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CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Evidence Development & Coverage Advisory Committee

March 21, 2012

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

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Panelists

Chairperson
Clifford Goodman, PhD

Vice-Chair
Steve E. Phurrough, MD

Voting Members
Wendolyn S. Gozansky, MD, MPH
Peter Heseltine, MD
Susan A. Levine, DVM, MS. PhD
Pamela R. Massey, PT, MS
Robert McDonough, MD, JD
Prabashni Reddy, PharmD
Art Sedrakyan, MD, PhD
Robert L. Steinbrook, MD

CMS Liaison
James Rollins, MD

Industry Representative
Robert W. Dubois, MD, PhD

Guest Panel Member
James E. Puklin, MD, FACS

Invited Guest Speaker
Robert N. Frank, MD

Executive Secretary

Maria Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:10 a.m., Wednesday, March 21, 2012.)

MS. ELLIS: Good morning and welcome, committee chairperson, vice chairperson, members, and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, MedCAC.

The committee is here today to discuss the evidence, hear presentations and public comment, and make recommendations concerning the currently available evidence regarding the intravitreal targeted treatment of diabetic retinal disease, diabetic macular edema,(DME).

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests.

Each member will be asked to disclose any financial conflicts of interest during their introduction. We ask in the interest of

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fairness that all persons making statements or presentations disclose if you or any member of your immediate family owns stock or has another financial, another form of financial interest in any company, Internet or e-commerce organizations that develops, manufactures, distributes and/or markets modalities used in the treatment of diabetic retinopathy, (DR), and diabetic macular edema, (DME). This includes direct financial investments, consulting fees, and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of 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 that 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 for the next speaker and please proceed to that chair when it is your turn. We ask that all speakers addressing the

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panel please speak directly into the mic and state your name.

For the record, voting members present for today's meeting are Steve Phurrough, Wendolyn Gozansky, Peter Heseltine, Susan Levine, Pamela Massey, Robert McDonough, Prabashni Reddy, Art Sedrakyan, Robert Steinbrook. A quorum is present and no one has been recused because of conflicts of interest. The entire panel, including nonvoting members, will participate in the voting. The voting scores will be available on our website following the meeting. Two averages will be calculated, one for voting members and one for the entire panel. I ask that all panel members please speak directly into the mic, and you may have to move the mic since we have to share. This meeting is being web-cast via CMS in addition to the transcriptionist. By your attendance you are giving consent to the use and distribution of your name, likeliness and voice during the meeting. You are also giving consent to the use and distribution of any personal identifiable information that you or others may disclose about you during today's

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meeting. Please do not disclose personal health information.

If you require a taxicab, there are telephone numbers to local cab companies at the desk outside of the auditorium. Please remember to discard your trash in the trash cans located outside of this room.

And lastly, all CMS guests attending today's MedCAC meeting are only permitted in the following areas of CMS single site, the main lobby, the auditorium, the lower level lobby and the cafeteria. Any persons found in any other area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

Now I would like to turn the meeting over to Dr. James Rollins.

DR. ROLLINS: Thank you. Good morning. My name is Jim Rollins and I'm the director of the division of items and devices in the Coverage and Analysis Group.

The MedCAC serves three main purposes for CMS. The first, to get input from experts on the topic in the field. Also, number two, it helps us to disseminate information to the

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general public, and as Maria just mentioned, this will be web-cast. And three, also, information from experts as well as information obtained from commissioned external technology

assessments help us strategize our efforts in terms of related future activities on this topic, including potential national coverage determinations, but let me just also say that we currently do not have an NCD open on this topic.

Because of the global nature of this topic, we have commissioned two external technology assessments. One of them will be discussing health-related quality of life measures for patients with diabetic retinopathy as well as patients with diabetic macular edema. And also, the second technology assessment will look at anti-VEGF therapy for patients with diabetic macular edema.

I would like to thank the chairperson as well as the vice chairperson, as well as the members of the MedCAC committee for today's discussion.

DR. GOODMAN: Thank you very much, Dr. Rollins, Cliff Goodman here. We have today

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a full agenda on a topic of considerable potential impact on the wellbeing of a large number of Medicare beneficiaries, so we expect that all of our guest speakers, those providing scheduled public comments and any who provide open public comments, as well as my fellow MedCAC members, will be on point and concise today.

When it's your turn to speak, speak into the microphone. If you don't do that, we are not going to be able to hear you and our trusted court reporter won't hear you either, which means that the very important things that you have to say won't get into the record.

We have today time for scheduled public comments. As I understand it there will be six such presentations, each of which will be allocated a maximum of seven minutes by CMS, so six such presentations, only seven minutes each. Given our tight agenda, we will need to adhere to those seven-minute limits.

Later on we're going to hear from any public commenters, each of whom will be allocated just the one minute. So we kindly but firmly suggest that each scheduled speaker,

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each public commenter think now about focusing your presentation on information pertaining directly to today's questions.

If you planned to present material that you find would be repetitive of a previous speaker or that is just background information

about the organization you represent, you might consider dispensing with that material and focusing instead on what you want this panel to know today about our questions. In any case, please do heed the traffic light system when you're speaking, and please do know that we will proceed to the next speaker once you've used your allotted time.

Any speaker, by the way, who has not signed a disclosure form, will have to do so. Please at this time silence your cell phones and any communications gizmos on or near your person.

Moving to disclosures, I apologize ahead of time, mine's a little bit longer than most. I am Cliff Goodman, I'm a senior vice president for the Lewin Group. The Lewin Group is one of multiple subsidiaries of an outfit called OptumInsight, which is a healthcare

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information and analysis firm. OptumInsight, in turn, is one of multiple subsidiaries of United Health Group.

Though not a conflict, I do want to note that a conference planning firm has engaged my employer, Lewin, to have me moderate an oncology symposium next month being sponsored by Genentech, which also manufactures certain products being addressed in today's meeting. Under that same type of arrangement, I facilitated a similar oncology symposium in 2010. I have no interests to declare pertaining to today's topic. Dr. Phurrough.

DR. PHURROUGH: Hi. I'm Steve Phurrough, from the Center for Medical Technology Policy. My company works in clinical trial design; as such, we sponsor various symposia around designs of clinical trials, and some of those symposia have sponsorship from some of the companies that make these products, but I'm unaware of a symposium that specifically looked at this particular product.

DR. GOZANSKY: I'm Dr. Wendolyn Gozansky from Kaiser Permanente Colorado. I'm

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an internist geriatrician and investigator in the department of continuing care of the Institute for Health Research, and I have no conflicts to disclose.

DR. HESELTINE: I'm Peter Heseltine, internist and infectious disease expert. My positions are, I'm a clinical professor of medicine at the University of California at

Irvine, and am also senior vice president and chief medical officer for Prometheus Laboratories. I have no conflicts of interest to declare.

DR. LEVINE: I'm Susan Levine, and I'm senior vice president of Hayes, Incorporated. Hayes is an independent company that does technology assessment and comparative effectiveness, and I have no conflicts of interest.

MS. MASSEY: I'm Pamela Massey, and I am retired from the University of Texas M.D. Anderson Cancer Center and the rehab services there, and I have no conflicts of interest.

DR. MCDONOUGH: I'm Bob McDonough, I'm head of clinical policy research and development for Aetna, I'm also cochair of our

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pharmacy and therapeutics committee and I have no conflicts of interest.

DR. REDDY: I'm Prabashni Reddy, I'm the director of the Partners Healthcare Center for Drug Policy in Easton, Massachusetts, and I have no conflicts of interest to declare.

DR. SEDRAKYAN: Art Sedrakyan from Weill Cornell Medical College, directing the patient-centered comparative outcomes research program, associate professor of public health, and no conflicts to disclose.

DR. STEINBROOK: Robert Steinbrook, Yale University School of Medicine, internist, no conflicts to declare.

DR. DUBOIS: I'm Bobby Dubois, I'm the chief science officer of the National Pharmaceutical Council, I'm the industry representative. The National Pharmaceutical Council is a member-sponsored organization and the members are major manufacturers, pharmaceutical manufacturers in the United States, and I have no other conflicts to report.

DR. PUKLIN: My name is Jim Puklin, I'm a professor of ophthalmology at Wayne State

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University Kresge Eye Institute. In addition I was the chair of the human investigation committee at Wayne State University for a period of four years, and I am still the chairman of the Phase I panel at Wayne State University's human investigation committee. I have no conflicts of interest.

DR. GOODMAN: Excellent, thank you, panel. We will now move to the CMS presentation and voting questions. This will

be Kimberly. Ms. Long.
MS. LONG: Good morning. CMS has called this meeting of the MedCAC panel to review the available evidence for intravitreal targeted treatment of diabetic retinal disease, diabetic macular edema, (DME).
CMS is most interested in meaningful changes to beneficiaries' visual function that enable their independent accomplishment of routine daily activities. We also seek the panel's input on the preferred measures for determining progression and clinical trials of DME treatment.
For the voting questions, please use the following scale identifying level of
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confidence, with one representing the lowest or no confidence, three representing intermediate confidence, and five representing a high level of confidence.
Discussion question number one: In a 2005 MedCAC meeting on wet age-related macular degeneration, the following commonly used outcomes or intermediate endpoints were discussed. Visual acuity, VFQ-25, dilated eye exam, grade of diabetic retinopathy, Amsler grid, extent and progression as measured by retinal photography, fluorescein angiography, visual field, ocular coherence tomography.
Please discuss the suitability of these measures for assessing DME treatment-related health outcomes, i.e., benefits and harms.
Question two: How confident are you that there is adequate evidence to determine whether or not DME management using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without intravitreal targeted anti-VEGF treatment?
Question three: If the result of question two is at least intermediate with a
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mean vote of greater or equal to 2.5, how confident are you that there is adequate evidence to conclude that DME management using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without intravitreal targeted anti-VEGF treatment. Please discuss any patient characteristics, treatment regimens of other factors that may have important impacts on the degree of patient benefit or harm from these treatments.
Question four: If the result of

question three is at least intermediate with a mean vote of greater than or equal to 2.5, how confident are you that there is also adequate evidence to determine whether or not there are clinically meaningful differences in health outcomes among the available intravitreal targeted anti-VEGF treatments for the management of DME.
Question five: If the result of question four is at least intermediate with a mean vote of greater than or equal to 2.5, how confident are you that there is adequate evidence to conclude that there are clinically

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meaningful differences in the health outcomes when comparing the following available intravitreal targeted anti-VEGF treatments, ranibizumab versus pegaptanib, bevacizumab versus pegaptanib, ranibizumab versus bevacizumab? Please discuss whether your conclusions are based on evidence of, A, different benefits with similar harm; B, similar benefits with different harms; and C, different benefits and different harms.
Question six: How confident are you that the conclusions above are generalizable to Medicare beneficiaries and community-based settings?
Discussion question seven: To what extent are the conclusions above generalizable to the management of other forms of diabetic retinal vascular disease beyond DME?
Discussion question eight: Are there significant gaps in the evidence base on the management of diabetic macular edema?
Discussion question number nine: What study designs would support the narrowing or closure of these gaps?
Thank you.

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DR. GOODMAN: Thank you very much, Ms. Long. Having heard the CMS presentation and voting questions, we will proceed with our first invited speaker. This is Dr. Robert Frank. He is the Robert Jampel professor of ophthalmology and professor of anatomy and cell biology at Wayne State University School of Medicine. Welcome, Dr. Frank.
DR. FRANK: Thank you very much, and it's a pleasure to be here to address this MedCAC panel. I should state at the outset, as others have before me, that I do not have any conflicts of interest or financial interests relevant to this presentation.

The questions that I have been asked to address are initially what is diabetic retinopathy and what is diabetic macular edema, which is the entity that we are to consider today.

Diabetic retinopathy, although we recognize it clinically as a disorder of the retinal blood vessels is actually, I believe, primarily a disease of the retinal neurons and glial cells, with the vessels becoming involved secondarily to the metabolic abnormalities of

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the neural retina. It usually develops after a number of years of diabetes. If you are a Type I diabetic with acute onset, it may be as long as five years at the minimum, and it is occasionally in individuals with Type II diabetes who have a more subtle onset of their metabolic disease, it may be seen at or very near to the initial clinical diagnosis of the systemic disease.

Macular edema is a form of diabetic retinopathy that involves the macula, which is the central area of the retina occupying a roughly circular area about six millimeters in diameter in the adult eye extending temporally from the temporal border of the optic nerve head, and between the superior temporal and inferior temporal retinal vascular arcades.

The center of the macula is the fovea, which is composed exclusively of narrowed and tightly packed retinal cone cells, and where there are no retinal blood vessels affording light or direct path to the photoreceptors, and affording the maximum visual acuity, color, sensitivity and so forth.

Macular edema is a disease in which,

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as one would expect from the name, fluid leaks from the retinal vasculature and perhaps also, though not as well recognized, from the choroidal vasculature underneath the retina, and causing the tissue to swell and disrupting visual function. Diabetic macular edema, then, there are many forms of macular edema, but diabetic macular edema is the form the disease that occurs in the setting of diabetes mellitus.

These questions are the next that I will consider and this, the data here comes from the National Health and Nutrition Examination Survey, the NHANES study, which is a federally financed study from the Centers for Disease Control and Prevention in Atlanta

that's conducted every several years. The most recent publication of this occurred in 2010 in the Journal of the American Medical Association.

Seven percent of the U.S. population is estimated to have Type I or Type II diabetes. Of those individuals, studies have shown that almost a third of these have some evidence of diabetic retinopathy, and nearly

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five percent of these have vision-threatening disease, that is, either proliferative diabetic retinopathy with new blood vessels or diabetic macular edema, both of which can cause severe and permanent reduction in vision and in the proliferative disease, even total blindness.

The disease is much more prevalent among minority groups, African-Americans and in particular among Mexican-Americans and native Americans, so that it affects a particularly sensitive and often disadvantaged portion of the U.S. population. So for those, in those regards diabetes and diabetic retinopathy are terribly important diseases from a public health standpoint.

This is an old slide dating back from a population, a classic, now classic population-based study in 1984 conducted by Ronald and Barbara Klein and their colleagues at the University of Wisconsin, showing that in Type I diabetes, the less prevalent form, about five percent of all diabetics are Type I requiring insulin, and ketosis prone, they don't make any of their own insulin, and showing that any retinopathy detected

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photographically affects nearly everyone after about 20 years or so of Type I diabetes, and proliferative retinopathy affects 50 to 60 percent of all Type I diabetics by 15 years of diabetes. Diabetic macular edema was not assessed in this initial trial.

These data are now, since 1984, and the numbers have probably been reduced as a function of the recognition that blood glucose control is an important pathogenic mechanism and better blood glucose control, as the Kleins have shown in more recent data, has decreased the incidence and prevalence of diabetic retinopathy and its -- of diabetes mellitus, diabetic retinopathy and other complications of diabetes.

Type II diabetes, the most prevalent form of the disease, about 90 to 95 percent of

all diabetics are Type II, usually adult onset, although there is some younger onset individuals, often not requiring insulin, the prevalence of retinopathy is a function of duration of the disease as shown here. This slide isn't labeled, but the red line are those who are taking insulin despite

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their Type II disease, the blue symbols indicate prevalence of retinopathy and a proliferative retinopathy in those who were not taking insulin, perhaps as a result of poorer blood glucose regulation in those who are required to take insulin with this disease. This slide just simply summarizes the data shown in the last two slides, but the middle portion shows, the middle and lower portion shows the incidence and prevalence of diabetic macular edema, (DME), which by 15 years of diabetes, essentially 15 to 20 percent of individuals with Type I or Type II disease will have macular edema. The incidence and prevalence increase is a function of the disease, and it has been shown by now two major controlled clinical trials, the Diabetes Control and Complications Trial for Type I Diabetes in the U.S. and the United Kingdom Prospective Diabetes Study or UKPDS, for Type II diabetes in Great Britain, both of which showed that blood glucose control is essential for preventing the development and progression of diabetic retinopathy in all of its forms.

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Blood pressure volume, at least in those who are hypertensive at the outset, is also critically important. Normotensive diabetics are not at any greater risk, and better control of blood pressure in normotensive individuals in several trials now, and will be summarized in a forthcoming Cochrane systematic review, normotensive diabetics benefit not at all from still further lowering of blood pressure. Several trials, most notably the ACCORD study in this country, showed that lipid control with a combination of a statin and fenofibrate are also beneficial overall for diabetic retinopathy and for diabetic macular edema. There are also some, in addition to these controllable factors, there are genetic factors that are strongly suspected that have not yet been ironed out.

These are severity scales that have been proposed and I will pass on with this. You have all of this in your handouts and can study these at your leisure. This is simply a montage of the standard photographic fields for

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assessing diabetic retinopathy and including diabetic macular edema that started in the 1970s with the first controlled clinical trial of laser therapy, the Diabetic Retinopathy Study or DRS and have continued ever since, although there have been modifications in this photographic protocol.

And here are some of the lesions. This is an early picture of a macular lesion, the optic nerve out to the dark area in the center, which is the center of the macula, the fovea, and then extending equally distant on the opposite side, showing some small lipid deposits with the white streaks and spots, and some little dot and blot hemorrhages and perhaps some microaneurysms, which are often small dilations of retinal capillaries.

This is much more severe retinopathy. In the left-hand photograph you see multiple blocked hemorrhages and some white arterioles near the bottom and top of the picture, which show evidence of larger vessel disorder. A much more severe picture is the one on the right, which shows irregularity of the caliber of the retinal veins, that venous loop or

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reduplication is typical of diabetes, I have not seen it in any other retinal vascular disease. The white patch is a cotton wool spot surrounding a partially occluded small arteriole, and there are little squiggly blood vessels which are called intraretinal microvascular abnormalities and may represent early forms of new blood vessel formation.

And here is some of the severe constant sequelae of proliferative retinopathy, new blood vessels on the optic nerve head at the left-hand side, new blood vessels not on the optic nerve head, so-called NVE or new vessels elsewhere on the right-hand side, and vitreous hemorrhage extending from new blood vessels on the optic nerve in the bottom slide. The dark pigmented marks to the right of that paragraph are laser treatment scars that this patient has previously had, and those are severe consequences of proliferative diabetic retinopathy.

This slide illustrates diabetic

macular edema. Often, though not always, macular edema is accompanied by clusters of these lipid deposits in the upper left

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surrounding the fovea or the center of the macula. The top right is a histologic section from an individual who died and came to autopsy, showing the fluid-filled spaces in the retina, and the dark red patches in this stain were not eliminated by the fixation process and those are lipid deposits.

In the lower left there is an optical coherence tomographic image, the latest and most wonderful technological advance, which allows for a noninvasive assessment of the macular region, and showing macular edema actually with almost the quality of a histologic slide, showing the fluid-filled space in the center. The horizontal green lines at the lower portion of this slide actually represent the visualization of the tiny photoreceptor cells, the rods and cones in the retina. The red line is the retinal pigment epithelium that underlies these structures.

On the right is a fluorescein angiogram, a technique that's been around since the 1960s, in which sodium fluorescein, a fluorescent dye is injected intravenously and

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rapid sequence, now digital photographs are taken showing that the dye leaks out of the blood vessels in the retina, which is not a normal circumstance, normally the blood vessels are tight to this dye. But when they leak out, showing a breakdown of the blood-retina barrier, fluid then leaks into the, in amongst the retinal neuron, causing this edema in the macular region.

Macular edema can occur in a number of diseases, it's not unique to diabetes, but the diabetic form of the disease is the one we are considering this morning.

There are a number of ways of assessing it. I've already mentioned optical coherence tomography, which is a wonderful technique which is capable of detecting the disease even when clinically, even skilled observers have a difficult time, but it has been shown to be quite accurate and it is quantitative, you can measure the thickness of the macula, and with adaptations which several of the technology companies and we ourselves are trying to develop, to actually measure the

thickness of the layers and measure the volume
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in each of the neural and glial areas of the retina.
One can clinically assess macular edema by slit lamp observation with special retinal lenses. This is the subject of assessment which has been the standard for a number of years until OCT came along. In clinical trials, however, retinal photography using stereoscopic technique have been used, but this too is subject to error because the two photographs are not taken simultaneously, they are taken by moving the camera slightly, and by the degree of movement of the camera you can either increase or decrease the amount of retinal thickening that you can visually assess. So OCT really is the standard of the world currently for assessing diabetic macular edema.
Fluorescein angiographic evidence is also helpful but does not always, it does not detect retinal thickening, only leakage of dye from retinal blood vessels. This is a comparison of OCT image at the bottom with a histologic section of the macular retina at the top, showing that the OCT really is a brilliant
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technique that can assess with almost histologic accuracy and quantitative accuracy macular disease. I often tell my colleagues and patients that it has one major major defect, however, and that is in my mind that I didn't develop the technique myself.
In any event, diabetic macular edema has been clinically divided into what is called non-clinically significant, and following the Early Treatment Diabetic Retinopathy Study or ETDRS, the first major clinical trial with laser therapy for diabetic macular edema in the 1980s, we have talked about clinically significant macular edema, which is edema which involves or is close to the center of the macula, the fovea, and thereby either causes decrease in vision or very nearly threatens decrease in vision over a relatively short time course without therapeutic intervention.
However, vision is not necessarily always affected in clinically significant diabetic macular edema, and sometimes one can have center-involved macular edema with normal or very nearly normal visual acuity.
A number of factors may be involved in
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the actual reduction of vision when macular edema is present. Duration probably is an important cause of vision loss, the longer the edema is present, the more likely that disorders will occur affecting function of retinal neurons and glial cells.

With the OCT techniques that we now have, as I have noted, it is actually possible to assess the integrity of the retinal photoreceptor cells themselves, not perfectly, but quite well. And it's become apparent that one can, with loss of photoreceptor cells, visual acuity is decreased even when macular edema is not present, but the presence of longstanding can affect the integrity of the photoreceptor layer.

Sometimes the edema is not only within the retina but underneath the retina, between the retina and its underlying retinal pigment epithelium, and this causes the photoreceptor cells to be detached from their base at the level of the retinal pigment epithelium and that can over time severely affect their function.

The thickness of the retina may not be

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the most important function to assess in terms of vision loss or the presence of cystoid spaces, they're not true cysts but they're those little focal open areas that you saw in the previous pictures, OCT pictures and histologic sections. They're called cystoid because a true cyst is surrounded by epithelium, which these are not, so we attach the suffix o-i-d to indicate that they are not truly cystic.

Other retinal layers in the photoreceptors may be affected, although that's a little bit hard to detect other than their thickness by OCT measurements, and metabolic abnormalities are difficult to assess by any of our clinical techniques at present, though there are some attempts, particularly by our colleague Dr. Victor Elmer and his associates at the University of Michigan down the road from us, to look at in vivo metabolic changes within the retina.

This is a larger photograph of an OCT image showing where the arrows are that there is vitreomacular traction from these fibrous membranes at the posterior base of the vitreous

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gel, and they can keep the retina elevated as perhaps shown here, even when one has

therapeutic modalities like laser treatment or anti-VEGF therapies.
DR. GOODMAN: Dr. Frank, you've got about ten minutes left and I believe you're about halfway through your slide deck.
DR. FRANK: We're going to run through this very quickly. You say ten minutes?
DR. GOODMAN: Yes, sir.
DR. FRANK: That shouldn't be difficult to do.
DR. GOODMAN: Give us the good stuff.
DR. FRANK: Okay, I'm going to try to get there as fast as I can.
These arrows simply show the photoreceptor layer or what is left of it in this individual who actually has good vision, but you can see that cystoid space causing the macular edema. Here is an individual with subretinal fluid illustrated on OCT scan and this individual was treated with anti-VEGF therapy with vitrectomy surgery because she had had an adverse cataract surgery with lens fragments in the vitreous which were removed.

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She was diabetic. She was treated with bevacizumab, one of the major anti-VEGF therapies, and this reduced the edema but did not eliminate it, but finally intravitreal steroid injections were done and that reduced the edema totally, but her vision did not recover. And the question is why is the vision still not back all the way to normal, and these are some of the questions that we need to consider in considering the efficacy of these therapies.
This is a comparison of the two eyes, they look almost identical, and yet the vision in the eye at the bottom, the right eye which has been affected, never did recover to the normal level shown in the picture above.
So what do we know about preventing diabetic retinopathy and what do we know about the prevention of macular edema? Well, this is the DCCT trial, which concluded in 1993 but the follow-up with the so-called EDICT, or Epidemiology of Diabetes Interventions and Complications Trial still continuing, tight control of blood glucose randomly selected among Type I diabetics, the others had standard

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blood glucose control as evidenced by the differences in their hemoglobin A1c measurement, and it shows that the two curves didn't separate for about three years and then

they separated, showing that tight blood glucose control was efficacious in preventing the progression of diabetic retinopathy. Visual acuity was not the principal endpoint to be assessed here.

This is the United Kingdom trial showing the differences in long-term blood glucose measurements on the left and the fact that the risk ratio with better control of blood glucose was well below one, as shown by the average, the dark symbols on the right-hand picture, with the 95 percent confidence interval not intersecting one.

These studies did not assess macular edema, so what do we do, what are the mechanisms of macular edema and what are the treatments? Well, until recently, laser treatment was the standard of care as assessed in 1985 in the Early Treatment of Diabetic Retinopathy Study, the ETDRS study. Major results were shown here for clinically

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significant diabetic macular edema. Loss of vision, doubling of the visual angle going from 20-20 to 20-40, 20-40 to 20-80, et cetera, shows the endpoint of this study, and the yellow line shows that eyes that did not receive focal laser treatment reached that endpoint at a much more rapid rate than eyes that did receive the treatment, the blue plot down at the bottom, and this is a highly significant result showing the efficacy of laser treatment for preserving vision, though in this slide not improving vision.

Then subsequently various, both specific, the anti-VEGF antibodies and most recently the anti-VEGF fusion protein, Eylea or aflibercept, are specifically targeted at vascular endothelial growth factor molecule presumably responsible for the disorder. Pegaptanib and aptamer, which also blocks some form, the major form of vascular endothelial growth factor but not all of its molecular forms, was the first of these specific treatments.

Steroids, triamcinolone or fluocinolone are also effective though they do

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have some adverse effects. Notably they cause cataracts in almost all individuals and cause elevations of the intraocular pressure in about 30 percent.

So these are several of the various agents that have been or are being tested in

controlled clinical trials. This is the result of the major clinical trial. There are two others sponsored by the company that makes these drugs, Genentech, but I think the Diabetic Retinopathy Clinical Research Trial sponsored by the National Eye Institute is the most important, because it compared ranibizumab with or without focal laser for macular edema or triamcinolone or laser alone, and it had a protocol that allowed for repeated injections for the first four months at monthly intervals, for the next two months if a certain endpoint was not reached after the first four months, and then treatments ad lib according to a specific algorithm after that time, and I think that protocol is most important for assessing the effects of these drugs, that type of protocol for assessing the effects of these drugs and their longevity of effect, rather

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than an every month over a two-year period required, as the Genentech trials did. The Y axis here is visual acuity in letters, and you see that with the ranibizumab, either with or without laser, there is a substantial increase in letter score in these individuals with diabetic macular edema. Steroids, triamcinolone improved vision almost as rapidly and almost as much, but then the vision decreased because nearly all of these individuals developed cataracts, and when the cataracts were removed, or in patients who were cytotactic from the start, the vision did much better. The violet line shows the improvement in vision with laser treatment, not quite so much, but still a modest improvement in visual acuity over the period of the trial. What's impressive to me is the comparison of that last slide on the left with the slide on the right, which is a measure of macular thickness, and you will note that the violet line for laser treatment shows that macular thickness decreased but at a much slower rate than it did with the injections, but eventually reaching almost the same level

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of macular thickness. However, the visual acuity results after laser were not nearly so good, so there is something more than simply the reduction of macular thickness that has its effect on visual acuity with these various therapies.

DR. GOODMAN: Sir, about two minutes.

DR. FRANK: We will wrap it up. The

other important point, and it's a good one to conclude with, is this. With the protocol of the Diabetic Retinopathy Clinical Research Network Trial where injections were required only over the first four months, you could assess how many injections here of ranibizumab were required over a period of two, and it's now up to three years, although the three-year follow-up has been submitted but not yet been published, the number of injections decreases over the period of this trial with this particular injection protocol.
That is, monthly injections for two or three years are not required in all patients, in fact perhaps in a minority of patients, so that these injections rather than simply fighting the smoke, blocking VEGF as it is

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formed, are having some other metabolic effect on the production of this growth factor that is much more long lived than simply the pharmacologic duration of the drug.
So the question is what is that effect, and the other question is, with which I will leave you, is this: These drugs are quite effective but they are not effective in all patients. There are some mechanical reasons, vitreomacular traction, epiretinal membranes and others that may mechanically prevent the reduction of macular edema, but there must be other effects as well, and it is going to be necessary not only to introduce these therapies but also to try to understand what some of the other causes of visual loss are and how to prevent them in diabetic macular edema.
I would like to conclude with several lines from the Four Quartets, the great poem of T.S. Eliot. Eliot was not a scientist, but these lines to me express what we do as scientists and academic physicians. We shall not cease from exploration and at the end of our exploring, we will return where we started, to this disease we have known for over a

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hundred years, but have only just now begun to understand. Thanks very much.
(Applause.)
DR. GOODMAN: Thank you very much, Dr. Frank. This was a very clear presentation, clear images and excellent explanations for us, and we hope that you will continue on our journey for the balance of the day, I'm sure we will have some follow-up questions for you.
Once again, thank you so much for a superb

presentation. Our next presentation is one of, the first of two technology assessments. This is Dr. Donna Dryden. She's the associate director of the University of Alberta Evidence-Based Practice Center. We call that in the trade one of the EPCs, this is one of 14 evidence-based practice centers under contract with the U.S. Agency For Healthcare Research and Quality. They do systematic reviews in the area of comparative effectiveness, technology assessments and similar evidence reports. Dr. Dryden is going to focus largely on health-related quality of life measures, which is one of the ways in which anti-VEGF and

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other treatments for DME are intended to improve the lives of patients, including Medicare beneficiaries. Welcome, Dr. Dryden, thank you for making the trip from Alberta.

DR. DRYDEN: Thank you very much. So as you've heard, the topic of the presentation is measuring health-related quality of life in patients with diabetic retinopathy, and this includes macular edema. I'm making this presentation on behalf of my colleagues at the University of Alberta. This technology assessment is based on research that we conducted at the university's evidence-based practice center under contract with the Agency for Healthcare Research and Quality, or AHRQ, and the report was requested by the Coverage and Analysis Group at CMS.

The authors have no -- I guess I have to push this, don't I. Sorry. Okay, there we are. The authors have no conflicts of interest related to the material presented in this report. Drs. Tennant and Rudnisky are directors and have financial interests in a company that manages teleophthalmology software for the diagnosis and follow-up of patients

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with diabetic retinopathy. No treatment is performed using the software.

So, this is the outline for my presentation today. You've had a good background about diabetic retinopathy and diabetic macular edema already so I won't spend much time on these slides.

Diabetic retinopathy is a leading cause of vision loss, it occurs as a result of pathologic changes in the retinal vasculature. In 2005 to 2008 the prevalence of diabetic retinopathy among Americans with diabetes who

are over the age of 40 was 28.5 percent. Among this group, prevalence of vision-threatening diabetic retinopathy was 4.4 percent and again, in this group of Americans with diabetes over the age of 40, the prevalence of clinically significant macular edema was 2.7 percent. Prevalence and severity of diabetic retinopathy increases with the duration of diabetes and it's inversely related to glycemic, or inversely related to the control of glycemia and blood pressure. The early identification and treatment of diabetic

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retinopathy is an important goal for patients and for healthcare systems, and the mainstay of treatment is aimed at reducing the risk of onset and limiting the progression of diabetes. Patients with diabetic retinopathy and with diabetic macular edema report that vision loss affects multiple areas of well-being, such as independence, self-care, mobility. Vision loss could be particularly debilitating to patients with diabetes because treatment success to limit the progression of their diabetes often depends on their ability to read a glucometer and to self-inject subcutaneous insulin. Diabetic retinopathy has also been found to impair functioning and overall health-related quality of life.

In recent years clinicians and researchers have recognized the importance of measuring the subjective experiences of patients diagnosed with chronic diseases such as diabetes. These patient-reported outcomes measure a variety of aspects of care, including health-related quality of life, treatment satisfaction and patient illness perceptions. These outcomes are distinguished from other

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outcomes because the report is from patients' perspective and without interpretation by another individual.

So health-related quality of life is one important patient-reported outcome, and a subsection of that would be health status which refers to the identification and acceptance of changes in activities and perceptions compared with normal life. Functional status is also a component. This focuses on the physical capacity to complete everyday activities at home or at work, and health-related quality of life measures the impact of disease and the treatments on the lives of patients. It's a

multifaceted measure and it takes into account the impact of physical, psychological, social and somatic domains of functioning and well-being.

Tools to measure health-related quality of life can be as simple as a single question asking the patient to state their quality of life, but that would be far too easy, so most of the measures take the form of questionnaires that focus on specific elements and domains under the subject of health-related

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quality of life.

They can divide health-related quality of life, they allow for broad comparisons across the domains that are part of the questionnaire, but they do not necessarily investigate specific aspects of a particular disease, and therefore, they tend to be less sensitive to changes in the quality of life of patients with particular disease.

On the other hand, there are specific quality of life tools that are designed to target particular disease or population or outcome. These tools have been found to be more responsive to changes in health-related quality of life in the patients or populations that they're developed for.

So an example of a generic health-related quality of life tool is the SF-36, and two examples of condition-specific tools that were identified in our review are the visual function 14 or VF-14, and the National Eye Institute visual function questionnaire or the VFQ.

So with that background, these were the three key questions that we were asked to

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identify, or asked to address. What health-related quality of life measures have been used in studies of treatments for diabetic retinopathy, including diabetic macular edema, and what are their psychometric properties? What is the evidence that health-related quality of life is improved for any intervention for diabetic retinopathy? And what is the evidence about the association between the improvement of health-related quality of life and other variables, including baseline visual acuity, age, sex?

Our methods for conducting the review were developed a priori and followed the guidelines developed for the EPC program, which is part of the Agency for Healthcare Research

and Quality. We developed a single search strategy to address all three of our key questions. It was originally run in July of 2010 and it was updated in January of 2012. In addition to the electronic databases, we searched clinicaltrials.gov to identify recently completed or ongoing trials, and there were no restrictions for language, date or study design for the research we developed.

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We used a two-step process for study selection, first screening the titles and abstracts of the records that were identified in our searches, and then reviewing the full text of potentially relevant studies. We included studies of adults 18 years and older with diabetic retinopathy, including diabetic macular edema.

For key question one we included studies that used any tool to measure health-related quality of life, and for key questions two and three we included prospective comparative studies with any intervention to treat diabetic retinopathy. The studies had to report health-related quality of life outcomes and they had to use a measurement tool that had reported psychometric properties.

For key question one, to assess the quality of the studies that measured the psychometric properties of the tools, we used the COSMIN checklist. COSMIN is an acronym for the consensus-based standards for the collection of health measurement instruments. It's a checklist that was developed in 2010 and includes seven items, contents and construct,

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validity, internal consistency, reliability, measurement error, responsiveness and interpretability.

For key question two we used the Newcastle-Ottawa tool to assess the quality of cohort studies, and we used a modified version of this to assess before and after studies.

There were no randomized controlled trials that matched our inclusion criteria.

To assess the overall strength of evidence we used the EPC grade approach for the outcome of health-related quality of life and this tool looks for broad domains, risk of bias which incorporates study design and the conduct of the study, consistency, directness and precision, and we assign an overall grade for looking at these four domains.

So our database search has resulted in

about 7,000 studies. For key question one there were 13 unique studies plus one companion study that met our inclusion criteria; from these there were nine studies that used validated measures to evaluate health-related quality of life. And to address key questions two and three, there were seven unique studies

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that met our inclusion criteria.

So there were, I know I said there were 13 studies that may have worked, but we'll talk about 11 studies first of all. So there are, 11 studies reported using health-related quality of life measures. There was one randomized controlled trial, six cohort studies, three before and after studies, and one case report. Out of these 11 studies we identified four health-related quality of life tools with demonstrated validity and reliability, and these were used in the context of a study that was looking at an intervention for diabetic retinopathy or diabetic macular edema.

The most commonly used health-related quality of life measure was the National Eye Institute VFQ, either the 25 or the 51-item tool, four studies used the VF-14 tool, one study used the diabetes treatment satisfaction questionnaire, and two studies used a combination of a generic tool and either the VF-14 or the VFQ. One study also used qualitative interviews to assess health-related quality of life, but they didn't use any

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particular tool.

So here's the other two studies. We also identified two tools that have been developed specifically for patients with diabetic retinopathy, including patients with diabetic macular edema. These are, these have undergone some psychometric testing but testing is still ongoing. So, the first one is called the retinopathy treatment satisfaction questionnaire or the RetTSQ, and the second one is the retinopathy-dependent quality of life measure or the RetDQol. Currently there is no literature describing these interventions or treatments for diabetic retinopathy.

In addition, our search of the clinical trials register identified seven studies that were either recently completed or were ongoing, and these were studies that identified specifically that they would use the VFQ-25 to assess health-related quality of

life.
So, this is a summary of the psychometric properties of the six measurement tools that we found, the four that have actually been used in the studies and then the
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two that are currently under development. Generally all of the tools showed good validity, as shown on the two columns on the left, content validity and construct validity. Generally they all show good reliability, which are the next three columns, so internal consistency, test-retest reliability, and measurement error. Some show fairly good responsiveness, and less work has been done on investigating the interpretability of the actual tools. So interpretability is basically the usability of the tool, and it's the degree to which the tool can be understood and made meaningful to clinicians and patients. The two tools that are under development, they've looked at some reliability and validity, and the rest of the elements or the domains are still under investigation.
So we identified seven observational studies that addressed key questions two and three. There were no randomized controlled trials that reported health-related quality of life outcomes. None of these studies were conducted in North America, they were conducted in Europe and Japan, and the sample sizes
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ranged from 55 to 327. Of the seven studies, four reported some results for patients with diabetic macular edema, two included patients with diabetic macular edema but the results weren't reported separately, and one study didn't report whether there were patients with diabetic macular edema included in their sample.
And of the seven studies, there were two studies that included patients with diabetic retinopathy, but the intervention that was under investigation was treatment for cataracts. The other interventions that were studied were laser photocoagulation, vitrectomy, and panretinal photocoagulation.
Overall the studies are at high risk of bias, primarily because of poor study design, so before and after cohort studies, and overall the strength of evidence to draw conclusions about the effect of any treatment on health-related quality of life was insufficient.

So, I will just briefly go through the results of the studies. For laser photocoagulation there were two before and
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after studies that looked at this intervention. The first one included 55 patients with diabetic macular edema. At three months post surgery, health-related quality of life as measured by the VFQ 51 improved from baseline measures, and the results were statistically significant for the confidence score, as were eight of the 11 vision-related domains of the tool.
In the second study, this is a mixed group of patients with either proliferative diabetic retinopathy or diabetic macular edema who underwent surgery. At nine months post surgery, 25 percent of the population reported improvement in visual acuity, and patient satisfaction as measured by the diabetes treatment satisfaction questionnaire was high, the mean score was 27 out of a possible 36, but the results for the two patient groups were not reported separately in this study.
There was one prospective cohort study and one before and after study that discussed the impact of vitrectomy on health-related quality of life. Both these studies took place in Japan and both used the VFQ-25 Japanese
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version. In the first study there were two patient groups, 99 patients with proliferative diabetic retinopathy and 38 patients with diabetic macular edema. For patients with PDR, the confidence score and most of the subscores of the VFQ improved significantly following the vitrectomy. For those with diabetic macular edema, there were no significant changes in the score.
In the second study there were three patient groups, 41 patients with vitreous hemorrhage, 21 patients with diabetic macular edema and 18 patients with fibrovascular membranes. For the patients with vitreous hemorrhage, their score, their mean score on the VFQ increased in 10 of the 12 subscales and the changes were, the results were statistically significant. For the other two groups, there were no statistically significant changes with the exception of the fibrovascular membrane group that improved on the vision subscale, but otherwise there were no significant changes.
One prospective cohort study followed

327 patients who underwent either vitrectomy or
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panretinal photocoagulation, so there were three groups, the third group is a control group that didn't undergo any treatment at all. At one year post intervention for the vitrectomy group, the health-related quality of life confidence score improved and the change was statistically significant. For the other two groups, their changes in the health-related quality of life score weren't statistically significant.

And then there were the two studies, these are cohort studies that assessed the impact of phacoemulsification cataract surgery in patients with diabetes and diabetic retinopathy. In the first study at three months post surgery, patients with either no diabetic retinopathy or mild nonproliferative diabetic retinopathy demonstrated significantly greater improvement in visual function compared to patients with more advanced diabetic retinopathy. In the second study patients with proliferative diabetic retinopathy and moderate to severe diabetic retinopathy improved marginally on the VF-14 but the specificity results weren't statistically significant.
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So, key question three looked at factors associated with health-related quality of life outcomes. There were two studies on laser photocoagulation. In the first study they used a multivariate analysis and found that age less than 65 years, more severe level of diabetic retinopathy and low preoperative quality of life were associated with improved health-related quality of life. The second study conducted a univariate analysis and found an association between age over 65 years and greater satisfaction with treatment.

In the study that assessed vitrectomy the authors conducted a multivariate analysis and found improvement in contrast sensitivity associated with changes in the health-related quality of life in patients with proliferative diabetic retinopathy and diabetic macular edema. Overall, however, the strength of evidence is insufficient for us to draw any conclusions about what factors are associated with health-related quality of life outcomes.

So in summary, this review identified evidence of the effect that interventions for diabetic retinopathy have on health-related
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quality of life. We identified one generic health-related quality of life tool that has been used to study these interventions. In general the SF-36 appears unresponsive to changes in visual acuity in patients with diabetic retinopathy and this is based on other studies, but this isn't a surprising conclusion since the SF-36 assesses a wide range of characteristics that are not directly related to visual acuity. There are other generic measures that do include an assessment of visual function and they might be worth considering if there's a need for a generic measurement tool.

There were two vision-specific measures that were included in our review, the VFQ-25 or 51 and the VF-14. These have both been validated and have shown some responsiveness and reliability, and vision specific measures have been shown to be sensitive to differences in vision status and functioning among patients with diabetic retinopathy and diabetic macular edema.

There was one study that looked at the treatment satisfaction from the diabetes

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treatment satisfaction questionnaire. This questionnaire was developed to measure patient satisfaction with treatment for diabetes, but it wasn't designed to measure satisfaction with other aspects of diabetes, diabetes care management, so it's a tool that's most useful used with other tools to assess other outcomes, including health-related quality of life.

As well, there were the two diabetic retinopathy specific measurement tools that we identified. These tools have been developed to enable patients to consider the specific aspects of diabetes-related eye problems and their treatment, rather than health generally or vision or vision loss, or the impact of diabetes. So the preliminary psychometric testing is promising for content, validity and internal consistency, and additional testing of these tools is ongoing.

There were no diabetic macular edema specific tools that we identified, although these two tools looking at diabetic retinopathy have included patients and intend to include patients with diabetic macular edema as their research is ongoing.

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So, there were no randomized controlled trials that we identified up to

January of 2012 that had reported health-related quality of life outcomes. We know from the clinical trials register that there are 14 ongoing or recently completed trials investigating the impacts of interventions for diabetic retinopathy and diabetic macular edema, and these have reported that they're going to look at health-related quality of life, but to date none of the trials have reached publication. The PKC-DRS2 trial has been completed but, again, the results for health-related quality of life haven't been reported.

So, our review did show that some studies showed or indicated that health-related quality of life improved following various interventions to treat diabetic retinopathy at different levels of clarity, but these results are based on one or two observational studies and the results weren't always statistically significant, so we concluded that the strength of evidence to reach conclusions about the effects of interventions on health-related

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quality of life in this patient population is insufficient to draw conclusions.

Furthermore, there is some concern about the applicability of these studies to the North American population. The studies were conducted either in Europe or in Japan.

So our recommendations for future research, RCTs are needed to assess the impact of interventions for diabetic retinopathy and diabetic macular edema on health-related quality of life. This systematic review should be updated in two years to incorporate the results of the ongoing or recently completed randomized controlled trials. Validated and reliable health-related quality of life tools should be used and the results should be reported in these trials. And the assessment of the psychometric properties of the diabetic retinopathy specific tools should continue, and as I said, these tools have included patients with diabetic macular edema in their research or in their study population.

DR. GOODMAN: Just one minute, Dr. Dryden.

DR. DRYDEN: Okay. Patients should be

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followed for at least six months post intervention to capture maximum improvement for visual acuity, and randomized controlled trials should be designed and conducted to minimize

risk of bias.
So in conclusion, we identified four health-related quality of life measurement tools that have been used to assess the impact of treatments in patients with diabetic retinopathy or diabetic macular edema. Current research is insufficient to draw conclusions about the effectiveness of those treatments on health-related quality of life. There is two -- well, the psychometric properties of those tools have been measured and there's two tools specific to diabetic retinopathy that are currently undergoing psychometric evaluation.
Thank you.
(Applause.)
DR. GOODMAN: Thank you, Dr. Dryden, and Dr. Dryden, before you leave the podium, just a point or two of clarification, we've got a couple minutes, and Dr. Phurrough had a question.
DR. PHURROUGH: Yes, Dr. Dryden. Did

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your comment not including any studies around anti-VEGF drugs, is that because you did not have reported quality of life measures?
DR. DRYDEN: Yes, that's right.
DR. GOODMAN: So it's not that you weren't studying anti-VEGF, it's just that when you looked at the studies involving anti-VEGF they didn't study these types of measures?
DR. DRYDEN: They didn't include a report on health-related quality of life outcomes.
DR. GOODMAN: Thank you very much. Okay, Dr. Dryden, thank you very much, and once again, thank you for making the trip from Alberta. We hope that you will be available for the balance of the day for follow-up questions as appropriate. Thank you so much. Our next presentation is another technology assessment and this will come from Dan Ollendorf. He's the chief review officer for the Institute for Clinical and Economic Review, otherwise known as ICER. Welcome, Dr. Ollendorf, glad to have you here.
MR. OLLENDORF: Thank you, Cliff, and thank you to the entire MedCAC and the Coverage

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and Analysis Group for allowing us to present, to conduct our review and present the results to you. Thank you also for the honorary doctorate, I'm actually just a lowly mister.
DR. GOODMAN: No one is lowly in this room, I assure you, especially if you've got

the podium in this room, Dan.
MR. OLLENDORF: I am presenting this on behalf of my team from the Institute for Clinical and Economic Review. As noted in our report, we have no conflicts of interest to disclose. We do receive funding from manufacturers for our operations but we receive no funding from any of the manufacturers that we will be discussing in this topic today.
So, we will go through an outline of what we will be presenting. You have now heard from two different and distinguished speakers about the background on diabetic retinopathy and DME, so I'm not going to bore you again with that, I will skip through that information. But then we will talk about the objectives and the methods of our assessment, we will talk about both the qualitative and quantitative synthesis that we applied to the

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data, and then we will provide results on both clinical effectiveness measures and potential harms of these drug treatments, and then finally summarize.
I thought this was still an important slide to show because unlike some of the other slides you've already seen, this shows retinopathy and DME from the perspective of a patient who is afflicted with the condition, and it comes from the National Eye Institute. And so as you can see, there is significant blurring of vision as well as dark spots in the visual field of the patient. So as you might imagine, this affects lots of activity for the patient, both in terms of near vision activities like reading and writing, but also distance activities such as driving.
There's some interesting research that actually suggests that this may affect diabetic self-care in these patients, because reading nutritional labels is difficult, reading instructions for glucose test strips, et cetera, is difficult, so there may be potential impacts on the overall condition even beyond just the visual impact.

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I'm not going to spend a lot of detail on this slide. Again, you've heard about laser photocoagulation and anti-VEGF therapy in some detail. One of the things I wanted to point out, and Dr. Frank showed this on the ETDRS slide, is that there is an established approach with laser photocoagulation, but it is essentially to stabilize vision and/or minimize

visual loss, but significant improvement in visual acuity with laser photocoagulation alone is rare, and that is not surprising given the clinical interest in other therapies to try to improve visual acuity.

Another thing that we heard from some consultant expert ophthalmologists that worked with us on this review was that there can be different protocols applied when anti-VEGF therapy is used in terms of laser photocoagulation, so these therapies can be used alone, or they can be used either before, concurrently with, or after laser treatment.

Nothing really earth shattering to report on this slide except that these, all of these drugs in terms of the U.S. are currently off label for DME. There are some products

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that have been submitted to the FDA for consideration in DME, but at this point they're all off label.

Another thing I wanted to point out is that in terms of the cost for these therapies, there are some differences there. It was actually brought to our attention that these estimates that are in this slide are a little bit inconsistent in that we took estimates of the cost of Lucentis and Avastin from a recent report of the Office of the Inspector General and the estimates we used in our reporting on this slide were net of patient copayment, whereas the costs for Macugen and Eylea are actually inclusive of copayment. So if you add those figures in, the cost for Lucentis and Eylea is about the same, the cost for Avastin goes up nominally, I think from $50 to approximately $60 per dose, so apologies for that oversight, just a little correction there.

And as you can see, that worldwide there have been approvals for these drugs in other ocular conditions with the exception of Avastin, which was approved as a chemotherapeutic agent and is used off label in

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all ocular conditions, but there are varying stages of regulatory approval for DME.

In terms of the project objective, essentially it was this. It was to conduct a systematic review on the clinical effectiveness and potential harms of anti-VEGF therapy relative to laser photocoagulation or other control in patients with diabetic macular edema. In terms of methods, we accepted patients or studies of patients with DME. We

did not put any other restrictions on the intensity or the severity of DME, so we looked at all studies that evaluated anti-VEGF therapies in patients with DME, and if these were studies of diabetic retinopathy they were required to have a named subgroup of patients with DME with outcomes and measures for that subgroup.

In terms of interventions we looked at any anti-VEGF therapy with at least one published RCT report in DME or, again, in that subgroup of DME. Comparators varied. These were in many cases laser photocoagulation either as a control arm or sham injection as a control arm with the ability of rescue laser

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therapy during the trial. We also looked at comparators, though, that involved intravitreal steroid use.

In terms of relevant time frames, these studies varied in duration anywhere from three to 24 months, so we collected data from all available time frames.

One important note in terms of the RCTs that we included, there were studies, principally of Avastin, and my apologies for switching from generic names to brand names, but I figured I'd spare you from having to trip over the generic names during the presentation, so apologies for that.

But, these trials were primarily of Avastin, but they involved a single injection only, and upon the counsel of our expert ophthalmologists we felt that this was not reflective of typical clinical practice in which repeat injections are given. These were studies that were either early experimental studies where there was just an observation seen with one injection to see if there was improvement in acuity, or they occurred in geographic settings where there was probably

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some sort of constraint on drug availability, so we excluded single injection RCTs essentially.

We did look at observational studies but only for information on long-term effectiveness and durability of benefit beyond 12 months, and we looked at observational studies for additional information on safety.

In terms of outcomes, the principal outcome that we focused on was best corrected visual acuity, and this essentially means visual acuity with any aid that the patient has

available to them, so this could be eyewear and/or artificial light to help with vision. This was typically measured as either a change from baseline in visual acuity in terms of letters seen, or it could also have been a threshold of improvement, 10 or more or 15 or more letters gained, for example. To give you sort of a layman's definition of what a 10-letter improvement might mean, for a patient who starts the study with essentially 20-80 vision, a 10-letter improvement or two lines of additional sight would bring that vision up to 20-40 and allow

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that patient to drive in most states, so that's one indication of how it would work. We also looked at health-related quality of life if data were available, and we actually did find two RCTs with information available on quality of life through the NEI VFQ-25, which you just heard about from Dr. Dryden, as well as the EuroQol EQ-5D, which is another generic quality of life instrument. We also looked at treatment utilization, so we heard before that patients may be required to get repeat treatment with additional injections so we looked at that. We also looked at the incidence of the use of laser rescue treatment in studies where that defined the protocol, and also the number of injections as well. So in terms of potential harms, these were both specific to the eye as well as other body sites. We looked at endophthalmitis, an infection in the eye or irritation in the eye, glaucoma. We also looked at systemic events if reported individually, like stroke and myocardial infarction. This again is something that has been reported previously in the

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literature with anti-VEGF therapy. We also looked at the incidence of death from any cause. Many of these studies also presented information in summary form, so it may be the incident of serious adverse events in the eye or ocular-related serious adverse events, these could be nonocular related, so anything outside of the eye, and cardiovascular events were often summarized as well. Our review was both qualitative and quantitative, so we focused in our quantitative analysis on all fair or good quality RCTs with outcomes reported at six to 24 months of

follow-up. So again, we heard counsel from our experts that three-month date, if those were the only data available, would not necessarily be considered a reliable indicator of long-term effects or longer-term effects. And we looked at comparisons in our primary analysis to laser photocoagulation as a control, or sham injection with laser as a rescue modality. We did sensitivity analyses as well and looked at multiple other comparators.

We conducted direct meta-analyses for

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each anti-VEGF therapy separately, and we also conducted pairwise indirect comparisons of the data, so we compared the evidence on Lucentis versus Avastin, Lucentis versus Macugen, Eylea versus Avastin, et cetera. Sensitivity analyses not only included additional comparators but also the inclusion of studies that we had designated as poor quality.

So as you can see, we don't have to go through the entire PRISMA flow chart here, but for all the full text references that we identified, we found a total of 28 study reports with 15 RCTs, and we also included data from eight observational studies, so a total of 23 individual studies in our analysis. In terms of evidence quality, 11 of the 15 RCTs were judged to be of fair or good quality.

Most of the evidence was available for Lucentis or Avastin, so we identified only one trial of Eylea in DME and only two trials of Macugen in DME. Importantly, these were all trials relative to some control other than another anti-VEGF, so there were no direct comparisons at all available to us.

Of the poor quality studies, three of

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the four poor quality studies were Avastin studies, so there was a relatively clear dichotomy between the either government or industry-sponsored studies that tended to be larger, Lucentis, Macugen and Eylea, and what tended to be small primarily investigator-initiated studies of Avastin.

One important note with the results is that while we saw a broad spectrum of patients enrolled in the analysis, so in terms of the range of visual acuity at baseline, in terms of levels of glycemic control, in terms of comorbidity, when we looked at the evidence for each anti-VEGF we found that those populations were relatively comparable, so again, a broad spectrum overall but when comparing the

evidence for each anti-VEGF, relatively comparable studies, and that clinical judgment led us to feel that we could attempt quantitative synthesis.

So this is just an illustrative example for one trial, or two trials, the recently published RISE and RIDE studies of Lucentis in DME showing some of the same results that Dr. Frank showed you earlier, in

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that one of the key findings with this information is that benefits seen at early time points tended to remain stable and relatively constant throughout follow-up. So you see in this slide the benefits were seen very early, maybe even as early as one week, and then increased for a certain period of time, but then remained relatively stable throughout the period of follow-up, and that's a pattern that we observed really in all studies of all anti-VEGFs that we identified.

DR. GOODMAN: Mr. Ollendorf, before you go to the next slide, I may be misinterpreting this. Does the key match up with the lines on the graph --

MR. OLLENDORF: Oh, it looks to be a color issue, I apologize. That might have been something that happened when this was submitted. So in terms of the colors it does not, but in terms of the --

DR. GOODMAN: The sham would be the lower blue line, right?

MR. OLLENDORF: The sham is the lower blue line, I apologize for that, I'm not sure what happened there. So the upper two lines

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are the anti-VEGF lines from the two trials and the bottom line is the sham trial. Actually, no, the other two lines are the two different doses from the two trials, and the bottom line is the sham line.

DR. GOODMAN: So those upper two lines which are pretty close to each other are the two doses --

MR. OLLENDORF: The two active --

DR. GOODMAN: Ranibizumab --

MR. OLLENDORF: Right.

DR. GOODMAN: And the sham is the bottom line.

MR. OLLENDORF: Right. I apologize for that, so ignore the key, focus on the difference between the upper two lines and the bottom line, and that's essentially the point we're trying to get across.

DR. GOODMAN: It may have been a software version issue. Thank you for the clarification.
MR. OLLENDORF: So that's one result that was particularly striking to us. Another was that the improvement in average, the average improvement in visual

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acuity from baseline to the end of follow-up ended up in a fairly tight range across the anti-VEGF therapies, so somewhere between six and nine letters of improvement at these points of follow-up across all of the anti-VEGF therapies, so those are really the two, the key features of the results that we focused on. For our quantitative synthesis, this is a presentation of the evidence network so it's a fairly complex one. You have the four active therapies that are of interest. Then you have multiple types of comparators. You've got triamcinolone as the intravitreal steroid that was used in some of these trials, laser photocoagulation as a control arm, and sham injection with laser as a rescue modality. And so you see that within each individual evidence relationship there is a relatively small number of RCTs available.
DR. GOODMAN: So the numbers on the previous slide refer to the numbers of relevant RCTs for that comparison.
MR. OLLENDORF: Yes.
DR. GOODMAN: Would you just pause for a second?

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MR. OLLENDORF: Yes.
DR. GOODMAN: So for example, there were three RCTs comparing Lucentis to the sham injection with laser rescue?
MR. OLLENDORF: Correct. These are not mutually exclusive because some of these RCTs could have multiple control arms, so that could be triamcinolone and sham injection in a single RCT.
DR. GOODMAN: Got it. So one would not add up all the numerals on that slide to arrive at total numbers of RCTs.
MR. OLLENDORF: It will be over 15, right.
DR. GOODMAN: Thank you very much.
MR. OLLENDORF: So we'll pause a bit and take you through this slide in some detail, and there are two versions of this. The first one here is the change in best corrected visual acuity at six to 24 months of follow-up. The

next one you see will be the portion of patients achieving a gain of 10 or more letters. So you see with the individual studies at the top, and so here when we're looking at the vertical axis, a value of zero

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essentially means that there's no difference between treatment and control in the change of visual acuity, so we're looking at the incremental change over control. You see that there is a fairly consistent result favoring treatment in all the available studies. It should be noted that although it appears this way in the graph, these are not meta-analyzed data for Eylea and Macugen of course, because we only had single RCTs available, and of the two Macugen RCTs, only one had sufficient data for us to be able to include it in this analysis. We then looked at the pooled results for those drugs where we could pool data and again found that there was a significant effect in favor of treatment within each anti-VEGF therapy. But then when we did our indirect comparisons comparing each anti-VEGF to another in pairwise fashion, we found no significant differences in that change in best corrected visual acuity, and that's notable essentially by looking at the diamonds in the lowest set, and those diamonds all cross the zero threshold in terms of their confidence intervals.

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So -- but I actually need to make a correction there. The analyses of Lucentis and Avastin, the analyses of Lucentis and Eylea, and Avastin and Eylea are not significant, but all of the comparisons relative to Macugen are. But as we noted in our report, these results really need to be, it's a caution, because of the two available Macugen RCTs we could only use data from one, so we didn't feel that we could draw any firm conclusions about this apparently significant effect. So moving into gain of ten letters or more, so here the vertical is one, and essentially we're looking at the proportion of patients who gained ten or more letters in the treatment arm relative to the proportion of patients who achieved that gain in the control arm, and so here the value of one indicates that that ratio, or the ratio of one indicates that there is no difference in the proportion of patients gaining ten or more letters for treatment versus control.

And again here, when you look at the studies individually, you see that, again, there are significant effects in most of these
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studies favoring treatment relative to control and that corresponds, then, to some pooled ratios with the exception of Macugen, some pooled ratios that are also significant with each anti-VEGF therapy.
But again, when indirect analyses were conducted, we found no significant differences in any of the pairwise comparisons in this case across each of the anti-VEGF pairs. So again, the significant treatment effects versus control in the individual studies as well as in most of the pooled results within anti-VEGF therapies, but when indirect analyses were conducted, comparisons were made, no significant differences.
So turning to information on harms, we did find two RCTs that evaluated the impact of treatment -- I'm sorry, not harms, other outcomes. We found two studies that evaluated the effectiveness of treatment on health-related quality of life, two RCTs, one of these was of Lucentis and one of Macugen. We found that in studies reporting the results of the NEI VFQ-25 that there was significant improvement in the treated group in
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vision-related activities on that instrument, but no significant differences in the generic domains, and we found in studies that looked at the EQ-5D that there were no significant differences on that generic quality of life instrument.
We also looked at treatment utilization and we found that, in terms of the measures around the numbers of injections and retreatment, this measure was hard to interpret and compare across studies because it was highly dependent on the protocol that was employed. When we looked at the percentage of patients who received rescue laser in studies reporting this measure, we found, again, across all anti-VEGF therapies, that there was a substantial difference in favor of anti-VEGFs relative to control therapy, so you see the ranges there.
Now turning to harms, one key piece of information to note is that we found a general underreporting of data on harms in those primarily single center investigator-initiated studies of Avastin, so three of those six RCTs

reported no data on harms whatsoever, and we
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saw low rates reported in the other available studies.
In general across anti-VEGFs there was a relative low incidence of ocular harms.
Nonocular harms were available in terms of results in terms of, in a very wide range, but it's important to note that even in studies at the high end of the range, so you see for, I believe it's nonocular SAUs, yes, total nonocular SAUs, you see an upper end of that range of something like 41 percent, but the incremental difference between that and the numbers in control arms was very small, so essentially this relates more to the inclusivity in the definition of serious adverse events than to some actual effect that could be attributed to treatment.
We also received some counsel from our experts that it would be relevant to look at safety information from the available trials and in these agents in other ocular conditions, primarily wet AMD, and of course there's one direct head-to-head comparison of Lucentis and Avastin that is available.
So when we looked at that information,
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we found that there were no differences in rates of death or thrombotic events, which are events that are often attributed to systemic VEGF inhibition. We did find a rate of systemic adverse events that were higher with Avastin versus Lucentis in this trial. These were events that included hospitalizations for any cause, and the authors of the study make note that when restricted to events that are known to be associated with VEGF inhibition, there were no differences.
These are one-year data from what's known as the CATT trial, and I believe two-year data are going to be released sometime in May of this year.
We also identified a study that was a retrospective analysis of Medicare claims data on approximately 150,000 patients, 150,000 Medicare beneficiaries, looking again in claims data with an eye towards the incidence of particular events, and we found that here there were no differences in mortality or systemic events for either Lucentis or Avastin when compared to other available therapies like laser photocoagulation or Macugen. When
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compared to each other, there appeared to be a difference in the rate of all cause mortality and stroke when comparing Lucentis versus Avastin, but the authors noted that because there is such a difference in the cost of these drugs to the patient, there may be some selection bias associated with the socioeconomic status of the patients presenting for treatment. And so there was a secondary analysis conducted that focused on providers who exclusively used one drug or the other, and found no differences there.

So essentially, to summarize the primary findings that we've seen, we do have available RCT data and observational study data that include more than 4,000 patients evaluated worldwide. The available data suggests that anti-VEGF agents are associated with substantial improvement in visual acuity relative to control therapies, but that there is no data to indicate a significant difference or a substantial difference in the effectiveness of one anti-VEGF agent over another. And the greatest element of uncertainty from our perspective is that the

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lack of rigorous and reliable safety data for Avastin is kind of the greatest element of uncertainty that remains with this evidence. Thank you.

DR. GOODMAN: Thanks, Mr. Ollendorf, if you could just stay at the podium for a moment. First, thank you very much, a very clear presentation, and thank you very much for addressing the key questions, very helpful. We have just a couple of minutes coming up to our ten a.m. break. If any panelist has a question for now that's brief, let's take it. Dr. Heseltine first, and then Dr. Dubois. Dr. Heseltine.

DR. HESELTINE: My question is really for Dr. Dryden. Can you explain why you did not include the two randomized clinical trials that reported health-related quality of life outcomes?

DR. GOODMAN: Dr. Dryden, if you could come to this microphone, and I'm sorry I didn't quite set you up for that. After the break I'm going to ask all the presenters to sit up front. Dr. Dryden.

DR. DRYDEN: No, I can't explain that.

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I would be interested in looking at the RCTs and take a look at why they weren't included in

our studies.
DR. GOODMAN: Thanks, Dr. Dryden.
Dr. Dubois.
DR. DUBOIS: Thank you very much for the presentation, Dan. I guess my question relates to the indirect treatment comparisons, so statistically you were able to collapse things and make comparisons. Sort of stepping back and looking at the graphs is one thing, but since you really played with the data and thought carefully about the studies, at some level you said okay, they're relatively comparable and we can combine them and do the indirect treatment comparisons. But you also mentioned that the studies did have significant differences, some were done in the U.S., some were outside the U.S., some were big, some were small, some were single center, some were multicenter. Advise this group of the strength in your comfort level about doing the indirect treatment comparisons across the different drugs.
MR. OLLENDORF: That's a very good

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point, Bobby. Essentially we acknowledged that for certain of these drugs, so with the small number of RCTs available for Macugen and Eylea, and for the quality issues we identified with the RCTs, Avastin, there is some limitations on the strength of evidence. What gave us comfort in the ability to conduct these analyses was essentially the remarkable consistency in the findings that we saw, again, regardless of treatment protocol, regardless of study population, regardless of setting. So we felt that by conducting sensitivity analyses, and one thing I neglected to mention is that we found no differences in those analyses relative to our primary analyses.
We felt that that would be one way to explore some of the heterogeneity issues with these studies, but at the same time we felt it was the clinical judgment of the consistency in the findings that enabled us to attempt this quantitative synthesis. Does that answer your question there?
DR. DUBOIS: Thank you.
DR. GOODMAN: Thank you very much, Mr. Ollendorf, and we'll see you after the

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break, I presume. Thank you all presenters thus far today, this has been very very helpful, and I think each of our three main speakers thus far have covered a very important

relevant part of our discussion. This has provided an excellent foundation. When we come back from the break, Ms. Ellis is going to ensure that our six scheduled speakers will be cued up. I believe the order is Ehrlich, Nickerson, Gonzalez, Topping, Bressler and Thompson, and we will start promptly at 10:15, so I hope you're back in the room before then. Thank you very much. See you then.

(Recess.)

DR. GOODMAN: Let's reconvene now. As I mentioned before the break, we're going to start out now with our scheduled speakers, of whom there are six. I remind the panel that the presentations submitted by this set of six speakers was bound together in this hefty document which you've got there. We've asked our three speakers from this morning to sit front and center just to the left of the aisle for questions a little bit later right before

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our break, and we're also asking our six speakers who are going to go now in sequence to come sit at or near the front row as well, so we can get at you as needed before the lunch break.

So with that, and these are seven-minute presentations, not eight-minute presentations, starting with Dr. Jason Ehrlich, who is the associate medical director for ophthalmology at Genentech. Welcome, Dr. Ehrlich.

DR. EHRLICH: Thank you, Dr. Goodman, members of the committee. On behalf of my colleagues from Genentech, I would like to thank you for the opportunity to participate in today's discussions. My name is Jason Ehrlich. Again, I'm an ophthalmologist and the lead medical director at Genentech for our studies in diabetic eye disease. Those are my financial disclosures, and obviously I'm an employee of Genentech.

So, Dr. Frank explained to us that macular laser has been the standard-care treatment for DME since the 1980s and it's important to emphasize, again, that the goal of

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macular laser is to stabilize patients' vision and that visual acuity improvements with macular laser are relatively uncommon, so anti-VEGF treatments directed to the eye have the possibility of significantly improving vision in many more patients and, indeed, the

clinical trials bear that out.
So ranibizumab, which is sold commercially as Lucentis, is an anti-VEGF therapy that was developed and is manufactured specifically for ophthalmic use. It is FDA-approved for other retinal vascular diseases, most notably wet AMD, where it has had a tremendous impact on reducing the risk of blindness from that condition.
As noted already, ranibizumab is not currently FDA-approved for diabetic macular edema, although an application has been submitted for that purpose and is currently being reviewed by FDA.
Ranibizumab has several unique pharmacologic attributes, notably it has a rapid systemic elimination, and it binds and inhibits VEGF with high affinity, it is roughly 10 times more potent than bevacizumab for that

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purpose.
So Genentech, bearing on question number six, Genentech has conducted two Phase III studies of ranibizumab in DME patients, both in community-based studies, these are called the RIDE and the RISE studies. In both studies we took patients who have vision loss from diabetic macular edema and they were randomized to one of three treatment arms, either monthly sham injections or monthly intravitreal injections of one or two doses of ranibizumab. All patients were followed through to their 24-month primary endpoint, and all patients, regardless of treatment arm, were eligible for standard-care macular laser. The majority of patients in the sham group, roughly 75 percent, received macular laser during the course of the study.
Both of these studies have good representation from important patient populations relevant to today's discussions. Over 43 percent were 65 years of age or greater, 22 percent were Hispanic, and roughly 12 percent were African-American.
Touching on question one, the studies

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around ranibizumab and DME include common and probably the most important outcome measures that are relevant for assessing treatment outcomes in DME. These include a variety of measures of visual acuity, patient-reported outcomes, the extent of retinopathy severity on color photos, as well as fluoresceins and OCT, and benefits relative to control were seen in

Phase III studies with ranibizumab for all of those different endpoints. Ranibizumab treatment results in rapid and sustained improvements, both in vision and in retinal anatomy. Again, touching on questions two and three, as you can see from the graphs on the left, the average change in vision from baseline over time in the sham group in white and the ranibizumab group in color, statistically significant improvements in vision were noted as early as one week after the first ranibizumab treatment, these results were durable through 24 months. And if you look at the graph on the right, subjects gaining significant vision, 15 or more letters on the standard chart or three or more eye chart lines, this outcome was

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achieved in just 12 to 18 percent of patients in the control group, as compared to 35 to 45 percent of the patients in the ranibizumab treated groups. Looking to the patient-reported outcomes on the VFQ-25, these were collected as part of the randomized studies and if we look at the graphs on the bottom, this looks at the change in the VFQ-25 composite score over time, and patients in the ranibizumab treatment groups had better improvements in the VFQ-25 than patients in the control groups. Touching also on question seven, sort of extending these results beyond diabetic macular edema, ranibizumab also appears to significantly slow the development of proliferative retinopathy, which is the end-stage complication of this disease. So this is a post hoc exploratory analysis, the graph in white shows development of proliferative disease over time in these studies, and this occurred in approximately 35 percent of patients treated in the control group as compared to fewer than 10 percent of patients in the ranibizumab groups.

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Looking to safety, ocular safety was generally consistent with other studies of ranibizumab in non-DME patients. With regard to systemic safety, we saw low rates of systemic adverse events that were potentially related to systemic VEGF intervention. In addition to the RIDE and RISE studies, there are a variety of additional data demonstrating that ranibizumab has benefits and improves outcomes as compared to other forms of

DME treatment. There's several Phase II studies comparing ranibizumab either versus sham injections or macular laser, and as Dr. Frank discussed, there's also additional Phase III type data, most notably on the DRCR network which is sponsored by the NEI, comparing ranibizumab with prompt or deferred laser on the blue and orange lines at the top of the left graph, as compared to intravitreal steroids or laser treatment alone. There is also additional data from Europe where Novartis has completed a Phase III study with ranibizumab looking at, again, ranibizumab with or without laser, as compared to laser alone.

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Touching on the questions of comparative efficacy, questions four and five, there's no level one evidence that directly compares outcomes of various intravitreal anti-VEGF agents in DME. As Dan has just discussed, the technology assessment does provide an indirect comparison, and we feel there are substantial limitations to that approach because of the differing nature of these studies. Several of the studies have, may not have had a sufficient number of patients with characteristics similar to Medicare beneficiaries, several of the studies were not multicenter, data was not necessarily collected or reported or analyzed in standardized ways which can minimize bias and variability, and the length of the treatment period may not have been sufficient to understand long-term outcomes with all of these different anti-VEGF agents. In addition, some of the patient population differed with regard to the baseline characteristics such as visual acuity. So if you don't correct or try to adjust for some of these differences, the conclusions that you can make from an indirect

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comparison are going to be limited. Now of course there is additional evidence that was level one in quality comparing anti-VEGFs directly in macular degeneration, particularly, for instance, the CATT study, but it's important to recognize that DME patients and AMD patients differ substantially, both with regard to the pathophysiology of their visual disease as well as the demographics and medical comorbidities of these patients. We typically think of DME patients as having multiple end-stage

complications of Type II diabetes, they are often a relatively fragile patient population, and so we feel that neither the efficacy results nor the safety results from wet AMD studies can be directly abstracted to potential results that would be seen in diabetic macular edema.

So overall in conclusion, we feel that there's robust evidence from multiple clinical trials to conclude that DME treatment with ranibizumab improves patient health outcomes relatively to DME treatment without ranibizumab. We feel the outcomes are broadly

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applicable to patients and in particular to Medicare beneficiaries and patients in community-based settings. And really most importantly, we feel that these results really underscore the need for appropriate screening, diagnosis and treatment of DME patients. Thank you very much and I will be happy to take any of your questions.

DR. GOODMAN: Thank you very much, Dr. Ehrlich. We won't take questions now, but if we could persuade you to sit in the front row here so we will know where to find you in the near future?

DR. EHRLICH: Sure.

DR. GOODMAN: Thank you. That was a very clear presentation, very nicely documented, and we appreciate your ability to prune down the original slide deck to get it into our time limit, but we're glad to have it in hard copy for our later reference. Thank you very much, sir.

(Applause.)

DR. GOODMAN: So, Dr. Helen Nickerson is the senior scientific program manager for JDRF, which is the Juvenile Diabetes Research

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Foundation, and I was told you --

DR. NICKERSON: I don't have slides.

DR. GOODMAN: You don't have slides, so we'll take these slides down. Welcome, Dr. Nickerson.

DR. NICKERSON: Thank you. My name is Helen Nickerson and I am program scientist at JDRF. I don't have any financial or other conflicts to disclose. I'd like to thank the panel for the opportunity to speak on behalf of JDRF and patients with Type I diabetes. JDRF is a global organization focused on Type I diabetes research. As many as three million Americans might have Type I diabetes, and our

organization is driven by passionate grassroots volunteers connected to children, adolescents and adults with the diseases. Since 1970 we've funded more than $1.6 billion in diabetes research.

So, Type I diabetes is also known as juvenile or insulin-dependent diabetes, but I should make the point that it can strike at any time in life, including well into adulthood. It's an autoimmune disease that attacks cells in the pancreas needed to produce insulin, and

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people with Type I diabetes face a lifetime of taking insulin just to stay alive, and the challenge of balancing their food intake, exercise and insulin to avoid dangerous high and low glucose levels, and as Mr. Ollendorf pointed out, the challenge of vision loss on this kind of management could be substantial. However, even with careful control, many people with Type I diabetes develop complications, including diabetic macular edema. Diabetic eye disease is as common in Type I as in Type II diabetes and in some cases it's more aggressive. And there was a recent international analysis, the Metro Eye Study, that showed that three-quarters of people with 20 years or more of diabetes have diabetic retinopathy, and the longer that someone has diabetes, the more likely they are to develop retinopathy, so we do believe this is a very significant problem for the aging population. So, diabetic eye disease can lead to significant loss of vision, and this is actually one of the greatest fears of people diagnosed with diabetes, and diabetes is the leading cause of adult onset blindness in the

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U.S. population.

Our chief scientific officer, Dr. Richard Ensor, submitted a letter to the panel that outlines our position on some of the questions being addressed today, and this letter does include specific references to some of the trials and points I'll mention even though I don't have slides.

So most importantly, in response to questions two and three posed to the panel, at JDRF we do have high confidence that there is sufficient evidence to suggest that one anti-VEGF therapy, ranibizumab, can improve the current standard of care for diabetic macular edema. We believe that the most important study was the study highlighted by Dr. Frank,

the Diabetic Retinopathy Clinical Network study, and this is important because it did directly compare standards of therapy, laser and steroids, with anti-VEGF therapy. A couple of other studies I'd like to mention, the RESTORE study did independently confirm that ranibizumab alone and combined with laser gave superior gain in vision compared to standard laser therapy in patients

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with vision impairment due to their diabetic macular edema. And the smaller short-term study called the RES-2 study which JDRF also supported, found that ranibizumab treatment had better visual outcomes with respect to laser therapy.

We think that these results are generalizable to other anti-VEGF therapies, although a small study did suggest treatment with bevacizumab resulted in better vision outcomes compared to a laser group.

So we feel on the whole that there's not enough evidence to determine whether there are clinically meaningful differences between different anti-VEGF therapies in terms of safety and efficacy, and that better designed research studies would be needed to address that question.

In response to question six, we are very confident that the studies conducted are generalizable to the Medicare population because there are many subjects in those studies older than 65. Also, the use of community-based practices in the DRCN studies should mean that these results are relevant to

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the general population with diabetic macular edema.

So in conclusion, we believe that there is evidence that one anti-VEGF therapy in particular, ranibizumab, improves patient health outcomes relative to current standard of care, but that there is insufficient evidence available to give good data on comparative safety and efficacy of outside VEGF treatments for macular edema. Thank you.

DR. GOODMAN: Thank you very much, Dr. Nickerson, very helpful and clear, and now, Dr. Nickerson, if you would as well, find your way to the front of the room if possible. Thank you.

Dr. Victor Gonzalez is representing the American Diabetes Association. Dr. Gonzalez.

DR. GONZALEZ: For all the 21 million Americans, men, women and children with diabetes in this country, I would like to thank you for the opportunity to address you today. As you may know, at the ADA we don't come to these sessions very often, and I think this was one that was of interest to us because we think

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there are some important changes that we can help you with in terms of the quality of life and other issues that our diabetics face in this country.

First of all, these are my disclosures, I do not own any stock in any of these companies, although many of these are doing research that is relevant here.

As we know, the laser has been the standard of care for over 30 years now and it served us well, you know, compared to the blindness, the issues associated with laser photocoagulation have been acceptable issues up to now. The mechanism of how laser works is something that we're still learning, but we do feel that somehow there is a decrease in the levels of VEGF in the eye, which results in some of the benefits we see with the laser.

Now then, why are we interested in looking at different options to try and treat these patients? Well, because laser has some limitations. Laser is intended to try and stabilize and prevent vision loss. Some of the side effects of the laser are unfortunate in cases of diabetic macular edema. Repeated

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laser photocoagulation can in fact result in some distortion or scotoma, some blind spots, and sometimes we can cause inadvertent disturbance of color vision. Laser photocoagulation also results in a reduction in the peripheral field and as a result of the loss of that peripheral field we can induce some problems with night vision function in our patients.

Fortunately, we know that there are some options. This has been my poster child in a sense as a young ophthalmologist or a young retinal doctor in training. This is a patient who has 20-25 vision, he has been stabilized for over 25 years, but this individual is what I call those individuals who are chart happy but functionally disabled, because there is very significant loss of visual field as a result of our treatments.

Although we know that the

pathophysiology of diabetic retinopathy is very complicated, there are a few factors that are important, and one of the most important is glycemic control, and we always at the American Diabetic Association make sure that we point

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that out, glycemic control is very important. But we're very fortunate that in all that conflicts in biochemistry, VEGF in fact does play an important role in some of the complications that we see with diabetes, including the diabetic macular edema and the proliferative diabetic retinopathy. There are experimental and clinical evidence that basically supports this concept and with this concept in mind, you know, a lot of the trials that have been discussed have already been carried out. This is one of the early studies where they were able to demonstrate that continued application of anti-VEGF could cause resolution of the macular edema and we could see all the vascular changes that were discussed earlier. You can see on the far left here the resolution of those complications without significant laser treatment. Of interest to our group has been the fact that, you know, in this study they were able to demonstrate also a regression of new revascularization, which came back once the drug was stopped, suggesting that in fact there

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was a benefit from application of this medication to the patients. We have been able to have access to this drug in Texas, fortunately we have had a local coverage determination and have been able to use these medications to benefit our patients. And here you see someone with very severe diabetic retinopathy as was described earlier, have resolution of the retinopathy, and here you have the long-term benefits of this individual, he's over five years out without requiring any laser photocoagulation. The benefits to this individual have been, you know, improved visual acuity and maintaining the periphery. So when we start talking about quality of life measures, I think that's important. You know, my patients come in and tell me, Doctor, I want you to do three things for me. I want you to give me a treatment that's going to keep me being able to drive, being able to work and being able to take care of myself, and

I think one of these anti-VEGFs satisfied all of those requirements.
This is just to summarize something
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that has already been pointed out. The studies have demonstrated the fact that those patients on the drugs tend to have better outcomes compared to their controls in terms of gaining ten letters of vision and also in terms of gaining letters as well.
So in conclusion, we at the American Diabetes Association feel that, you know, we have reached a crossroads, that there is a shift in the paradigm in terms of how we treat these patients. I think that use of the anti-VEGFs is a game-changer in terms of benefitting our patients, and we support a national coverage determination that allows physicians to have access to all of these drugs so they can continue to preserve the independence and improve the quality of life for these 21 million diabetics in this country.
Thank you.
DR. GOODMAN: Thank you very much, Dr. Gonzalez, and thank you for representing the American Diabetes Association. We're pleased that you've taken an interest in this topic for obviously very good reasons. I might add as well, thank you very much for that highly
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visually stimulating slide there. That was, it lit up my visual cortex, I can assure you. And if you would sit near the front of the room, we may want to bother you in a bit. Thank you, sir.
Our next three speakers all come from, or represent the American Academy of Ophthalmology, and we will start with Dr. Trex Topping. He's the chair of the health policy committee of the AAO. Welcome, Doctor.
DR. TOPPING: Good morning, it's a pleasure to be here. I will be followed by Dr. Neil Miller, director of the retina services at Wilmer Institute, and then John Thompson, who is president-elect of the American Society for Retina Specialists.
The leading causes for blindness in the American population in patients over 65, i.e., our Medicare population, include wet macular degeneration which does not relate to diabetic retinopathy, to cataract, and to diabetic retinopathy. In this population, in this age group the major cause is going to be diabetic macular edema, and glaucoma also is an

issue.
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You all know about the anatomy of the retina, and we've talked about the macula being the area where central vision is located, and good macular function is important to have good visual function, and you all recognize the eye chart from your most recent visit to the eye doctor and the 20-20 line down below is what you see and hopefully you all saw on your exam. We've heard about three lines of visual loss and 15 letters of loss. Three lines and 15 letters of loss takes you to 20-40, which is okay, because at 20-40 you can still read, you can still drive. However, if we go from that point and take three lines of visual loss or 15 letters, we go to 20-80 and that is not okay, you cannot read, you cannot drive, you are losing your independence. And then as we go further up the chart to the 20-200 line, if that is the vision in your better eye, you're legally blind and very handicapped.
Our visual function obviously is usually assessed using visual acuity. Now, when your visual acuity in an eye chart is taken, if you were in the bad part of the eye
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chart then you have very diminished functional acuity, functioning in the upper area trying to read, or lower area, recognize faces. Near activities are very important for our activities of daily living, for reading, for knitting, for going to the store and selecting the right objects to buy, being able to read your insulin pump or your insulin monitor, or reading the insulin syringe.
And distance activities, can you see the stairway, do you trip over sidewalks, can you function nicely and can you have fun, can you watch television or sports events.
As you know, the macula is the center part of the retina and it is damage in the macular intrinsic blood vessels that makes the problems in diabetic macular edema. Seen here with angiography, leakage of these vessels results in pooling of fluorescein, which is then documented using OCT, which you heard about already. And as we pass further into the process from the left screen where there's a nice little depression in the fovea, no edema, to a little Mount Vesuvius, which is macular edema on the right side, and this is used for
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quantitating the degree of edema. If we look at the United States population and their body mass index and their obesity, and we start in 1990 and we go up to 2010, we see we're going from blue, less than 10 percent, to 10 or 15 percent obesity, to now 20, to almost over 30 percent in some areas, and with this increase in obesity goes an increase in diabetes. The U.S. population in the last 10 years has increased by 10 percent, and if we look at what's going on within our population 10 years ago, 10 million diagnosed Type II diabetics, about a million Type I diabetics, and about 5.9 million undiagnosed diabetics, as well as another 24.5 million people with impaired glucose tolerance. The prevalence of complications is significant, and let me just identify in this slide that 49 percent of retinopathy is based on seven-field funded photographs. The previous records that have been described to you come from a study, the ME study which only used one center field, and therefore the numbers are higher. As time passes, the

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prevalence of diabetic retinopathy increases. There are 8.5 million people in the U.S. right now with diabetic retinopathy and 2.9 percent of the U.S. population has diabetic retinopathy. And if we look at our diabetic patients, what are your big concerns? Two of the top four are visual concerns, going blind number one, and number four, blurriness and other vision changes such as cataract. If you take patients who are diabetic and somewhat visually impaired and ask them how much of your future life are you willing to trade to get back good vision, if you're in the good range of 20-20, 20-25, 15 percent of future life. If it's 20-30 to 20-100, 22 percent of future life. Legally blind patients are willing to give up over a third of their future life, and patients who are counting fingers giving up half of their future life, and those who are totally blind, no light reception, give up three-quarters. Okay. Now that we have this background, are there other things that we can do to change the outcome in diabetic

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retinopathy other than just laser, are there treatments that can be done that go from

macular edema to normal retina? Thank you.
DR. GOODMAN: Thank you very much, Dr. Topping, very helpful. We will now move to Dr. Neil Bressler, if I'm correct. He's the chief of retina services at the Wilmer Eye Institute at Johns Hopkins Hospital, also representing the AAO. Welcome, Dr. Bressler.
DR. BRESSLER: Thank you, Dr. Goodman. Yes, Dr. Neil Miller is an excellent neuro-ophthalmologist that I strive to be, but we'll stick to the retina for today. So, I do chair the Diabetic Retinopathy Clinical Research Network, but also am representing the Academy of Ophthalmology. I have no financial conflicts of interest as reviewed by my university, but my university does get numerous research grants to support my efforts for many of the research areas that we're doing here. The network is to facilitate clinical trials as new treatments come on, to be able to plug them in right away and test what we're going to do in terms of reducing the magnitude of blindness and the public health problems

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from diabetic retinopathy. We take our orders from Congress and they have set as a high priority trying to attack this problem that Dr. Topping was discussing.
As recently as 2010, the Senate Appropriations Bill has four examples, one of the examples was the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trials that we're going to discuss today. This involves community-based and academic-based centers. About 75 percent of the patients in these trials come from community-based centers, because our idea was let's penetrate about one-third of all the retina practices in the United States to try to be representative of the treatments and to teach those.
The life cycle of the network is it's constantly bringing on new studies and new trials and this just shows you what we're going to discuss, just this one trial right now.
This was discussed earlier. I want to highlight some important facts based on what was discussed.
This was comparing the prompt laser on

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the left, which was our standard care, two different ranibizumab trials, one involving laser and ranibizumab right away, the other deferring it for at least six months, possibly

forever if it's not needed. And unlike macular degeneration, this does not require treatment month after month after month. As was highlighted by Dr. Frank, it's possible that following treatment you may get resolution of the edema and it may take months or years until it comes back.

So we ask ourselves if it's improving based mainly on OCT and visual acuity; if it's improving, we treat again. Once it's no longer improving we withhold the treatment, and if it thickens again, we resume the treatment. But once it's no longer thickening, we withhold and double the follow-up time to two months and then at least to four months, and this has resulted in a difference in treatment compared with what we do with macular degeneration.

It already was highlighted that laser improves, shown in purple here, but the ranibizumab arms with the arrows have a 50 percent relative improvement, and this is also

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important to look at the losses, this was not highlighted, but here you can see fewer than five percent of the ranibizumab arms lose ten or more letters of vision, and that's critical. If you walk in at 20-40, you want to stay there, you want to avoid having that loss of vision.

This highlights the number of injections that are needed. There could have been -- I'm sorry, the number of lasers -- I'm sorry, there we go, the number of injections that were given. There could have been a maximum of 26 injections. In the first six months to get it under control there were a median of six injections, but in the second six months about three, and in the second year two to three. We have no biological rationale to suspect that this is going to change, so it appears that once it's under control, a little edema comes back, we treat, and then it takes care of it again.

This looks at the number of lasers, and on the right-hand side you can see that by the second year, the eyes that were in the deferred laser group, only 30 percent got any

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laser, so the majority of eyes are getting zero lasers, and this is because the edema completely resolves, and when it comes back it resolves again with the treatment.

And as was mentioned by Dr. Ehrlich, it also may have a role in preventing

proliferative retinopathy whether you start with moderately severe or better retinopathy, or even if you start with severe retinopathy, there are few eyes, while they're getting treated with this drug, that go on to either vitreous hemorrhage or receive PRP compared with sham.

Now one last thing I want to highlight from the trials, and that is that starting visual acuity is the only thing we found among a myriad of risk factors across all of our trials that influenced the outcome. So we had a median visual acuity of 20-50 walking in, and this divides the subgroup by a preplanned above the median and below the median. I point out, either way the ranibizumab arms were superior. But when we were less than 20-50, the median was 20-80, and you can see on the right-hand side they have a 10- to 15-letter average

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improvement.

That's important because in the BOLT trial which looked at Avastin, the median visual acuity starting was not 20-50, it was 20-80, and so they only improved six lines, which we saw in our trial which started at 20-50, but in our subgroup of 20-80 we had a greater improvement.

Therefore, the network is embarking upon a comparative effectiveness trial. Now that we know anti-VEGF works, now that we have confidence in ranibizumab, starting in June we're going to do a comparative trial of Eylea and Lucentis and Avastin in one trial to control for these factors hopefully with randomization and look at the outcome. As was mentioned, we do have great confidence in this because it was also shown in the RESTORE trial and was shown in the RIDE and RISE trials.

And one last thing is, we did look both in the RESTORE trial, this was published in the April 2011 Ophthalmology journal, showing that whether we look at all eyes or most importantly the better seeing eye, even in the worse seeing eye, the ranibizumab arm has a

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better quality of life outcome.

So I'm not going to show you the other quality of life results, I'm going to turn it over to Dr. Thompson, who on behalf of the Academy of Ophthalmology will give our opinions on the questions that you asked, and thank you to the panel for letting us share that information.

DR. GOODMAN: Thank you very much, Dr. Bressler. If you would join the folks towards the front of the room, that would be very helpful. Our next speaker, also with the AAO, is Dr. John Thompson. He's the president of the American Society of Retina Specialists.

DR. THOMPSON: Thank you. I'm president-elect actually, I don't want to put the president out of a job too quickly. My financial disclosure is that our practice has participated in some of the trials with Genentech and Regeneron, so we've received grant support for the practice. I have no other financial disclosures.

So in terms of the questions, looking at the questions that the panel has been asked to look at, for the macular degeneration we

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probably see it a little different than diabetic retinopathy, but if you want to pick out at those things that are most important for treatment of diabetic macular edema, visual acuity is extremely important, so is the VFQ-25 as it relates to visual function, and then towards the bottom, the OCT, ocular coherence tomography, are critical things, and those are probably the most important tests in our patients with diabetic macular edema, but there are other important things.

The dilated examination allows us to see what the level of retinopathy is and we grade that level of retinopathy. The Amsler grid is not that useful for diabetic macular edema. Measuring the extent and direction of diabetic retinopathy is useful by photography because that predicts the likelihood of progressing to proliferative diabetic retinopathy, which is a different problem and different issue which needs to be treated differently, at least at this point.

Fluorescein angiography is not used frequently for diabetic macular edema, but it is often helpful at baseline to see is this

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macular edema. There's another thing called nonperfusion, and these eyes don't respond particularly well to anti-VEGF and so you want to establish that the problem is diabetic macular edema rather than nonperfusion.

The visual fields are not particularly useful for diabetic macular edema treatment since this involves the center of the vision, and so that's the suitability of these particular tests.

In terms of question two, how confident, the three of us are very confident that we do have enough evidence to indicate that we can make an informed decision based on scientific evidence about the use of the anti-VEGF agents, and the related question number three, we feel confident that the anti-VEGF agents are useful and do result in improved patient outcomes, meaningful improvements in visual acuity and visual function compared to the other therapies, laser photocoagulation.
For number four, do these give meaningful changes in health outcomes and yes, again, we don't have as many studies, we just

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have the RESTORE study in terms of the VFQ-25, but I think it's very likely that with some of these other studies when they report, the ones that are the RISE and RIDE study which was presented by Dr. Ehrlich, and also when the DA VINCI, which is the Eylea study, reports visual function, and that has not been reported yet to my knowledge, that we are going to see similar sorts of statistically significant improvements. So we do have data which will be available very shortly that's in the process of coming out.
And in terms of question number five, the comparison, we don't have this data. You know, putting these studies and doing the meta-analysis is nice, but it's not the value of a randomized controlled clinical trial, and this is an area where we really need to have data to compare ranibizumab to bevacizumab and to aflibercept. It is the impression of the three of us that the pegaptanib doesn't give quite as much improvement. There is not a head-to-head trial on that, so this not proven science, but it's our clinical impression that it does not give as much improvement in

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diabetic macular edema treatment, but certainly the other three anti-VEGF drugs need to be compared, and as Neil alluded to, there is a DRCR Net study starting in June which is going to do this very comparison.
In terms of the different benefits and similar harms we think that the risks of these various anti-VEGF agents are similar, but it would require a very large trial to try to tease out small differences in arterial thrombotic events between one drug versus another drug. So we really can't say at this

point whether the risks of these three drugs, Avastin, Lucentis and Eylea, are different in terms of systemic risks. The point has been made and it's very important that we not just generalize the macular degeneration data because they are these are different patients. They have different medical histories, different conditions. They tend to be younger. In terms of the generalizability of the results, we think that these are generalizable to the Medicare population. The RISE and RIDE studies as well as the DA VINCI study included Medicare age patients. This

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was. About 70 percent were community-based practices and about a third were university-based practices, so these are typical patients that we see in our offices. We believe that this also applies to the younger population. This problem affects many patients that are not Medicare age yet unless they are disabled, and we think that these also apply to that. So these results are generalizable to the broad community of patients. These also included minority patients, which are an important component since they tend to have more severe diabetic retinopathy, at least with black and Hispanic patients.

In terms of other forms of diabetic retinopathy, there is some tantalizing evidence that these anti-VEGF drugs help to prevent or slow the progression of diabetic retinopathy, but we do not have Level I data that really indicates that. That would be a bonus, but we don't know that yet.

In terms of gaps in medical evidence, for management, really the biggest gap is the one that the DRCR Net is going to fill for us

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in terms of comparative effectiveness studies for the different anti-VEGF agents, and this will be very important data.

And question number nine is what studies are needed, and I would say really comparative effectiveness studies are needed to try to determine the both systemic risks of these three different drugs as well as the response to treatment. It's important to remember that, with macular degeneration, the disease is new blood vessel membranes which occur at the level of the corti capillaris, and, in diabetic macular edema, the damage occurs with the retinal blood vessels within the

retina, so pathophysiologically these are very different diseases and it's the anti-permeability effects of the anti-VEGF agents that are helping us in these two very different retinal conditions that cause vision loss. Thank you very much.

DR. GOODMAN: Thank you very much, Dr. Thompson, very helpful, and thank you for the coordinated series of slides from the AAO. What we will do now, if Ms. Ellis says we're ready, is to move to our open public

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comments. Are we ready, Ms. Ellis? Thank you. Ms. Ellis, I know, had to get disclosures from all the folks that signed up today and I will do my best to get the names pretty close to right, and I apologize ahead of time for my inability to read certain handwriting, which should be good enough. We have four speakers in our open public comment section. CMS says that they get a minute apiece. Correct, Ms. Ellis? It doesn't mean we might not come back to you later on in the day.

Our first speaker is John Magliocchetti, from Regeneron Pharmaceuticals.

MR. MAGLIOCCHETTI: Thank you, Mr. Chairman, members of the committee. Again, my name is John Magliocchetti, and I am in full disclosure a full-time employee of Regeneron Pharmaceuticals, and Regeneron appreciates the opportunity to correct the public record regarding several misstatements that were made with regard to our product Eylea aflibercept injection in the technology assessment report prepared by the Institute for Clinical and Economic Review.

Please note that Eylea is not approved

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for the treatment of diabetic macular edema. It is indicated in the United States for treatment of wet age-related macular degeneration.

As you know and as we heard earlier today, Medicare beneficiaries are responsible for 20 percent of drugs administered in direct physician's office costs. Regeneron would like to thank Mr. Ollendorf for pointing out the inconsistencies and to correct the public record earlier in his presentation with regard to the Medicare cost information provided earlier for Eylea and Lucentis. In the presentation of the cost assessment report for anti-VEGF therapy in DME Mr. Ollendorf cited 2008-2009 Medicare cost estimates for

Genentech's Lucentis or ranibizumab injections which appeared to reflect 2008-2009 Medicare reimbursement payments of 80 percent of average selling price plus six percent, whereas the report also used the currently listed 2012 average selling price plus six percent of Medicare calculations for Eylea to compute an average cost per dose for these two products. As was pointed out in the presentation

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earlier, these costs are not a correct description of pricing of either therapy and not appropriate for the comparison. More specifically, as of today, a current wholesale acquisition cost for a dose of Lucentis is $1,950 as compared to what was presented as a figure of $1,624, and the wholesale acquisition cost per dose for Eylea is $1,850, as compared to the reported figure of $1,961 in the report. The most recent published average selling price plus six percent for Lucentis is $2,009 and for Eylea it is $1,961. Our genuine concern is the use of these inconsistent Medicare cost estimates for Lucentis and Eylea may have resulted in erroneous Medicare budget impact numbers relative to these two products on page 56 of the report.

DR. GOODMAN: Mr. Magliocchetti, you may want to finish.

MR. MAGLIOCCHETTI: Yes. In conclusion, we would like to thank you very much for this opportunity to address the panel today with this, and we do respectfully request that these corrections be added to the public statement.

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DR. GOODMAN: Thank you very much, Mr. Magliocchetti, for your presentation. I would just remind the panel that notwithstanding any discussion about price, none of our questions, none of the questions before us today discuss economics, pricing or otherwise. Thank you, sir.

Next is Jeff Todd, from Prevent Blindness America. Welcome, Mr. Todd.

MR. TODD: Thank you. Founded in 1908, Prevent Blindness America is the nation's leading voluntary eye health patient advocacy organization dedicated to preventing blindness and preserving sight.

As it relates to the treatment of various eye conditions, we strongly believe in policies that encourage treatment options and flexibility for patients and physicians. We

believe that treatment decisions should be left to the treating physician and his or her patient. However, we also believe that these decisions must be fully informed with all of the available knowledge related to efficacy and safety. I understand and appreciate this is why we are here today.

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There are others in the room who have spoken to the specifics of the efficacy and safety of anti-VEGF treatment of diabetic macular edema. I simply want to highlight how important the expansion and availability of effective and safe treatment options is for eye conditions, particularly those related to the retina.

When I began working with Prevent Blindness America less than 10 years ago, we routinely received inquiries from patients who were diagnosed with conditions for which there was little or no treatment at the time. All we could do was provide a caring unknown voice of comfort on the other end of the phone, and to suggest that they start looking at options for low vision devices.

Now less than a decade later due to advances in care, most prominently anti-VEGF treatments, we are able to offer hope to these patients, hope for a fulfilling lifetime of vision. So thank you for your time today.

DR. GOODMAN: Thank you, Mr. Todd, and thank you for making your point within the minute, we appreciate that.

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Our third speaker is, I believe it's Narinder Sharma, from AMD Alliance International. Welcome, Mr. Sharma.

MR. SHARMA: Thank you, good morning. Today's discussion is important for people affected by macular disease worldwide. I am here today as CEO of AMD Alliance International in support of maintaining and expanding access to safe and effective treatment options for people with diabetic macular edema and related conditions.

AMDAI represents a coalition of patient and older person organizations across the globe. We essentially raise awareness, support research and clinical advances, and try to improve the lives of people with serious vision disorders through our affiliates. We have a simple request of you today; we wish you to make your decisions to encourage innovation, to encourage informed choice, and three, to

ensure all treatments are available for patients and for clinicians. We all remember how just a handful of years ago there was not much hope for preserving eyesight for people with macular

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diseases. Then the anti-VEGFs came along. Eye doctors thought at first that patients would never agree to injections into their eyeballs. Lo and behold, as patients found they could read again, and even drive, everything changed. I ask you, what is better than this type of success where a treatment not only restores biological function, but also restores quality of life and potentially would reduce the economic cost of vision impairment. Now that's a victory if ever I heard it. And I thank the panel and everybody here for working towards improving the lives of patients. I thank you for all that you do.

DR. GOODMAN: Thank you, Mr. Sharma, and thank you for your clear remarks, and I can assure you that we join in your wish that this benefits patients, including but not limited to Medicare beneficiaries. Thank you, sir. Our fourth speaker is Daniel, first letter of the last name is R.

MR. ROBERTS: Roberts. I don't write any better than I see.

DR. GOODMAN: That makes me feel a little bit better about my vision. You're from

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MD Support?

MR. ROBERTS: I'm the founding director of MD Support, Macular Degeneration Support, and I have no conflicts of interest, just that we do get an educational grant periodically from Genentech. Other than that, no other conflicts, and speaking as a patient I am essentially just supporting what the two gentlemen before me said. As a patient with both AMD and with diabetes Type II, on behalf of the worldwide low vision community that we support, if the evidence shows no significant safety issues and the evidence is equal on both sides, all we ask is that the final decision whether to treat or not treat be left to the doctor and the patient. In return, MD Support, MD Alliance, all the rest of us in this field vow to continue our efforts to empower the patients with enough knowledge to make appropriate decisions based upon their own individual circumstances. Thank you very much for

allowing me to come and witness this excellent process.
DR. GOODMAN: Thank you, Mr. Roberts,
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and thank you for your on-point comments. Ms. Ellis, I believe that concludes the set of open public comments, correct?
MS. ELLIS: Correct.
DR. GOODMAN: And you've gotten disclosures from all four?
MS. ELLIS: Yes.
DR. GOODMAN: Excellent, thank you, thank you all.
Well, panel, now we're going to move to the next item on our agenda, which is labeled questions to presenters. We're a few minutes ahead of time, thanks to the prompt and to-the-point comments of our speakers thus far, and as noted before we've arranged to have all of our scheduled speakers to date, to this point, sitting in the front row so we can have them available.
I have just a couple of suggestions about how we might pursue this discussion, and we will take this right up to just a few minutes before noon. It would probably help if, one type of question would be, you might seek clarification from our speakers regarding something they said that is relevant to their
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questions, that's worth pursuing, and another would be if you want to ask particular questions regarding evidence or data or study design or what have you pertaining to, once again, our question, either the voting questions or discussion questions, that would be good. So again, we want to focus as much as possible on the voting and discussion questions, because we are going to face up to those sometime after lunch.
So let's start with that. If there's any panelist that has a question to get started, and I will start with Dr. Phurrough, followed by Dr. Dubois.
DR. PHURROUGH: Can we ask Dr. Dryden and Dr. Ollendorf to address the studies that were not in her technology assessment?
DR. DRYDEN: I have copies of the studies that were identified and I would like to take some time over the lunch hour to review them, and I may then be in a position to summarize the evidence from my perspective.
DR. GOODMAN: We can table that question until later, unless another person has

a response.
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DR. PHURROUGH: And I had a question for you, Dan, if I may.
MR. OLLENDORF: I can just let you know what the studies were that we used. So, the RESTORE study was discussed already and that did have a quality of life component, and the Macugen 1013 Study Group also had a quality of life component, so those were the two studies that were part of our review. You also saw that RISE and RIDE had quality of life data collected, but those data were only presented at scientific meetings and not published in the peer reviewed literature.
DR. PHURROUGH: My other question for you is, of the various studies that you looked at and then included within your systematic review, I'm interested in sort of the selection criteria, what were the areas, levels, disease, how was that assessed for inclusion, and can you use that to -- and this is going to be a question that goes back to the research network, how well can you use those studies in choosing which patients need therapy. So your question is how close do they match the inclusion criteria, and the follow-up question
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is how do you use them to select patients.
MR. OLLENDORF: So again, in terms of our own inclusion criteria for selection of studies, we did not have, as some systematic reviews have done, we did not have precise criteria around level of visual acuity required or progression of retinopathy or other clinical values, we simply looked for studies that diagnosed populations with DME.
In terms of the types of patients that were in these studies, as I mentioned in my presentation, there was a broad spectrum of patients included in terms of both visual acuity, level of glycemic control, comorbidities, et cetera, across the entire sample of studies that we looked at.
When we looked at these studies comparing the anti-VEGF evidence, we found that many of those characteristics were relatively similar, looking from one anti-VEGF to another. So for example, most of the baseline visual acuity levels were between 55 and 65 letters when looking at the evidence for one anti-VEGF as compared to another.
DR. GOODMAN: Thank you very much,
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Dr. Phurrough. This is Dr. Bressler.
DR. BRESSLER: Thank you. So the cases that were, all the trials that were presented, all involved edema in the center, that was confirmed on OCT, and they all involved some level of vision impairment starting at 20-32, so starting at 20-32 or worse. And then as was mentioned, the mean ranged from a score of 55 to 65, as good as 20-50 for the mean and as bad as 20-80, and that's why we pointed out the outcomes may differ by where they start but all the anti-VEGFs worked, so they were all superior to no treatment and also superior to laser, but the magnitude is yet to be determined between or among the anti-VEGFs.
DR. GOODMAN: Thank you very much. Dr. Dubois and then Dr. Heseltine.
DR. DUBOIS: I guess this is for Dr. Frank. I would like to get your views on whether the safety data from AMD can be extrapolated to this population or whether the intrinsic differences between the patients would suggest that you shouldn't extrapolate, not on the efficacy side, but specifically on

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the safety side.
DR. GOODMAN: This is Dr. Frank.
DR. FRANK: Well, of course other than simply differences in age, there are certain differences between AMD populations and diabetic populations, the latter of which has a much greater prevalence of systemic renal, cardiovascular and other diseases. Nevertheless, to the best of my own ability and I think the data and safety monitoring committee of the Diabetic Retinopathy Clinical Research Network on which I sit, the systemic adverse events related to any of these treatments, and of course the network has not yet tested Avastin or Eylea, but they certainly have tested ranibizumab, Lucentis, and have tested steroids, and the systemic adverse events associated with those treatments given intraocularly have been extremely small and not really significantly different from the control of the laser alone groups. But of course very small incidences of adverse effects may not come out until many many more patients are treated over a much longer time, so to that extent the answer has to be indeterminate.

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The most severe event is, from my way of thinking at least, which is directly related

to the injection, is intraocular infection and ophthalmitis or a posterior injection leading to retinal hemorrhage or retinal tear could lead to retinal detachment and those events, too, are extremely rare. The maximum frequency from most of these studies has been about one in 1,000 injections, not one in 1,000 patients but one in 1,000 injections, so if a patient gets multiple injections, the risk may increase.

DR. GOODMAN: Thank you, Dr. Frank. Other responses to Dr. Dubois' question? Yes, Dr. Ehrlich.

DR. EHRLICH: If I could just add a brief point about ocular safety, I agree with what Dr. Frank said, and one of the reassuring things we found in the ranibizumab studies was that even though you tend to think of diabetic patients, particularly with complications of diabetes, being disposed to infections, we happily did not see a significant difference or an uptick in the rate of endophthalmitis in the DME studies as compared to the studies in wet

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AMD, so that is somewhat reassuring. In RIDE and RISE it was four out of 10.5 thousand injections that resulted in endophthalmitis and that was very similar to the rate that was seen in studies on macular degeneration.

DR. GOODMAN: Four out of 10,000?

DR. EHRLICH: Yeah, four out of 10,000 injections.

DR. GOODMAN: Thank you, Dr. Ehrlich. Dr. Heseltine.

DR. HESELTINE: My question is probably for Dr. Bressler, but anybody else could answer too. I'm sensitive to the concept that treatment choices in the absence of very definitive information often is based upon local phenomenon or local preference, and one of the comments that was made suggested that pegaptanib might not work as well as the other therapies, and I'm curious to know, is that a worldwide phenomenon or perception, in other words, in Europe and other parts of the world, and is it something we should pay attention to or be concerned about, or is it an area for research?

DR. BRESSLER: The perception that

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pegaptanib is probably not on par with either ranibizumab, bevacizumab or aflibercept is twofold. Number one, in the diabetic macular edema studies that were presented, although

there was just one Phase II trial, they started with a visual acuity as low as 20-100, and so the magnitude of improvement was nowhere near the magnitude seen in the lower or bad visions in Lucentis, Avastin or Eylea, so it just doesn't seem likely that they will be close. The second thing is the magnitude of improvement for avoiding vision loss with macular degeneration, while it is a very different disease, still is quite different with pegaptanib than we see with either Avastin or Lucentis.

So we can't test everything. As you know, these are very expensive trials in a way, we hope they're cost effective in the end, so that we have taken and been supported by our external reviews, the decision not to pursue pegaptanib. Although it has an effect, we don't think it's large enough compared to the other three available.

DR. GOODMAN: Thank you, Dr. Bressler.

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On that point? This is Dr. Thompson.

DR. THOMPSON: Yes. I would say also in the clinical view as a clinician, very very few retina specialists are using pegaptanib now, so that drug is very infrequently used, we almost always use ranibizumab, bevacizumab or aflibercept and so, you know, on our radar screen that's off the radar screen now.

DR. GOODMAN: Thank you, Dr. Thompson. I'll just remind the panel that while it is interesting and relevant to understand what may or may not be on the radar screen among clinicians, that's not necessarily the same as what the evidence might suggest, and we like to make that distinction as appropriate. Thank you.

Dr. Sedrakyan is next, followed by Dr. Steinbrook.

DR. SEDRAKYAN: I have a question about the systemic effects. I assume in the Genentech funded trial you have seen a substantially higher chance of death in your treatment arm, and we haven't seen that in DRCR trials because of the this issue about selection criteria that Dr. Phurrough started

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with, particularly patients with severe cardiovascular diseases, and also patients who are older.

So are there any differences in your trials, and also, intensity of therapy seems to be different in the DRCR versus Genentech

funded studies, so these are important considerations when I see intensity has any effect on potential systemic side effects, and I worry about whether regular regimen might also in some subgroups of people be harmful, so can you comment about this issue?

DR. GOODMAN: I see Dr. Ehrlich first and then I believe Dr. Bressler. This is Dr. Ehrlich.

DR. EHRLICH: Thank you for that question. So in the pool of data out of 750 patients in RIDE and RISE, when we looked in terms of overall mortality, death from any cause, I believe there were three in the sham group versus seven and 11, so .3 and .5 in the ranibizumab groups. But if you look in more detail at what the cause of the deaths were, some of those are ones that we would typically think of as potentially related to systemic

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VEGF intervention, despite the fact that the doses of these drugs in the eye are very very low. So things such as myocardial infarction, for instance, that have been seen in studies of ranibizumab or other anti-VEGF systemically. Some of the other deaths were things that were, that happened in the .5 milligram dose group were things that were not typically related to VEGF interventions, so carbon monoxide inhalation, for instance, is an instance of that. So, you know, I think that first off the numbers are small, and if we look at the numbers of vascular deaths, for instance, the numbers are fairly consistent between the two different anti-VEGF groups. With regard to the question of treatment intensity, we have obviously looked very carefully at all of the safety issues that might arise. We don't see that that, for instance, the rate of mortality seems to increase, and there was other morbidity as well over the course of the studies while we were still masked, so it's quite possible that you could use the shams. And if we look in the DRCR network

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studies I think we actually saw the opposite relationship where overall incidence of patients we see with these events was roughly twice as high in the sham group as compared to the ranibizumab groups, but I don't think anyone would suggest that ranibizumab is cardioprotective. So I think, you know, we're dealing with very small numbers, even despite

the fact that the study has 750 patients, so it's hard to have a high degree of confidence of whether it's related to intensity of treatment, or even if it's a true effect or not.

DR. GOODMAN: Thank you, Dr. Ehrlich, Dr. Bressler, to this point.

DR. BRESSLER: I would support what Dr. Ehrlich said. We are very attuned to these concerns about whether there could be a systemic effect because there is, when you put 400 times the dose of bevacizumab in to treat people with metastatic colon cancer you do get a slight but definitive increased risk of stroke, and now we're dealing with people who have diabetes. Nevertheless, in the network studies the numerical numbers were actually

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less in the ranibizumab groups than in the laser only group.

And the few numbers, the numerical numbers that are increased in RIDE and RISE, I think are just that at this time. It could be due to chance. It could be that there's an effect there. We have too few numbers of events to be able to tell, so one trial may see it go one may numerically, one trial another way. The cumulative data so far do not suggest a problem, so this has to be watched and we'll have to look, I hope, at Medicare beneficiaries for example, databases in the future that are exposed to these various drugs or not exposed at all, to see if we can tease this out. That's not the same as controlling for all factors in a randomized trial. In a randomized trial we have not been able to identify a systemic harm and so we believe that at least a moderate or large risk has been ruled out, a small risk we just cannot rule out yet.

DR. GOODMAN: Thank you, Dr. Bressler. Dr. Sedrakyan, what's your take-home from the two responses to your question?

DR. SEDRAKYAN: I have a follow-up

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question, because I think you addressed the questions, but from my point of view we need to have more information about entry criteria difference in Genentech versus the DRCR trial, but also if I may ask a question as to the, out of population that you screen, what percentage ended up being randomized. Otherwise, how representative it ended up being after you screened so many patients, did these groups of patients end up being?

DR. BRESSLER: So the first question, the network chose not to exclude people who have prior cardiac or stroke history unless it was just within the previous month or two, when in fact we were worried about them being able to come back for the immediate follow-up, not that there was necessary risk. I believe, and Dr. Ehrlich can confirm this, this was different where perhaps the Genentech study was more risk averse and excluded people with these histories.

So given that we accepted those people, we wanted to be broad, generalizable, not exclude people unless we had a strong reason to exclude, and in that population we

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didn't see it. I do not have formal numbers because of the way practices work and a lot of community-based practice participated in these trials, to tell you what this represents, so it would be unscientific for me to tell you it probably represents about half of the people that walked in that had vision impairment, at least a little, and edema in the center of the macula. That's our guesstimate.

DR. GOODMAN: Thank you. That was Dr. Bressler, by the way. Dr. Ehrlich, on this point.

DR. EHRLICH: With regard to the systemic inclusion and exclusion criteria, particularly with regards to cardiovascular disease, we excluded patients who had had a history of a recent MI or stroke from the RIDE and RISE studies, the reason being within the past three months. And then again, that was mainly because of the possibility of them having recurrent events and exiting the study quickly, and we wanted to get follow-up on everybody who was enrolled.

With regard to the screening failure rate, I honestly don't recall the number off

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the top of my head, I would say it's probably 50 percent or less. We typically would try to minimize the number of screening failures to the extent that we can.

DR. GOODMAN: Thank you, Dr. Ehrlich. Dr. Sedrakyan, before we move on, what do you get from this line of questioning that you might share with us?

DR. SEDRAKYAN: I'm reassured that the events that we see. In fact I was calculating yesterday night, and in the combined studies it's .06 if you combine these two trials, and I

was reassured that in the DRCR study you don't see that effect, and it's more inclusive and a more representative population, so I'm less concerned now about this.

DR. GOODMAN: Thank you, Dr. Sedrakyan. Dr. Steinbrook and then Dr. McDonough.

DR. STEINBROOK: I wanted to ask about the health-related quality of life tech assessment, but I think this could really be responded to by anyone who wanted to. I'm struck by the fact that on the one hand we have a lot of information about

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two-line, three-line improvement on the eye charts, and to someone who is not an ophthalmologist and is not a quality of life methodologist, it seems to me that there is some real quality of life predicates there which are pretty obvious. I mean if you can drive and you couldn't drive before, you can probably do a better job with diabetes self-care, you could probably read some labels that you couldn't have read otherwise, so I'm wondering if there's any ability to speak about quality of life just based on that.

Or to phrase it slightly differently, is there some correlation which is found between some of these quality of life measures which have been used in the retina/diabetes/retinopathy field to sort of say okay, if you have this sort of improvement on the eye chart, what does that likely mean in terms of some of these scales which we may not have data for, and some of these could be used as a surrogate in some of them.

DR. GOODMAN: Thank you, Dr. Steinbrook. Let's have Mr. Ollendorf, and I might want to call on Dr. Thompson as well,

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depending on these remarks. Mr. Ollendorf first.

MR. OLLENDORF: I don't want to steal Dr. Ehrlich's thunder, but I believe in RISE and RIDE there was a measure looking at the proportion of patients who achieved a level of visual acuity equivalent to 20-40, is that correct? So that was found to be significantly in favor of ranibizumab and that is, as I mentioned, the threshold for driving in 45 of 50 U.S. states, so that's one sort of measure that speaks to the benefit related to a specific activity.

DR. GOODMAN: Before you proceed, Mr.

Ollendorf, when you asked the question is this correct, you made an assertion and asked if this is correct, and I note for the record that Dr. Ehrlich nodded his head in the affirmative. Our court reporter couldn't see that subtle gesture. Dr. Thompson.

DR. THOMPSON: Yes. I mean, there is a correlation between improvements in visual acuity and quality of life, but it matters where you start in terms of your visual acuity. If somebody goes from 20-100 to 20-80, they

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still can't drive, and their quality of life assessments try to capture some of those things, but it matters much more if you go from 20-80 to 20-40 because all of a sudden you can drive, and that's why although the quality of life assessments are extremely useful to us, you have to dissect out where the patient started in that continuum of vision, because at certain levels of vision it's going to matter more in terms of the quality of life than at lower levels of vision.

You're also more likely to get improvement at lower levels of vision. If you start in one of these studies at 20-32 and you improve to 20-20, your quality of life probably doesn't improve that much in this situation because you have had pretty good vision to begin with and now you have even sharper vision, which makes you happy when you're looking at the telephone directory, but it doesn't make a huge difference in terms of your ability to read your insulin syringe.

DR. GOODMAN: Thank you, Dr. Thompson. Dr. Steinbrook, does that address your point?

DR. STEINBROOK: Well, yes and no. I

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guess, I raised this in the context of, we talked at the end about where we're going and things of that sort, but we have a lot of information about health-related quality of life in the TA and we don't have a lot of data related to particular studies, but if some of the more general points are we really ought to focus on where people start because if you start too bad vision or too good vision, it doesn't really matter, maybe we should be calibrating and trying to understand better exactly how these rather formalized things which don't seem to get done that much in a formal way, or maybe they get done but don't get published, where can they really help us and where should we really be looking for that.

DR. GOODMAN: Yes, point well made, Dr. Steinbrook, so it isn't merely the delta, it's an individual's baseline from whence did he or she start. Dr. Thompson, did you want to make a concise addition to this point? This is Dr. Thompson.

DR. THOMPSON: Dr. Chambers reminded me of an important other thing that I neglected to mention, and of course it depends upon what

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your other eye is. You know, if your other eye is really really good, then helping your one eye that is down somewhat from diabetic macular edema matters less. So for all of these quality of life studies, they typically report for where the study eye is the good eye versus the study eye is the bad eye. If the study eye is the better eye, then the effects are more robust.

DR. GOODMAN: Thank you. And I believe you were referencing Dr. Chambers, who is a colleague from the FDA, is that correct? Just for the record, thank you. Next is Dr. McDonough, followed by Ms. Massey. Dr. McDonough.

DR. MCDONOUGH: One of the questions I guess is related to Dr. Steinbrook's point about the relationship between visual acuity and quality of life. You mentioned baseline as being one factor. What about, does an improvement in visual acuity as a result of, say, cataract removal, or an equal improvement in visual acuity given equal baselines in AMD, would that have a different quality of life implication than diabetic macular edema?

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And then my second question, because I want to get them both in, you talked about the importance of ocular coherence tomography as being critical in terms of health outcomes, and on the other hand we heard evidence that retinal thickness might not directly relate on a one-to-one level in improvements in visual acuity, so why is that so important?

DR. GOODMAN: This is Dr. Thompson first.

DR. THOMPSON: Let me try to answer your first question. In terms of the different conditions, diabetic macular edema and macular degeneration have some similarities because they affect the center of vision, and you cannot correlate one-to-one what may be a 20-80 in macular degeneration is to a 20-80 macular edema, but they have more similarities than

differences. I'm not aware, Neil might know of some studies that have tried to directly correlate quality of life for 20-80 with macular degeneration versus diabetic edema, but I'm not aware of those correlations. Do you have a comment?
DR. GOODMAN: This is Dr. Bressler.

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DR. BRESSLER: We have published the quality of life outcomes using these anti-VEGF drugs in macular degeneration and there you can see the effects of 20-80 or 20-50 better eye. We have presented them, those were the slides we shared with you, but you were too fast in scheduling this meeting because we haven't published it yet, so I'm optimistic it will be published in terms of RIDE and RISE showing the same effects, and that is more robust when it's the better seeing eye that's treated, but even with the worse seeing eye, these translate into people answering that they can drive better, that they're reporting that they're driving, that they perceive that they're reading better. So unfortunately, it's not published yet, fortunately it's on its way, and we shared the slides with you that were presented at the scientific meetings.
DR. GOODMAN: Thank you. We will await those findings. On this point, Dr. Thompson.
DR. THOMPSON: Your second question, I wanted to address that. Could you --
DR. MCDONOUGH: Why is OCT important?

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DR. THOMPSON: OCT is important because it is the most sensitive way to determine diabetic macular edema, but there have been studies that have looked at OCTs with a particular thickness, say 400 microns, just to pull a number. You can have a patient with a 400-micron thickness that's 20-20, 20-25, but you can also have that same patient at 20-80. And so the OCT is an important sort of surrogate and it's a very good way of determining when the retina is starting to leak again, but the correlation between the OCT and the visual acuity is imperfect at best.
DR. GOODMAN: Thank you. So, Dr. McDonough, what do you take from that interchange?
DR. MCDONOUGH: Well, it seems to me if you're thinking about outcomes that are important to patients, it's not clear to me that OCT is important. It is an important

diagnostic measure but it's not something that I think that to a patient would necessarily matter. I would think what would matter to them is their visual acuity.

As far as the first question, I think

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it would seem to me intuitive that improvements in visual acuity from one disease to another of equal magnitudes might have equal quality of life outcomes, but I guess that's a matter that needs to be proven because the diseases are different.

DR. GOODMAN: Understood. So, we see this from time to time. There are distinctions to be made among biomarkers, true surrogates for outcomes, clinically important outcomes and patient-reported outcomes, and your questions raise that distinction once again and is very helpful. Next is Ms. Massey, followed by Dr. Reddy.

MS. MASSEY: Thank you. My questions are also related to quality of life and I have two questions. One of them is related to what you mentioned, is the minimal clinical significant change in a quality of outcome measurement, does the literature describe that, are there some standards to that? I know that there's reference to these studies saying they're statistically significant, but sometimes some of these measures actually have done some research and can show if you have a

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change of this magnitude, regardless of whether or not you start with low vision, high vision, whatever your vision is, but that amount of change is considered clinically significant. Does anyone know if any of that has been done?

DR. GOODMAN: So in part this addresses clinical versus statistical. This is Dr. Dryden.

DR. DRYDEN: There's a rule of thumb, so there isn't any evidence that applies to the tools that we looked at in our studies, but the rule of thumb is that a .25 of the standard deviation may translate into a clinically meaningful difference. So for example, if the change in the VFQ-25 is 4.4 with a standard deviation of 8, .5 of the 8 is 4, so we would say that there is a clinically significant difference in that change.

DR. GOODMAN: Thank you, Dr. Dryden. So you said .25 of a standard deviation.

DR. DRYDEN: .5.

DR. GOODMAN: .5 of a standard

deviation, thank you.
MS. MASSEY: Actually, I have another question for you. In your look at the tools
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that were out there, you mentioned that there were two that were being developed specific to the disease but have not yet been published or used. There was one other tool that I found in the literature, and I didn't know if it wasn't included in yours because it didn't meet your criteria, and that tool was the assessment of disability related to vision, and it was a performance-based measure, It was developed and looked at in diabetic retinal neuropathy. Did you come across that tool, is there some reason that was excluded?
DR. GOODMAN: And this was Ms. Massey's follow-up question. Dr. Dryden.
DR. DRYDEN: Unless it has been used in a study that was looking at the effect of an intervention on a diabetic retinopathy or macular edema, it would not have met our inclusion criteria.
MS. MASSEY: Okay. So it could be a possible tool, it may just not have been in your criteria for inclusion?
DR. DRYDEN: Yes.
DR. GOODMAN: Thank you. I believe Dr. Bressler had a response to an earlier
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question. Dr. Bressler.
DR. BRESSLER: The NEI in conjunction with the FDA has had an endpoints meeting where they look at this very question about the translation of 15 or more letter loss with NEI VFQ changes in several disease, it's published in the Investigative Ophthalmological and Visual Sciences. In general it tends to be around four to seven letters, or four to seven points corresponds to about a 15-letter change. This is similar to the different approach that Dr. Dryden was using and we tend to think, then, across all the literature, that at least a five-point change is probably a clinically relevant change for a dichotomous outcome.
DR. GOODMAN: Thank you very much, Dr. Bressler. Next is Dr. Reddy.
DR. REDDY: This question pertains to the indirect meta-analysis. Was there any consideration of adjusting for what I hear from other panelists, some patient population differences when you conducted that, one of the recommendations in the internal guidance on how

to do indirect meta-analysis.

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DR. GOODMAN: This is Mr. Ollendorf.
MR. OLLENDORF: We actually considered several approaches for looking at this, including Bayesian frameworks evaluating mixed treatment comparisons with multiple adjustments for follow-up time points, for differences in baseline characteristics, et cetera. We had a great concern given this evidence network that I presented earlier and its thinness, about what sort of additional utility would be yielded by such analysis. I think it's something we would still consider in any open publications. We were also constrained by time. But again, I think the big take-home for us was that even after acknowledging, before a quantitative analysis, even after acknowledging heterogeneity of study populations in the starting point of some of these patients, we still saw remarkably consistent findings in terms of treatment effect across the studies, so that based on that we decided to take a more parsimonious and relatively transparent approach of doing these pairwise relatively simplistic indirect comparisons as a double check on what we were seeing just based on

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clinical judgment, so that's the approach we took.
DR. GOODMAN: Thank you. Dr. Reddy, does that address your question satisfactorily?
DR. REDDY: Yes, it does.
DR. GOODMAN: Thank you, Dr. Reddy. Dr. Phurrough is next.
DR. PHURROUGH: I would like to come back to the first selection criteria, and this is a bit for clinicians. Because we're talking about an area where there isn't an FDA-approved technology, we don't have FDA guidance of who gets treated and who doesn't. We have these various studies which have some differences in inclusion and exclusion criteria. We have outcomes that show differences based upon where treatment, where the patients, what the patient's status was when treatment began. So I guess my question is, based upon all the data, who should get treated and when? And then add for my benefit, not in terms of our questions, are you following that, or are patients getting treated at other particular times? And I guess the question involved in that is how do you determine if it's better at

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a lower level, when do you start assessing, so this is for any of you.
DR. GOODMAN: Let's start with Dr. Thompson, Dr. Ehrlich, and then Dr. Gonzalez. Dr. Thompson.
DR. THOMPSON: The treatment from a clinician's standpoint is typically when the visual acuity is decreased. One of the things that's a fine point that the panel may not understand is that clinically significant diabetic macular edema, per the ETDRS study, could be a 20-20 eye that had edema near the fovea, but not in the fovea, and those eyes still benefited from laser photocoagulation because it prevented them from losing vision loss, or losing vision later. In these studies, and I'm talking about the aflibercept, you know, the Genentech ranibizumab studies, the patients had to have center-involved edema and be around the 20-40 level with best vision that they allowed into the study.
And so from a clinician's standpoint applying results of these studies, I would like to start treating the patients when they're 20-40, 20-50, because I have a real chance of

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getting their vision back to 20-20, 20-25. If they come in with a visual acuity of 20-200 I might get a number of lines of visual acuity improvement, maybe 20-60, 20-70, but that won't matter as much to the patient as the patient that I saved earlier.
So I think as clinicians, we're trying to catch these patients earlier, trying to educate the referring ophthalmologists, optometrists, internists, to send these patients before they have severe vision loss.
DR. GOODMAN: Thank you, Dr. Thompson. Dr. Ehrlich and then Dr. Gonzalez.
DR. EHRLICH: I would just make a few points about this. First, all of the clinical studies are designed to be able to statistically detect differences in vision change, all right, so part of the reason that the patients are enrolled with 20-40 vision or worse is that they need to have enough room to improve so that you can determine if one treatment is better or worse than another.
So the other important point clinically is that, you know, when we look at patients who are 20-40 or worse, if we treat

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them with any of these anti-VEGF agents, it's not that a hundred percent of them come back to

you 20-20 or better than 20-40, so there is already a certain amount of potential irreversible vision loss once vision loss has occurred. So, you know, potentially it might be appropriate to treat some patients with better vision, but, you know, we haven't studied that yet. I think the DRCR network has the most inclusive vision range and that was only down to 20-30.

So whether it's appropriate to treat patients with clinically significant macular edema but without vision loss is speculative and we don't know, and it's probably worthy of further investigation. But I would just make the point that once you've already had vision loss, it's not necessarily 100 percent recoverable.

DR. GOODMAN: Thank you, Dr. Ehrlich. Dr. Gonzalez.

DR. GONZALEZ: I think most of the points have already been made and the important thing here is that yes, in our studies we did use center involvement, but we need to be

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careful because we have not had the opportunity to study what happens if you have edema right next to the fovea that's coming in, so I think one of the concepts that we've been using up to now, if it's visually threatening, if it's right up against the central vision, we do want to intervene, because as was pointed out earlier, if you wait until you lose vision, you may not have the same outcomes as if you intervene earlier.

DR. GOODMAN: Thank you. Dr. Phurrough again.

DR. PHURROUGH: If they don't have visual acuity changes, the question is, how are you identifying these patients? Are you screening every patient, are you doing OCTs? If they don't have visual change, then how are you selecting patients for treatment?

DR. GONZALEZ: Up to now what was happening is we have been using the ETDRS criteria in our practices, and if you recall, the data from the later treatments in the past, as was already mentioned, you were selecting these patients based on meeting what was called clinically significant macular edema, so in the

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studies we did in fact change that. The reason is that although we can have clinically significant macular edema, if it's not interfering with the central vision

and causing some visual impairment, we have an option of observing those patients, so we do follow them. If you think a patient needs treatment, obviously if you send them for treatment you think they're at high risk, then we have some follow-up protocols that we have been able to determine and be very successful that we don't lose those patients to follow-up, and treat them if they should become involved with central vision. But as the studies have shown, even if there is some edema there, we can use the anti-VEGF and have some improvement.

DR. GOODMAN: Thanks, Dr. Gonzalez. Dr. Gozansky is next.

DR. GOZANSKY: A quick question getting back to the health-related quality of life issues for Dr. Ehrlich. It looks like in RISE and RIDE we're seeing very quick changes in visual acuity that persist over the entire 24 months. However, when you look at the

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quality of life outcomes, you start seeing that the sham group also appears to be improving over time but we don't see any improvement in their visual acuity. Can you speak to what you think that reflects?

DR. GOODMAN: This is Dr. Ehrlich.

DR. EHRLICH: I can try. So, I think there's a couple of points. You know, vision was assessed at day seven, and then monthly. The VFQ-25 was only administered every six months or so, because it takes a while in the setting of a clinical study to administer, so these results are going to be somewhat delayed. You know, it's hard to know exactly why the patients in the control group start to show improvements.

Part of that is that some of the patients do have some improvements in vision, part of that is they're in a clinical trial so they may feel like, or they're actually doing a better job of looking after their diabetes, they have physicians looking after them every month, so all of those things may also contribute. And then also, you can see that there's a fairly wide standard deviation, so

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you know, the change you're seeing on average could actually just be a fluctuation of the comments.

DR. GOODMAN: Dr. Gozansky, what do you take from that?

DR. GOZANSKY: I guess, I mean I'm

somewhat concerned, so if I could sort of ask a follow-up question to Dr. Dryden. In the assessment, the technology assessment, you suggested that there was really just intermediate, or indeterminate, I'm sorry, responsiveness for both the VFQ-25 and 14, and I'm wondering if you could say why that was rated as such, and not actually showing that there was high quality evidence. Is it that evidence is lacking? Because I think this comes to the question of are these measures truly responsive to change.

DR. GOODMAN: Dr. Dryden.

DR. DRYDEN: I would have to go back to the studies that were used to make that assessment. I don't have that information at hand.

DR. GOODMAN: Okay.

DR. DRYDEN: As I recall, there was an

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X, or no, a question mark, which means that there were data, it's just that they weren't as clear.

DR. GOZANSKY: In reading the details it looks like there was only moderate changes in visual acuity and changes in these measures, and I wasn't sure if that was in fact the reason for the sort of indeterminate nature, but I think that also speaks, then, to the issue with RISE and RIDE where we're seeing increased visual acuity and stabilization, but then the health-related quality of life measure just doesn't track along with that, and I think that gets back to the question of what does this really mean for patients.

DR. GOODMAN: Any response at this point, Dr. Dryden, or do you want to add that to the list of homework that you've taken on?

DR. DRYDEN: I think that's a reasonable assumption, that the evidence isn't strong to make conclusions about the long-term, but I can certainly add that to my homework.

DR. GOODMAN: Thank you, Dr. Dryden, you're in for more than you bargained for. Dr. Ehrlich, on this point.

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DR. EHRLICH: I just have three quick additional points. First, at least in macular degeneration it's been published, as Dr. Bressler mentioned, that the VFQ is responsive to changes in wet AMD. Second, I think it's to a certain extent a question of statistical power. You know, the studies are designed and statistically powered around

visual acuity changes, and the statistical power and the standard deviations that affect those measures are sufficiently wider. And then third, again, just a reminder of the point that Dr. Bressler had made, is that typically in a clinical trial you are really dealing with the worst seeing eye, at least in RIDE and RISE, the majority of the eyes that were enrolled were the worst seeing eye, where the VFQ change may not be as pronounced as if you were treating both eyes.

DR. GOODMAN: Good, thank you, Dr. Ehrlich. Was Dr. Dubois next?

DR. DUBOIS: My question has to do with heterogeneity of response. You guys talked a bit about baseline severity as a predictor, so if you take all the covariates

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that you guys can work with, how much of the heterogeneity can you explain and how much remains that you can't explain, and why it's so difficult to tell the benefit at all.

DR. GOODMAN: Dr. Bressler looks like he's about to take a go at that question, again, with heterogeneity and effects, Dr. Bressler.

DR. BRESSLER: We attempted to look at all the baseline factors to see if one predicts a better outcome than the other, and the only thing we could find, again, was the baseline visual acuity. The only homogeneous effect was that almost no one loses vision now, so that's a great step forward. The fact that only 50 percent have substantial vision improvement is, putting aside where the starting visual acuity is, is probably a reflection of undetectable at this time damage to the retinal tissue that we can't yet dissect out on OCT or other parameters, so that we fail to know which eye might improve and which ones will just simply stay the same. Even in the ones that stayed the same, though, that was a benefit, because without treatment they had a greater loss, a

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greater chance of losing vision.

DR. GOODMAN: Thank you. Dr. Dubois.

DR. DUBOIS: But with the baseline severity, do you know what percentage of the variance you could explain?

DR. BRESSLER: No, I don't.

DR. GOODMAN: Dr. Dubois, what do you take from that, then, with regard to your questions?

DR. DUBOIS: That it's hard to predict

which patients are going to be the best responders and which are not, and although maybe they didn't get worse, the ones that didn't really respond are faced with adverse events. So again, if you can identify the subpopulation that would respond, that's great, they will accept the risks for that, but for the people who aren't likely to respond, they have to be very wary of the potential adverse effects, and at this point it seems like the science is such that we can't really predict who's who at this point, other than with baseline severity.

DR. GOODMAN: Thank you very much. Dr. Dubois, just to follow up, anticipating

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that one of our discussion questions is about gaps in current evidence, might you anticipate that would be an area that could use some further evidence?

DR. DUBOIS: From my standpoint, I think there are two things that I feel would be very helpful to know. One is the predictors and that is difficult, and maybe it will turn out to be genetic subtypes that might explain it, or maybe other pathophysiologic issues. The other one for me is not being a psychometrician, it is very difficult to say what five points means. I believe that more of a dichotomous representation of quality of life would be helpful. So for example, what percentage of people could drive that previously couldn't. Add to that the number of people who couldn't shop because they can't read the labels. Add to that the number of people who really can't read the newspaper and now can.

So I would actually want to ask that the future studies dichotomize things into sort of a composite index of things that truly matter, and to be able to say 10 percent of

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people flipped from not being able to, or if it's 50 percent or 80 percent, that would be extremely helpful.

DR. GOODMAN: Good, thanks for that thought, Dr. Dubois. Ms. Massey.

MS. MASSEY: I would like to add to that. I think what you're alluding to is what I am also trying to get at. We have really three different types of measures that can be used in this population. One of the things are, the majority of the measures that we have right now that are

looking at the effect of the disease itself, the assessment tools that we have for that, the second level of measure are the ones with the patient's perceptions about the quality of life measures, and those measures are very important, but they often come with some risk because they are the patient's perception. There's a third level of measure, which is a performance-based measure, which is what you're implying, is how well can this patient do that on a quantifiable level, some standard measurement, and we don't appear to have that right now in this field, so that's

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something maybe we can discuss later. And my question earlier was related to that, are there any measures out there that are performance-based measures?

DR. GOODMAN: Thank you, that's a very helpful point, Ms. Massey. Not to answer now, but to think about over lunch are the following two questions, and we will probably lead with these when we get back from lunch. One has to do with indirect comparisons. It would seem that thus far the comments from Mr. Ollendorf on indirect comparisons, you seem to be pretty confident in those at this point, and I heard some comments from Dr. Ehrlich that he is less confident in those indirect comparisons. Certainly the indirect comparisons loom large to us because of the absence of direct comparison data from RCTs among the anti-VEGFs. So one thing we're going to want to ask you to address after lunch is, starting with Dr. Ehrlich and then back to Mr. Ollendorf, is why you do or do not have confidence in those indirect comparisons, one

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thing to think about over lunch. Another thing to think about over lunch, and we will probably want to start with Dr. Frank, and I will want to know what Dr. Puklin's view is on this, is to return to this issue of the relevance of the clinical trial findings for AMD comparing anti-VEGFs to our considerations for DME. In other words, we want to hear a little bit more about how confident you are that the trial findings in those comparisons for the one indication are applicable to what we need to infer for diabetic macular edema. It's not clear to me, for example,

whether you would take in their entirety the AMD comparative findings from the trials and say those apply fully to DME at one end of the spectrum, or at the other end of the spectrum you would say look, the AMD findings are just absolutely irrelevant for making those comparisons with DME. We would like to hear where we are on that spectrum, so we will start with Dr. Frank and then, again, I would be very curious to hear what Dr. Puklin has to say to that.

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It's a few minutes before noon. Take my advice. It's a good idea if you're going to use the cafeteria to get there now as opposed to 10 or 15 minutes from now. So we're going to take advantage of the prompt responses of our participants thus far, take a break for lunch, and we'll see you at the top of the hour, one o'clock. Thank you very much. Very helpful this morning thus far.

(Recess.)

DR. GOODMAN: Welcome back, everyone. I'm glad everyone could make it back from lunch pretty much on time. There was a crowd down there and it seems most people got through it pretty well.

We're going to reconvene now and in so doing, we're going to finish up some general questions to presenters and then we will probably move into discussion of the questions themselves. So for the next I don't know how long, we're going to take some general questions from our panel as we did prior to lunch, and then when it seems like we're kind of topping out on that, we will move to the formal questions.

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And just to pick up on where we left off before lunch, I wanted to pose two questions. One has to do with the importance of the indirect comparisons. Harkening back to Mr. Ollendorf's slide 15 where he had the boxes and the arrows representing the trial comparisons and number of trials, it was obvious that there were no arrows between any of the anti-VEGFs with regard to direct comparisons, so as he pointed out, we need to look at indirect comparisons.

And it sounded as though there was a bit of a different perspective from, for example, Dr. Ehrlich and from Mr. Ollendorf on that, and I just want to briefly, not in great detail, revisit what your main points are

vis-a-vis the significance or how accepting we might be of those indirect comparisons. Dr. Ehrlich, would you mind starting, sir?

DR. EHRLICH: I guess I would just reemphasize what I had spoken to earlier this morning, which is that there is no level of direct comparative evidence, so we're faced with the need to go through essentially indirect treatment comparison, and the

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difficulty is that the studies that are available for this potential indirect comparison are also very different in scope, and with regard to a lot of the qualities that you would find important for a really robust indirect treatment comparison.

So again, you know, whether the study contained a sufficient number of patients with similar, you know, Medicare patients, whether or not the studies clearly documented how they randomized patients, what the inclusion-exclusion criteria was, what the safety findings were, and without doing all of those things, you increase potential bias into this type of comparison.

So I think it's, you know, given the evidence that's available, I think it's very reasonable to show, as was apparent from some those slides, what the treatment outcomes were for those different things, that clearly directionally all anti-VEGF drugs trend towards showing some degree of benefit in visual acuity outcomes, but there's no good evidence to understand how they compare one to the other in terms of efficacy or safety.

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So I think that the conclusion we can make from an ITC, especially when you don't have studies with sufficient depth and rigor to really be able to adjust for those differences, the conclusions that you can make are necessarily limited.

DR. GOODMAN: Thank you very much. We understand indirect isn't always as good as direct, so your points are well taken. Thank you. Mr. Ollendorf, you seemed to think that the studies comparing the respective anti-VEGFs to other treatments, that they were all pretty much consistent in the same direction and order of magnitude, and that helps to suggest to you that those indirect comparisons were reasonable to make. What else would you like to say about that?

MR. OLLENDORF: I think that when we

were considering the types of analyses we wanted to undertake with this body of evidence, the first thing we looked at was, and admittedly it's anecdotal, but the conversations we had with the three expert ophthalmologists that consulted with us, and essentially their opinion, relatively

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unanimous, was this.
So as we've heard from some of the other clinicians here, there was a feeling that Macugen was not as effective as the other anti-VEGF therapies and it was rarely used. They felt that, because Eylea only had one trial published in DME, that it was potentially too new to be fully evaluated.
And so the decision on what to use came down to Lucentis versus Avastin, with them, and, essentially from their standpoint, the feeling was we view these products from an effectiveness standpoint as very very similar. We feel that the evidence from wet AMD is applicable, and even more so the evidence in DME suggests that magnitude of effect is about the same, so the decision on what we use comes down to questions about, around risk and possibly questions around cost, and so that was kind of thought process we used when we then took our own look at the evidence.
And I think that we acknowledge a lot of what Dr. Ehrlich just said, that these studies do differ in terms of their scope, they differ in terms of the measures used, they

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differ in terms of the time points at which these measures were conducted. But despite all that, I harken back to the remarkable consistency if you look at Figures 6 and 7 in the report, or slide 15 on the slide deck, the remarkable consistency in that magnitude of effect.
So there potentially could be an argument made that because Eylea only has one trial associated with it, maybe that is too little evidence to make a judgment on, but with regard to the anti-VEGF therapies for which there was sufficient evidence, we felt that the findings of both the direct meta-analyses within each drug and the indirect comparisons were relatively telling.
DR. GOODMAN: As someone who conducts meta-analysis, presumably you would look at matters of heterogeneity and homogeneity when considering whether a meta-analysis should be

undertaken and how valid the findings are. What can we infer from what you've done regarding sufficient homogeneity?
MR. OLLENDORF: So, when making a decision to conduct an indirect comparison, as

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noted in some of the guidelines, including the EPC guidelines that Dr. Reddy mentioned, the first order of business is to make a clinical judgment on how similar the results appear, acknowledging issues of differences in study design. Conduct of tests for statistical heterogeneity can be informative, but primarily you make a decision to conduct an indirect comparison based on how similar the results look. So that's the approach that we took. And we tried to understand how heterogeneity contributed to our results by conducting our sensitivity analyses, and we included poor quality studies in one of those analyses, we included other control arms other than laser and sham in another one of those analyses, and we added both in in yet a third sensitivity analysis, and the results were consistent across all of those analyses.
DR. GOODMAN: Across all of them.
MR. OLLENDORF: All of them.
DR. GOODMAN: I just wanted to make sure, because, looking at your slide 15, the two anti-VEGFs did track pretty closely, but that could have been an artifact or due to some

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other factors, but you're telling us you examined those trials for the extent of heterogeneity, and it seemed to be consistent with the clinical opinions, that's interesting and useful information, thank you. Any other comments on this issue before we move to another issue? Dr. Sedrakyan, on this issue?
DR. SEDRAKYAN: On this issue, a point question. With the level of Level I evidence brought out, so I want to revisit that question here, because this really in the question here you have compared effectiveness in the same class of anti-VEGF agents. So I really would like to hear if there is any observational data that you looked into, because this might be very valid, unless clinicians tell us that there's a substantial confounding indication for using one VEGF agent versus the other, which I don't believe is the case based on your presentation.
MR. OLLENDORF: We did look at

observational data as well. We looked, in terms of effectiveness, at data that had long-term outcomes, because we felt that the

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RCTs were the best source of data on shorter-term outcomes. We found very little in the observational data sets on either effectiveness or effect on safety. Most of these studies were of Avastin, I believe one of them maybe was Macugen, but there was very little to add to our analysis.

DR. GOODMAN: Thank you. Any other points to be made on this particular question? Dr. Gonzalez, on this point, yes, sir, please approach the mic.

DR. GONZALEZ: You know, in terms of from a clinical standpoint, and I don't know, this might be important to you. You know, basically having had an opportunity to use all the drugs, you know, my observation and my perception is basically very similar to what Mr. Ollendorf has, and that is at least clinically, there doesn't seem to be a clinically perceptible difference between medications.

DR. GOODMAN: Thanks for that clinical perspective, Dr. Gonzalez. The next question that we kind of hinted at going after before the lunch break

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has to do with the applicability of the clinical trial findings comparing anti-VEGFs for AMD to the case of DME, which is on our plate right now, and we wanted some sense along the spectrum of they're entirely fully relevant and applicable on one end, to forget it, the AMD findings have nothing to do with the DME. So I was hoping, Dr. Frank, if you would come up and start that for us, that would be very helpful.

DR. FRANK: Of course the short and sweet answer, as you suggested, is they are different diseases, but both of them, and we've seen this already clinically, do respond, do evolve as part of their pathogenesis the elaboration of excessive amounts of the growth factor VEGF, and they both respond to anti-VEGF agents.

But clearly there are differences and I think this means, again, going back to indirect comparisons, an indirect comparison of for example, the results of the comparative trials for wet AMD are probably translatable to DME, but I wouldn't be so quick as to say

25 absolutely for sure unless you have done
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1 something further to test that hypothesis. That
2 is, a direct comparison for DME.
3 And the reason is, the pathogenesis
4 for the diseases is different, they develop in
5 different parts of the ocular and vascular
6 beds, and they respond in different ways. As
7 we were talking at lunch, if you don't inject
8 an anti-VEGF agent for the individual with a
9 choroidal neovascular membrane in wet AMD, that
10 patient is almost surely going to get worse
11 over a relatively short period of time. I don't
12 think I'm too far off, don't think I will get
13 too much disagreement if I say they're going to
14 get worse within less than a year, or even less
15 than that.
16 People can putter along with diabetic
17 macular edema, clinically significant macular
18 edema, without substantial loss of vision.
19 Some may have center-involved macular edema
20 and, as was said earlier in this conference,
21 quite good vision for quite some time, though
22 they may well get worse over a period of time,
23 and spontaneous recovery is small.
24 DR. GOODMAN: Dr. Frank, just to steer
25 back to a narrower point, and that is to the
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1 extent that we are missing evidence, that we
2 don't have evidence, head-to-head comparisons
3 of anti-VEGFs for DME, are we to find that the
4 AMD evidence is relevant or do we dismiss it
5 entirely, and/or are we looking for more
6 studies for head-to-head for DME, what do we
7 want here?
8 DR. FRANK: My personal bias is we're
9 looking for more studies. I would like to see
10 that direct head-to-head comparison.
11 DR. GOODMAN: But what we have for AMD
12 is not at all relevant, partially relevant,
13 perfectly relevant?
14 DR. FRANK: I would have to say
15 partially relevant.
16 DR. GOODMAN: Good, thank you. Yes,
17 Dr. Heseltine, on this. Dr. Frank, we're not
18 done with you yet.
19 DR. HESELTINE: So you've spoken
20 eloquently about the efficacy between, the
21 judgment we might make on efficacy between AMD
22 and, age-related macular degeneration. What
23 about the toxicities? Can we infer from the
24 toxicity studies that were done on AMD, can we
25 actually infer something about those toxicities
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for the purposes of DME analysis?
DR. FRANK: Now you're talking systemic versus ocular?
DR. HESELTINE: Systemic.
DR. FRANK: Well, this relates a little bit to an answer that I gave much earlier today, which is that although they are older patients, they are above the age of 60, there is much less likelihood of considerable systemic cardiovascular disease in AMD patients than there is in patients with macular edema, who very often will have renal and significant cardiovascular disease that may be the target of some unwanted adverse effect of an anti-VEGF drug, even with a small amount injected into the eye.
DR. HESELTINE: So on the Lewin scale of one to three, would you say no relevance, partial relevance or a lot of relevance?
DR. FRANK: I would have to fudge that and say partial relevance.
DR. GOODMAN: Okay, thank you. Dr. Puklin, we're interested in your view on the matter of AMD relevance to DME for the clinical trials of anti-VEGFs.

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DR. PUKLIN: Well, I don't know exactly what to say, because I think that the speakers have covered all of the clinical trials very adequately and the panel members have been asking all of the appropriate questions.
I would only say that they are a bit different in how they're approached. Before we had anti-VEGF medication, patients with macular degeneration all lost vision, and if they were treated with laser, which was the standard of care, the laser frequently made them worse, depending on where their macular degeneration on the vascular membrane was located. So laser treatment didn't make anybody better.
If they were subjected to a survey about the quality of their life, many of them would have said immediately after the laser treatment the vision was much worse, because the clinical trials at the time showed that over a 10-year period their vision would be better with the laser photocoagulation than if they had left it alone and had it not treated.
So when the anti-VEGF drugs came along, this was a situation in which patients

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had symptoms and the anti-VEGF drugs made them better, and many of them smiled and smile today

because they actually perceived such dramatic improvement with these injections. The question that has come up is that Avastin, which is a drug that was approved for use in terminal cancer originally by the FDA, was administered to patients who had bowel cancer and it was terminal, and it was another adjunctive therapy and it prolonged life approximately three or four months, perhaps less, and it had associated with it significant cardiovascular and cerebrovascular accidents. So it was a higher incidence of those unexpected events with systemic Avastin. The diabetic patients, and this has already been brought up by all of our speakers, the clinically significant macular edema, which was part of the ETDRS study, involved leakages and exudates, and vascular changes adjacent to the macula, but in a situation where the patient might not have known that they had something that was bothersome, and so consequently these people that were injected with Avastin or Lucentis, their perception

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might be that their vision hadn't improved, but we did treat these lesions with photocoagulation. For the patients who have macular edema, and as Dr. Frank pointed out, for patients who have neovascularization, the anti-VEGF drugs can cause an infiltration of the neovascularization into the macular edema. So I think based upon the macular degeneration study, I think it's perfectly logical to make the transition to diabetic maculopathy for the reasons that were expressed, but I think the issues of quality of life have to be refined a little bit better. The nature of these surveys seems to actually have some gaps in them, but I'm not an expert on quality of life surveys, but I have learned, you know, what they mean. So I think these are all relevant issues and I think that the treatment experience from macular degeneration does relate to diabetic maculopathy, but the issue that keeps coming up is the complications of the injections. So, the major complication of the injection is an infection, and we have been

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injecting medication into the eyes of patients for over two decades now. We started injecting in patients who had HIV disease and had cytomegaloviral retinitis but in the AIDS

population many of those people couldn't get systemic medication, so personally I injected loads of patients for a decade before the heart treatment came along, and one of the risks that was involved was getting an infection. Currently that's one of the major risks of intravitreal injections of all drugs, is the infections, and in the proper hand under proper septic guidelines, this should not occur.

DR. GOODMAN: So that applies to all injected drugs?

DR. PUKLIN: All injections, correct.

DR. GOODMAN: But your take on the relevance of the AMD comparative data is that they are at least partially relevant, it sounds?

DR. PUKLIN: I think they're partially relevant to DME, I think the benefits are great, and the risk level is quite low.

DR. GOODMAN: Okay, thank you. Other points on that issue? Yes, Dr. Bressler.

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DR. BRESSLER: I only want to highlight the partial relevance to consider from CATT relative to DME. The two things to consider are there was a greater systemic adverse event reported in the bevacizumab group than in the ranibizumab group in that trial, and the conclusion in the New England Journal article appropriately was this requires further study. So when we have a very important common debilitating disease like diabetic retinopathy, that's exactly why we want to compare them head to head, just to see, was that just a fluke or was that something that may be brought out more in diabetes.

The second thing was that bevacizumab when given as needed gave an inconclusive result in the non-inferiority comparison to ranibizumab in the CATT study comparing it to ranibizumab every four weeks. The inconclusive result means it might have been superior, it could have been equivalent, it could have been inferior. That worries us because we use these drugs not every four weeks in DME but we use them until resolution, and then we resume using them when it comes back. So there's doubt in

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our mind as to whether they work exactly the same, last exactly the same, and it's because it's an important disease when we had this doubt that we have decided to prioritize our funding and do a comparative effectiveness trial, because we have these gray areas in an

important disease.
DR. GOODMAN: So you are going to devote resources for a comparative effectiveness trial comparing anti-VEGFs, and in the meantime you are using the available data from the AMD studies?
DR. BRESSLER: In the meantime for DME we use the available studies both in AMD and in DME to say all of these appear to work, and we cannot conclude from the available evidence whether one leads to less injections, greater safety or better or equivalent visual acuity outcomes.
DR. GOODMAN: Thanks. All this discussion is relevant to at least questions four and five, so we want to make sure we got some of that in. Any questions in general for our speakers seeking clarification of points that they made or in pursuit of some of our

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questions? Dr. Reddy.
DR. REDDY: I had a question on the doses used in the CATT study between bevacizumab and ranibizumab, and the frequency, I was a little confused about that.
DR. BRESSLER: The CATT study used 1.25 milligram bevacizumab, Avastin, and that's the same dose we're going to use in the comparative effectiveness trial in DME. They used .5 milligrams of ranibizumab and that's the same dose we're going to use in the comparative effectiveness trial in DME. The frequency in CATT was two different approaches, either an as-needed approach based mainly on OCT evaluations for resolution anatomically, not for outcomes and visual acuity, versus every four weeks.
In the DME comparative effectiveness trial we're using only one regimen approach and that is the deferred laser approach, where you use it initially for four doses and then as needed based on whether it's improving, inject again, if it's stable or resolved, stop, resume if it begins to thicken or worsen again, and that would be the same regimen in all three

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drugs tested.
DR. GOODMAN: Dr. Steinbrook.
DR. STEINBROOK: This may be a small point, but there was some publicity within the last year about the compounding of bevacizumab and some problems introduced by the compounding of it. Can some people enlighten us as to where that stands, is that still an issue or

has that been solved?
DR. GOODMAN: Dr. Thompson.
DR. THOMPSON: Yes, there still are issues with the compounding pharmacies, and just to bring everybody up to speed, there was an outbreak in Florida, there were also outbreaks in two VAs, one in Nashville and the other in Los Angeles, and it appears that there were some compounding problems. There are rigorous standards that are supposed to be followed by the compounding pharmacies, but it appears that sometimes those standards are not followed by some of the technicians and there have been some isolated outbreaks as a result of that with endophthalmitis.
And one of the things that we're very vulnerable as ophthalmologists is that every

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time I inject Avastin in a patient, I'm depending that my compounding pharmacy made the Avastin really well, and if they didn't I could end up getting in big trouble, because in the Florida case there were multiple lawsuits. And that's not the purview of this committee, but the answer is the Avastin supply chain is clean when it leaves Genentech, but then it touches the compounding pharmacy and you don't have the same assurances about the quality, although there are rigorous standards that the compounding pharmacies tell us that they adhere to.
DR. GOODMAN: So, has anything been done since them to correct this on a systematic basis, guidelines, et cetera?
DR. THOMPSON: Well, the American Society of Retina Specialists has on their website a listing that is voluntary from compounding pharmacies stating that this is the criteria that they use to compound, and there are a set of criteria, and they are saying that we adhere to these criteria in compounding, so this is sort of a Good Housekeeping seal of approval type of thing, but we still depend

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that they're doing what they self-report that they're doing.
DR. GOODMAN: Understood. They're self-reporting. Dr. Heseltine.
DR. HESELTINE: I have one question, Dr. Thompson. Is there any product that's manufactured in a single dose?
DR. THOMPSON: Yes, the Lucentis and Eylea are manufactured as single dose ampules, not really an ampule, but a rubber stopper, and

you use it once and you throw it away, so those two are prepared in single dose containers.
DR. GOODMAN: Thank you. Let me go to something Dr. Bressler said in an earlier discussion about different dosing. I had a question about a threshold effect of when to use anti-VEGFs and maybe when not to use them, so whether it's from the network trials or other sources, this regards frequency of dosing. Are there any criteria or thresholds for discontinuing anti-VEGF treatments if initial treatments don't seem to work, or small series don't seem to work. I know we talked about when we would use them, but is there a threshold point at which we say well, we have

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tried them and we think we can withdraw them. Is there any information on that from the trials or other sources.
DR. BRESSLER: The only work that has been done is that the protocols were designed at least in the network, not in RIDE and RISE where it was every month, but in the network, where once you no longer had improvement over three doses, it was judged it's probably not going to improve further, and only resume if when you stopped. It happened to worsen again, so maybe it stabilized and it was stable because of the drug and if you stopped, you would resume.
However, based on the results of the trial, the network recommended in their paper that if this regimen is followed, you would tend to withhold treatment once you're no longer improving, maybe not based on one OCT, but perhaps based on two OCT evaluations.
DR. GOODMAN: Is that something for which, Dr. Bressler, you think more evidence would be helpful, or do you think we know the answer to the start or withdraw question?
DR. BRESSLER: It would be nice to

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have more evidence as to what we should do when it's no longer improving, so there are other trials being considered and different regimens to test that. All we have right now are the either every-month regimen or the based on OCT resume and stop depending on results.
DR. GOODMAN: So the rule of thumb, which may not be fully evidence-supported, is to try it three times, if you don't see improvement, withdraw. If withdrawal leads to further deterioration, perhaps resume.
DR. BRESSLER: That's a fair summary,

yes.
DR. GOODMAN: That's very helpful, thank you. Dr. Thompson, on this point?
DR. THOMPSON: A comment kind of related to that is that we truly don't know, because I think that a lot of very bright people like Dr. Bressler, you know, developed these guidelines for the DRCR network, but the pivotal randomized trials use monthly dosing in large part. And so we really don't know, when we extrapolate from the monthly dosing in randomized trials to some type of PRN treatment schedule, we really don't know if that's as

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good.
I think for diabetes it's not going to be as much of a problem for diabetic macular edema, but I'll tell you, it's a huge problem in macular degeneration because in those patients I'm not convinced that as-needed dosing really does work as well in spite of the CATT trials, and the CATT trial will report the two-year results very shortly.
But in macular degeneration, if the patient develops a recurrent leakage and you start treatment again, many times you don't get back the visual acuity. So I'm saying for diabetic macular edema it's possible if you get too lax about the treatment, you know, there's too many months between treatment, a patient misses a visit because they're hospitalized and the retina swells again to 500 microns and you start treating them again, you may not get back the same visual acuity that you would have had had you been able to treat the patient monthly, as was done in the Genentech and the trials with Regeneron for Eylea and for Lucentis?
DR. GOODMAN: Monthly forever, even if you don't see a response?

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DR. THOMPSON: That's how these trials were designed, and I think if you don't see a response at some point you may say maybe we have futility here and we shouldn't do anything further, but in somebody that I'm seeing who's responding to the treatment, at what point can you back off and treat them less often? And with the DRCR network they have a protocol that they adhere to that's somewhat complicated, and you back off a little bit each time, but at some point you may back off so much that the edema recurs, you start treating them and you don't get the vision back.
So we as a retina community need to

try to figure out better algorithms for just how much we can back off on the treatment without getting burned in a subset of patients who do develop recurring edema and do have decreased visual acuity when the edema recurs.
DR. GOODMAN: So a considered evidence-based judgment on backing off distinct from a further considered, evidence considered judgment about when you reach the point of futility and therefore withdraw?
DR. THOMPSON: I don't think we've

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reached that consensus yet in the retina community.
DR. GOODMAN: Have not.
DR. GOZANSKY: Could I just clarify? Is this treatment regimen uncertainty, are the guidelines really being driven completely by the OCT, OCT plus visual acuity? I mean, we've heard that the OCT and visual acuity do not track necessarily. Can I get a response to that?
DR. THOMPSON: Yes, and that's an excellent question, and they are based on the clinical assessment, and this is why we don't just have the patient come in and get an OCT and not bother to look at the patient, and just inject them or not inject them, so you have to look at the whole clinical picture.
I would say that the visual acuity and the OCT are the most useful things, the OCT is probably the more useful because you see early recurrent macular edema with the OCT that you can't pick up clinically that has not decreased the visual acuity yet, and that's the time you want to treat it, before the visual acuity starts declining again.

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DR. GOODMAN: Okay. Thank you. Dr. Sedrakyan and then Dr. Steinbrook.
DR. SEDRAKYAN: We keep going back to the evidence related to glucose management, blood pressure management and lipid management, so I'm not sure how good ophthalmologists are at managing these conditions.
DR. THOMPSON: They're terrible at managing these conditions and we don't manage them truthfully. We send them to their diabetologists.
DR. SEDRAKYAN: So in these trials, in your opinion, how well were these patients managed? I mean, if there were aggressive management for lipid control, for blood pressure control and glucose management, do you

think the benefits of VEGF therapy might have been less?
DR. THOMPSON: I think in the trials, these are real world situations, but the fact that these patients are in a trial indicate in general they're taking better care of themselves. So if you measure the average triglycerides of a patient that's in one of these randomized trials, it would probably be
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better on average than just the average diabetic patient with macular edema. So I think this is a subset, and I'm not aware of the literature specifically looking at how these anti-VEGF agents work in patients with an A1c of nine versus an A1c of six. But I can tell you my clinical experience is when patients get religion, so to speak, and they start taking care of themselves, often the macular edema improves whether or not they're getting anti-VEGF injections. So absolutely, management of blood pressure, lipids, triglyceride treatment, all those things are very important, and the better the patient takes care of themselves, the less retinopathy they're going to have, the less nephropathy, the less neuropathy they will have.
DR. GOODMAN: Okay, thank you. Dr. Ehrlich, did you have a point on this issue? Okay, briefly.
DR. EHRLICH: Just a couple of comments. First, at least in RIDE and RISE, the average A1c in the studies was 7.6 to 7.7, so the patients actually had relatively reasonable levels of glucose control, and it
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did stay fairly consistent during those two years of data that we have. We've run subgroup analyses looking at efficacy based on A1c of greater than 8 or less than 8, and they're certainly very comparable in terms of outcomes in either of the subgroups. But, you know, I think you're talking a little bit about different patient populations. Focusing on lipid control, glucose control and blood pressure control is for preventing worsening of retinopathy and now, you know, probably all diabetic patients with retinopathy should be doing those things. But the patients who have macular edema have already had the worsening that you're trying to prevent with those other metabolic control issues.
DR. GOODMAN: Good, thank you,

Dr. Ehrlich. Dr. Steinbrook.
DR. STEINBROOK: Just to follow up the earlier discussion with Dr. Thompson, this is what I'm hearing, and tell me if I'm hearing right or not. It seems like for some of these second level questions about how you use the drugs, how frequently you inject them, that

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there may be issues that you really need to study directly in diabetic macular edema and not extrapolate from another disease, because when we go back one level further it doesn't work, the two diseases, that there's more that you can share the information for.
DR. THOMPSON: Yes, there is the need for additional studies. The DRCR Network protocol is a very reasonable approach that's based on some data, but we really don't know whether a treat and extend protocol, which is what the DRCR network is doing. If you look good you can extend the visits between, or whether we should have something that says patients should get treated every two months, let's say, or every 2.5 months. We really don't know between those two different treatment protocols whether one is superior to the other.
DR. GOODMAN: Okay, thank you. Let's move to discussing our first question. Our first question is a discussion question, and you know that this one has to do with the outcomes of interest, so I just want to make sure that everybody has that preface.

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Right above where it says discussion question on our MedCAC questions it has a phrase, outcomes of interest, and let's take a look at the relationship between the different kinds of outcomes here. It says that CMS is most interested in meaningful changes to beneficiaries' visual function and most, and perhaps all of the items under 1, i.e. 1.a through 1.i, some of those deal with visual function.
But in any case, changes to beneficiaries' visual function that enable their independent accomplishment of routine daily activities, and that latter part of that sentence seems more to refer to things like health-related quality of life measures, but we're starting with these changes in beneficiaries' visual function, so that's kind of the context here.
You don't see under 1."a" through "i" any

HRQL measures, you don't see SF-36 or whether visual acuity can be taken that way. Visual acuity, excuse me, can be taken that way, it doesn't say explicitly that one. Oh, excuse me, b is the only quality of life measure, it's

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a disease-specific one?

DR. DRYDEN: No, it's a generic one, but the --

DR. GOODMAN: Yes, the VFQ is vision-specific, right. But just to clarify, none of these, "a" through "i", to be more clear, is a generic health-related quality of life index or measure but at least this one, b, is a disease-specific quality of life measure. Okay, good. Thanks for the clarification. So that's what we're looking at in 1.a through i. The purpose of our discussion now is to address the suitability of these measures, the suitability of these measures for assessing DME treatment-related health outcomes, benefits and harms, and we might also think of this a couple ways. One is, this is relevant to the subsequent questions insofar as the subsequent questions talk about impacts of interventions on some kind of endpoint or outcome, and which of these might be more or less relevant. This question is also useful to the extent that the MedCAC may want to, may identify gaps in evidence that need to be filled by clinical trials or other studies which might employ one

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or more of these measures, so this pertains to our, the discussion questions and the evidence we've got in hand. It also pertains to if we have any thoughts about evidence that might need to be generated in the future that might address some of these outcomes. So, sorry for the long preface there. Dr. Dubois.

DR. DUBOIS: Okay. I'm a little confused about what we're actually discussing, because if you look at the preamble it refers to beneficiary visual function, and then at the bottom it says treatment-related health outcomes, which is broader than just visual function. So if I was to look at just the first part, I would say well, I don't care about OCT because that's not patient function, but if I look at the thing at the bottom and say is it a relevant health outcome, I would say yes. So which do we address?

DR. GOODMAN: Part of our discussion will address that distinction. Dr. Phurrough,

can you fill in on that?
DR. PHURROUGH: My interpretation of that is that CMS is interested in changes to
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visual function that enable quality of life things to improve. So it's not, the first sentence is not necessarily saying we're interested in measuring changes of visual function, we're interested in changes in visual function that improve independent accomplishment of routine daily activities.
DR. GOODMAN: That's the meaning of that phrase, that enable.
DR. PHURROUGH: I think that includes in that sentence, my interpretation of that sentence included health-related quality of life outcomes.
My question on this particular question to this group is, I think what CMS is asking us to do is to tell them both within, particularly within clinical trials, what should be measured. Here's a list of "a" through "i", are these appropriate measures, and are there other things that ought to be mentioned. Dr. Thompson talked to this list particularly in his presentation, and outside this list.
And I think there's a separate question of, are there appropriate measures to
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be tracking in patients who are getting treated who may or may not be in a clinical trial. So, could you --
DR. GOODMAN: Before you do that, Dr. McDonough has a comment immediately, and then we'll go to our speakers. Dr. McDonough.
DR. MCDONOUGH: Actually, to elaborate on that point, are we focusing on health outcomes that matter to patients, is that what we're trying to discern, or, I think the other part of your question is whether there are measures that are important to management of patients but that may not be useful as sort of outcome measures in the clinical study.
DR. GOODMAN: That's a fair question, and you might be able to distinguish some of the items "a" through "i" to the latter as opposed to the former. I emphasize that CMS is most interested, as they say, in meaningful changes to beneficiaries' visual function, which sounds pretty patient-oriented to me anyway, that enable their independent accomplishment of routine daily activities, which strongly implies to me patient orientation, so I think

CMS really does care about the Medicare
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beneficiaries' experience.
Some or all of the items "a" through "i"
may be closer to patient-oriented or reported,
some may not be patient-oriented at all but may
be relevant for other purposes, and our
discussion can make those distinctions right
now.
Dr. McDonough, on that point?
DR. MCDONOUGH: So we're also supposed
to answer whether they're relevant?
DR. GOODMAN: Well, we care less about
DME.
DR. MCDONOUGH: Okay.
DR. GOODMAN: Dr. Heseltine.
DR. HESELTINE: I just wanted to
confirm that as an example, hemoglobin A1c is
inapparent to patients but it's used as an
outcome measure for management of diabetes and
is widely adopted by CMS for that purpose, so I
looked at this list and determined not only
those things that are directly connected to
patient observations with their visual acuity
but also the things that might lead to
progression or non-progression, and that's I
think the tough part of this question, because
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I haven't seen an enormous amount. I
understand that our perception is that OCT
actually correlates it absolutely, but that
might be because it's earlier.
DR. GOODMAN: Right. We use the term
biomarker, we use the term intermediate
endpoint, there are biomarkers that are useful
as intermediate endpoints, but they're not
predictive or prognostic of a health outcome.
We use the term surrogate, and I'll be
redundant and say true surrogate, but a
surrogate endpoint is one that is demonstrated
as highly associated or correlated with a
health outcome of interest, and HDMC has kind
of waxed and waned so far as the confidence of
surrogacy. Dr. Puklin.
DR. PUKLIN: I just wanted to ask a
question here. I don't think we actually
discussed the issue of the Amsler grid as a
test that typically is employed with patients
with macular edema, but the reason I raise this
question is because I was a member of the panel
in 2005 when we discussed age-related macular
degeneration, and unless I'm wrong, the
technology assessment that was produced by I
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think the Duke group found that the Amsler grid was the most unreliable clinical test for macular degeneration.

DR. GOODMAN: That may have been on the table and discussed at the time. It still doesn't mean that we can't address it as appropriate here. So your view on this is certainly accepted, that is part of our discussion.

DR. PUKLIN: I didn't think there was a great deal of information, and we haven't discussed it with regard to the Amsler grid.

DR. GOODMAN: That may be correct, yes. Dr. Phurrough.

DR. PHURROUGH: Which is, I think what we're attempting to get now is what are our expert opinions on these particular tests, are they valuable both in a clinical setting and in a research setting in evaluating DME versus AMD, and are there others that are on the list.

DR. GOODMAN: Yes, exactly, and do know that items a through i is kind of a mixture of things that are tests of things that are outcomes and endpoints. The test often is known to be conducted for the purpose of

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assessing a particular intermediate endpoint, for example. So we're interested in feedback on these, and I see Dr. Thompson and Dr. Bressler for starters. Dr. Thompson and then Dr. Bressler.

DR. THOMPSON: Well, if I had to rank these in terms of importance, I would say the visual acuity is number one, the most important, and I would say that for diabetic macular edema, we're talking about ocular coherence tomography as the second most important, and the other things are less important.

I would say that Amsler grid and visual field are really not at all important for this particular disease process. There are other reasons, you know, that you might do it, but it's not going to help you with the diabetic macular edema.

The dilated eye exam I would say is third most important, because you learn other things. If the patient has a new vitreous hemorrhage that develops that looks like diabetic retinopathy, that's important to know, and you give them a panretinal laser, so that's

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important, and I would say that's probably third, and these are my clinical

interpretations. And closely along with that is the grade of diabetic retinopathy because when you do the fundus examination internally you're grading it as moderate, nonproliferative, proliferative, whatever. And then I would say the fluorescein angiography is next on my list because it's useful for finding that small subset of patients that have macular nonperfusion, it also confirms if they're leaking. If you believe they have diabetic macular edema and you don't see any leakage on the fluorescein angiogram, then if you see a very thick OCT with lots of fluid and yet the angiogram is not showing leakage, then you have this disconnect that you need to reconcile. And I would say that the -- I think that covers everything. Oh, fundus photographs without angiography are less important.

DR. GOODMAN: I don't think you addressed the disease, the condition-specific health-related quality of life issues, the VFQ-25.

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DR. THOMPSON: We don't do that to a practical extent. You know, I'm thinking of what I do in my office, and this is very important from a research standpoint and helps to validate what vision acuity is doing, but I'm not going to do VFQ-25s routinely on my patients coming into the office. Hopefully, if all is right in the world, the visual acuity and VFQ-25 should correlate some.

DR. GOODMAN: How about VFQ-25 in clinical trials?

DR. THOMPSON: Yes, very important for clinical trials.

DR. GOODMAN: Okay, thank you. Dr. McDonough, and then we'll go to Dr. Bressler.

DR. MCDONOUGH: Just as a follow-up to that, I think the question you're answering is whether the tests are important in clinical practice, but what about clinical endpoints? How would you interpret a study that showed improvement in OCT without overall improvements in visual acuity, versus, you know, where they're discordant? So I'm just wondering, what is the importance in terms of the clinical endpoint of OCT or what you see in the dilated

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eye exam, as far as the study endpoint.

DR. THOMPSON: Well, the OCT is a good marker for determining when the edema is recurring but at the study, if the clinical

study of the new drug showed just improvement on the OCT, but no improvement in visual acuity, I think that the retinal community would say does this drug really matter, because it's not improving visual acuity or it's not stabilizing visual acuity.

But the OCT in clinical practice is extremely important because it is like our Doppler radar of seeing what's on the horizon, you know, is the edema recurring or not, and so we use that to determine, does this patient need a treatment today or can we say come back next month.

DR. GOODMAN: Okay, thank you. Dr. Bressler, on this, and then we'll return to Dr. Steinbrook.

DR. BRESSLER: In clinical practice if you are going to just treat every four weeks indefinitely then you don't need the OCT except initially to confirm that indeed the retina has thickened. Almost every physician treating

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diabetic macular edema does not treat every four weeks indefinitely. Rather, they treat until the OCT appears to have resolved, and then they withhold and then they follow the OCT to see if it's thickened.

In order to see improvement, real improvement beyond just the measurement error alone is a 10 percent or greater change on the OCT, for example, going from 400 microns to 360 or less microns. We cannot detect that with our eyes with any sort of reliability, so we need the OCT if we are going to use a treatment strategy that does not involve every-four-week indefinite treatment, which is the typical approach.

We need visual acuity because we do use that to determine is there improvement, but visual acuity is not as objective as OCT. So we put greater weight on the OCT. But someone who has substantial vision improvement with very little change on OCT, we might think is still improving in some way and consider an additional treatment, so those two really are indispensable from a clinical practice point of view.

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They're indispensable from a clinical trial point of view because visual acuity is our endpoint that does have very strong correlation with how a person functions. Now it may not match the NEI VFQ because we have to deal with both eyes, and so you have to look at

the subgroup where it was the better seeing eye that you were treating, and then we see a very tight correlation with the visual acuity. But we want that so that we can share with our physician colleagues, our policy-makers, what this 10-letter or more improvement of 10-letter or more loss means. So we need the NEI VFQ only for clinical trials, but it's important to validate the visual acuity outcome.

And finally, the fluorescein angiography is one of those things that there are rare circumstances that we do need it in certain cases, and I won't go into the details now, but it's needed to differentiate if there's tremendous nonperfusion to the macula explaining the vision, where you might say I shouldn't be treating this edema, there's something else going on, so occasionally we need that. And the fundus photographs are a

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helpful management to, is the person progressing to proliferative retinopathy, a different complication, but needed to know if that's happening, that might influence your whole decision of how closely you're following them or treating their edema.

So it gets to the complexity of just the one complication of DME itself versus the multiple, so I don't know if that's helpful, but that is our approach.

DR. GOODMAN: Thank you, that is very helpful. Other comments from clinicians or researchers, people that design clinical trials with regard to these? Dr. Frank, did you have a point, sir?

DR. FRANK: First, I want to endorse Dr. Bressler's very elegant statement. The only modification I would make is from the clinical trial point of view, not from the clinical management point of view, how frequently one might want to do a VFQ assessment. Certainly you wouldn't do it at every single visit, but at least perhaps three or four times a year in patients who are being followed as they usually are in these kinds of

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trials, monthly.

DR. GOODMAN: Dr. Frank, that's helpful, but for OCT, ocular coherence tomography, that is useful as an initial basically biomarker clinically as well as for clinical trials?

DR. FRANK: Both, although it should be emphasized, and I, Dr. Bressler and others

would certainly agree, that in no clinical trial that I can think of was OCT measurement the primary endpoint because the correlation with visual acuity, although approximate, is so poor.
DR. GOODMAN: Yes, and that's an excellent example of a surrogate, something that may not be a surrogate. It's certainly a biomarker. It's apparently clinically important, but it may not be a surrogate for a healthcare outcome.
DR. FRANK: I would, however, emphasize that there are other things to look at besides macular thickness on OCT and hopefully as the technology improves we will be able to look at this better and to state things like the status of the photoreceptor layer,

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which must be very important in visual acuity, where macular thickness itself is not.
DR. GOODMAN: Got it. Great biomarker, not a patient-reported outcome. Ms. Massey.
MS. MASSEY: I would like to follow up on your point about the surrogates. When we go back to look at our charges, again, it says the visual function that enables an independent ability for self-care, and we don't have that strong a correlation between the OCT and the visual acuity, and then we make the jump to function. And so for me, I'm still, I'm having a hard time figuring out how with the measures we have here, we're going to be able to say it makes a difference on the visual functions that improve the independence of these patients, with the limited tools that we have.
DR. GOODMAN: That's a point well made, Ms. Massey. Dr. Phurrough, what would you say to that?
DR. PHURROUGH: I believe I heard it a bit differently, that we believe that visual acuity is correlated with these larger measures of function and that as the visual acuity changes one way or the other, then that

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correlates to patient function, accomplishment of routine daily activities. Is that what you were trying to say?
DR. GOODMAN: Yes, four of our invited speakers are nodding their heads, and Dr. Bressler is approaching the mic.
DR. BRESSLER: We don't have the information published yet, but as an example, at an upcoming scientific meeting looking at the RIDE and RISE trial, we looked at the sham

group to see who was driving that wasn't driving at the beginning of the trial and that was about four percent, and then we looked at the ranibizumab arm and that's about 20, 21 percent. Why isn't it 50 percent? Well, because many of the people were still able to drive because of their first eye, but it's an example where we have seen that function, not just patient-reported function, but actual function is there.

But I would agree, it's also limited, we don't have good tests of, the patient says they're reading better, but do you really test them and are they reading better, that is definitely limited. But so far, there seems to

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be good tracking in everything we've looked at. If the visual acuity improves, then their function improves. It's why the ophthalmologists are very comfortable, the FDA is very comfortable using visual acuity as the outcome, because of this historical approach of matching with function when it's the better seeing eye, but we only are scratching the surface in terms of proving the direct links that you mentioned, absolutely.

DR. GOODMAN: Thanks, Dr. Bressler. Ms. Massey, thank you very much. It sounds as though visual acuity does not equal patient functioning, but it may track pretty closely is what it sounds like, but that's a very important distinction that you made.

I wonder if we could ask our vice chair, Dr. Phurrough, since he led this off, if he might, in order of 1."a" through "i", just tell us what he thinks the high points are of what we've heard about the utility of these items. Just a few words, starting with visual acuity, what's kind of the synthesis of what we've heard, Dr. Phurrough?

DR. PHURROUGH: I think what we've

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heard is that for clinical trials, the key aspects, the key measures on this particular list are visual acuity, VFQ-25 and OCT, that other things may be used, but these are key functions that need to be measured and assessed in a clinical trial.

In practice, visual acuity and OCT are the clear measures that seem to make a difference. The dilated eye exam and the grading of retinopathy are important things to track in DME since that may be the entrance to the next step and may change treatment as the

disease progresses from just DME to more of a normal retinopathy. Cliff, that's my take on what I heard.

DR. GOODMAN: My notes track to that pretty well. I would add, it sounded as though Amsler grid and visual fields, items "e" and "h" respectively, are not that much in demand for either purpose.

DR. PHURROUGH: One other question I would have is that we focused on this list. Are there things not on this list that should be on the list, particularly perhaps the question of Dr. Dryden, is the VFQ-25 the test

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to use when you're looking at health-related quality of life, or should there be others on this list that aren't, based upon your analysis?

DR. GOODMAN: And to this point, as you said, Dr. Phurrough, the VFQ sounds like it's useful for clinical trials, perhaps less so for clinical management, but let's proceed now to the question to Dr. Dryden.

DR. DRYDEN: Based on the work that we did, I believe that the VFQ 25-is a reasonable condition-specific tool to use. You wouldn't, even in a trial setting you wouldn't necessarily use a generic health-related quality of life tool unless you wanted to compare the results of your study with the results of health-related quality of life in the general population. It's not going to inform health-related quality of life for patients with diabetic macular edema. The other tools that are under development, I think it's too premature to say yea or nay, they are the ones to include.

DR. GOODMAN: Okay, very helpful. Thank you again for making the distinction

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between the generic health-related quality of life outcome and a condition-specific one, thank you. On this point, Dr. Ehrlich?

DR. EHRLICH: Just in terms of areas of future research, I think that there is some interest in developing additional screening tools and technologies. This may be more a topic for the 2020 MedCAC, but things like macular FNG, which is sort of flicker sensitivity, it's a direct measurement of retinal sensitivity, but it's applied to patients to get further use from glaucoma, and might be looked at for retinopathy and macular edema.

DR. GOODMAN: Because it would tell us what?
DR. EHRLICH: It potentially could identify which of the patients among your patients with diabetes or earlier retinopathy were starting to see subclinical changes that could identify them potentially before they would need any of these more invasive treatments.
DR. GOODMAN: So potential early detection.

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DR. EHRLICH: Yeah, exactly, and then in terms of other patient-reported outcomes, I'm not an expert on this, but I know there's also some work in addition to the retinal TOL which is still being validated, like item banking, there's some work with sort of more computer-based adaptive testing for measuring visual function.
DR. GOODMAN: What banking?
DR. EHRLICH: Item banking, like a computer-based banking.
DR. GOODMAN: Any final points on question one before we move on from this discussion question? Final concise points, Dr. Gozansky, and then Dr. McDonough and Dr. Steinbrook.
DR. GOZANSKY: I would just quickly say that the other thing I heard was that I think when we come up with these items, what we really want that they are necessary for initial diagnosis, so that's sort of what I was hearing as far as angiography as well as the level of diabetic retinopathy, so we really need that to classify folks at baseline and make sure we have the right measurements to get people into

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trials and to stratify them.
And I would also suggest that perhaps a general health-related quality of life measure where it may not be an outcome, may be an important baseline stratification for folks and have something to do with that issue of whether or not people are going to show an improvement or not depending on whether they are going to drive or not drive, fall or not fall, et cetera.
DR. GOODMAN: I see no one disagreeing with your statement, thank you. Dr. McDonough.
DR. MCDONOUGH: A few panelists brought up the idea of performance measures, and I think we're left with that, in addition to patient-reported outcomes and quality of

life, that we actually have performance measures included in the clinical trials.
DR. GOODMAN: Who brought that up originally? Oh, Ms. Massey did, yes.
MS. MASSEY: I would think the item bank could easily be applied to obtain performance-based measures, if those would test the patient's ability to perform a certain function that requires a visual function, but

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it's based upon some quantifiable data and would be validated, so I would encourage the field to take a look at developing something along that line that is quick, that can be done easily in a clinical setting and in a research setting that, again, gives you the patient's outcome measure, but the difference is not the patient's perception but the actual ability of the patient to do that.
DR. GOODMAN: Good, thanks for the clarification. Dr. Steinbrook.
DR. STEINBROOK: I heard visual acuity really being more than two words, you have to remember there are two eyes and they each have a visual acuity, which has implications, and also, what is the number, because I clearly hear that that's going to have implications for prognosis when you tend to start, so I think that's something where two words really don't emphasize the value of visual acuity here.
DR. GOODMAN: Point well made. I think that captures all of our comments. Dr. Dubois, still on question one?
DR. DUBOIS: Yeah, following on what Dr. Steinbrook said, with respect to the

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functional measures, this issue of whether it's the better eye or the worse eye, it seems to me one of the reason why it's not as good a measure is that in some cases that may be the worse eye, in which case it doesn't really matter because you've got one good eye. But in the future studies if its utility can be directly related, are we looking at the best eye, and is it at the meat of the curve where changes actually will make a functional difference?
DR. GOODMAN: That's a good point and reflects the point made earlier that it's not just the delta, it's a starting point, where are you on the scale. Okay. Dr. Thompson, a closing comment on question one.
DR. THOMPSON: It's very important to

remember as an ophthalmologist that the good eye today may be the bad eye tomorrow, and this is why we as ophthalmologists try really really hard to save vision in both eyes, because bad things happen to the good eye in the future.

DR. GOODMAN: Thank you, point very well made.

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Panel, any final comments on question one, the discussion question? This is very helpful because we talked about these outcomes insofar as they're used in clinical management, clinical trials and other aspects, and I hope we've provided sufficient grist for CMS.

Let's move to our first voting question, and that is question two. I see Ms. Ellis is coming around with the high-tech gizmos, and CMS has actually given us orange ribbons, presumably so we won't lose these.

And so what we're going to do with these questions now, similar to what we just did. We're going to ask a few of our speakers to, if they want to provide a quick synopsis of the evidence that they discerned, particularly I would say in the eyes of the technology assessment, to just kind of give us a quick wrap-up of what they saw, and then we'll have further panel discussion, and if any of our speakers want to chime in direct and to the point on the question at hand, that would be welcome as well.

Dr. Phurrough, did you have a comment?

DR. PHURROUGH: Yes. As you're asked

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to make these comments, I think the information that we need to be providing back to CMS in all of these questions is focused on DME management. As I have listened today and read, we're not talking about all DME management, we're talking about DME management in patients who have visual acuities that are not normal, and I think we talked about 20-40 or worse. So I think we need to have, as we comment on this question, I think we need to understand that our recommendation back to CMS is not all management of DME. It's management of DME in these patients who have visual acuity that is not normal.

DR. GOODMAN: That's an important point of clarification. Dr. Bressler, would you mind commenting on that, and perhaps Dr. Frank.

DR. BRESSLER: At this point we like to use the term visual impairment rather than a

direct cutoff. 20-32 in someone might be their first impairment, but someone else with 20-25 vision might be impaired because their normal vision might have been 20-15 or 20-12. Dr. Chambers pointed out to me that half the

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population is really better than 20-20, that's just the mean for the group. So we tend to think in terms of using anti-VEGFs when there is vision impairment and the edema involves the center of the macula.

DR. GOODMAN: So you don't want to go any further insofar as defining visual impairment?

DR. BRESSLER: Defining it as an absolute cutoff of 20-32 or 20-40, or 20-25, I think would be dangerous, because the reliability of those measurements within a clinic, not within a clinical trial but within a clinic, can be variable to plus or minus five letters, and I would be reluctant to say that there's an absolute cutoff, so I would think we are far better off saying when there is vision impairment from diabetic macular edema.

DR. PHURROUGH: Can you define what's visual impairment?

DR. BRESSLER: It's a loss of the person's normal central vision that you believe is due to diabetic macular edema.

DR. PHURROUGH: And loss is defined as?

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DR. BRESSLER: From where their best vision was.

DR. PHURROUGH: Not correctable.

DR. BRESSLER: That's not correctable with glasses, it's from some other problem, it's due to the macular edema.

DR. GOODMAN: And this is judged by what instrument?

DR. BRESSLER: Well, it is judged by the visual acuity measurement and your history with the patient. So someone who is 20-25 and says, and they have been 20-20 their whole life, and has a large amount of edema, and tells you over the last four months their vision has gone downhill, is different from someone who's 20-25, maybe they were a little tired today, maybe they had a lot of allergy as spring approached and a little mucus in their eye, and they said oh, I probably didn't measure that quite as well. Same visual acuity, different circumstance.

DR. GOODMAN: Thank you. So

Dr. Phurrough, just to help us as we proceed with these questions, when any question refers to DME management, would it satisfy you if we

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were to imply that whenever we said DME management we were referring to people with vision impairment as determined by visual acuity and personal history?

DR. PHURROUGH: I think it's important for us to understand that, so we are not suggesting that there is adequate evidence to determine anti-VEGF treatments in people with DME who don't have visual impairment.

DR. GOODMAN: So it's visual impairment as determined by some combination of a falloff in visual acuity and their history. That's a fair rendering of your concern and your point?

DR. PHURROUGH: That's fine.

DR. GOODMAN: Thank you. Dr. Heseltine.

DR. HESELTINE: To follow up on your statement, I recognize that OCT is perceived as being very specific, but is it absolutely required for every case? Because it's important that we understand that too.

DR. GOODMAN: What do you think, Dr. Bressler?

DR. BRESSLER: It is specific in many

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cases, first of all, but there are cases that are thickened, and then when you look in the eyes, so looking in the eye is also critical besides visual acuity and OCT. When you look in the eye, you might see some other cause of thickening, for example traction of the vitreous gel on the macula. So if it is indeed thickened, you have to confirm that there are other factors looking in the eye that it is from diabetic macular edema. That being said, you could look at an eye and say that's diabetic macular edema and it's thickened without having the OCT. However, in order to determine at follow-up that there's improvement worth continuing anti-VEGF therapy, you would need the objective measurement of the OCT. Our eyes are not good enough. So even if I see it's there, so I know that person has DME without the OCT, I still obtain it so I can determine if there's improvement.

DR. GOODMAN: So when we're talking about DME management, talking about DME, you've looked into the eye using perhaps OCT --

DR. BRESSLER: Or ophthalmoscopy.

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DR. GOODMAN: Or ophthalmoscopy. You have found DME, that's not sufficient, because you're also looking for vision impairment as determined by some combination of a drop-off in visual acuity and a patient's history.

DR. BRESSLER: That's correct.

DR. HESELTINE: I'm really speaking to the sensitivity of OCT. So in other words, I think I'm hearing you say unless, if you do OCT and unless there's edema on OCT, it cannot be DME; is that correct?

DR. BRESSLER: That's correct, assuming technically the OCT was performed adequately, yes. If it looked thickened to my eye and the OCT was flat, I'd think my eye was off.

DR. GOODMAN: That's very helpful, and as Ms. Massey and others established earlier, an OCT that might look like a problem is not necessarily evidence of a drop-off in visual acuity. So I think -- thank you very much, Dr. Phurrough, that helps us a lot. So when we see that phrase DME management, we just elaborated on what is meant by that phrase.

I will read the question and then I'm

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going to ask Mr. Ollendorf, if you don't mind, if you would come give us a synopsis on what you found for this. This is a how confident are you question. Question two pairs with question three, by the way. Question two is going to ask what we think about how good the evidence is. It doesn't ask us what the evidence tells us. It's just asking how adequate is the evidence to determine something. The next question will be how adequate is the evidence to conclude something. That's the difference. So two and three go together.

Two says, how confident are you that there is adequate evidence to determine whether or not DME management, we just discussed that, using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without intravitreal targeted anti-VEGF treatments? So we're comparing the anti-VEGFs to something else insofar as treating or managing this condition.

Mr. Ollendorf, would you comment on what your TA might have discerned pertaining to that question?

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MR. OLLENDORF: Pertaining to this question, with the availability of 15 RCTs, 11 of which were fair or good quality across all of the anti-VEGFs, our evidence review concluded that there was adequate evidence to be able to make a determination as to whether anti-VEGF treatment improves.
DR. GOODMAN: That there was adequate evidence.
MR. OLLENDORF: That there was adequate evidence.
DR. GOODMAN: Okay. Does any other speaker care to elaborate on Mr. Ollendorf's observation? I see a couple heads nodding in the affirmative of agreement. Panel, any further discussion on question two, the adequacy of the evidence to make this determination? Yes, Dr. McDonough.
DR. MCDONOUGH: Yeah, just kind of remind me, did all of the anti-VEGFs have quality of life data in their trials?
DR. GOODMAN: This is Mr. Ollendorf.
MR. OLLENDORF: Very few of them did in fact, so there were only two RCTs out of the 15 that measured quality of life, one of

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Lucentis, one of Macugen, in our review.
DR. GOODMAN: Very good. And you'll recall that we had, in question one, discussed a range of outcomes and types and the role of utility and so forth for clinical purposes and research purposes. Any other points to be made on question two? It sounds like we're poised to vote on it. Any other points?
Okay. How confident are you, then, that there is adequate evidence to determine whether or not DME management using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without that, without targeted anti-VEGF treatment? Low, intermediate or high, a Likert scale of one to five, your confidence in the adequacy of evidence, not what you conclude from it but the adequacy to make a determination, one to five.
Do we have defective software or hardware, Ms. Ellis, perhaps.
MS. ELLIS: No, if everyone could just press their buttons one more time.
(The panel voted and votes were recorded by staff.)

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DR. GOODMAN: Very good. Thank you.
I see a mean that is greater than 2.5, 4.1, so

that means we've got, this group has pretty high confidence in the adequacy of evidence to make that determination. Any follow-up points on this? I think we've all registered our vote and our comments earlier.
Okay. Now we need to do, we have to go down the row, Ms. Ellis, starting with Dr. Phurrough, we've got to announce our votes.
DR. PHURROUGH: Four.
DR. GOZANSKY: Four.
DR. HESELTINE: Peter Heseltine, five.
DR. LEVINE: Four.
MS. MASSEY: Five.
DR. GOODMAN: Wait, I'll stop you right there. Ms. Ellis, do we need people's names?
MS. ELLIS: Yes please.
DR. MCDONOUGH: Robert McDonough, four.
DR. GOODMAN: Thank you.
DR. REDDY: Prabashni Reddy, four.
DR. SEDRAKYAN: Sedrakyan, four.
DR. STEINBROOK: Steinbrook, five.

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DR. DUBOIS: Dubois, four.
DR. PUKLIN: Puklin, five.
DR. GOODMAN: Thank you. Do you think we captured all that, Ms. Ellis? Between the transcript and the camera, we probably know who said what, and given that we went in order. Thank you, and thank you for the reminder.
That was question two. Let's go to its pair now, or I should say its fraternal twin, question three. So we are going to ask question three, because it asks when the result of question two was at least 2.5, and indeed it was. Now we're going to move. The question is almost the same except now it's adequate evidence to conclude, and in a moment we'll ask Mr. Ollendorf to come up and make any additional comments, and others as appropriate.
So if the result of question two is at least intermediate, that is a mean of 2.5 or greater, it was, how confident are you that there is adequate evidence to conclude that DME management using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without intravitreal targeted anti-VEGF treatment?

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Again, we're going to vote on a scale of one to five where one is low and five is high. Mr. Ollendorf, what does the evidence tell us, do you suppose?

MR. OLLENDORF: The evidence tells us that based on the consistency of findings that we saw, primarily in terms of improvement in visual acuity as well as large improvements, ten-letter or more gains in visual acuity, that we would say with high confidence there is adequate evidence to conclude that DME management with anti-VEGF improves health outcomes relative to management without.
DR. GOODMAN: Thank you very much. Do any of our speakers have a cogent comment to make on this issue number three? Any panelists have anything further? Yes, Dr. McDonough.
DR. MCDONOUGH: Dan, do your conclusions differ for the different agents?
DR. GOODMAN: I'll point out that in a later question we probably will make that distinction, but Dr. Ollendorf, you may want to comment on that, since I think we're looking probably at a group effect here or a class effect, if you will.

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MR. OLLENDORF: Yes, my comment relative to this question is related to the class effect, so we can deal with the separate agents when we get to that question.
DR. GOODMAN: Thanks, Mr. Ollendorf. Any other points or questions by the panel on this before we vote? Any of our speakers have anything to add to this? Seeing none, let's go ahead and vote on question three. This is your confidence regarding adequacy of evidence to conclude that DME management using intravitreal targeted anti-VEGF improves patient health outcomes compared to DME management without those.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: The mean is 3.8, thank you very much. Dr. Phurrough, your score.
DR. PHURROUGH: Phurrough, four.
DR. GOZANSKY: Gozansky, three.
DR. HESELTINE: Heseltine, four.
DR. LEVINE: Levine, four.
MS. MASSEY: Massey, four.
DR. MCDONOUGH: McDonough, four.
DR. REDDY: Reddy, four.

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DR. SEDRAKYAN: Sedrakyan, three.
DR. STEINBROOK: Steinbrook, four.
DR. DUBOIS: Dubois, four.
DR. PUKLIN: Puklin, five.
DR. GOODMAN: Thank you very much. Before we proceed to question four, as CMS

asked us here, when you made this consideration and entered your vote, were there any particular thoughts you had regarding patient characteristics or treatment regimens, or any other factors that may have important effects on the degree of patient benefit or harm from these treatments. When you think about whether these things work or not versus the alternatives, is there anything about those characteristics or factors that would weigh more or less heavily on the findings, if there is a difference in outcomes? Dr. Puklin.

DR. PUKLIN: Well, I think that the speakers all touched upon significant alternatives of management that would go a long way with regard to preventing or reducing the severity of that macular edema which is what we're talking about, but it is not relevant to ophthalmology management, it has to do with

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tight glycemic control, weight loss, lipid control and all these features, and it can be beneficial to these patients.

DR. GOODMAN: Point well made, thank you. Any other considerations? If you don't mind, Dr. Dubois, I'll sort of ask you. You certainly talked about heterogeneity of treatment effects and so forth. Anything you discerned with regard to HTE to add to this question, or any other attributes of note?

DR. DUBOIS: Well, I think that's sort of collectively what we have all heard. Your baseline severity of deficit is certainly one of the predictors. It's not officially in this one, but part of the outcome can be dependent upon which drug you got, and I don't think we know the difference between and amongst them, so I think that's the second one.

And I think depending on which outcome measure you look at. It will differ depending on whether it's your good eye or your bad eye as to whether it translates into health-related quality of life. And then there is the unmeasurable which would be very nice to know, if you took all of your abilities you know,

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whether we can explain 20 percent for the variance or 80 percent, would be useful.

DR. GOODMAN: That's a good point. Dr. Steinbrook.

DR. STEINBROOK: Just add to that the earlier comments that baseline visual acuity may have something to do with this.

DR. GOODMAN: Yes, absolutely, that

was a point well taken earlier. Any other points to be made about these particular distinctions? So, what the panel has just done basically is said there's enough evidence to determine whether anti-VEGFs work compared to the alternative treatments, and the answer was yes, largely. What does that evidence say? The evidence says the anti-VEGFs, at least as a group here loosely defined, are better as far as improving outcomes.

So having found that, panel, we're going to move to the next pair of questions, four and five. The pattern here is similar again. In question four we're going to ask about the adequacy of evidence to make some determination, and if that level is sufficient, i.e., 2.5 or greater, we would then move on to

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question five which would say, "Well, is it adequate evidence to make some conclusion about the comparison?" And this time the comparison is among the anti-VEGFs themselves, that group of therapies, and in a moment we will ask Mr. Ollendorf again to tell us what he thinks about the adequacy of the evidence to make some determination.

And the question is, if the result of question three is at least intermediate, a mean of 2.5, which it indeed was, how confident are you that there is also adequate evidence to determine whether or not there are clinically differences in health outcomes among the available intravitreal targeted anti-VEGF treatments for the management of DME?

Mr. Ollendorf.

MR. OLLENDORF: Based on the review and the analyses that we conducted, I would say that we are confident that there was adequate evidence to be able to analyze or determine whether or not there were clinically meaningful differences in health outcomes among the individual anti-VEGF patients.

DR. GOODMAN: Would you say,

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Mr. Ollendorf, that the evidence for any distance between these, between any two or among the set, varies?

MR. OLLENDORF: Yes.

DR. GOODMAN: It does. Can you tell us where it might vary, without telling us what the answer is, but where might we see some, be more confident of differences as opposed to other comparisons?

MR. OLLENDORF: Well, certainly as we

discussed, the bulk of the evidence from the RCT perspective is with Lucentis and Avastin, so there were only two available RCTs with Macugen and one only one with Eylea.
DR. GOODMAN: So the distribution of available RCTs varies.
MR. OLLENDORF: Yes.
DR. GOODMAN: Okay. Any other comments about adequacy of evidence to make these distinctions?
MR. OLLENDORF: I think certainly the other commentary we've had, both from myself and others about differences in trial designs, differences in study populations all have to be taken into consideration, but my read of the

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question is was there enough evidence to be able to attempt to make a determination, and yes, there was.
DR. GOODMAN: Thank you for that viewpoint. Do our speakers have other things to add of note here with regard to the adequacy of evidence to make some determination here across the anti-VEGFs? Yes. This is Dr. Ehrlich.
DR. EHRLICH: I think you probably know what my position is on this.
DR. GOODMAN: I do, but I'd like to hear it.
DR. EHRLICH: I don't believe that there's adequate evidence to determine whether there's clinically meaningful differences or not, both with regard to efficacy and with regard to safety of the various anti-VEGFs for diabetic macular edema.
DR. GOODMAN: You need to speak up, Dr. Ehrlich.
DR. EHRLICH: Sorry. I do not believe that there is adequate evidence to make the determination if there's clinically relevant differences or not, because of the relative

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differences in the various studies that were considered.
DR. GOODMAN: Do you make that observation, do you think that observation applies to any pair at all or, excuse me, to all pairs of these, do you think for no pair of anti-VEGFs there is adequate evidence to make some determination about some delta?
DR. EHRLICH: Yes, I believe it applies to all the anti-VEGFs.
DR. GOODMAN: Thank you, Dr. Ehrlich, for that viewpoint. Other speakers care to

comment on this? Dr. Bressler, it looks like Dr. Bressler is approaching the mic.
DR. BRESSLER: I will use my good eye. So, we are putting the NIH's money toward the comparative effectiveness trial because there are gaps in the evidence in our opinion, but we are not including pegaptanib in that because we believe there is adequate evidence to suggest that we don't have to add that one for the costs that would be involved to have all four in the mix.
DR. GOODMAN: So you do not see the need in designing this trial to try to discern

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differences between all of these, just some of them.
DR. BRESSLER: That is correct, in terms of the efficacy, the safety and the number of injections needed.
DR. GOODMAN: Okay, thank you. Dr. Steinbrook and then Dr. Dubois.
DR. STEINBROOK: I guess there may be a tsunami question here, at least in my mind, but this is what we're asked to answer. I don't -- there's no quarrel that there's adequate evidence maybe for one, but not for all four, but leaving that aside. If there was adequate evidence, just plain logically here, there wouldn't be a reason to do the study that you're doing, so it's almost a tautology that because the evidence is inadequate, therefore we need to do the study. I mean, that's how you do clinical research.
So I'm sort of struggling with that as to how to translate this. And I can understand the point, the notion of putting together the tech assessment, that there was adequate evidence to go through the exercise to see what could be teased out, but that may be different

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than what we're being asked here, to determine whether clinical meaningful differences. This doesn't mean that the tech assessment is not well done and that there's some value from what is in the tech assessment.
DR. GOODMAN: Interesting. Dr. Dubois and then Dr. Sedrakyan.
DR. DUBOIS: I don't know if this is helpful or not but I will say it anyway. So, we've wrestled with the question all day of is there enough evidence to say that these agents differ? I'm thinking about this as some sort of a null hypothesis. Let's just assume they're different. Is there anything to

suggest that they are enough different that we should worry about those differences, and that to me is a critical element. Rather than wrestling with maybe they're different, maybe they're not, they probably are different. The question is, are they enough different that patient benefits and harms would be affected in a clinically meaningful way.

DR. GOODMAN: So, just to underline something, Dr. Dubois, the question is not only about statistical significance, it does say, as

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you know, clinically meaningful differences. I would add that judging from previous MedCACs when we've looked at questions like these, it's not necessary that we think that there are differences among all pairs of these or any possible comparison. If there are clinically meaningful differences between at least one pair of these, that's enough to answer this in the affirmative.

We're trying to draw some distinction, not necessarily confirm that they're all the same, if that helps you as far as framing the question. If there's some difference somewhere, that's adequate, and it's supported by adequate evidence as clinically meaningful, then you would probably answer in the affirmative. You don't have to hold out for differences among any set, or any pair of these. And by the way, we get to discuss those further for any clarification. Dr. Sedrakyan.

DR. SEDRAKYAN: I'm having a hard time thinking that we have adequate evidence based on indirect comparisons alone, and because this is what it boils down to. Is indirect comparison good enough for us to conclude that

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there's enough of a body of evidence for determination? And based on prior knowledge and evidence from, say Main Street, and those people who leave us indirect comparisons are certainly important, but without even having one head-to-head even large observational comparison, I'm having a hard time thinking that we have adequate evidence for this.

DR. GOODMAN: Thank you, Dr. Sedrakyan. Other points by the panel on this? This is one reason why we asked earlier about the indirect comparisons and so forth. Having reflected upon that since then, and Dr. Sedrakyan raised it again, and so did Dr. Steinbrook, I want to ask Dr. Ehrlich and Mr. Ollendorf one more time here with regard to

these indirect comparisons.
Mr. Ollendorf, it seems to me that you put together a set of factors starting with clinical judgment that led you to think that you could conduct a meta-analysis and make certain findings, and Dr. Ehrlich was pretty confident that the indirect comparisons were wanting. Any additional comments or summary comments you want to add to this question about

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making distinctions among any of the anti-VEGFs, Mr. Ollendorf first.
MR. OLLENDORF: I guess this may come from the bias of living in the world of technology assessment, but the world we inhabit is unfortunately often one of indirect comparisons. We are often not asked to answer any questions about evidence where there is a lot of direct comparative data because that would be a worthless exercise in many situations.
So given that, and acknowledging that there are issues with the evidence base that we have to work with, we still did believe that, as Dr. Steinbrook put it, that it was worthwhile to go through the exercise, to look at the body of evidence we had available and to see if indirect comparisons led to any new insight beyond looking at the studies of the individuals.
DR. GOODMAN: And those indirect comparisons yielded what?
MR. OLLENDORF: Yielded the suggestion that there were no clinically meaningful differences between the drugs.

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DR. GOODMAN: Between the anti-VEGFs?
MR. OLLENDORF: Right.
DR. GOODMAN: Okay. So it sounds like you've got pretty good confidence in this indirect evidence, but what that indirect evidence in which you have considerable confidence showed, was that there wasn't any discernible difference.
MR. OLLENDORF: Right.
DR. GOODMAN: Which is our subsequent question. So the question for now is on the adequacy of the evidence, you are putting forth that you consider the evidence to be adequate.
MR. OLLENDORF: Given the evidence available to us at this moment, yes.
DR. GOODMAN: Okay, other comments? Dr. Ehrlich, did you want to add to what you said before or not? If you're just going to

repeat yourself, you don't have to. Come on up to the mic. It sounds like you're going to talk, so you might as well say it into the microphone.
DR. EHRLICH: I'm not sure I have much else to add. I think the comparisons you can make from these types of data, the differences
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among the studies really limits the adequacy of any comparison that you can make. I think other than saying that the anti-VEGF drugs directionally show benefits in vision relative to laser treatment, I don't think that you can conclude that there's enough evidence that there's clinically relevant differences among them.
DR. GOODMAN: Okay, thank you, Dr. Ehrlich. Panel, any other comments on this one, the adequacy of evidence to determine question? Let's take a vote on it, then, and obviously we can have some discussion further. This is, we do take on this vote because of the previous question. How confident are you that there is adequate evidence to determine whether or not there are clinically meaningful differences in health outcomes among the available intravitreal targeted anti-VEGFs for the management of DME? One is low, five is high.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: So we have a mean vote of 2.1, which falls short of the 2.5, which
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suggests that at least average across the panel, you do not consider that there is adequate evidence to make that determination, three would have been intermediate and we're at 2.1. Any comments to make before we proceed? Dr. Phurrough, go ahead, vote.
DR. PHURROUGH: Phurrough, three.
DR. GOZANSKY: Gozansky, two.
DR. HESELTINE: Heseltine, one.
DR. LEVINE: Levine, one.
MS. MASSEY: Massey, three.
DR. MCDONOUGH: McDonough, three.
DR. REDDY: Reddy, two.
DR. SEDRAKYAN: Sedrakyan, two.
DR. STEINBROOK: Steinbrook, two.
DR. DUBOIS: Dubois, three.
DR. PUKLIN: Puklin, three.
DR. GOODMAN: Okay, thank you very much. Well, Dr. Phurrough, if I read this as you're reading it, it would appear that we

don't need to discuss question five; is that correct?
DR. PHURROUGH: That's the way I read it.
DR. GOODMAN: Before we leave question five, just in case anyone has anything to say about it from a discussion standpoint, briefly, we will take any discussion points. We're not going to vote on it, however. Dr. Heseltine.
DR. HESELTINE: A point of record. Should we be spelling pegaptanib with two P's? I think there's a P missing.
DR. GOODMAN: There is indeed, pegaptanib. Thank you for the correction of that typo. Dr. Steinbrook.
DR. STEINBROOK: Yes. This is a discussion point, but 5.c, while we may not feel that the evidence is adequate to reach a conclusion about this, I certainly haven't heard anything to say that there are clinically meaningful differences, that's really the reason for this topic, but I think that's clear from the discussions to that point.
DR. GOODMAN: Okay, thank you. Any other points on this? Dr. Phurrough?
DR. PHURROUGH: In regard to the second half of the question, I would assume that if there was adequate, the evidence that we do have suggests that the differences are based upon different benefits and not harms, so that among the VEGFs, at least from what we know now, it's a benefit issue and not harms, so we may determine at some time that it's a systemic event.
DR. GOODMAN: Is that a question you're posing for our speakers?
DR. PHURROUGH: No, that's more of a comment.
DR. GOODMAN: Dr. Bressler.
DR. BRESSLER: Clearly we want to be confident of the efficacy. When these trials have 80, 100, 150 people, and there are tens of thousands if not more people getting treated each year, for ophthalmologists we're not comfortable with the level of evidence to say I should use A versus B, especially when there is a large cost difference involved as well, and there's compounding risks that we have to take into consideration.
That being said, it is both efficacy, because I told you in our presentation that some of these eyes started with 20-80 and had a

six-letter improvement, whereas, with Avastin, whereas with Lucentis when they started at 20-80, the average improvement was 11 to 15

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letters, so it's putting into question whether the efficacy is the same. Finally from the systemic point of view, the CATT trial had this outcome with systemic adverse events that requires further study, that is, there were greater systemic adverse events in the bevacizumab group than the ranibizumab group, and we want additional information that might come from our comparative trial or might require other studies to understand the systemic risks. It's more likely that the comparative trial will pick up efficacy differences or equivalency rather than pick up systemic differences.

DR. GOODMAN: Okay, thank you. Dr. McDonough, and then Dr. Sedrakyan.

DR. MCDONOUGH: It almost is, at least with respect to Lucentis versus Avastin, I mean, you do have a direct comparative study for a different disease, but it does give you more information than we have about comparative harms that we have from some of these other comparisons.

DR. GOODMAN: So we should infer what from that, Dr. McDonough?

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DR. MCDONOUGH: That your answer about the confidence and the adequacy of evidence might be different when you're talking about the health outcomes being harms of these two specific agents, than efficacy, where we have no direct comparative data in DME.

DR. GOODMAN: Right. Dr. Sedrakyan, did you have a further point?

DR. SEDRAKYAN: Just a clarification, and I think Dr. Steinbrook covered it, this was in the same class of anti-VEGFs, but that the third comparison, Lucentis versus Avastin is potentially, it needs to be proven that one has advantage over the other. Unless that evidence is out there, it's reasonable to assume that they're similar.

DR. GOODMAN: So what you're saying there, then, is based on the evidence that we've heard thus far and as summarized at least by the average vote, we can't draw a distinction between those two anti-VEGFs for either effectiveness or safety?

DR. SEDRAKYAN: While the evidence is not substantial perhaps, as we voted on number

four, the position I'm coming from, it needs to
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be proven that one has advantage over the other, rather than the other way around.
DR. GOODMAN: I see, so there's a burden of proof to depart from the null hypothesis and no difference.
DR. SEDRAKYAN: Exactly.
DR. GOODMAN: Thank you, got it. Okay. Any further points to be made on this issue? Okay. We will move to question six. Let me take a state of the panel's preference here. We've got question six, which is a voting question that's two-part, and then we've got three discussion questions. Would you like to take a ten-minute rest break now and then finish it all, or do you want to push through and have all the remaining questions now? Is there anybody that wouldn't mind taking a ten-minute break, or how do you feel about that? Dr. Steinbrook, do you want to take ten? Oh, he doesn't want to take ten, or excuse me, Dr. Heseltine doesn't want to take ten, pardon me. Do you want to kind of just push through, panel? It looks like a yes. If I don't hear otherwise, we'll assume that our court reporter and other technical staff
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are cool with that.
MS. ELLIS: I just checked with everyone.
DR. GOODMAN: Oh, you were ahead of me on that. Let's proceed then. Question six is a voting question, it is two parts, and it has to do with generalizability, sometimes we call this external validity. The point being that for the questions to this juncture, we haven't been specific about certain types of beneficiaries or settings of care and so forth. The idea here is we just made some determinations about adequacy of evidence to determine and the evidence of adequacy to conclude, and now does this stuff play or is it relevant to Medicare beneficiaries and community-based settings. So the first one asks, how confident are you that the conclusions above are generalizable to Medicare beneficiaries in particular? Mr. Ollendorf, would you care to comment on that? What you'll probably want to tell us is if you looked across the studies, do they generally include Medicare beneficiary aged population or not, or any kind of other
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differences of which you might make note.
MR. OLLENDORF: That was, we didn't look at any subgroup by age specifically, but in general the study populations, one of their characteristics that was relatively similar across study populations was age. As we heard from some of the clinicians, it does affect a somewhat younger population than wet AMD, so I think the mean age was somewhere between the high 50s and low 60s in most of these studies. Though there are studies, and the clinicians that are here can talk in more detail than I can, RISE and RIDE for Lucentis, and the DA VINCI study for Eylea, that had a substantial amount of patients who were age 65 and older, so the outcomes, I believe, were quite similar in the older population compared to the overall.
DR. GOODMAN: Okay, thank you. Yes, Dr. Heseltine.
DR. HESELTINE: What I'm interested in knowing is were in fact the patients in the clinical trials randomized by age? Certainly they were included, but if they were unbalanced, that might have influenced the

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outcome.
DR. GOODMAN: Dr. Ehrlich is approaching.
DR. EHRLICH: So in RIDE and RISE at least, the randomization stratification factors were A1c, previous treatment for DME and baseline vision. But the age, the average age was very consistent across all three of the subgroups, the sham, .3 ranibizumab and .5 ranibizumab. There didn't seem to be any systematic differences with age.
DR. GOODMAN: Thank you. Do any of our speakers, including our clinicians, have any reason to think that the clinical trial data in particular are not applicable, or are, there is some important subgroup differences that were not discerned or discussed thus far that would say they were not relevant to the Medicare beneficiary populations? Folks are shaking their heads in the negative, okay. Other comments on the Medicare beneficiary population applicability, panel? It looks like we're ready to vote on 6.a on a scale of one to five, where one is low and five is high.

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How confident are you that the conclusions above are generalizable to Medicare

beneficiaries, scale of one to five?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: Thank you, they come in at 4.1. Dr. Phurrough.
DR. PHURROUGH: Phurrough, four.
DR. GOZANSKY: Gozansky, four.
DR. HESELTINE: Heseltine, five.
DR. LEVINE: Levine, four.
MS. MASSEY: Massey, four.
DR. MCDONOUGH: McDonough, four.
DR. REDDY: Reddy, four.
DR. SEDRAKYAN: Sedrakyan, four.
DR. STEINBROOK: Steinbrook, four.
DR. DUBOIS: Dubois, four.
DR. PUKLIN: Puklin, five.
DR. GOODMAN: Thank you very much. It looks like our standard deviation was pretty narrow there, thank you very much.
Okay. Let's proceed to question 6.b, a similar question, except this asks about community-based settings. Sometimes when we look at topics in MedCAC meetings, the evidence

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has all been accumulated in a certain kind of setting, hospital-based or outpatient-based, and may not be more broadly, and so we want to ask again this question. If you consider the evidence which you heard today, do you find it applicable to community-based settings in particular?
I just would remind the panel that some of our discussions dealt with things like relevance to certain minority populations, so you might want to think of the population type, the geographic distribution, where people get care and so forth.
Mr. Ollendorf, do you have anything to submit on this one? He's shaking his head no.
DR. HESELTINE: One population at risk, pregnant women. I don't think any of the studies included pregnant women that I'm aware of, but that's a group I understand who are at risk for this disease. Is that correct?
DR. GOODMAN: Dr. Bressler.
DR. BRESSLER: There are some people with no diabetes that get gestational diabetes so all of a sudden it appears during pregnancy, or more commonly someone with diabetes when

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they become pregnant, they can be exacerbated. We did exclude them because we didn't know if it worked. Now that we know the benefits and risks, we make individual judgments as patients

walk in and are losing vision, perhaps from diabetic macular edema, which exacerbates perhaps in certain pregnancies, and so we can at least make a patient-by-patient decision with a doctor-patient decision there. But no, they were all excluded from all of these trials, is my understanding.

DR. GOODMAN: Thank you, Dr. Bressler. Dr. Thompson.

DR. THOMPSON: I just want to make the follow-up point that we do try to avoid using these drugs in pregnant women because of possible concerns of the fetus. There really have not been adequate studies done to look at these risks, so as Neil alluded to, you would have to make a very difficult decision if we had a person that was losing their pregnancy while losing their vision. Severely from diabetic macular edema you might do it, but otherwise we try to avoid these drugs in pregnant women.

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DR. GOODMAN: Dr. Phurrough.

DR. PHURROUGH: So really the question is, since we weren't presented data that segregated any of the treatments by setting, we really didn't discuss that. And then Neil, your study does do that. Are there studies that look outside, are there other studies where the treatment is done outside the non-community setting?

DR. GOODMAN: I'm sorry, the non-community setting?

DR. PHURROUGH: Yeah, is there data in the community setting, as opposed to the non-community setting where most of the studies are done?

DR. GOODMAN: Such as well managed, carefully managed clinical trial settings and so forth.

DR. BRESSLER: Okay. So, the only data are from the clinical trial settings, which I would agree in general tend to have healthier people, are chosen to last the two to five years that a trial will go. I will point out there is a strong drive in the network to keep it simple, to allow most patients that

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walk into the community-based setting to be included in these trials, which, for example, we did not do the NEI VFQ because it was important for clinical research, but it wasn't part of clinical management, as an example. So we have some evidence that no matter where

these trials were done among these various settings, there were similar outcomes that we're seeing.

DR. GOODMAN: Thank you.

Dr. Gonzalez.

DR. GONZALEZ: Just one clarification also. Aside from being a retinal specialist in private practice, I'm also part of the DRCR network. So similar to what Dr. Bressler has explained, we try to as much as we can to have a clinical community approach. It's not exactly like, you know, because there are some restrictions in terms of who we do enroll and who we don't.

What I can tell you is that there are a few concerns obviously that we have. The first one is, you know, a lot of these studies did not include a large population of minorities, and I think we have already

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discussed that earlier. While we do have some of these enrolled in our trials, you know, as the in particular Hispanic population grows, it's continuing to be more important.

One of the unique things about our study is that you know, our population, about 25 percent of them are diabetic, and about 85 percent are Mexican-Americans, so we get to see a lot of diabetic retinopathy. We've had the ability to see how these individuals respond both in a clinical trial setting, and we have the opportunity to also see them and treat these patients outside of clinical trials, and basically the data and the experience that we have within the clinical trials has been applicable.

And as I pointed out earlier, when we look at all the different anti-VEGF agents, whether it's Avastin, whether it's Lucentis or pegaptanib, at least in that population, we tend to agree with the observations of Mr. Ollendorf, that there doesn't appear to be a significant difference, even when it's outside of a clinical trial.

DR. GOODMAN: Dr. Gonzalez, let me

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make sure I understand. When you consider the involvement of clinicians and patients in these trials, it sounds like many of those trials are conducted in what you could characterize as a community setting.

DR. GONZALEZ: Correct.

DR. GOODMAN: Is there any reason to think that the selection of patients, the

management of the therapies, the delivery of the therapies or how patients were followed up in these settings, these clinical trial settings, would depart greatly from what might be seen in the community where these things diffuse more broadly, or are you confident that even though they diffuse more broadly, all those things line up pretty much the same?

DR. GONZALEZ: Well, you know, of course everything we do in clinical trials sometimes is not in the community. For instance in our DRCR net we have very clear-cut algorithms as to how we determine when a patient was to be treated. I can tell you that out in the majority of the community at least at this point in time, that's not the way diabetic macular edema is being treated, but I

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think we're evaluating to see what's the simplest algorithm that we may be able to demonstrate benefit and communicate to our practitioners.

Is it going to be exactly like what we have within the clinical trials? I don't think everything is going to be applicable and feasible, just because of the constraints that we have, you know, within our clinics outside of the clinical trials.

DR. GOODMAN: But when we think about the kinds of outcomes that are being achieved now in clinical trials both for effectiveness, efficacy and/or effectiveness and safety, efficacy and safety, would you expect to see similar improvements, similar effects or impacts on effectiveness and safety in the field as you are seeing now, or would you expect that those might be completely different?

DR. GONZALEZ: I think the efficacy and safety will be similar.

DR. GOODMAN: Will be similar, okay. Thanks, that's very helpful. Dr. McDonough first, and then Dr. Heseltine.

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DR. MCDONOUGH: I'm having some confusion about the question. The question asks about community-based settings, so like the DRCR net, I heard, is 80 percent of the patients were managed in the community that were included in the clinical study. I think that's a different question than what are the protocols that are used in the community-based setting in actual practice, or the question of would any inclusion criteria in the clinical

trial allow us to generalize to people who are not included in the clinical trial? It seems like we're just creating a lot of different questions on this.

DR. GOODMAN: It's true that much of the research done to date has been done in what one might characterize as a community-type setting. The question here is to what extent are the findings of those studies to date regarding in particular how well the thing works and what its adverse effects are, would it be generalizable or seen should this diffuse more broadly into community-based settings. That's the main issue.

There may be reasons why there might

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be variations, it might be population-based or other things, but can you basically take the findings thus far and say yeah, we're going to see these, very similar findings once these things diffuse into the broader community. That's the main thrust of the question. Dr. Heseltine.

DR. HESELTINE: I just want to be sure that there are no additional data we should consider. We have opinions about these drugs obviously, or these biologics. They have, however, been in use for some time, and we are about to do a clinical trial to compare toxicity and efficacy. So I want to know from the manufacturers if in fact in their records, do they have either a registry, question number one, particularly for on-label use. And secondly, what is the experience in adverse outcomes that you reported to the FDA?

DR. GOODMAN: Any knowledge of that, Dr. Ehrlich?

DR. EHRLICH: With regards to the first question there is no registry, at least at Genentech, for diabetic macular edema, nor is there currently a registry for wet AMD

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either.

And then with the rest, postmarketing safety, obviously we have an extensive postmarketing safety surveillance program, but I think that the data that are available to that specifically for diabetic macular edema is very limited at this time because the drug is not approved for that, and it's difficult for us to track any sort of non-approved uses of the drug. We often don't know if a patient, in a postmarketing safety report, we don't always know what the patient is being treated for.

DR. GOODMAN: Okay, thank you.
Dr. Phurrough.
DR. PHURROUGH: I'm not sure we're all functioning with the same definition.
DR. GOODMAN: Give it a try, Dr. Phurrough.
DR. PHURROUGH: I'm not sure I know what that is. My assumption is when we were looking at these questions in a community-based setting, it's a setting outside a typical medical center or a very large specialty-based ophthalmological practice, those would be not community settings, and anything else would be

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a community setting. I'm not sure that's the definition that CMS has, or the definition that clinical trial people have.
DR. GOODMAN: That is the usual distinction. You are correct. In this instance, it seems as though much of the clinical data has been collected in what has been characterized by our speakers as community-like or community-based settings.
DR. PHURROUGH: I think it would be helpful if they would tell us, is that your definition, or have the retina specialists been outside these large ophthalmological practices?
DR. GOODMAN: Dr. Bressler.
DR. BRESSLER: When we started the DRCR Network, large trials included 70 percent of community-based practices. Our definition was that it did not, it was not an academic health center as defined by the federal regulations, which is usually a university, and there's one or two exceptions to that as well. Otherwise, it is the community-based private practice, two, three, five, ten-person ophthalmology practice or whatever, that was our definition.

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DR. PHURROUGH: Then all of the studies that we looked at, where did they fit in?
DR. BRESSLER: I'd have to have them comment because I don't know the details, but I think they used a combination, but I would not be able to quote you as to what I know from the network.
One other quick point and that is, in extrapolating this to the world, it's not laser where you have to understand where do I laser, how good are my eyes, and experience laser. Everyone is going to get the drug. What may vary in the community will be are they

following a specific algorithm, treating until it's no longer improving, recognizing that it's thickening again, and resuming treatment. We think that will be the same if we do our responsibility correctly and educate our colleagues, so we think will be the same. It's not that complicated but these results are very recent, which is why, some of them are, you know, just a month or two old, but we don't think this will be difficult to extrapolate and educate our colleagues. I wanted to add that

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to your discussion.

DR. GOODMAN: That's helpful. Thank you. Dr. McDonough.

DR. MCDONOUGH: There's also the issue of the type of people who volunteer for a trial tend to be healthier. I know that in cardiovascular trials and clinical trials when we evaluate things, we emphasize more compliance in the clinical trial, making sure that they're followed up, and so there is a lot of differences. So that, I am interpreting, Cliff, the question to be, can we generalize these results outside of the clinical trial setting, as opposed to can we generalize these results outside of an academic hospital.

DR. GOODMAN: Yes, I would concur with that. Dr. Gozansky.

DR. GOZANSKY: If I could just have some clarification, so OCT, every ophthalmologist is going to have that?

DR. GOODMAN: Dr. Ehrlich, briefly.

DR. EHRLICH: I just want to say that the community that we're probably talking about is the community of 1,500 retina specialists practicing in the United States, so you've

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actually already got almost all of the intravitreal injections, for instance, for wet AMD. There are some general ophthalmologists who do these types of treatments, but by far the majority, at least in wet AMD, is retina specialists, so that's sort of the community, right?

With regards to RIDE and RISE, the vast majority of patients were in what we can call community-based practices, most of them were not in academic centers, some of them, but mostly not.

DR. GOODMAN: Thank you. So Dr. McDonough, just to get back to your point, in this instance, not in the case for other conditions and trials, but in this instance, it

sounds as though 70 to maybe 80 percent of the clinical trial data were collected in what are generally characterized as community-based settings as defined by the speakers. The further question would be, even those these were conducted in community-based settings, might there have been anything going on in these clinical trials in those community-based settings which would

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systematically differ from any performance or use of these interventions in a broader community-based setting not part of clinical trials? That's one of the distinctions you're trying to discern here. Dr. Frank and Dr. Thompson. It's usually an easier matter for us because a lot of these clinical trials are conducted in academic medical centers, but in this case there are a lot that were community based. Dr. Frank.

DR. FRANK: A couple of points relevant to this issue. As to whether the actual procedures would differ in a clinical trial or outside, I would suspect that other than the more meticulous data collection and the performance of various other assessments, for example, the VFQ-25 examination, the performance of the procedures and the diagnostic tests probably, and I'm just guessing at this, but I think with pretty good confidence that it does not differ. But the other thing that's of interest, certainly with the DRCR Net trial, and Dr. Ehrlich can tell us a little bit more

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about the RISE and RIDE trials, is the population that was assessed. I think one of the problems with many previous clinical trials, certainly in diabetes with which I'm most familiar, is that they really did tend to get a more select population, perhaps economically and educationally better off than the average population, and hence one might be concerned as was commented earlier, maybe they're in better health, maybe they're better able to follow a strict clinical trial regimen as far as taking medication, coming in for follow-up visits and so forth. The ethnic distribution in the DRCR trial really mirrors the distribution in the entire U.S. population, I think, which is good evidence that that trial really is community based and reflects the expire population and

not a select group of that population, contrasted with the Diabetes Control Complications Trial, the earlier trial for folks with Type I diabetes. 99 percent of the patients in that trial were Caucasian and all of them had to pass certain tests of being able to follow

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instructions and a standardized written test before they were allowed to enter the trial, which really selected that population very highly, even though the results have now been generalized to Type I diabetes overall.

DR. GOODMAN: So there were differences among the trials with regard to the representativeness of the patient population vis-a-vis the national population.

DR. FRANK: That is correct.

DR. GOODMAN: Thank you very much. I believe Dr. Thompson is next.

DR. THOMPSON: I kind of feel like we're getting stuck on this particular issue and I will just give you a brief example in the AMD world. I reported in a paper not published yet of everybody who wasn't in clinical trials getting anti-VEGFs, about 180 patients followed for several years, and the results were very very similar to the MARINA and ANCHOR results of 800 patients. So I think, you know, this group of trials was not done mostly in the ivy-covered academic institutions, this was real world medicine, these trials were done in the community by many many private

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practitioners and some academicians as well.

DR. GOODMAN: Okay, thank you. Any further points to be made here? By the way, we got stuck on this on purpose, Dr. Thompson, because CMS does care a lot about whether the evidence that it has seen thus far is going to apply more broadly to Medicare beneficiaries and others, and in the population more broadly. There have been cases where interventions are very nicely validated with great outcomes in vary regimented studies, but once they got out in the community, gosh, those numbers, effectiveness does not look like efficacy at all, the safety protocol in the real world is not the same, so I want to make sure we understand this aspect of generalizability. So I'm glad we spent a little time, thanks for your patience on this. Any other points to be made? Great. Thank you, speakers, for your comments.

Let's go to vote for item 6.b now, a scale of one to five, one is low, five is high, how confident are you that the conclusions above are generalizable to community-based settings?

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(The panel voted and votes were recorded by staff.)

DR. GOODMAN: Good. I see a mean of 3.6, thank you. Dr. Phurrough, your vote?

DR. PHURROUGH: Phurrough, three.

DR. GOZANSKY: Gozansky, four.

DR. HESELTINE: Heseltine, four.

DR. LEVINE: Levine, four.

MS. MASSEY: Massey, four.

DR. MCDONOUGH: McDonough, three.

DR. REDDY: Reddy, four.

DR. SEDRAKYAN: Sedrakyan, two.

DR. STEINBROOK: Steinbrook, four.

DR. PUKLIN: Puklin, five.

DR. GOODMAN: Excellent, thank you very much. That handles our voting questions, and we've got three discussion questions to go here. Just as a time check, I'm confident on a scale of one to five, I'm confident at 3.5 that we will be done before four o'clock. I give a 2.5 to three that we will be done at 3:45, but I'm highly confident that we will be done before four.

So, discussion questions, we've got three of these, and I don't think we need long

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discussions of all these. However, I do want some high points and key points from as many of you as possible. This has to do with, let's take the first discussion question, and I want to emphasize as well that CMS truly does care not only about our voting questions but our discussion questions, they often weigh heavily in determinations about taking on an NCD or what an NCD might conclude.

First, to what extent are the conclusions above generalizable to the management of other forms of diabetic retinal vascular disease beyond DME? So we've been trying to focus as much as we could on DME and we've been sometimes looking at DME evidence and asked about how AMD evidence might spill over to DME. In this case, are the conclusions we made generalizable to management of other forms of diabetic retinal vascular disease, i.e., beyond DME? Any takers on this? Dr. Steinbrook to start.

DR. STEINBROOK: Well, this is not to

address the issue of generalizability, but we certainly heard some post hoc analyses and other interesting possibilities that there
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could be a role of these anti-VEGF agents in forestalling the development of more general diabetic retinopathy, and to the extent that some of the trials are going on, that would obviously be very important if it turned out to be true, and would have implications, I think, for how these agents might be used, and it would be nice if the people who are doing trials sort of worked that into their thinking going forward.
DR. GOODMAN: Very useful point. Other points to be made here? Dr. McDonough.
DR. MCDONOUGH: I think this is a really important point, I mean, do we need to have separate trials for all the different types of causes of macular edema or can we extrapolate, in addition to the question of whether these results can be generalizable to other types of diabetic retinal vascular disease. I mean, that's something that we always have to struggle with in our managed care company, so it's a good question.
DR. GOODMAN: And let me just be more pointed about that. Dr. Frank, could we call on you to address this in short here? We
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looked at the body of evidence thus far with regard to DME, we looked at the spillover from AMD to DME, but in your judgment, considering the evidence we've looked at today, how applicable is that to some other sorts of diabetic retinal disease, is this pretty useful stuff for these other conditions or not?
DR. FRANK: It certainly portends a happy answer. You're referring only to diabetic retinal vascular disease and not to other, for example, other forms of macular edema.
DR. GOODMAN: Diabetic retinal vascular disease.
DR. FRANK: Okay. By which I would think primarily a proliferative diabetic retinopathy, and although that has not been addressed directly by any of these clinical trials and I don't think I'm saying things I'm not supposed to say, but Dr. Bressler can grab a big hook and drag me off if I do say something --
DR. GOODMAN: You are your own man, Dr. Frank, I assure you.

DR. FRANK: Okay. I'm saying things
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from the unpublished results of the Diabetic Retinopathy Clinical Research Network trials, and that is that there is ancillary evidence in some of those trials that both intravitreal corticosteroids not being considered here, and also intravitreal ranibizumab, Lucentis, do seem to forestall the development of peripheral diabetic retinopathy when the totality of retinal photographs are used in that study, the seven standard stereo fields, not just the macular photographs are considered. That has not been a direct endpoint of these trials but it certainly suggests very strongly, as well it should, because these are anti-VEGF agents, and VEGF is certainly considered to be the major player in the department of proliferative retinopathy as well as diabetic macular edema. If such were the case, it could eventually avoid some of the complications, for example, Dr. Gonzalez showed us earlier with his photograph of extensive panretinal laser photocoagulation, which is now the standard treatment for proliferative diabetic retinopathy, but which has as its almost
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inevitable result, sometimes more severe than others, a great restriction of the peripheral visual field with limitation of visual function even though the central visual acuity is good. The disadvantage, of course, is the requirement for multiple injections, and probably a higher cost of individual treatment if anti-VEGF injections were used for treatment of proliferative retinopathy.
DR. GOODMAN: But Dr. Frank, if you were to look at the body of evidence that has been shared with us today, to which form of diabetic retinal vascular disease would it be most applicable? We can take it -- aside from DME, it's most applicable to what?
DR. FRANK: Two things. One, proliferative diabetic retinopathy, and two, it's end stage consequence, which is neovascular glaucoma, in which it is already being used.
DR. GOODMAN: Got it. Thank you very much for that answer. Dr. Heseltine is next.
DR. HESELTINE: Well, this is more of an impression than a question, but I don't, I understand that we're beginning to appreciate
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the biology here of proliferative retinopathy, but I still am not convinced that the link between VEGF and proliferation has been made sufficiently to allow me to say oh, because I know this works reasonably well in DME, it's going to work in the others, and at this point we need additional trials. I think we need to include those patients because those are very likely to be patients in the community setting that get treated, because we as physicians tend to do things rather than not do things, and it would be nice to know that it actually worked and by how much.

DR. GOODMAN: Great point, Dr. Heseltine. Dr. Frank, would you like to respond?

DR. FRANK: To your point as to whether the link between vascular endothelial growth factor, VEGF, and proliferative diabetic retinopathy has been established, it was actually, although not therapeutically, but in a very well-run basic science study, it was, the link was established earlier for proliferative retinopathy than it was for

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macular edema in a now classic 1994 paper in the New England Journal of Medicine by Lloyd Paul Aiello and associates. It was shown that vitrectomy specimens from patients with active proliferative diabetic retinopathy had very high concentrations of VEGF in the vitreous cavity, whereas those with inactive retinopathy and other diseases in which vitrectomy was performed did not. And that was an absolute, that's been very rigorously --

DR. HESELTINE: I'm not disputing the association, I'm really talking about the exact biology at a molecular level.

DR. FRANK: Well --

DR. HESELTINE: But leave that aside, and the question still remains, is it going to improve these patients and by how much?

DR. FRANK: I think that would require a clinical trial.

DR. GOODMAN: We don't have enough evidence on it. Thank you, Dr. Frank. Other points to be made on management of other forms? Oh, Dr. Bressler, yes.

DR. BRESSLER: So, we hopefully will have the evidence for you. We started a

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randomized trial a month ago to compare prompt panretinal photocoagulation, which is the

standard of care for proliferative retinopathy, to anti-VEGFs, in this case we were using ranibizumab. We've already enrolled 15 people in the past month, I think we will finish enrolling them by the end of this year, and we will do at least one to two years of follow-up so that we will have that information. I agree we need it.

In terms of neovascular glaucoma, this is a devastating complication of diabetic retinal vascular disease where it's too infrequent, it's too rare, we think, to make it feasible to do any sort of clinical trial, so we will depend on our judgment of observational studies, our retrospective evidence that we have, and use likely anti-VEGF drugs as an adjunct to panretinal photocoagulation until we learn more about the scientific setting of this protocol that I told you that we have just embarked upon.

DR. GOODMAN: Good, thanks for that information, Dr. Bressler. Any other points with regard to question seven? This has been a

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very helpful discussion. We got to the point on that and had some specific discussion. Let's move to question eight, also a discussion question, and this has to do with the gaps in the evidence base. We've seen a couple of technology assessments, we saw reports from trials, we've compared anti-VEGFs to other interventions, we've compared anti-VEGFs to each other. What are the main gaps in the evidence base? And our following question is what kind of trials would we like to see to address those gaps, but let's talk about the gaps first. Dr. Reddy.

DR. REDDY: I think one of the most striking things that came up in some of the suggestions from the speakers was the duration of therapy, so what I was hearing was that the clinical trials lasted from 12 to 24 months, while in the community these treatments are ongoing for extended periods of time and I'm assuming well beyond 24 months.

So I think, for me, I feel that's a huge gap of evidence across all agents, and I think an analogous situation was diphosphonate where analogous agents have been around for a

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long time and people are sort of wrestling with this issue, when do you stop them, or do you, and so I feel for me that's a major cost issue question.

DR. GOODMAN: So just to clarify, the diphosphonate is important because we were taking other therapies that may complicate these --

DR. REDDY: In a similar situation, with diphosphonate, I'm just using it as an analogy, that people are wrestling with this issue ten or 15 years later, "Do we stop them?" "do we continue them?" and I'd hate to see us in that situation 15 years from now.

DR. GOODMAN: Understood. Dr. Heseltine was next.

DR. HESELTINE: I would like to return to the issue of quality of life measures and associating them with what we know about the biology and the tests that we do. There isn't anybody out there using the term best corrected vision, but we all intuitively associate that with improved sight, but I do think if we're going to recommend that CMS aggressively pay, and outreach, and get people treated with this,

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that we need to understand exactly who we're treating and what's going to be the benefits to those individual patients.

As you pointed out, to move from 20-200 to 20-100 may not make a lot of difference to an individual's life, and obviously at the other end the reverse may be also true, so we need to understand other things related to quality of life.

DR. GOODMAN: Yes, that does recall the discussion we had earlier about biomarkers, about clinically relevant outcomes, about patient-oriented or patient-reported outcomes, including but not limited to health-related quality of life outcomes which may be condition-specific and sometimes assessed through generic instruments. So there's a whole range of questions about how we measure how well this stuff is doing what it's supposed to. Thank you, Dr. Heseltine, great point. Other major gaps in the evidence that you would like to address? Dr. Gozansky.

DR. GOZANSKY: Just following up on that point, I would also suggest that when we're looking at quality of life outcomes that

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we are looking at actual measured functions. I think that that's an important point that has been brought up.

I would also suggest that we need endpoints and trials that are powered to detect these quality of life issues.

DR. GOODMAN: Right, we've got to be able to design trials that have the power to draw these things. Dr. McDonough.
DR. MCDONOUGH: I would like to see an actual study that looked at the actual performance outside of the clinical study setting, maybe some registry observational kind of thing, to see how much of a difference it is when you get the average patient and average follow-up, and whether that makes a big difference.
DR. GOODMAN: So those are study designs, but you're interested in using those study designs to discern --
DR. MCDONOUGH: To find out how well this performs in the community.
DR. GOODMAN: More data in the community setting. Dr. McDonough, allow me to push on you for something else, and that is, do

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you care in the standpoint of your role at Aetna, any more about differences between the anti-VEGFs, are you looking for more data or evidence that might distinguish among those, or are you not concerned about that?
DR. MCDONOUGH: Well, let me put it this way. We are considering, and not just Aetna, but many insurance plans are moving toward establishing formularies on the medical benefit and this is where it would fall, because it's a physician-administered medication.
And if there is no good data of differences and it's based on an assumption that they're equivalent we're going to, there may be a decision to choose the least costly equally effective alternative. So I think it's an advantage to those who do believe there are important differences in patients in certain subgroups to prove it.
DR. GOODMAN: Thank you, Dr. McDonough. Dr. Dubois and then Dr. Phurrough.
DR. DUBOIS: So we've talked a fair bit about predictors and how we don't know much about predicting who does well. I think

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there's also predictors of adverse events, systemic adverse events. Is there any way to sort of figure out who the people are that are likely to have adverse events and then make some choices based on that.
DR. GOODMAN: Thank you.
Dr. Phurrough.
DR. PHURROUGH: I suspect that as this

has diffused, there's significantly more patients who are not in good control of their diabetes when they show up with their DME, and I'm not sure we had the evidence from our study of how well additional control of those factors in diabetes affects the need for long-term recurring anti-VEGF treatment.

DR. GOODMAN: Good, thank you, Dr. Sedrakyan.

DR. SEDRAKYAN: I'm going back to that generalizability to community-based settings. I think we know little about these rare side effects and issues that you talked about, but the potential is still there, and we have to reserve and watch until we will be able to view in a community-based setting in larger studies potentially to be able to put some kind of

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surveillance in place in the form of registry or as a study design issue, but that's an important gap in terms of rare side effects, heterogeneity of effects, but again, we can't really get to the subgroups of people who might not or might benefit more from these therapies. So that, again, will probably have to do with the generalizability to real world populations, so called.

And I'm also thinking that there's a potential now that there's effectiveness, there is substantial evidence of effectiveness, we might lower the threshold for therapy, and a different population of patients will be undergoing this therapy in the community-based settings than what happens in trials. So I don't think, if there is such risk for going to intervene, that may be changing based on availability of the treatment. Sorry to say that, but certainly an important consideration in every changing populations to be able to look at those effects.

DR. GOODMAN: Thank you, good point. Dr. Bressler, did you have a concise point on this?

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DR. BRESSLER: Only to emphasize as someone who treats these patients, works with the NIH and testifies before Congress on how we're using the NIH money, it will be great to have these documented, because all of these trials are necessary information that you mentioned and they cost money, and we need to identify the ways of efficiently, economically getting the answers you need. I'm glad we're doing this comparative effectiveness trial, it

was not easy to set up, so to speak, but it's critical, as an example. So I'm thankful on behalf of the research community and our colleagues that use this that you're pointing these out, and we will do our best to prioritize and to do them.

DR. GOODMAN: Great, thank you very much, glad that you're listening to the input, another good reason to hold MedCAC meetings. Yes, Dr. McDonough.

DR. MCDONOUGH: Another thing that will come up as a question on these drugs as they are entering clinical practice, are there patients that once you get maximum benefit from Lucentis might get additional benefit from

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trying Eylea. Because what usually will happen is you hit a wall with Lucentis and now you want to try Eylea, or maybe you want to combine them, and use of that isn't studied, and I think it would actually be a worthwhile question.

DR. GOODMAN: Good, I think you're the first person to raise that today. Dr. Heseltine.

DR. HESELTINE: So we're sort of slipping into, I guess between eight and nine, but I think to your point, we've seen this happen with other biologics in other conditions. So what concerns me is that we need in fact to both design and conduct future investigations, and I'm using that word carefully and not saying trials, because in fact if you look at what the rest of the world is doing, particularly the European community compared to the PhRMA regulations, they work really hard trying to attack the question of utility, how is it actually going to benefit people in the community, as opposed to the more traditional randomized trial. We're probably not going to be able to do a randomized trial

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with a placebo arm, I guess from this point on, I think it would be inappropriate.

So the question is, "How do we tease out the toxicity issue?", "Do we do it through a registry?", "Do we do it through comparisons?". And also specifically, are there subgroups who were underrepresented in terms of the potential toxicities that we might see in these? I think we both know that diabetic pregnant women who come in reporting vision loss will get this treatment. We need to know what happens to the fetus.

DR. GOODMAN: Excellent point. Ms. Massey.
MS. MASSEY: This is back to the quality of life outcome measures. As we do take a look at these measures, I would just caution that we not focus in on just one measure of activity and use that as the only measure. For example, driving is one that is often talked about, but there's other things that go into driving and as an age group and the Medicare population, there may be other factors for slowing down in the driving category that isn't related to vision, like

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neuropathy. So I would just want to see something that assesses all levels of function, not just the driving.
DR. GOODMAN: Great, good point. Dr. Steinbrook, yes.
DR. STEINBROOK: Just briefly trying to incorporate a different point, we haven't heard a lot in the presentations about other medicines which may be on the horizon. Obviously if there are some, they wouldn't be ready for clinical use now, but I don't know whether the state of the medicines which are now being compared are sort of it for a while, or whether there are scientific opportunities to have other medications where they might do a better job in answering these issues.
DR. GOODMAN: Anything? Dr. Thompson, why don't you comment on that? We're not going to dwell on it.
DR. THOMPSON: What all retina specialists would like is a long-acting anti-VEGF so we don't have to see these patients so frequently, and there's a lot of work done, you know, Dr. Ehrlich can probably talk about it, to try to look at those

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long-acting agents.
The other thing is that there is a small set of diabetic patients who just don't seem to respond to anti-VEGFs, which sort of goes to your question, and there may be a role for steroids in some of those patients. I have a few patients who are getting intravitreal triamcinolone injections because they just don't seem to get touched. So there is still an unmet need out there in terms of treating the small percentage of patients that don't respond to anti-VEGF agents who have diabetic macular edema.
DR. GOODMAN: Great, thank you. So

among the evidence gaps, and I know the transcript has them all, but we talked about more evidence regarding duration of therapy, the range of endpoints from biomarkers all the way to health-related quality of life measures and how those apply in real life. There would be some interest in seeing evidence regarding comparisons of the anti-VEGFs, more community-based data, more in the follow-up on adverse events, better definitions of adverse events and side effects, toxicity and so forth.

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Thresholds of effectiveness, when to start and when to maybe withdraw these. The sequence or steps of care involved. So those are just some of the kinds of evidence gaps that our panel has discerned thus far.

Question nine, panel, some of you have already talked about this so far as the types of study designs that would support the narrowing or closure of these gaps. I know that one or two people have already mentioned registries, comparative trials and so forth. I would assume, though, Dr. McDonough, with regard to differentiating among anti-VEGFs, you're probably looking for carefully designed RCTs.

DR. MCDONOUGH: That would be the best, if you can.

DR. GOODMAN: Okay. Dr. Phurrough.

DR. PHURROUGH: RCTs are not going to tell us all that we need to know about all of these drugs. They're for a limited period of time, limited number of patients; even though they study a lot of people, it is not going to answer all the questions. So there is a tremendous need for us to take the learning

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that has occurred over the last three or four years and other methods of collecting data, and analyzing that data and drawing conclusions from that data, and incorporate that into these processes, so that you don't run a randomized trial that's well done and then sort of quit. Those patients have a lot of information to continue to provide.

How do you do that? How do you take patients who are in a similar place who did not get enrolled, and we have some data on those through electronic records and our claims forms, so how do we merge that data? There's been a significant amount of work on how to do that and we ought to take advantage of that.

And then we ought to, speaking of

regulatory and industry, you can't stop collecting information. There needs to be a really strong requirement that's funded enough to do it in some manner or fashion. Once something new comes on the market, we can't raise the victory flag and move on from there. We've got to, there's a lot to know and a lot to learn, and we can't depend upon a single postmarket surveillance study to find that

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information.

DR. GOODMAN: Dr. Phurrough, are you talking about prospective registries when someone is treating with these, to put them in registries?

DR. PHURROUGH: There's all sorts of ways to do that. Registries is one of them. There are lots of techniques that have been introduced into, at least into the conversation. There are foundations that have been kind of looking at funding some of these where these kinds of methods are being developed and used, and seemingly have some potential benefit, so we need to be thinking of those as you're ending your trials now, what do we do as these trials end to continue to collect information.

DR. GOODMAN: Good, thank you. How would we track, the three of you that mentioned adverse events, side effects and toxicity, would these be long-term follow-up trials, registries, how might we track those potentially long-term adverse effects?

DR. PHURROUGH: There's a number of ways. There are national registries, many of

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the specialist societies have been establishing national registries. Cardiologists have done it vigorously. The orthopedists are doing it now. There's a good one up and running in California, the American Academy is working hard to establish that. Plastic surgeons are working on it, radiation oncologists are working on it. These are specialty-based societies.

AHRQ had some work in it, and there's international collaboration registries. Outcomes Inc. is attempting to develop sort of a registry of registries, so you can see what data is located in a number of different places. There are fairly simple changes to claims forms that can add information on specific harms that may happen when these are implemented.

When ICD-10 happens, if that ever does, it has now been delayed to past my Medicare card, but when ICD-10 happens there's going to be changes in claims forms, the Medicare claims forms, which are then, similar changes will happen outside Medicare that will allow a lot of clinical information to be

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added. So if the question is a fairly simple one, it might not come up with that particular outcome. Visual acuity, I mean, it's fairly simple to put visual acuity into a claims form, it's actually not difficult in the first place to list visual acuity, but that is a significant piece of information that would be simple to track, and there's various ways to do this, but we have to be innovative.

DR. GOODMAN: Great, thanks, Dr. Phurrough. Dr. Dubois.

DR. DUBOIS: I agree with Dr. Phurrough that to track efficacy is going to require changes to the claims forms. But I think more on the safety side, because the real worrisome events are things that probably would require hospitalization. That data is probably fairly accurate, and I think you can link together how many injections did this person get, because those are all billed events, so it's pretty easy to keep track of those. And the major thrombotic events are going to end up in a place where the diagnosis is probably valid.

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So that's something that doesn't take a whole lot of money. You don't have to build up a whole registry, and it can be followed. Where we might get a little bit of challenge is what the clinical indication was, but if you know the patient has diabetes, you're at a higher suspicion that it's one of the things that we're talking about.

DR. GOODMAN: Good point, Dr. Dubois. Dr. Gozansky, on the design aspect?

DR. GOZANSKY: So, I would just like to tie those two ideas together, and I think one of the important things that we're talking about here is that we really want to know what kind of quality-adjusted life years we're giving to our patients, and so making sure that they're actually tying those quality measures to our visual acuity or MI increases would be nice, and so I would advocate for something that incorporates patient-reported outcomes in

a registry type model as well.
DR. GOODMAN: Patient-reported outcomes in a registry type design, thank you.
DR. PHURROUGH: But Congress has figured that Medicare is not interested in
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cost.
DR. GOODMAN: Well, not cost, but quality. At least that's what Congress would say.
Any further comments about study design? We've answered it under question nine, but some of your comments under question eight also touched on study design. Any other points on study design here? Okay.
Before we adjourn, we've got a closing question, and I'm going to start with Dr. Puklin and move this way, and here's the closing question and a few restraints around that. The closing question is this, starting with Dr. Puklin. You can take your choice of the target of your answer, okay? Either for the Medicare program or for stakeholders in the best treatment of DME, either for the Medicare program or for other stakeholders in the management of DME, what's the single most important thing they better have heard today from our deliberations? If there was a single take-home point that Medicare needs to have about how they consider improving beneficiary outcomes for DME in managing the health of the
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beneficiaries, or for stakeholders that manufacture these treatments or deliver these treatments, or even patient advocates, what should be that take-home message that they got today that may provide input into their further decision-making or policy making in the future? You may address either the Medicare program or some other stakeholder represented here today, and please do it in a sentence, or just a couple of points, no speeches. Dr. Puklin.
DR. PUKLIN: Either Medicare or a group of targeted individuals in the Medicare population in a formal prospective randomized clinical trial utilizing the anti-VEGF drugs that are currently at stake with well-thought-out quality of life questionnaires that could be relevant to making determinative decisions.
DR. GOODMAN: Thanks, Dr. Puklin. Dr. Dubois.
DR. DUBOIS: That not only do the anti-VEGFs work, but they work substantially and in a relatively small NNT, and they do in

fact change people's lives.
DR. GOODMAN: Good. Thanks,
Dr. Dubois. Dr. Steinbrook.

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DR. STEINBROOK: Comparative studies, as we heard about, talked about, not just the agents, but also designs of how to treat people with the most sparing of injections possible.
DR. GOODMAN: Thank you.
Dr. Sedrakyan.
DR. SEDRAKYAN: More duration evidence is probably needed to advance comparative effectiveness, and making sure that there is a surveillance system to ensure that evidence in trials continues to be applicable to the ever-changing population of people that is going for this treatment.
DR. GOODMAN: Great. Thank you, sir.
Dr. Reddy.
DR. REDDY: Based on the current evidence, anti-VEGF agents work in patients with DME, but we need to be vigilant about monitoring continued efficacy and safety of these agents.
DR. GOODMAN: Excellent, thank you, Dr. Reddy. Dr. McDonough.
DR. MCDONOUGH: We need to be concerned about heterogeneity of effects and see if we can come up with some predictors of

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which patients will do better on which agents.
DR. GOODMAN: Thank you. Ms. Massey.
MS. MASSEY: There's a real promise of hope for improving the quality of life for people with this disease, and as we continue to go forward we should continue to focus on patient outcomes with valid and reliable measures.
DR. GOODMAN: Thank you very much.
Dr. Levine.
DR. LEVINE: There's been a lot of talk about the quality of life and patient outcomes, and I think it would be important as we design clinical trials to make sure that patients are consulted about what outcomes are most important to them, you know, up front when the study is designed, as opposed to us trying to make judgments as to what's most important to them.
DR. GOODMAN: Thank you. Dr. Heseltine.
DR. HESELTINE: The great majority of diabetic patients are managed by generalists, and while the instructions are to refer them

for review by ophthalmologists, I'm not at all
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convinced that that's happening frequently enough. And now that we have good treatment for DME, it becomes even more important that we get the word out to generalists that there's something that can be done to save sight, and I think that's essential.
DR. GOODMAN: Great, thanks, Dr. Heseltine. Dr. Gozansky.
DR. GOZANSKY: I think the idea that the anti-VEGF drugs truly do have meaningful and proven improvements in visual acuity, and that we need to optimize treatment regimens.
DR. GOODMAN: Thanks. Dr. Phurrough.
DR. PHURROUGH: It's difficult for me to take off my payer hat even though it's been three years, but we have heard today that we have significant advancement in the treatment of DME. We have evidence, though, that in a fairly limited population, people who may have visual impairment, and new and exciting treatments commonly have indication leap, not creep, and Medicare needs to be concerned about that.
DR. GOODMAN: Thank you, Dr. Phurrough. Before I turn it back over to
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Dr. Rollins, a few comments. First is that there is a very challenging epidemiology out there for this condition. The number of people that have diabetes is increasing rapidly. We're seeing diabetes in younger people much more than we have in the past, so even the etiology may be different here, so the epidemiology and the etiology out there are very challenging. They are affecting an increasing number of beneficiaries. This is a very important issue to Medicare.
Do anti-VEGFs work? Yes, they seem to work as a class. Are we done figuring out how well and in whom they work, not anywhere near. We don't know enough by far about which outcomes are important and how we can use those outcomes to differentiate among these products in a way to best treat individual Medicare beneficiaries in a personalized way.
In order to continue to collect this information we can't rely on any single type of study design, we're going to need a tool kit of study designs, randomized control trials, comparative effectiveness trials in the real world, we're going to need registries,
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prospective registries to follow patients to understand how patients of certain types, not that you've just got DME, but if you are a male of a certain age with the following set of comorbidities and other environmental conditions and personal preferences, people like you tend to do well or not so well with intervention A, B, C or D. We need to be able to track that on an ongoing basis.

So this is a multivariate problem for a larger and larger population that is very much at risk. We have a lot of work to do. It's not enough to say that we found that these things seem to work, we have a long long way to go. This panel today has carefully identified the evidence gaps and provided some insight about what sort of studies we need to generate that evidence on an ongoing basis.

Panel, thank you very very much. I'll turn it back over to Dr. Rollins.

DR. ROLLINS: Yes. I would line to thank the chairperson, the vice chairperson, the members of the MedCAC committee as well as the presenters today for this great discussion. And as I said earlier today, we do not have an

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open NCD on this topic. If there's nothing more to say, we call this meeting adjourned. Thank you again.

(Whereupon, the meeting adjourned at 3:51 p.m.)