I can make a suggestion that we have a list and then we vote one, two, three.
DR. GARBER: Okay. Is everybody comfortable with that? So we'll have a list, and right now, Avastin is on that list. So the proposal is to vote one, two and three for these. Mark is shaking his head.
DR. FENDRICK: If we keep it the way it is, it's an easy question. If there are others, we can say yes, and move on. I think that would be in the spirit of other MCACs.
DR. GARBER: What would be most useful to you guys, Steve, would you rather us just say yes, there are other things and leave it at that?
DR. PHURROUGH: It might help if you just identify what you're thinking of.
DR. GARBER: Mark has the earliest flight.
DR. FENDRICK: No, no. Now we have to

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make the list and vote on each one?
DR. GARBER: Yeah. Is there anything to add to Lucentis and Avastin?
DR. ABECASSIS: What about the previous list, that's a steroid.
MR. CLARKE: Was there any discussion about the steroid?
DR. ABECASSIS: Yeah, but we can vote one, two or three.
DR. GARBER: So what do you want to add to the list.
SPEAKER: Anecortave acetate.
DR. GARBER: All right, anecortave acetate, and do people want to include triamcinolone? That was discussed.
DR. ABECASSIS: You can number it.
DR. GARBER: So now I have four things on the list, Lucentis, Avastin, anecortave, and triamcinolone. Okay, one, two, three. Lucentis, how many ones?
(Hands raised.)
DR. GARBER: Two, for Lucentis.
(Hands raised.)
DR. GARBER: And three.
(No response.)

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DR. GARBER: Avastin, one?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: Three.
(Hands raised.)
DR. GARBER: Anecortave, one?
(No response.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: Three.
(Hands raised.)
DR. GARBER: Triamcinolone, one?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: Three.
(No response.)
DR. GARBER: That's 2B, so moving to 3, based on 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 1?

I'll suggest we don't go outcome by outcome, but the intent to your answers of the previous question is clearly stated. Is that the intent of your question?
DR. ABECASSIS: I'm not sure this is different from 2A.
DR. GARBER: 2A was the evidence showed it works, but I would not be surprised if you answered the same way.
DR. PHURROUGH: Does it have a positive effect on outcomes.
DR. GARBER: Yes or no. Okay. The first one was did you think the evidence was sufficient to make a judgment, and this is just saying do you think it has a positive effect.
DR. BURKE: It says how confident are you, so stick with the one, two, three thing.
DR. GARBER: Okay, we will do one, two, three. First, verteporfin, one?
(Unanimous response.)
DR. GARBER: Two.
(No response.)
DR. GARBER: Three.
(No response.)
DR. GARBER: Okay, that's a one. Laser

photocoagulation, one?
(Unanimous response.)
DR. GARBER: Two.
(No response.)
DR. GARBER: Three.
(No response.)
DR. GARBER: That's a one.
Intravitreal Macugen, one?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: Three.
(No response.)
DR. GARBER: And then the combination of vitamins, antioxidants and zinc. One?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: And then three.
(No response.)
DR. GARBER: Okay. Number 4A, we have a request from CMS to delete 4A.
4B. Based on evidence reviewed, how confident are you that the other treatment modalities, used singly or in combination, and

those are the four that we just discussed, produce clinically significant net health benefits in the treatment of AMD? So we will do one, two, three. Starting with Lucentis, one?
(Hands raised.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: Three.
(No response.)
DR. GARBER: Avastin, one?
(No response.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: Three.
(Hands raised.)
DR. GARBER: Anecortave, one?
(No response.)
DR. GARBER: Two.
(Hands raised.)
DR. GARBER: Three.
(Hands raised.)
DR. GARBER: Triamcinolone, one?
(No response.)
DR. GARBER: Two.
(Hands raised.)

DR. GARBER: Three.
(Hand raised.)
DR. GARBER: Question 5, what are the knowledge gaps in current evidence pertaining to the usual care and outcome measurements of AMD?
Bryan.
DR. LUCE: Patient preference and utility.
DR. FENDRICK: Linkages between surrogates and clinically meaningful outcomes.
DR. WEINER: Guidelines relating to sequencing, the combinations, the real practice outside of trials.
DR. GARBER: Should we say treatment algorithms?
DR. WEINER: I think treatment algorithms would be fine.
DR. ABECASSIS: Pathophysiology of disease.
DR. PRICE: Diagnostics of progression.
DR. GARBER: Any others?
DR. GOODMAN: Patients subclinical responses to specific therapies.
DR. BURKE: Indicators of treatment response.

DR. ELLWEIN: Adverse side effects and economic data, direct and indirect costs.
DR. LUCE: Cost effectiveness?
DR. ELLWEIN: Yes, cost of treatment versus not treating.
DR. WEINER: The California list and there are some good questions there, they were really very clinical, but can we just suggest Dr. Stout's list.
DR. GARBER: We can suggest that.
DR. WEINER: Why don't we suggest his list.
DR. GOODMAN: Genomic cell biology and stem cells, vascular permeability, that said it.
DR. GARBER: Any others.
MR. CLARKE: Clinical quantification that can be digitized down and made very easy.
DR. FENDRICK: Let me be clear; are you prioritizing the second therapy over the first and the order in which they're given?
DR. GARBER: Yeah, that would fit in with the algorithm and combination of therapy question. Okay. That was a great suggestion. Number 6, what trial designs will support the development of such evidence to

determine the appropriate treatment of AMD?
DR. BURKE: RCT trials, I think should really be the bedrock for this, you know.
DR. LUCE: Are we going to talk about registries, I don't think, or modeling studies?
DR. BURKE: Well, sufficient evidence, you know.
DR. GARBER: Maybe a specific example of what Bryan is concerned about is, well, the registry could be used for adverse events even outside the trial and would produce useful information. Another issue is comparative effectiveness, because I doubt very much that we're going to see many head-to-head trials of VEGF inhibitors, for example, but there may be some questions about that, and do you think there are types of study designs other than head-to-head trials that might address some of those questions?
DR. ABECASSIS: Could I suggest studies showing superiority versus nonsuperiority studies.
DR. BURKE: But how are you going to control in any non-head-to-head trials or non-head-to-head studies that you're proposing?
DR. GARBER: We're not going to resolve the question of what you do, but the question is,

do you want to foreclose the possibility that there is any design other than a randomized trial?
DR. BURKE: I'm wide open. If you want to you do one, I'm wide open.
DR. GOODMAN: RCTs are necessary, though.
DR. ABECASSIS: Steve, maybe you can clarify the question.
DR. PHURROUGH: The question is what other ways, what are various ways that can be provided to us that will help inform those who are asking us in making our coverage decisions and for practitioners in treating patients.
DR. GOODMAN: RCTs are necessary, to be followed up as appropriate by comparative head-to-head trials, to be followed with registries, to be followed with perhaps meta-analysis of RCTs. But you can't get on the board without an RCT. Thereafter, as Bryan just whispered in my ear, claims analyses, registries and so on. You've got to get on board with an RCT. After that, head-to-heads might be good in certain cases, also randomized. Registries, claims analysis and meta-analyses of RCTs.
DR. WEINER: And I think with a lot of

the networks that are in place, we want to foster the new technologies but not everybody can get everything, so I think we need to monitor and get back to the algorithms and figuring out when it is appropriate, and monitoring not only efficacy but also other outcomes. This is complicated stuff, this is a good one, because it will only increase in terms of the impact on Medicare society and the technologies will also be increasing.

DR. GOODMAN: Technologies are swell, but you still can't get on board without an RCT.

DR. GARBER: There's going to be a question here, I think. I don't know how many RCTs there are for Avastin as a treatment of AMD, there are plenty of toxicologic indications, but if you say you can't get off the floor without a randomized trial, then Avastin will never get off the boards. Now that may be the conclusion you want to reach, but I want to make sure that people are comfortable with that, because we heard from ophthalmologists who are currently using Avastin to treat AMD and if you want to just say CMS shouldn't consider reimbursement for this without a randomized trial, we have to make sure that we're explicit. There are people who would

advocate using it based on indirect evidence, and if you are going to say it has to be an RCT and foreclose that practice, that's fine, but we should be clear about what we're doing.

DR. FENDRICK: There was something about strength of evidence between RCTs and indirect evidence, and obviously there are people on this panel with strong feelings about that. Steve, when I saw these questions, I thought this was probably the question that lurked in the past to essentially help prioritize not only the trial design, but also to start to get various opinions not only about things without an RCT, and it seems that what they're saying is the RCT is to be backed up with a non-RCT design, but you would not be very interested in some of these other designs without an RCT to put it on board.

But the other thing in Question 6 is, I feel that we didn't prioritize these 11 things, and I'm wondering when I read this question about trial design, if it's not only the type of trial, but also to hear from the panel about what would be the minimum amount, and Neil stuck around for so long, and I think we could probably help by saying what we would find to be that minimum set

of outcomes that panels would like to see.
DR. GARBER: Our vote on Question 1 was intended to answer that question.
DR. FENDRICK: But there still could have been -- I may be wrong. None of us would accept a trial without visual acuity being looked at, one without that, but I think some of us voted highly for other outcome measures, but I think some of us have different priorities, but I may be wrong.
DR. PHURROUGH: The question is a broad definition of designs and a broad definition of trials. We have a newer drug on the market, a newer procedure. Verteporfin has had its RCTs, should we stop collecting data on it? Is there not more data to collect that will help inform both us and the world about how it should be treated? Maybe we can answer that question. Macugen has finished its two RCTs, what's next for it, how should it be followed, what should be the next kind of evaluation?
DR. GOODMAN: How about biological plausibility, Steve?
DR. PHURROUGH: There are various levels of treatment that are already out there

with various amounts of information we would continue to like to receive about those, and not just us, but treating physicians, and what are the different kinds of evidence collecting tools that we should use. And design not only includes RCTs versus comparative trials versus registries versus claims databases, but what are those things that we should be measuring when we are putting those products together, or when people are putting those trials together.

DR. ABECASSIS: I think if you restrict it to RCTs, you may be doing some drugs that are out there and that people are using a real disfavor, because there may not be sponsors for those RCTs and I think that, you know, we're talking about some drugs that are very promising that if that's required, they may not be allowed to show their efficacy even though the practitioners think they are efficacious.

DR. BURKE: I have to take a little bit of exception to that. I mean, we've sat on these MCACs where that rationale, you know, we don't do clinical trials because the clinicians say it works so we're not going to do a clinical trial, and that becomes a factor in determining whether

in fact the drug works or not.
DR. ABECASSIS: I didn't say not to do a clinical trial, I was specifically talking about a randomized controlled trial.
DR. BURKE: Right, a randomized controlled trial, and they will actually say because our clinicians already know it works, we're not going to do that, it's unethical in some cases. We're asked to know whether the treatment that they're using is effective or not, and there is no real evidence to support it. So I think in this day and age we have to have actual evidence, and I think a randomized controlled trial is the evidence that we need.
DR. GOODMAN: I think we are all aware of certain limited instances where pulling off an RCT is impractical and some might say unethical. I suggest those are very unusual circumstances. But for answering the question so far as it affects AMD, which I don't think is a fatal disease, for which there are no alternative treatments and no one is willing to be randomized, I think for the purpose of this disease for the available treatments and other things in development, that the presumption should be RCT

first. And if the sponsor has a real strong compelling reason why something other than an RCT would suffice, let that sponsor make their case.
DR. ABECASSIS: I'm not an ophthalmologist, I have no conflicts. The way it looks to me is, there is a drug out there called Avastin which is probably as good as another drug called Lucentis, and I want to know who is going to sponsor a randomized clinical trial to check the efficacy of Avastin. If there is anybody in the room who wants to volunteer to sponsor that trial, I would like to hear it, because the way I read it, that drug will not be tested as rigorously as it probably should be tested.
DR. KLEIN: What if there are no RCTs to show the efficacy and also what's been happening, there is no sponsor and someone else has to step in.
DR. GOODMAN: Lack of a sponsor or facilities is not a cause for Medicare to decide to pay for something.
MR. CLARKE: Specifically with regard to Avastin, if a company knows that, if they make a decision to sponsor it, they do; if they don't, they don't. The problem with not doing an RCT is

you don't have pharmaco-vigilance.
DR. ABECASSIS: There is a randomized trail for Lucentis and therefore, is the reason for them not to do that based on financial realities? I'm just putting that on the table.
MR. CLARKE: We also are glossing over the power of drugs and an RCT with pharmaco-vigilance in a structured orderly ongoing way, and we can't minimize that. That is the burden that people must carry when people do a trial.
DR. SEMBA: Genentech is developing Lucentis and also does manufacture Avastin for cancer therapy.
DR. ABECASSIS: Are you saying that Genentech would be willing to put Avastin into a randomized clinical trial to test its efficacy against a much more expensive drug, Lucentis?
DR. SEMBA: Genentech did not develop Avastin, it was not intended for individual use. It will have to be reformulated, the clinical trials will take another five to seven years, so the short answer is no.
DR. GARBER: Alex.
DR. KRIST: All I was going to say is I believe in the RCT theory, and I understand the

dilemma that we have here as well, and maybe one solution is to list this in gaps of our knowledge, and I hate to step back a question, but this specific one might be a gap in our knowledge.

DR. BURKE: This is what?

DR. ABECASSIS: The difference between RCTs.

DR. LUCE: Alan, I think the solution to our problem is the wording of the question itself. It says, what designs will support the development of sufficient evidence to determine. It's a very open ended question and we don't have to prioritize here, unless you think we need to.

DR. GARBER: If we eliminated the word trial and before the question came up, I should have reviewed it, and should it say what, study design? Are people comfortable reformulating the question so it says what study instead of what trial?

DR. LUCE: It doesn't matter.

DR. GARBER: Okay.

MR. BURKE: Well, I would suggest that randomized clinical trial would be an answer to this question.

DR. PHURROUGH: For what?

DR. BURKE: For any appropriate treatment of AMD, for any appropriate treatment, a randomized clinical trial will suffice.

DR. PHURROUGH: RCT has demonstrated benefit of PDT, so there is no further evidence or any other trial design that would help inform physicians on how to use PDT?

DR. GOODMAN: Yes, there are other study designs.

DR. WEINER: RCTs are necessary, but we have to go beyond that, and the difference between the FDA and CMS is that for FDA, that might be enough, but not for CMS. Some things are beyond our control, and we're not allowed to talk about cost/benefit and value to society.

DR. PHURROUGH: Nothing prevents you from talking about it.

DR. WEINER: But it terms of capturing data on preferences and looking at costs and looking at population benefits, I think every country in the world does it and maybe one day we'll do it here, but CMS is within its regulatory purview in saying that we can't.

DR. BURKE: The RCT can be used for utility analysis, it can be used for safety and

efficacy, it can be used for anything you need to know. It could be your intermediate endpoint validity test, it can be a fertile ground for finding all these things.

DR. ABECASSIS: Who's going to pay for it?

DR. GARBER: Cliff, and then Bill was next.

DR. GOODMAN: I don't know that we want to suggest to CMS that something other than an RCT would be sufficient evidence to determine appropriate treatment. I think a suggestion that they do an RCT, that's the starting point. That doesn't mean that other things might support sufficient evidence, but not comprise it. So these other studies that have been described, not necessarily trials, but these other studies would certainly support an evidence base, but we have to start with RCTs, and then supportive studies are the ones that include the registries, the claims analyses, meta-analyses of RCTs and so forth.

DR. GARBER: Bill.

MR. CLARKE: I just second that. I mean, RCTs are necessary but not sufficient. They may concern a certain population base, but there

are other effectiveness, cost effectiveness sort of determinations that are needed, so ongoing studies that have registries, maybe even coverage determination studies could be extraordinarily powerful here. As we get into study design, as we see in any technology, we'll see technology creep. So it is ultimately a disease that should be covered, and that's the power of these ongoing registry studies, we want to be able to say to CMS that it's a powerful thing to require us as providers and industry to do, to continue to acquire data like that. That allows an understanding of the use and utility of this in an extended population where RCTs will normally not do that.

DR. BURKE: We could require them to do Phase IV follow-up afterwards, after the RCT. I don't know about increased data, but with added criteria and the RCT, there is a cornucopia of things you could do.

DR. GARBER: I don't think there's any disagreement that RCTs are important. The question is just, are there important supplemental studies like claims analysis. Patrick.

DR. PRICE: I think one of the problems

that Steve is alluding to is that we have verteporfin's RCT, we now have Lucentis' RCT. Now together, though, when we're going over both in unison, does that require another RCT or is that what we need to derive from registries? These are important questions because it is not the single drug necessarily that's the endpoint, it's the combination of drugs, triamcinolone with OPT. And these are difficult questions that CMS is having to deal with, so where does, you know, if it has an RCT, that drug has an RCT, does that therefore mean that we have to use both of them simultaneously or outside of an RCT? That's number one.

Number two is that this is more specific, but it would be helpful since we don't have very many or hardly any head-to-head analysis, that CMS would be encouraged, or could ask for this same method of reporting the data, whether it be quality of life, in other words, a template where you plug in the number and if you want secondary outcomes, that's fine, that's your decision. That would be helpful.

DR. GOODMAN: We've discussed this in enough detail to answer this question. RCTs

should be required, I think we all agree on that. I think we also agree that there are a set of other kinds of study designs that will supplement this information, and I think that is an answer to this question.

DR. BURKE: I agree.

DR. GARBER: Okay. So, I think the discussion has answered the question and we don't need to vote on the question; is that correct?

DR. PHURROUGH: Agreed.

DR. GARBER: Number 7. Based on the evidence presented, how likely is it that studies using valid measures of outcomes in treatment of AMD will result in conclusions that can be generalized to the Medicare population? This is basically effectiveness and internal validity.

DR. BURKE: No, it's entry criteria.

DR. GARBER: Well, actually that is presupposing the answer to that question. What it's trying to get at in the question, do the results apply to the typical beneficiary treated in a typical practice?

DR. BURKE: Patients over 65, right?

DR. GARBER: Right.

DR. BURKE: That's it.

DR. GARBER: Any discussion?
DR. WEINSTEIN: A quick discussion.
That's why we need the other studies. In other words -- I'll wait until we vote. We're allowed to comment afterwards, right?
DR. ELLWEIN: There was that point made that the studies are done perhaps in clinics that are not representative of clinics in general, that is to say that the eye care providers in a study may be nonrepresentative of the eye care providers for the general Medicare population, so paying attention to the study sites is probably an issue, not to mention entry criteria, exclusion criteria, the patient population itself, so the study needs to be looked at across all the dimensions to ensure that it is truly not a special population, a special set of providers, with a nongeneralizable or nondoable, nonpractical protocol.
DR. GARBER: I think that's a really good point, and one of the aspects that we often worry about when we talk about generalizability is how the intervention was delivered, and although there may not be a lot of variation in how an intravitreal injection is given, we heard today

about a lot of variation in how people decide to monitor response to treatment and how they decide to give another treatment, whether it's the same one given again or a different one, and that clearly could be at least potentially different at different sites, different between the places in published studies and the rest of the world where this is administered.

DR. LUCE: I just want to make the point that unlike a lot of products that come to the market, this product undoubtedly was tested in the elderly population because it is the elderly population that is at risk for this, so to a great extent what we see is clearly generalizable to the Medicare population. The real question is, is it generalizable to community practice patterns, so you may even want to change the nature of that question.

DR. WEINER: Again, we are dealing heavily with the elderly, but also as I understand the concept here is mainly retinal specialists, it's not going to be something that diffuse primary care doctors or even primary care ophthalmologists in most cases, so that part I'm not concerned about.

But we all know that an RCT has all kinds of external validity problems and I'm worried about one thing in the controlled RCT by retinal specialists, it's another one that's out there, open, all paid for, no algorithms and so forth, and demanding boomers are on the march, so it's not like the trials we're seeing today.

DR. GARBER: Any other business? Thank you, panel members, thank you, speakers and attendees. We need a motion for adjournment.

DR. BURKE: So move.

DR. ABECASSIS: Second.

DR. GARBER: All in favor.

(Whereupon, the meeting adjourned at 3:02 p.m.)