FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

(CDRH)

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SUPPORTING INNOVATION FOR SAFE AND EFFECTIVE

MINIMALLY INVASIVE GLAUCOMA SURGERY (MIGS)

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PUBLIC WORKSHOP

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WEDNESDAY

FEBRUARY 26, 2014

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The Workshop met in the Washington Marriott Hotel at Metro Center, Grand Ballroom, Salons A-C, 775 12th Street, N.W., Washington, D.C., at 1:00 p.m.

PRESENT

JOSEPH A. CAPRIOLI, MD, Moderator
MALVINA B. EYDELMAN, MD, Moderator
RONALD L. FELLMAN, MD, Moderator
DAVID S. FRIEDMAN, MD, MPH, PhD, Moderator
RICHARD A. LEWIS, MD, Moderator
JEFFREY M. LIEBMANN, MD, Moderator
MARLENE R. MOSTER, MD, Moderator
RICHARD K. PARRISH II, MD, Moderator
THOMAS W. SAMUELSON, MD, Moderator
KULDEV SINGH, MD, MPH, Moderator
HUSAM ANSARI, MD, PhD
JAMES D. BRANDT, MD
REAY H. BROWN, MD
DONALD L. BUDENZ, MD, MPH
BRIAN E. FLOWERS, MD
BRIAN A. FRANCIS, MD
PAUL HARASYMOVYCZ, MD, FRCSC
LEON W. HERNDON, JR., MD
DALE K. HEUER, MD
HENRY D. JAMPEL, MD, MHS
MURRAY A. JOHNSTONE, MD
MALIK Y. KAHOOK, MD
L. JAY KATZ, MD
TINA KIANG, PhD
CYNTHIA G. MATTOX, MD
ROBERT J. NOECKER, MD
DOUGLAS J. RHEE, MD
EVA RORER, MD
STEVEN R. SARKISIAN, JR., MD
GREGORY L. SKUTA, MD
GEORGE L. SPAETH, MD
ROHIT VARMA, MD, MPH
STEVEN D. VOLD, MD

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

1:03 p.m.

DR. SINGH: Well, welcome, everyone, to the second workshop that the AGS and the FDA have partnered on. We had one imaging about a year and a half ago.

Today I think we have a very important and exciting workshop. I just want to say a few words about the American Glaucoma Society. Many of you are members of the Society; others are guests, and we also have a lot of FDA personnel here.

The mission of the Society is to promote excellence in the care of patients with glaucoma and preserve our enhanced vision in supporting glaucoma specialists and scientists through the advancement of education and research.

And with all the exciting things happening in glaucoma, we find opportunities, such as the one we have now, to partner with the FDA to have an open discussion about a very, very important and exciting area where cutting-edge technologies have brought us new glaucoma operations. And today we're going to hear about these procedures, and we will also have three panel discussions relating to various aspects of studying these newer devices that are being used concomitantly with cataract surgery currently and also have potential to be used as standalone procedures.

With no further ado, I would like to introduce Malvina Eydelman, who heads the Ophthalmic Devices Section of the FDA, along with many other hats she wears. And I will ask Malvina to come up and say a few words about the FDA's perspective on this event.

DR. EYDELMAN: Thank you, Kuldev.

And welcome, everyone. Thanks for putting up with our D.C. weather and still making it here today.

In the last few years there has been almost an exponential increase in the number of literature articles dedicated to the novel glaucoma surgical devices. We have also heard quite a number of abstracts, papers, courses, and seminars at annual professional meetings. As a matter of fact, it just was in the last year the numbers almost doubled.

However, it comes to minimally-invasive glaucoma surgery devices, we still have more questions than we have answers. When we review the literature, there is a lack of consensus trials of what is a MIGS device, what is the appropriate patient population, what are the safety endpoints and targets, and what should be the effectiveness endpoints and targets. As many of you know, lack of common understanding of basic terminology always leads to problems.

At FDA Center for Devices and Radiological Health, we have seen an increasing number of submissions for MIGS devices. Unfortunately, as of today, there's a lack of FDA guidance or recognized standard. And therefore, we cannot clearly delineate safety and effectiveness endpoints for investigation of these devices, and we end up having quite extensive discussions with each individual sponsor.

What we would like to do is to be able to provide industry with a predictable, consistent, transparent, and efficient regulatory pathway that will allow us to facilitate medical device innovation. That's our goals for today's workshop, to discuss the best clinical trial design for MIGS devices and try to identify the appropriate patient population, safety assessment, effectiveness assessment.

We hope that today's discussion will be a foundation for development of leapfrog guidance for MIGS devices. That's a mechanism via which we can share our initial thoughts regarding the content of pre-market submissions for such emergent technologies. Such leapfrog guidance will help speed the development and approval of future submissions and

help us achieve our vision of bringing high-quality, safe, and effective medical devices of public health importance first in the world to U.S. patients.

So, today let's challenge the definitions, generate some ideas, develop solutions, and change MIGS devices from moon shots to reality.

Thank you.

(Applause.)

DR. SINGH: Thank you, Malvina. I just want to say it's been an absolute pleasure working with Malvina and her team in putting this workshop together. It has been an incredible amount of work, but it has been fun all the way along, just because the FDA has been so helpful and cooperative and fun to be around.

So, with that, I would like to introduce the first session, and our co-moderators for this first session are Marlene Moster from Wills Eye Hospital and Tom Samuelson from Minnesota Eye Consultants.

So, I am going to ask either Tom or Marlene to come up and introduce the session.

DR. SAMUELSON: Well, Marlene is our first speaker for the session. So, I'll let her get settled.

I'm Tom Samuelson. I'm from Minneapolis.

This is fantastic, to have a forum between the FDA and physicians and the American Glaucoma Society, really a dream come true for this space.

So, Marlene Moster is going to lead us off. This session is going to basically give an overview to the procedures involved in MIGS.

DR. MOSTER: Good afternoon, everyone.

On behalf of the Introduction Committee, I would like to talk to you this afternoon

about leaving the past behind and why we are so looking forward to minimally-invasive glaucoma surgeries. I have nothing to disclose regarding this lecture.

Now why are we so interested in MIGS? Remember that glaucoma is the second leading cause of blindness in the United States, where 2.3 million Americans have glaucoma; only half are aware that they actually have this disease. Twenty percent of eyes treated for glaucoma may require in their lifetime surgical care due to progressive visual field loss and optic nerve deterioration.

Glaucoma also has serious economic impact and accounts for over 10 million visits to physicians each year. In terms of Social Security benefits, lost income tax revenues, and healthcare expenditures, the cost to the United States Government is estimated to be over $1.5 billion annually.

So, then, doesn't it make sense to treat glaucoma efficiently, so visual loss does not occur? Just how do we do that? Well, of course, we have medicines. We have lasers. And, ultimately, we have surgery, if needed.

Although roughly 75 to 80 percent of patients could be controlled with medications, compliance with medicine is a huge issue. People just do not use their glaucoma drops reliably and, therefore, continue to go blind.

Now lasers certainly help treat glaucoma, but they are not the answer, as the pressure may not come down sufficiently, and often medications are still needed.

So, then, we are left with traditional glaucoma surgery called a trabeculectomy. This is done under local or topical anesthesia, and a block is removed, meaning taking out part of the trabecular meshwork and adjacent structures to form a new conduit between the anterior chamber under the scleral flap that is created. This fluid, then, goes under the flap under the

conjunctiva and forms a bleb or a reservoir, so that the intraocular pressure comes down and this fluid is then absorbed by the system. Once the block is removed, an iridectomy is often necessary at the time of surgery.

Another alternative is to use a tube shunt. This is a Baerveldt 350 tube shunt. It is a plastic device that is placed under the muscles, affixed to the sclera. The tube is then cut, placed in the anterior chamber, and aqueous is shunted from the anterior chamber over the plate. Thus, the intraocular pressure is lowered.

Now would you personally want to undergo a surgical procedure that has significant risk? You would, of course, if there weren't many alternatives. However, perhaps if the glaucoma were not so severe and newer devices and procedures with acceptable efficacy and safety were available, might that not make more sense?

Remember that trabeculectomy is still the gold standard, and complications from trabeculectomy occur with sufficient frequency that this surgery is usually reserved for severe disease. Why is that? Not because it doesn't work, but because of the risks.

These risks include problems with anesthesia, scarring with high pressure of the bleb and failure, problems with cyst formation and astronomically-high intraocular pressure, large blebs with foreign body sensation and possible deformity, blood everywhere, under the conjunctiva, in the anterior chamber, and even under the retina.

Not only can the pressure be too high, but the pressure can be too low following trabeculectomy, and this is called hypotony, due to overfiltration.

The anterior chamber can collapse, causing visual compromise and anatomic distortions.

Astigmatism can be a sequelae of hypotony with decreased vision.

And if the lens is not nourished due to too low an intraocular pressure, all kinds of cataracts can develop, again with decreased vision.

Holes can develop over time in the bleb, and this can lead to serious infection, which we call blebitis or endophthalmitis. And this often results in permanent, irreversible visual loss.

So, then, if possible, we are ready to leave the past behind us. And by way of introduction, we are now looking forward to discuss the pros and cons individually of the newest minimally-invasive surgical glaucoma techniques.

I would now like to introduce Dr. Brian Francis, who will talk to us on non-implantable MIGS devices.

I think I'll stop here. Thank you very much.

(Applause.)

DR. FRANCIS: Thank you very much, Marlene.

My talk today is going to be about non-implantable MIGS procedures.

This is my slide for I'm on the Medical Advisory Board for NeoMedix and EndoOptiks.

First, I want to have a quick case presentation, why we're doing MIGS. And it kind of follows what Marlene was saying.

But this is a patient I saw two weeks ago in clinic. So, it is really fresh in my mind. We have a 78-year-old Caucasian female with POAG, .9 cup in the right eye. IOP was 24 on three meds. She underwent a Baerveldt implant tube shunt, which we believe is safer, according to TVT, than trabeculectomy.

However, upon tube opening, she had hypotony and flat AC, led to choroidal effusions with a mixed choroidal hemorrhage, and eventual corneal decompensation. We did a tube

exchange for an Ahmed to give a floor for the IOP and we did a corneal transplant.

But, despite all these interventions, she goes from 20/70 pre-op on the upper left; now she's bare light perception. So, this, in a nutshell, is why we're looking at MIGS. And this is my patient. So, this is my surgical technique. So, I can't blame it on anyone else.

So, what we're looking at in this talk is three different procedures: ECP or endoscopic cyclophotocoagulation, which has been FDA-approved for many years; trabeculectomy ab interno with a trabectome, which has been FDA-approved since 2006, and ELT or excimer laser trabeculostomy, which is under investigation currently.

The ECP we'll start with. It's one of the cilioablative procedures, but, as opposed to traditional external ablation, this is done with an endoscopic device. And you can see that device here. This is the console on the upper right, and here's the endoscope with the laser, image and light, as well as aiming beam.

So, this is what the procedure looks like. You inflate the ciliary sulcus space and you go in between the lens and iris, and you ablate the ciliary epithelium of the ciliary processes. And this can be done -- it's titratable in the sense that you can control how many clock hours you're performing and how deep the ablation is.

So, advantages of ECP:

It's a titratable treatment of the ciliary process. It's a unique mode of action in MIGS. So, it's the only MIGS procedure that decreases aqueous production.

It may be additive to other procedures, other outflow procedures, because of that.

It can be used in any glaucoma. It doesn't have to be an open angle. It's not an angle-based surgery.

And the endoscope that's used in this procedure can also be useful in other anterior

segment and posterior segment procedures.

A couple of disadvantages:

No. 1 is inflammation. Inflammation postoperatively can be severe and needs to be treated aggressively.

And there is a learning curve for endoscopic surgery. It's not your traditional surgery where you're using the binocular microscope.

So, shifting gears now, we're looking at surgeries in the angle. And basically, we're looking at surgeries that are bypassing the trabecular meshwork.

And this is a slide from Doug Johnson which shows the collector channel ostia after trabecular meshwork has been removed.

The first procedure is a trabectome. You're probably familiar with this. It's an electrocautery device that permanently ablates part of the trabecular meshwork, and thereby, unroofs Schlemm's canal and exposes the Schlemm's canal and the collector channels to the aqueous in the anterior chamber.

This is the surgical procedure. It's done via gonioscopic surgical approach. Here's a temporal corneal incision. And the gonio lens is placed back on the eye, and the hand piece is inserted into the anterior chamber. The tip is inserted through trabecular meshwork into the Schlemm's canal and the ablation is carried out. And you can see the area where there is ablation to the right here of the trabecular meshwork.

And this is what you're looking for postoperatively, where you have the trabecular meshwork removed here and you have what we call a trabectome cleft.

So, advantages: it opens a continuous pathway from anterior chamber into Schlemm's canal. The cautery removes the tissue to prevent closure of the canal again.

There is no conjunctival scarring, as with other MIGS procedures. The clear corneal approach combines well with cataract surgery.

Disadvantages: the cleft may close with peripheral anterior synechiae or may close downstream. And the access to Schlemm's canal circumferentially is limited. You're only treating whatever clock hours you have access to.

The final procedure is ELT or excimer laser trabeculostomy. And we'll show you the procedure here.

This is the excimer laser. It's, again, done with a clear corneal incision. This time this is an indirect gonioscope. So, you're looking straight down instead from the side.

The excimer laser probe is abutted all the way out to the trabecular meshwork and, then, activated. And you can see, when there's a bubble formation, you're actually cutting a hole through trabecular meshwork into Schlemm's canal. And several different entry sites are made with this procedure.

And at the end of the procedure, you can see the reflux of blood from Schlemm's canal, which is pointed out by the arrow here.

Advantages: it opens multiple pathways from the anterior chamber to Schlemm's canal. There is no conjunctival dissection again. There's a controlled ablation with excimer lasers. There's no heat damage to surrounding tissues. And again, easily combined with phacoemulsification cataract surgery.

Potential disadvantages: the outflow pathway is limited to the size and number of the openings. And again, flow in Schlemm's canal is limited circumferentially. You're only accessing the Schlemm's canal in the area that you're treating.

So, in conclusion, the non-implantable MIGS procedures have the advantages of the

other MIGS procedures which you'll hear about today in terms of reduced risk versus traditional glaucoma filtering surgery, but there's no implant-related complications, such as possible corneal iris damage, scarring or fibrosis of angle tissues beyond the postoperative period due to the implant itself, and no problems with extrusion or dislocation of an implant.

Thank you.

(Applause.)

DR. SAMUELSON: Now we're going to have a series of three talks, each addressing a specific reservoir for aqueous egress for MIGS.

The first, Schlemm's canal, will be discussed by Reay Brown, who, by the way, is the 2014 Innovative Award recipient for the AGS.

DR. BROWN: Tom, thank you very much.

Oh, I do have my slides. Thank you.

I'm going to be talking about, as Tom said, the implantable MIGS devices, canal-based.

These are my disclosures.

We're basically talking about two devices, the iStent, which is the first MIGS device to be approved, and also, the Hydrus, which is still in studies.

And I want to deal with three questions: why does trabecular bypass make sense? What can we expect? And which patients will benefit the most?

And I want to start off with a case, and this is somewhat like Brian's, but I'm going to be talking about the good eye. This is an 87-year-old monocular patient with pseudoexfoliation. She has a moderate cataract in her good eye. Her last four pressures have been around 30 on maximum medications, including pills. But she has a full field.

So, what should I do? I have many surgical options, a tube or a trab, a combined

cataract and a tube or a trab, cataract alone, or cataract with an iStent.

And as we have already heard, we don't want to do a trab or tube because of the high risk, unless we really need to, especially in a monocular patient. And like Brian's case, she had lost her other eye due to complications of a tube.

So, I decided to do the iStent and cataract. This is her iStent procedure. And we've all seen these.

The sharp tip pierces the meshwork, and I'm going to flatten out the body of the device and slide it along the canal. It's now in good position. I'm going to release and push it down along the canal to make sure it's properly seated.

So, on postop day one I was a little surprised. Her vision was 20/20 uncorrected, which would be quite rare with a trab or a tube. Her pressure was 21. And at three months her pressures had been in the mid-teens on two drops and no pills. And we're both, obviously, very grateful to be able to control her pressure without having taken the risks of a tube or a trab.

So, I want to get back to the questions. Why does trabecular bypass make sense? Well, if the site of resistance is the meshwork, it would be wonderful if a device like the iStent or the Hydrus could open that pathway, so that aqueous could bypass the meshwork and go directly into the canal and, then, on to the distal outflow system.

And this is what we hope is happening. A tube is already in the canal, and blue dye is being pushed along the canal at one place, right here. And you can see how the whole outflow system lights up in a matter of seconds. So, that is available to us if we can just tap into it. And that's what we see as the promise of trabecular bypass.

I wanted to spend a couple of minutes talking about EyePass, which was the first

trabecular bypass device. It was developed by my wife, Dr. Mary Lynch, and I in 1999. And we did the first FDA study in humans.

But this was a challenging study because the FDA told us that we needed to do 10 functionally-blind eyes. And that was really a body blow to a small company trying to develop a new device for glaucoma.

But I bring it up also because now we have 13 years of follow-up on these patients. And this is a case that was done 13 years ago, and we've seen no erosions, no migrations, no corneal decompensation, and no chronic inflammation. So, the EyePass was a very safe device, and the canal is a very safe and stable place.

We have seen data from the iStent and also Hydrus showing excellent pressure response to those devices, but is there any clinical evidence for trabecular bypass?

And I want to show this case. This is the snorkel of the iStent and the stent is pointed this way. And you can see there's more pigment downstream along the course of the iStent than in the other direction. And pigment suggests outflow.

This is another case showing more pigment downstream than upstream and, again, suggesting outflow is improved with the iStent.

But what can we expect with these devices? The pressures are not going to be as low as with trabs and tubes. We can't below episcleral venous pressure. So, the best pressures that we can get are probably in the mid-teens. This is going to be enough for most patients, but it may not be enough for patients with advanced disease.

But the good news is that trabecular bypass takes these complications off the table. No more hypotony and no more blood infection.

Well, which patients are going to benefit most? On this graph, we see the

distribution of which glaucoma patients take how many medications, one drop, two drops, three, and four drops. Seventy-five percent of glaucoma patients take one or two drops, and these are the candidates for the iStent.

The safety of bypass devices could make glaucoma more of a surgical disease. And this would have many advantages. It's much simpler and avoids the problems of eye drops like compliance, expense, and side effects.

This is a patient who has good pressures in both eyes. He has surgery on this eye and is on two drops in this eye. But he has all the complications of eye drops. He has the long eyelashes, the darkened skin, the sunken orbit, and the very red eye. And yet, we think of this as successful treatment because the risks of surgery are just too great.

But trabecular bypass devices can change this paradigm. They can safely make glaucoma more of a surgical disease and reduce the need for medical therapy, so that we have fewer glaucoma eyes looking like this and more looking like this.

Thank you very much.

(Applause.)

DR. MOSTER: Thank you, Reay.

I would like to introduce Steven Vold, who will talk about implantable MIGS devices within the suprachoroidal space.

DR. VOLD: Thank you, Marlene and Tom. It's a real privilege to be here.

I get the privilege today to talk a little bit about suprachoroidal outflow as a surgical target for the treatment of glaucoma.

And just as a means of disclosure, there we are. I had an opportunity to work with many of the companies that developed these devices.

As we talked about already to some degree, there's really two main outflow pathways for aqueous humor. We have the trabecular pathway, which Reay has so nicely elucidated. We also have the uveoscleral outflow. And this is something where it has really been considered pressure-independent and contributes up to 57 percent of total aqueous outflow.

And I remember when I was in my residency training we actually thought that uveoscleral outflow was closer to 10 percent. But the studies more recently have shown it's a much larger proportion of outflow, and we have seen the prostaglandins, that it's really a powerful way of getting fluid out of the eye.

And if it goes through the sclera and choroidal blood vessels, we have found that really the most resistance is at the level of the ciliary body. So, the question is, how can we really improve our pressure control?

Well, we believe this pressure differential between the anterior chamber and suprachoroidal space is 4 millimeters of mercury at physiologic range. And so, we have this robust pressure gradient.

Also, we have this large space that's really 160 pounds more surface area than the trabecular meshwork. So, potentially, it's a very powerful force for lowering intraocular pressure.

And then, we also have the precedent of the prostaglandins, which we know is right now probably our most powerful medical treatment for glaucoma.

In the past we have had cyclodialysis clefts, and one of the problems that we have faced is this issue of scarring with the suprachoroidal space. And so, people with cyclodialysis clefts, which people actually in the past have done with surgery, sometimes it would work really well and, then, other times these things would close; we would have incredible high pressure

spikes, and sometimes patients would not do as well. So, the goal here is, by using a stent, we can have a much more controlled cleft there, and, then, also, hopefully, prevent the closing-down of this space over time.

We currently have two devices that are undergoing investigation from an ab interno approach. There is also one that has been attempted from an external approach. Today we are kind of talking about the ab interno approach.

We have the CyPass Micro-Stent, which is a fully-enrolled FDA clinical trial with over 500, I think 505, patients enrolled in this study. We are now a year out in this study. So that, we are really coming and very shortly will have some real answers on this topic. Also, we have the iStent Supra, which is a very similar device which is currently in FDA trials as well.

Here is the approach of surgery. And one of the things that is no nice about the suprachoroidal approach here is really you just have to go to the base of the scleral spur. And rather than sometimes the challenges of putting a device in trabecular meshwork, this is really a very simple approach to do. You just have to have good visualization and gently slide this device into the suprachoroidal space, and it really just slides in like butter if you're in the right space.

And the trick there is at the end of the device I really like to have the device end up between the pigmented trabecular meshwork and Schwalbe's line. That way, the tube is not going to be resting on the corneal, and we don't want it to go down too deep as well because, then, you potentially could end up with some synechiae and close off the tube.

Some of the challenges that have faced, and Reay was kind of talking about this. I think in more advanced disease we know that the longer you are on medications and the more advanced your glaucoma, sometimes the downstream resistance is quite high. We assume

that about 70 percent is at the level of the trabecular meshwork, but the reality of it is that in some patients it's probably significantly more, even downstream, and potentially can make for challenges with the device.

Also, we're still learning as to where to place these devices. There's some variability in collector channel location. Sometimes we can look when we do trabecular stent devices; we want to place them near the largest collector channels. And it will be interesting to see as we learn and get more experience and data on this, to see if we can be more precise in our precision in placing those devices.

The other thing is here it's really the only thing we have to do in placing a suprachoroidal device is you just want to avoid the large blood vessels. And really, that's something that's very simple to do. And so, it just makes it a little bit easier to place for most surgeons.

So, really, in summary, this appears to be a very promising target. We still have a lot to learn about it. But the potential it has for potentially lowering IOP more efficaciously than anything we have had as far as a micro-invasive approach.

Preliminary safety results from the international experience is in line with other MIGS devices. And I speak from personal experience to say that it appears to be a very safe procedure as well.

The anatomic approach makes for an elegant procedure. Overall, suprachoroidal represents a very promising MIGS approach.

Thank you so very much.

(Applause.)

DR. SAMUELSON: The third target, blood flow, the subconjunctival space, is

certainly the most familiar to us. And Steve Sarkisian is going to review MIGS procedures using the subconjunctival space.

DR. SARKISIAN: Good afternoon.

So, here's my disclosure.

So, trabeculectomy, what's the big whoop anyway? Marlene did a great job on packing some of the major problems with trabeculectomy.

Here's a photograph of a patient who has had a trabeculectomy and has a bleb leak; as you can see, the aqueous pushing the fluorescein out of the way there.

And she unpacked it very nicely, but I'll just reiterate it because it's a large part of the reason why we're having this discussion. Endophthalmitis and blebitis, bleb leak, hypotony and the problems that happen therein.

Bleb dysesthesia is a big deal. We see lots of patients 10 years out who, by our standards, have done beautifully. They have this wonderful-looking bleb, and we're just so happy with ourselves for having helped them. And they have these long lists of chronic problems that make them miserable, but we just say, "You're doing great," you know.

And astigmatism is another problem. So, really, after we have this successful surgery, we are really helping our patients live with disability almost, with having this bleb here.

So, let me talk a little bit about the subconjunctival space. The first procedure is the AqueSys XEN Gel Stent. Currently, it's the only true MIGS device being investigated that's implanted into the subconjunctival space because it's ab interno.

Now my apologies to the InnFocus people because they have a device that's similar, but it's ab externo. And so, for the sake of this talk, I have excluded it. However, it has a similar philosophy.

The ab interno implantation has been, personally, it seems to me, up for discussion a little bit with MIGS, but it has been my personal bias about how to define MIGS. And so, as Dr. Eydelman said in her great talk, the very first thing we're doing is kind of discussing what defines MIGS. And so, that's a discussion I would like to have.

AqueSys XEN Gel Stent is soft. It's a compressible implant that is the size of a human hair. It bypasses the conventional outflow pathway by filtering aqueous into the subconjunctival space.

So, it is made of this hydrophilic cylindrical implant of porcine gelatin cross-linked with glutaraldehyde. And this gives it some permanence. And really, it hydrates, swells, and creates this drainage channel.

And here you can see a picture of it, both the device in a photograph and an OCT where it's placed. This, as well as the InnFocus device, which I am a consultant for -- I'm not for the AquaSys -- follows this law, this Poiseuille's law of laminar flow that dictates that, if you have a skinny-enough tube and a long-enough tube, that the rate of flow will be managed.

This particular implant does have an injector that you can use one hand for. It is somewhat like an intra-ocular lens inserter.

This is a complicated slide. I'll direct your attention to the right, where you can see the slit lamp view of the device, a gonioscopic view of the device, and, again, an OCT view of the device. And then, I have a video that will show these multiple steps here.

This figure I believe is courtesy of Len Byae.

Here you can see through a paracentesis, going across the eye, engaging the angle, using a second paracentesis to hold the eye still, and going into the subconjunctival space from an ab interno standpoint. You can see the bevel of the needle come through. And once

that's been visualized, pushing on the injector to release the implant into place.

So, when you think about this, the differences between an ab externo bleb and an ab interno bleb, they're fairly significant. If our motivation is to minimize complications from issues with a bleb, then the differences here are a low-lying diffuse bleb that seems to be having been demonstrated with the XEN ab interno bleb compared to an elevated and focal bleb, due to ab externo dissection.

The wall of the bleb with a conventional trabeculectomy is typically thin, and this allows for a higher potential risk for complications, like we have discussed. And the studies will, hopefully, bear it out, but these are some sample pictures of what the blebs might look like for the XEN ab interno.

Currently, the XEN Gel Stent is an investigational device within the U.S. So, there's not much data to present. But AqueSys is conducting two studies in refractory glaucoma subjects in the U.S. as a standalone procedure. One study completed enrollment and follow-up is ongoing. The second study is currently enrolling subjects. It has obtained CE mark in Europe, and Phase 4 studies are ongoing, and a limited commercial launch is underway.

Thank you very much for your time.

(Applause.)

DR. MOSTER: The next speaker will be Tina Kiang from the FDA to talk about the FDA's regulation of glaucoma devices.

Dr. Kiang?

DR. KIANG: Thank you.

So, let's begin at the beginning. What is a medical device? Something is considered a medical device if it diagnoses, cures, mitigates, or treats or prevents disease or a condition,

affects the function or structure of the body, and it does not achieve the intended use through a chemical action, and it will also have not metabolized.

This slide shows the broad diversity there are in what is considered a medical device, from band-aids to a fully-implantable artificial heart. So, with such a diversity, how does FDA determine how to regulate these things?

So, the law gives us the flexibility to calibrate our regulatory approach to a level of potential risk by new products. So, it is a risk-based paradigm by which we regulate these products.

Through this risk-based paradigm, we have classified devices under one of three classes: Class 1, which are usually the simplest and lowest-risk devices; Class 2, which are more complex and have a slightly higher risk, or Class 3, which are the most complex and the highest-risk devices. In the next few slides I am going to describe each of these classes individually.

So, Class 1 devices are those devices that are considered able to be regulated by use of general controls. General controls are establishment registration with FDA, medical device listing with FDA prior to marketing, manufacturing that is regulated through quality system regulations. There are labeling requirements for these devices for use, and medical device reporting by companies or by patients when something goes wrong with the device. Most Class 1 devices are exempt from pre-market notification.

Class 2 devices are devices for which general controls are not enough to provide sufficient reassurance of reasonable safety and effectiveness of devices. So, in addition to general control, special controls are implemented in order to provide this assurance.

Special controls consist of performance standards, guidance documents issued by FDA,

device tracking, and/or patient registries. Most Class 2 devices, but not all, require pre-market notification or 510(k) submission prior to this marketing of the device.

Class 3 devices are the most risky devices or have the potential for most harm if used. So, the Class 3 devices are those devices which are regulated by both general controls plus the submission of a pre-market application.

So, these are usually reserved for devices that support or sustain human life, have a substantial importance in preventing health impairment, or have a potential unreasonable risk of illness or injury. And again, it requires a pre-market approval application with data to assure reasonable safety and effectiveness.

So, I mentioned it a little bit in the past couple of slides, but I'm going to go into the specific regulatory submissions in the next few slides.

Any devices that are non-exempts Class 1 or Class 2 devices require the submission of a 510(k) before marketing of the device in the United States, and all Class 3 devices require the submission and approval of a PMA prior to marketing of the device in the United States.

So, what is a 510(k)? It's called a 510(k) because the definition is written out in Section 510(k) of the Food, Drug, and Cosmetic Act. It is a marketing clearance application that should be submitted to FDA at least 90 days prior to marketing of the device.

It allows FDA to determine substantial equivalence of a legally-marketed device to a legally-marketed device that is not subject to a pre-market approval. So, what is substantial equivalence then?

When we look at a device, we determine if its substantial equivalent if, in comparison to a legally-marketed predicate device, another 510(k) device that's already been cleared and on the market, it has the same intended use and has the same technological characteristics as

that predicate. Essentially, almost identical or, if the device has the same intended use and, if it does have different technological characteristics, the information in the 510(k) does not raise new types of safety and effectiveness questions, and that the performance data provided in that 510(k) demonstrates that it is safe and effective as the chosen predicate device.

For pre-market approval application, or PMA, this is an application for Class 3 devices to request approval before going to market. The application needs to contain sufficient valid, scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use.

When we are reviewing applications to determine safety and effectiveness, we take a number of considerations. First, the intended population for the device; the conditions of use for the device; the probable benefit to health versus the probable risk of injury or illness from use, in other words, that the benefits of the device outweigh the overall risk of the device, and the reliability of the device overall. And this is only based on valid scientific evidence that is submitted in the PMA.

So, we're here to talk about glaucoma devices today. And generally, we look at the glaucoma devices in two different ways. We have diagnostic tools which typically require 510(k) and we have therapeutic glaucoma devices which can come in under 510(k) or PMA.

So, on this slide are listed diagnostic tools. I'm sure many of you are familiar with them. Diagnostic tools are typically indicated for the aid in the diagnosis of glaucoma. Since the subject of this workshop is not diagnostics, I will pass over.

For therapeutic glaucoma devices, we kind of look at them in two separate categories as well. We have the lasers for surgical procedures. These typically come in through 510(k). And we also have implantable glaucoma devices which can come in under 510(k) or PMA,

depending on the indications for use and the intended population.

We look at the populations as either refractory or non-refractory, and Dr. Eva Rorer will discuss these a little bit further in her talk which is after mine.

I do want to note that there are no surgical tools that have been specifically cleared by the FDA with their treatment of glaucoma indication.

So, under the category of implantable therapeutic devices, for the first population, refractory, these are devices that are intended for subjects who have failed medical treatments and filtering surgery and for subjects who are likely to fail filtering surgery.

All of the previous glaucoma shunts have been cleared with indication for IOP reduction, and all the previous glaucoma shunts have been cleared through the 510(k) process.

For the non-refractory population, which is for the less severe glaucoma, we currently have two devices approved, the Staar Aquaflow Collagen Glaucoma Drainage Device and, of course, the Glaukos iStent.

As Malvina has shown you, there are many devices that are under investigation and have been many papers and talks about in the recent years. And all of these devices would require PMA approval before coming to market.

So, how would one go about coming to FDA in order to discuss one of these devices? Well, we have a mechanism for that, and we very much encourage you to use this mechanism. So, we have this pre-submission program, the final guidance, which was issued, in fact, last week, which is meant to facilitate device development and innovation by providing informal feedback on, for example, proposed preclinical testing or trial design.

When we receive these, we have a goal of 75 days to provide you formal feedback either in written form or if you wish to come in for a face-to-face meeting. And it will provide

an open discussion on your trial design, either at the very beginning or while you're in development or as you're moving along, moving towards your trial.

So, if you have a copy of my slides, you can click on the link to look at it.

And we look forward to your submissions.

Thank you.

(Applause.)

DR. SAMUELSON: Thank you.

The next talk is by Dr. Eva Rorer from the FDA, ANSI standards for implantable glaucoma devices: a framework for clinical evaluation.

DR. RORER: Hello. I'm going to be speaking to you today about the clinical trial recommendations and the American National Standards Institute, or ANSI, Draft Standard for Implantable Glaucoma Devices.

FDA has been working with ANSI as well as the International Standards Organization since the 1980s to develop ophthalmic device standards. There are 36 FDA-recognized ophthalmic standards. These standards help assure consistency and predictability, reduce data-reporting requirements and pre-market approval applications, PMAs, but also in 510(k)'s, and result in decreased review time.

A working group was convened to revise an outdated ANSI standard for aqueous shunts to make it more applicable to innovative implantable glaucoma devices. That work was recently completed, and the product of that work, the Draft ANSI Standard for Implantable Glaucoma Devices, Z80.27, passed a vote, and its publication is pending.

The scope of this standard applies to devices which are implanted in the eye to treat glaucoma by facilitating aqueous outflow. And the purpose is to describe the physical,

mechanical, and biocompatibility properties, as well as the elements of clinical protocols that may be useful in assessing the clinical performance of these devices.

The majority of the information in the Draft Standard regarding the clinical investigation of implantable glaucoma devices is in informative annexes, meaning it is there to provide recommendations or guidance, and it's not required per se.

Recommendations for enrollment criteria, sample size, length of follow-up, and clinical evaluations vary by intended target. This has been divided into refractory glaucoma and non-refractory glaucoma. Analyses and adverse events are similar for both of these targets.

So, the definition of refractory glaucoma that is put forward in the standard is glaucoma that is uncontrolled by medical therapy and the eyes that have this condition have to meet at least one of the following criteria as well:

They have to have failed one or more incisional intra-ocular glaucoma surgeries, failed one or more cilioablative procedures, have neovascular glaucoma, or have any other condition in which a conventional incisional glaucoma surgery would be more likely to fail than for an eye with uncomplicated primary open-angle glaucoma. So, failing laser trabeculoplasty alone is not enough to meet the definition of refractory that is included in this Draft ANSI Standard.

For non-refractory glaucoma, the Draft Standard defines this as eyes diagnosed with glaucoma which do not meet any of the criteria for refractory glaucoma. They may or may not be treated with medications or laser trabeculoplasty, and they may be candidates for medical therapy, laser treatment, and glaucoma filtering surgery. They may have undergone uncomplicated cataract surgery, retinal laser or extra-ocular muscle surgery.

So, for refractory glaucoma, the Draft ANSI Standard recommends that the inclusion criteria in the protocol specify the minimum and maximum IOP allowable, the maximum degree

of visual field restriction in the non-study eye, and the type of glaucoma.

The exclusion criteria includes no light perception vision, need for a combined procedure, or anticipated need for ocular surgery or retinal laser within the follow-up period, best corrected visual acuity worse than 2200 in the non-study eye, and conditions and mechanisms that could confound the outcome or decrease patient safety, and, also, inadequate space in the anterior chamber and/or angle for safe device placement.

So, the clinical evaluations that are recommended are typical for what you would expect with glaucoma, except perhaps the diurnal IOP assessment and, also, a validated patient questionnaire that covers the symptoms and the conditions that are described there on the slide.

The draft ANSI recommendations for refractory glaucoma also say something about what should be the sample size in terms of there should be at least 50 evaluable investigational device subjects at the final time-point. Follow-up should be a minimum of 12 months, and criteria for preoperative and postoperative discontinuation and reinstitution of IOP-lowering medications and additional laser surgery or laser treatment or surgery postoperatively should also be specified.

So, for non-refractory glaucoma, the first three recommended inclusion criteria are the same as those for the refractory clinical trial. However, criteria for confirming the diagnosis should be specified in order to avoid enrollment of subjects with pre-perimetric glaucoma or ocular hypertension. In addition, minimum endothelial cell density based on age at the time of enrollment is also an inclusion criterion.

As you can see, the exclusion criteria are more numerous for non-refractory than for refractory glaucoma. Please note that the need for a combined procedure is the reason for

exclusion unless the protocol specifies that a cataract extraction should be performed in conjunction with implantation of the device.

The clinical evaluations for non-refractory glaucoma are similar as for refractory glaucoma, except that specular microscopy should be performed on all subjects enrolled in the initial phase of the trial and, also, subsequently on additional subjects, if warranted by the risk analysis and the early data.

For non-refractory glaucoma, the number of subjects should be a minimum of 300 evaluable subjects in the investigational device subject arm for safety at the final time-point. Follow-up is recommended to be 24 months, although this can vary with the risk analysis.

And concomitant IOP-lowering interventions, again, there are similar recommendations in terms of specifying when medications and laser treatment and surgeries should be stopped and started. However, in addition, it's also recommended that consideration should be given as to whether to specify in the protocol a washout period of all topical IOP-lowering medications before the baseline visit and before or at the visit window once the primary endpoint is assessed, if subject safety, of course, will not be unduly compromised.

The analyses annex of the draft standards applies to both the refractory and non-refractory clinical trials and includes a list of analyses to consider as applicable to that particular trial.

The recommended analyses included subject accountability, safety analyses, efficacy analyses, and some additional analyses. I won't be discussing subject accountability any further. However, let's move on to the safety analyses.

The analyses include best corrected visual acuity loss as well as lens opacification,

endothelial cell density changes and the rates of adverse events, including intraoperative complications.

So, the clinical protocol should include a list of possible adverse events, and that list should take into consideration the intended study population in terms of how to define those adverse events.

The other things that should be taken into consideration when defining adverse events is such things as the grade of severity, the degree of involvement of the anatomical structure, the timing, and the duration of the event, as applicable, in order to distinguish findings that should be reported as adverse events from those observations that should be routinely recorded.

So, during the workshop today, we will be actually focusing on three particular adverse events: hypotony, increase in IOP, and visual field loss.

The efficacy analyses include change in the number of ocular hypotensive medications, distribution in terms of the percent reduction and mean diurnal IOP from baseline, changes in mean diurnal IOP, which should be characterized in terms of mean, median, standard deviation, inter-quartile range, and minimum/maximum across the entire study cohort. Box plots should also be provided and, also, scatter plots. Survival analyses are also recommended. In addition, changes in patient-reported outcomes from baselines should be noted.

And finally, the Draft ANSI Standard has limitations for MIGS devices. It doesn't define implantable devices for minimally-invasive glaucoma surgery. It doesn't define what the patient population for such trials should be. It doesn't indicate what the primary or second endpoints for safety should be and leaves definitions of some adverse events ambiguous. And it also doesn't say what should be the primary and secondary endpoints for

effectiveness, whether composite endpoints should be used, or how to define study success.

So, we're all looking forward to hearing the rest of the program and the discussion on these topics.

Thank you.

(Applause.)

DR. MOSTER: Before moving forward to more in-depth panel discussion, we're going to hear from Tom Samuelson, who is going to talk to us about a working definition for MIGS and panel groundrules.

Tom?

DR. SAMUELSON: Thank you, Marlene.

So, I was asked to somewhat define MIGS, at least for this afternoon, and discuss some groundrules for the panel discussions.

So, I do have some disclosures. I do consult, investigator advise many of the devices and companies discussed this afternoon.

So, in terms of defining MIGS, it's clearly an evolving space. You have heard a variety of talks already discussing a very diverse group of procedures. There's no well-accepted definition, at least to date. But suffice it to say that MIGS is, indeed, a diverse group of alternative glaucoma surgeries that are intended to be safer and induce considerably less tissue disruption than traditional procedures.

In general, surgical safety and efficacy are related to the mechanism of IOP reduction, the reservoir of aqueous egress, the complexity of the surgical maneuvers that are performed, and the extent of tissue manipulation. And clearly, safety and efficacy are helped defined by the frequency of complications and/or adverse events.

MIGS are diverse, and I think they are best categorized by the recipient reservoir which has a significant influence on both safety and efficacy. And the three reservoirs we have heard about, Schlemm's canal, the suprachoroidal space, and the subconjunctival space, are the three that are currently utilized, but you can imagine there are other reservoirs that will be coming.

So, first, Schlemm's canal. It's the most physiological of the three. It's synergistic with the innate outflow pathway, and its mechanism maximizes safety. The episcleral venous pressure that the canal drains into provides a safety-net barrier in limiting the risk of hypotony. But, accordingly, there are similar efficacy limitations then.

The success of Schlemm's-canal-based procedures also is dependent on the viability of the distal outflow system. Well, how about the suprachoroidal space. It is less synergistic to the innate mechanism. Hypotony is theoretically possible. There is no theoretical limitation to efficacy. So, that's a plus. If hypotony is possible, that's something you have to deal with, but on the efficacy side that's an advantage.

Disuse atrophy of the physiological system is possible post-operatively, and there is greater theoretical risk with suprachoroidal space procedures, but large trials may prove or disprove this premise for any particular device.

The subconjunctival space, likewise, not synergistic to the innate mechanism. There is no theoretical barrier to efficacy. Hypotony is theoretically possible. Disuse atrophy of the physiological system could occur. Extra-scleral egress introduces the risk of endophthalmitis, and there is at least theoretical greater risk than canal-based procedures. But, again, large trials may prove or disprove this premise for any particular device.

Ultimately, I believe a MIGS classification may need to be earned, not just granted.

And it's based on at least modest efficacy, and I believe, more importantly, based on an enhanced safety profile, as determined by well-controlled clinical trials.

So, for today's panels -- and I emphasize today because there are other definitions of MIGS and other procedures that might be considered MIGS -- so this is today's working definition. And I also want to emphasize we're talking about devices today. As per the FDA request, we're speaking to MIGS procedures that involve devices.

So, we're going to define MIGS for today's purposes as procedures that are intended to lower IOP via an outflow mechanism that can be either an ab interno or ab externo approach. We would like to see limited or no scleral dissection. Certainly, needle penetration or device penetration or perforation of the sclera is allowed. But procedures involving significant scleral dissection will be included for today's discussion.

Minimal nor conjunctival manipulation, limited peritomy is allowed or a small conjunctival incision is allowed, but not significant conjunctival dissections.

So, based on this definition, some examples of existing MIGS -- and this isn't by any means comprehensive -- the Glaukos iStent and the Ivantis Hydrus. In terms of canal-based procedures, the suprachoroidal-based procedures would be the iStent Supra or the Transcend Cypass. For the ab interno transclera, it would be the AqueSys XEN and possibly the ab externo transclera would be the InnFocus MicroShunt.

Procedures excluded from today's discussion, but certainly included in other MIGS discussions are listed here, and there's many more as well.

So, to conclude, in-person comments for the panel, safety and efficacy are inexorably linked. While all procedures should have at least modest efficacy, safer procedures might be held to more modest efficacy standards, while procedures with greater risk may be expected to

have greater efficacy. The indication for each MIGS may differ based on both efficacy and safety considerations.

So, despite the diverse nature of the procedures collectively known as MIGS, the panels are challenged, as much as possible at least, to establish some uniformity of clinical trials involving MIGS implantable devices, uniformity based on eligible patients and severity endpoints, safety endpoints, and efficacy endpoints. It's quite a challenge.

I'm looking forward to hearing the panel discussions.

Thank you.

(Applause.)

DR. MOSTER: Thank you, Tom.

Well, this concludes the overview of MIGS procedures. I would like to call up Dave Friedman and Rick Lewis to begin the panel discussion on defining the patient population for clinical trials.

DR. SINGH: Thank you, Marlene and Tom, for just an excellent opening session and, also, for staying right on time. We're actually exactly on time.

And Dave Friedman, from nearby Baltimore, Wilmer Eye Institute, and Rick Lewis, from Sacramento, who is past AGS President and current President of ASCRS, are here to lead this next session.

Now Dave is going to be the moderator. Rick is the Co-Chair. All of these sessions are going to be moderated by one individual, but the two Co-Chairs will be involved. They have been involved in the program and will be participants.

In addition, I would like the panelists to all come up for this first session. So, Henry Jampel, also from Johns Hopkins, Wilmer; Don Budenz from North Carolina; Husam Ansari from

Boston; Rohit Varma from Los Angeles, I think this week -- (laughter) -- and Brian Flowers from Dallas. I want them all to come on up.

And I'm going to turn it over to David.

I just want to point out that the FDA and AGS have agreed on certain questions that we have to get through. But, after those questions have been covered on the panel, if there's more time, we will have open mic; people from the audience can ask questions and comments. And I'll let Dave and Rick lead that, lead the discussion.

Thank you.

DR. FRIEDMAN: All right. So, I guess we'll get started. At the beginning we will have our first talk, which will be how to just determine disease severity, which Rohit will be giving.

DR. VARMA: Could I get my slides, please? Okay.

So, actually, a little wrong; I'm from Chicago this week.

(Laughter.)

But I will be from LA, in fact, in about a couple of weeks. The snow just scared the heck out of me.

(Laughter.)

Sixty-eight inches of it this year.

So, anyway, when I was given this particular topic, in fact, I was wondering where I would go with this because there's really no good way for trying to classify disease severity.

And I'll actually go through two sort of approaches which we know of and which we use. And then, I will propose a third one which is just a draft which I've just spent the last sort of two-or-three-odd months, in fact, trying to think how we can incorporate various things,

which is that we use two specific things when we treat people with this disease. One, IOP-lowering, how much do we want. And two, we sort of tailor it based on how much existing damage there is in the patient. And so, I think as we go forward, in fact, I just want to have you all give some thought to how we can incorporate those two and how we classify diseases.

So, how do I get to the next slide? Ah, there you go.

These are my disclosures.

So, there are three main reasons why one ought to try and classify a disease. One is to provide better guidance to us in how we treat our patients. Two, to help the patients, in fact, understand their disease in a better way, how far advanced it is, how minimal it is. And third, in fact, a plan for what future outcomes of the disease is going to be, whether they're going to go blind or not or whether they're going to be visually-impaired.

The first one, which you have already heard a lot from Malvina about, is what the FDA evaluates, which refractory versus non-refractory. And I'm not going to go into it because she's really detailed it out for you, in fact, very well.

But, if you use the three sort of criteria which I've outlined as to what is the purpose of classifying a disease, it sort of doesn't fair particularly well. You know, maybe it had outcomes in terms making better treatment recommendations, but not really. We don't select a particular approach because refractory glaucoma or not.

We don't particularly understand the disease better, but particularly with regard to patients. They don't really know what that means.

I mean I think, three, it does not give us any idea about what the future outcome of the disease in that patient is going to be. You may have people with minimal disease. You

may have individuals with advanced disease. We believe usually that people that end up in the refractory group may have advanced diseased, but that may not be the case.

The next sort of general criteria or classification which we use -- and this is based on work that Ron Fellman and Cindy Mattox have done, and I have used some of their images here -- is what I think we will be asked to use in the next version ICD, which is ICD-10, where we are going to be asked to have a disease staging in terms of how we diagnose individuals. And that's mainly mild, moderate, and severe.

Mild is where you have evidence of optic nerve damage, but minimal white-on-white perimetry change, or maybe just some short-wave automated perimetry change.

Moderate stage is where you have both, which is optic nerve changes as well as visual field changes, but the visual field loss is minimal and it does not come within 5 degrees of central fixation and it only involves one particular hemisphere.

And last of all, in fact, there severe, which is it involves both hemispheres and/or is within 5 degrees of central fixation.

The advantage of these, of this particular one, I think it does help patients better understand where they are on the disease severity spectrum. It does help them plan what is going to happen, in fact, going forward. But it doesn't particularly help us make better treatment decisions because there's no relationship to IOP or how much we need to lower IOP.

And so, in what I am going to propose is to see whether or not we can have a disease-staging mechanism where we can include IOP-lowering and we can use the amount of field loss. Now I've just picked these arbitrary, these IOP-lowering endpoints, and arbitrarily, in fact, did the amount of visual field loss.

And what I have out here are three particular groups. Group one, where you want

sort of a small, where you have about a small lowering of IOP, under 4-odd millimeters, minimal amount of damage. Two, where you need greater IOP lowering and there is also a minimal amount of damage, in fact. And, three, where you need greater IOP lowering, but there is a significant amount of damage.

So, I just wanted to actually say that this particular, if you will, staging approach allows you to meet all three criteria. We may have to, I guess, to refine it. But this is just an initial draft for you all to, in fact, consider, change, modify, alter, in fact, but it does give us some guidance, in fact, in terms of what to do.

So, I'm going to stop there.

DR. FRIEDMAN: That's great. That will set off the conversation beautifully. Thank you so much, Rohit. That was really nice.

The next speaker will be Henry Jampel, who is going to talk about cutoffs for entry into clinical trials.

DR. JAMPEL: Thank you. Well, I appreciate being invited to give this talk.

I may not have the most disclosures, but I've got the disclosures in the largest fonts, I think.

(Laughter.)

So, in terms of clinical measures of severity, glaucoma specialists consider visual field loss, of course. We look at structural measures of ganglion cell loss, such as the optic nerve appearance, the retinal nerve fiber layer thickness and macular thickness. And then, there are associated measures such as the intraocular pressure and the number of IOP-lowering medications used because these may be surrogates for the amount of damage to the outflow system.

So, when we are thinking of whom we should include in clinical trials, we want to exclude those whose disease is too mild, just protect them, and we want to also exclude patients whose disease is too severe, to protect them as well.

So, we're going to start with the too severe category. We need a too severe cutoff in these trials to prevent subjecting patients to a procedure that is unlikely to be effective enough for the degree of their disease, to allow inclusion in a randomized clinical trial of patients who are not going to receive the intervention and not compromise their safety. And also, as Dr. Rorer mentioned, washout of medications has become an integral part of these trials. So, the patient's disease can't be so severe that they could not tolerate not only a washout before entering the trial, but also a washout at one or two years into the trial.

So, I looked at the published literature. I looked at what is in clinicaltrials.gov. And I spoke to some of my colleagues in industry to see what sort of cutoffs are in use.

And, in general, the too severe cutoff for visual field has been an MD worse than minus 12 dB. For optic nerve, cutoff is cup-to-disc ratio of greater than 0.8 vertically. In terms of intraocular pressure, a treated IOP of greater than 24 would be an exclusion criteria, and an individual eye using more than three medications. And on the lower part of the slide is an example of a visual field with a mean deviation of minus 12.

So, given this, I would propose some modification to these too severe cutoffs. For visual field, I would add a criteria of fixation not threatened. For intraocular pressure, I'm okay with a 24 or greater and no more than three medications. And then, I would get rid of a too severe criteria for the optic nerve.

This shows the fixation threatened criteria. This is an eye that would qualify if we were just looking at mean deviation of minus 12. But if we were to include the fixation

criteria, we would see that this point here is highly statistically-significantly abnormal and is 10 dB below where it should be.

So, now we're going to turn from the too severe criteria to the too mild criteria. I think we need a too mild cutoff to prevent recruitment of individuals without disease. They don't belong in these trials.

What are the too mild cutoffs currently in use? Well, a mean deviation greater than zero. I think that's too permissive. An optic nerve with no characteristic signs of damage. I think that's too subjective. And I don't have any problems with an intraocular pressure that's less than 21 millimeters of mercury after a washout. I think that's okay.

So, my proposed modifications for the too mild cutoffs is I would get rid of the visual field mean deviation greater than zero and replace that with defined visual field loss, perhaps a GHT that is outside normal limits or perhaps a more regional criteria, such as three statistically-abnormal contiguous points.

In terms of optic nerve, if we're going to use, I think no characteristic signs of damage, as I said, is too vague. And I would replace that with objective OCT evidence of neurofibrillary thinning, if the visual field does not meet the criteria. If the visual field meets the criteria, I don't really care about the optic nerve appearance. And again, one could also, for the optic nerve, look at average RNFL being abnormal statistically or an inferior or superior sector or segmental abnormality. The intraocular pressure I have no qualms about.

So, to summarize, my recommendations are on the too mild side we ought require some defined visual field loss. And if there is no visual field loss, the eye could still be enrolled if there were OCT-defined structural damage. On the too severe side, I don't think we need optic nerve criteria. I think visual field would suffice, and I would recommend including a

fixation threatened criterion in addition to mean deviation.

Thank you.

(Applause.)

DR. FRIEDMAN: So, that was very helpful and I think will help focus the panel discussion.

I am going to put out a quick question for the panel. And then, we can have others or I have a few more that I would like to ask.

So, Henry pretty strongly stated he didn't want people without glaucoma in these studies. And let me just imagine a patient. A patient comes into you, very healthy optic nerve, relatively young, long life expectancy, pressure is 34, and they're on all the meds they're going to take.

So, I'm just wondering if the panel feels that person should not be allowed to get lesser surgery than a trabeculectomy or a tube shunt or can they be involved in a study that involves one of these new devices, or are we saying we can't have them have no treatment in that arm because that's the problem? What excludes precludes including somebody who we are going to do something fairly invasive to? Who doesn't have defined glaucoma?

DR. LEWIS: I would like to jump in on this one. You know, maybe even more fundamental than that question you raised was the issue of the relationship of visual field loss in cupping-to-pressure. These devices are strictly geared to lower pressure. All of our treatments are geared only to lowering pressure. And yet, we jump ahead and exclude patients who have field loss or have either too mild or too severe field defects to be included, when the overwhelming majority of our patients are in the mild category and they cannot be included in these studies.

And part of me feels that visual fields have almost nothing to do with this other than a safety monitor, that it should be part of the inclusion criteria. It is a safety measure only. And even within that, there's so much noise in a visual field test that we can't believe what we're seeing half the time anyway. So, I have a real issue with how we include/exclude patients in a study.

DR. FRIEDMAN: Yes. So, let's hear somebody who feels differently.

DR. FLOWERS: Well, that wouldn't be me because I've got similar --

DR. FRIEDMAN: So, give your similar opinion and, then, we'll get somebody who might feel differently.

DR. FLOWERS: Well, I also agree that the goal of these therapies is to lower IOP in a safe and effective manner. So, I think an IOP criteria, you know, I think is the most important thing. And I do agree that patients with OHT really should be permitted in these trials.

DR. ANSARI: I would add that all of our clinical trials have safety nets, in that if we think a patient is in trouble because of whatever on their randomized, too, we can do what we need to do. So, the patient scenario that you presented, Dave, I would love to see that patient in a trial because, if they get randomized to the observation arm or the non-implant arm, we're still going to watch them and we're going to need to do what they need. We're going to do what they need if they're progressing in that arm.

DR. JAMPEL: This is quite a radical thought -- (laughter) -- that we would take ocular hypertensive patients and put them in a surgical trial. I don't quite get that. That is so far from the criteria that are currently being used in the studies underway, where if you have a cup-to-disc ratio of 0.85 and a normal field, you are excluded.

So, it's great to hear that we're going to have a vigorous discussion here. And if the FDA approves these minimally-invasive glaucoma surgeries for the treatment of ocular hypertension, I may come around to that. I'm usually a dozen years behind the time, but that's too big a leap for this old guy.

DR. ANSARI: Can you sort of describe more in detail what the concerns should be in that patient population?

DR. JAMPEL: Okay. Well --

DR. ANSARI: I mean, I know some of them are obvious.

DR. JAMPEL: Most ocular hypertensives don't need treatment. I mean, there's a subset that do. Okay. So, that would be one thing.

And David's example, I mean to start the discussion, well, there's an extreme -- he said pressure of 34 on maximum eye drops. I mean, that's not typical. And one could make an exception in that instance, and you can go to the safety monitor, and maybe you can get an exception in a clinical trial. But that's not your typical ocular hypertensive patient.

And if you think that someone whose pressure is -- and what's ocular hypertension? Let's say over 21. You take someone with a pressure of 22, normal disc, normal field, and you're going to put them in this study?

DR. ANSARI: No, I wouldn't.

DR. JAMPEL: Not my relative.

DR. ANSARI: No. I'm not even --

DR. JAMPEL: Then, let's set up the groundrules.

DR. FLOWERS: I don't think anyone is talking about that type of patient. Because, like you, true ocular hypertensives don't need treatment at all.

I think we're talking about patients who are on multiple medications. You have decided that they require treatment, and they're on not one, but maybe two or three medications. And then, they are approaching a cataract surgery event. Should that particular patient that you would love to rid of the eye drops be eligible? And that type of patient, I would assert, should be eligible. But an ocular hypertensive with a normal nerve and a pressure of 24 on no meds doesn't require any treatment of any kind.

DR. JAMPEL: Okay. So, here's another argument for not doing that. This is in terms of wanting to have a clinical trial with results. If you have both groups, have no disease, and you randomize them to treatment or phaco-plus, and if they all have no disease to start with, it's going to be extremely difficult showing an important clinical outcome.

DR. LEWIS: But, anyway, we have to define what -- is it the disease that we're treating with these devices the visual field or are we treating the pressure? We're really trying to treat the --

DR. JAMPEL: Eye pressure isn't a disease.

DR. LEWIS: But that's what these devices are really intended to do, is to lower pressure. Hopefully, they're going to slow down the glaucoma's process, but that's whole other study that's going to take years to validate.

All we're trying to do is find a way, whether it's with medications or laser or surgery, of lowering the pressure. And hopefully, we're going to also in the long run manage the glaucoma.

DR. JAMPEL: I would like to protect the patient without disease from being involved in a clinical trial.

DR. VARMA: So, can I just add two things to that? One, I think the group

that you may consider treating, Henry, would be those that may, by whatever, existing data from the OHTS and others, have an extraordinarily high risk of conversion within the next two, three, five years. Those you can potentially argue are -- let's say they have a risk which is in the 30 to 40 to 50 percent range, that there is a better risk/benefit ratio in terms of treating them. And even getting beyond the medication-only arm into something which has minimal intra-op and postop, if you will, issues and does lower IOP significantly beyond what you can get with medication.

Two, I would say that the one other exclusion you had which was an IOP under 21 which is washed-out, I'm a little bit uncomfortable with that. And I'm uncomfortable with that because, you know, about 80 percent of all people with glaucoma sit in that below-21 range. They don't sit in the above-21 range.

And we have forever in glaucoma gone down this path because we can see adequate IOP by lowering -- we have sort of limited it to, well, it has to be 21 or higher or 24 or higher, or something like that. Well, that is such a small proportion of the glaucoma group out there. No wonder it's hard for us to, in fact, enroll patients in these trials. It takes us years and 20 centers, and so on and so forth, and that's not where the vast majority of patients sits.

So, I would just urge you to maybe reconsider that, maybe lower it, maybe something like that where you include the vast majority of patients. So that, when you have ultimately a result from your trial, it's applicable to the vast majority of glaucoma patients.

DR. JAMPEL: Right. So, what I put out there is what is currently being done in conjunction with the FDA. And my recommendation was to loosen up in terms of the optic nerve criteria, but to ensure that the patient had disease by having -- you didn't have to have visual field loss, but you had to have some evidence of damage. And it could be OCT.

So, that's fine.

The problem with opening it up to glaucoma patients, half of glaucoma patients at least with eye pressure under 21, is that, boy, it's going to be super hard to prove an effect of the device because the device you know is not going to lower the eye pressure below 14. So, if you're including patients whose eye pressure is 16 and 17, you know, as an advisor to industry, I would say that's not the way to go.

DR. VARMA: No, but you're saying that that's what can work with what exists out there. I'm sort of viewing this as what's best for the patient. I don't care if you don't have, as of now, a device which won't lower it below whatever. I mean, that ain't the goal. The goal ought to be let's have a device which does lower it significantly below it, so that you can actually do a benefit or give some additional, in fact, if you will, treatment beyond what exists now.

DR. JAMPEL: Yes. Well, also --

DR. VARMA: We're not trying to prove what industry has.

DR. JAMPEL: We have defined MIGS as having modest IOP lowering. We're not asking for moderate. I mean, that's a definition. That's what Ike Ahmed and Saheb wrote, modest --

DR. FRIEDMAN: So, let me take the moderator's privilege here for one sec.

(Laughter.)

I just want to summarize a couple of things. One is a lot of these questions are really for IRBs and I'm not sure they're for the FDA. I mean, that's a whole other question.

These are, is it safe -- you are talking about protecting patients in research. And a lot of that safety decision is more based on determination that the risk/benefit ratio is appropriate

for the patient. And depending on your device, it may be that that device so far in preclinical and all those other things shows so little risk that, even though it's surgery, whatever.

So, that's one piece that I'm not sure on, and I'm not sure the FDA prescribes what everybody is doing. I think everybody is doing the same thing because they're all doing the same thing. They look at the other protocols and they decide those are good.

I think the point Rohit is making personally is completely valid, that all these technologies will be applied not just to the people in the studies. We all know that's what happens. They get expanded beyond that. And many people with lower pressures will be treated with whatever technology gets approved.

And so, we need to think about having some of those people in these studies. So we know, does it do anything? Is it at all useful in the patient with a pressure of 18 on two medicines?

So, I would personally think that would just be better science. It's not great for industry because industry, my guess, would prefer to have higher pressures that would show a larger drop. And so, that becomes sort of a balancing act of what populations you can afford to study and how much data we can afford to obtain.

I want to open it up a little bit. I did want to make one comment. I think Rohit's way of segregating is very helpful, and I would propose that we think about things in that way. And not every procedure needs to lower pressure 10 millimeters. If it lowers it 4, that's a good hit for some people.

But in other patients, lowering it 4 is a complete loss, and we didn't want 4 when they started at 28 with end-stage glaucoma. So, I think that point of the severity and the amount of pressure and lowering should definitely be included in future thoughts about how to design

this stuff.

I did want to open up opportunities, because I saw some people kind of looking like they wanted to -- I saw George almost get up. George, did you get up? Yes.

DR. SPAETH: Thank you, David.

George Spaeth.

One of the things you've got to take into account, Henry, is asymmetry. You've got a patient with a pressure of 40 in one eye and 20 in the other. And the eye with the pressure of 40 has got a bad disc but no field loss. And the eye with the pressure of 20 has a healthy-looking disc. Do you call that ocular hypertension? Is that glaucoma?

I think one of the problems is this whole nomenclature that we're using. But it would seem to me that that patient would be -- that you want to get that pressure down.

And on the other hand, talking out of the other side of my mouth, Rick, it was really kind of scary hearing, well, we want to lower pressure, in hopes that sometime somewhere in the future maybe the patient's going to benefitted by that. That's a pretty scary indication for surgery.

DR. LEWIS: Let me respond. Let me just respond because I'm trying to be controversial, sitting up here.

But, also, we all recognize that we could classify glaucoma in a multitude different ways, whether it is POAG or secondary glaucoma or pseudoexfoliation. But we also have a large group of patients that we could classify by saying they have pressure-sensitive optic nerve and those who seem to be pressure-insensitive. And there are those who a large segment of patient populations have a low-tension glaucoma in which it doesn't matter what we do with the pressure; their disease seems to progress.

And so, my point, what I was driving at -- and again, sort of to be provocative here -- was that these devices are strictly intended to lower pressure. Everything else, we have to assume that, by lowering pressure, we are going to help the glaucoma. And if we could prove that these lower pressures, then all the better. We have one way of doing it.

And I think when we get off-track and starting saying these devices are going to stabilize visual field and help the OCT, I think we're taking a big leap forward.

DR. FRIEDMAN: Go ahead, Joe.

DR. CAPRIOLI: Joe Caprioli from UCLA.

First, I would like to agree, believe it or not, with both Rohit and Henry in the following way:

(Laughter.)

I think patients without disease should be protected. Patients with advanced disease should be protected. But there shouldn't be any pressure levels that are excluded or necessarily included.

For the point that Rohit made, most of the patients are going to be in normal -- I would like to know how those patients do, if this is valuable in, as you said, 80 percent of our patients.

It also avoids, if you don't set a cutoff, it also avoids problems with regression to the mean, which is always problematic. Even if you have appropriate controls, it sort of muddies the water sometimes.

So, I think that's what I propose, some kind of compromise between your two positions.

The other thing I would like to say is a comment which is apropos to the first session. We saw all the horrible things that can happen after trabeculectomy, nasty-looking blebs that

get infected. And I understand the strategy of setting up a strawman to dismember and burn.

But I have to object to a slide that says blebitis is a common complication, that bleb leaks are common complications, that hypotony is a common complication, when all of the well-done studies that included trabeculectomy show these to be uncommon complications. And for well-done trabeculectomies, I think they're actually fairly rare complications.

So, I am all for new techniques, but I would also like to have some sort of a balanced discussion of it as well.

DR. FRIEDMAN: So, Don, do you have some thoughts about it so far?

DR. BUDENZ: Yes. I think Henry's points are very well-taken because I think this cup-to-disc ratio is a very poor way to judge glaucoma severity. You have different sizes of optic nerves themselves, and we don't take that into account. And doing some arbitrary upper limit to judge somebody as too severe seems really nonsensical to me.

But including something about visual field defects that approach fixation, I'm just surprised that that's not included because, you know, study after study has shown that severe defects near fixation start to affect foveal threshold, which, of course, affects vision. So, I would like to see those things included.

And let's not forget in the OHTS trial investigators were not allowed to even use laser trabeculoplasty to lower IOP. That wasn't part of the treatment protocol. And the feeling among the investigators was these people don't have disease and we shouldn't even be exposing them to laser trabeculoplasty in that case.

And I'm certainly with George and Henry that people without disease should not be exposed to incisional surgical procedures. As low-risk as we think they are, there's still endophthalmitis postoperatively and other things that are, yes, rare in these situations. But in

a patient just with a risk factor for disease, and when we can detect the earliest signs of disease with visual fields or changes in OCT and optic disc photographs, that we should really be waiting to protect those early patients from even low-risk procedures.

DR. FRIEDMAN: And in terms of the severity scale, do you have any other thoughts about severity levels that Rohit was putting forth?

DR. BUDENZ: I think that I like the criteria that Cindy Mattox and Ron Fellman put forward, really basing severity on functional measures of the visual field. Because, really, we're trying to prevent blindness here. We're not trying to prevent the earliest detectable sign of glaucoma.

So, I think we have to get some perspective. Yes, we can reduce risk by reducing IOP, but we are trying to prevent blindness, not the earliest detectable sign of glaucoma.

DR. FRIEDMAN: Do any of the panel members think that that's not a fairly-useful severity scale for determining who should be in these studies at this point? I mean, that seems like a very reasonable approach.

The other question I would have around this is the optic nerve criteria. I'm in agreement personally with Henry's proposal. I just want to know, is there anybody who feels strongly or feels at all that that's not appropriate, that if you have a .9 cup-to-disc, you shouldn't be in a study because it's too severe, your glaucoma? Your field is not threatening fixation.

You know, it satisfies -- so, I think in terms of giving FDA advice, we feel that those things certainly, at least among this panel -- and I'm not seeing a lot of disagreement anywhere in the room -- that the cup-to-disc ratio is not a very useful single criterion and that the severity levels that Rohit put forward might be interesting.

Tom?

DR. SAMUELSON: I would love to hear the panel discuss further what Joe was talking about, about eliminating pressure criteria. With corneal thickness and corneal biomechanics and hysteresis, and all the things that might make pressure measurements erroneous, I like the idea of going by the disease characterized by the visual field and let particularly the device manufacturer decide what cutoff they might want in their particular trial.

One of the things that limits innovation considerably is how long it takes to enroll the number of patients needed. It takes far too long. And if we could expedite that, expedite enrollment and get answers much faster, that would be terrific.

And I think Joe nailed it when he said that one of the most erroneous aspects of these trials is the fact that there's a number that the recruiters have to hit. You know, it has to be 21. It invites, "Well, your pressure didn't qualify today. Let's see you back in a month, and maybe you'll qualify then."

And then, all of a sudden, you have a perfect storm for regression of the mean. And so, I would love to hear the panel discuss that, maybe eliminate specific pressure cutoffs and go more by disease characterized by visual field and nerve --

DR. FRIEDMAN: Husam, do you have something?

DR. SAMUELSON: I'm willing to give up -- I think Henry's right; I would like to see patients have some evidence that the pressure has caused some harm. Terrific. If it's pre-perimetric, fine, but it show some abnormality in the nerve fiber layer or something indicating -- or George's comment, disease in the other eye -- something that indicates that this isn't just ocular hypertension and a corneal thickness of 640 or something.

So, I would love to hear the panel discuss that no pressure criteria.

DR. FRIEDMAN: So, Husam, no pressure on you.

(Laughter.)

There's always pressure.

DR. ANSARI: I have to admit I like the idea of there being no pressure requirement delineated in, say, an FDA rule book, and one that may be determined by the industry, you know, the sponsor and the FDA together, based on the actual device, and so maybe preclinical data. I think it would really open us up to --

DR. FRIEDMAN: Rick?

DR. LEWIS: Well, this is slightly an extension of the issue, but part of the problem in these trials is that the forced duration of a two-year trial in glaucoma is an awfully long time. And the goal, of course, is safety and efficacy in these trials. If we were able to show in a year that the device is both effective and safe, and then, monitor them without them continuing the study -- by the time they get to the second, third, and fourth year, there's so many other variables that kick into this, that calls other types of diseases. I wish that we could just have a one-year trial and, then, accept that as a safety/efficacy endpoint.

DR. FRIEDMAN: Brian, you had something?

DR. FLOWERS: Yes, one point of clarification is that I'm enrolling patients in Transcend, Glaukos, and Ivantis. And I think all of them have fixation criteria for enrollment. So, that is already established.

DR. LEWIS: I couldn't find it.

DR. FLOWERS: Yes, it was, if you have points close to fixation, you're excluded, two points close to fixation certainly for Transcend's trial.

You know, thinking about what we're trying to accomplish with these trials, which is trying to show if a device has a pressure benefit, which is really what we're trying to show -- we're not trying to show if it prevents visual field loss.

Really, I think it comes back to not having pressure criteria I think is challenging. I think you really have to have pressure criteria because that's what you're trying to show.

And when you're in the trenches recruiting patients for these trials, one of the biggest challenges to the physician in the clinic is if all these trials have these wildly-different criteria. When you're at this point when we have two different trials we're recruiting for, and they have surprisingly different criteria, it makes it challenging to remember who fits which one. And so, I think that's something we should really be in this session seeking to eliminate and try to have uniform criteria for entry into these trials. And that way, it will not only be easier to recruit for them, but much easier to compare one trial to the other, which I think has always been a challenge because every trial, whether it be pharmaceutical or surgical, they've all got different entry IOPs and different outcome measures, and it's impossible to compare. It gives us lots of fodder for dinner meetings, but it is really not terribly useful to be that way.

DR. JAMPEL: So, if all trials that you are participating in had this same criteria, how do you choose which trial to enroll a patient in?

DR. FLOWERS: I'm not sure how I would answer that question, actually.

(Laughter.)

Because that's really an atypical situation for me personally because most of them don't overlap one another.

DR. JAMPEL: Oh, you're not doing --

DR. FLOWERS: Currently, that is the case, where there are two trials that are

overlapping. Of course, Transcend finished recruiting a year ago. So, we're done recruiting for that. But I don't think I have a specific way to choose one compared to the other.

DR. FRIEDMAN: So, a quick question. Rohit, what do you think of that?

DR. VARMA: Right. Brian, I'm not against not having any standards. I mean, yes, we should. I'm just against 21.

(Laughter.)

I think that has been one of the worst things we have done in glaucoma because it has become the -- you know, it has completely permeated our entire conversation on this. You know, for screening, 21; for this -- and we have shown over and over, time and time again, it has no relevance to people that have real disease, which is visual field loss and optic nerve damage.

So, pick whatever you want. I'm open to it, in fact. But I think what I had proposed, which was to lower it somewhat, not just have it at 21; maybe have it at 18 or something like that.

You will, then, include a much greater proportion of the real-world population that has this disease as opposed to this kind of --

DR. FRIEDMAN: And it would help enrollment for sure.

DR. VARMA: Yes.

DR. FRIEDMAN: And it would avoid some of the regression that we were talking about.

Yes?

DR. AYYALA: Ramesh Ayyala from New Orleans.

I would like to present a case that I saw about a month ago. And I want you to place

it in the category of mild, moderate, or severe.

It is a 37-year-old military sergeant referred with pressures of 40 in both eyes, history of phakic intra-ocular lens implantation about three months, four months prior to that. Patient is on Diamox, Combigan, and Travatan and Pred Forte. Constant release of pigment, 4-plus pigmentation at an angle. The optic nerves are 3.6 I think. OCT is normal. Vision fields with SWAP is normal. So, how do you manage this? In what category is this?

DR. FRIEDMAN: Frankly, you can always come up with a weird exception. That's truly like a secondary to something else having been done. And generally speaking, for these trials we don't really want the unusual secondary. So,

I think that is really moving outside of --

DR. AYYALA: The reason why this is important is this discussion with FDA requirements will permeate into the insurance companies. And then, they will start asking questions. They denied -- I did canaloplasty on this patient. They wanted me to do a trabeculectomy on this patient who happens to be a minus 16, myopia in both eyes.

What did I do? I took those phakic lenses out. With pressures of 40 on Diamox and three medications, I don't expect 4-plus pigmentation with angle. I'm not expecting that pressure to drop down.

DR. FRIEDMAN: Sure, sure, yes.

DR. AYYALA: So, I went ahead and did the glaucoma procedure, and the insurance company has not paid.

DR. FRIEDMAN: Right.

DR. AYYALA: And that's the point: I think we should be very careful in defining glaucoma. This, in my mind, is a severe glaucoma. If the treatment is to prevent

the disease from progressing or even from appearing, then what I did is correct.

But, in your mind, in Henry's definition, the disease has not appeared, so let this progress to a vision field loss before you offer the treatment.

DR. FRIEDMAN: Right. I mean, I brought that up at the beginning, and we have had a little bit of a discussion. I don't want to focus too much. We all agree there is this kind of unusual category of very high pressures, so high that we think that person is at extreme risk. And there is some discussion about whether those people should ever be allowed in these studies. And I understand your point.

I'm going to move on. Steve?

DR. SARKISIAN: Just a quick comment. As many of you know, I have been involved really with the gamut of all these studies from both advanced glaucomas to the mild to moderate. Let me just make a couple of observations.

We know, No. 1, enrollment for these studies is challenging. It has been that way for every company. And I actually think the FDA has done a good job of really trying to work with the sponsors on trying to make reasonable protocols.

Let me just say on the mild-to-moderate glaucomas, when we're talking about the phakic-plus procedures that we're talking about, a couple of things that I think are really important.

No. 1, we want to first establish that these devices work. And I do think I agree with Brian in the sense that having some standard of a pressure of 21-22, it's not to define the glaucoma, but we want to make sure that the device actually can lower pressure, I think is a reasonable thing.

I also agree with Henry in the sense that you like to have these patients have

glaucomatous disease, and that's what is in these trials. As you know with ocular hypertension treatment study, some patients presented with visual field loss first. Others -- in fact, the majority -- presented with optic disc changes first.

If we can define them either by imaging, by changes in our exam, we want to have that damage there, but we don't want them to have advanced visual field loss in these patients because you're doing washouts at these at both the baseline, one year, and two years.

So, that's kind of my thoughts on that. We want to have real glaucoma, but preferable in the mild-to-moderate range. And by definition, at least according to the American Academy of Ophthalmology's preferred practice patterns, the moment you have a visual field defect, by definition, you have moderate glaucoma.

On the other hand, I have been doing refractory glaucoma and advanced glaucoma trials. And it's interesting, they have been very difficult to enroll. First, just coming up with a standard definition for refractory glaucoma has been challenging. There's been a wide range of that definition over the course of these three different trials that I have been involved with. And now, it's tidying up a little bit, but that has been a challenge for the FDA.

And it would be helpful if we, as a community, a glaucoma community, could really say, "Here's what the definition needs to be."

And then, the other thing is, you know, I'm doing one with the InnFocus now. We have had to do a washout on patients where it is trabeculectomy versus an InnFocus device. And I don't know about you, but if people have got more moderate-to-advanced glaucoma, which is the only times that I am going to do a trabeculectomy, I'm a bit uncomfortable doing washouts on some of these patients. And it makes it more of a challenge there.

And so, we really have to -- and yet, the visual field criteria are such that it can't be real

mild, which would be more likely to do -- I would feel a little bit more comfortable doing a washout with as opposed to more advanced.

And then, the other thing you have a challenge with is not only do you have the eye that is being in the study, you have the fellow eye. And so, if the fellow eye has any significant damage, which a lot of these patients do, it can make it very difficult.

And I've got a tertiary glaucoma practice, and in our practice, I mean, it's almost -- I mean, these patients are -- I mean, when you see a patient that actually meets their criteria, as one of my partners said, they're like a unicorn. It is something that is very rare and you have to work really hard to find these.

And so, we just have to kind of work to find these. We want to protect those, but we also want to make sure that these studies can be enrolled, so we can potentially, hopefully, come up with devices.

And then, one last comment I want to just make. You know, we talk about a modest effect with these MIGS devices. You know, these are the very first generation ones. And I don't know about you guys, but I'm kind of hoping we get more than 2-3 millimeters from these devices as we go along.

These are the very first steps, and my hope is that we are going to be able to end up getting 30 and 40 percent IOP lowering with some of these devices as we become more knowledgeable about this space.

Thank you.

DR. FRIEDMAN: So, a quick discussion about refractory. Rohit, did you have any further thoughts based on what Steve was saying just now in terms of your --

DR. VARMA: No. In fact, I disagree with him on the fact that we want to

stick with this refractory business. I mean, I don't know. I would ask anybody, in fact, in this group as to, you know, do you ever treat people based on whether or not they are refractory versus not? I mean, we treat people based on how much IOP lowering they need to have and how much preexisting damage they have. Those are the things that figure into our thought process when we treat individuals.

But I would think that we want to move away from that, and we want to move into an area where we use those aspects of the disease that we use to treat them in our everyday practice. So, I would get away from it because, also, as I said, it doesn't help us, one, either educate the patient, educate ourselves, or know where the patient is going to go. Because you want to know what amount of visual field loss, and so on, they had at the outset.

DR. SARKISIAN: Refractory in the glaucoma trials, is that what you're saying?

DR. VARMA: I'm disagreeing on having that as a group at all.

DR. SARKISIAN: Oh, as a group at all?

DR. VARMA: Correct.

DR. SARKISIAN: Okay. Because this is what has been given to us. Okay?

DR. VARMA: That's exactly right.

DR. SARKISIAN: I mean, it's not like I said, "Hey, this is what we want to do."

DR. FRIEDMAN: Yes, no one is blaming you, Steve.

DR. SARKISIAN: This is kind of what has been set out before us. This is the group that's going to be looking --

DR. VARMA: Right. No, I'm arguing to sort of think outside the box --

DR. SARKISIAN: Okay.

DR. VARMA: -- and go beyond where we are now, because I think we have

an opportunity to, in fact, explore that, the whole spectrum, if you will, as opposed to stick with what's already there.

DR. SARKISIAN: So, redefine it, kind of like you did in that third category?

DR. VARMA: Yes.

DR. SARKISIAN: I understand. Okay.

DR. ANSARI: I just want to say, just so that nobody thinks that Rohit's the only one that thinks that, I completely agree. I never think about my patients as non-refractory and refractory, not even once. The first time I heard it was when I sat on the ANSI committee.

And so, I like the idea of saying let's base a study protocol on what's our target population, the patient with severe damage who needs a low pressure, a low of lowering, or all the way to the mild patient who doesn't need a lot of lowering. And maybe there could be three categories, as we have suggested, and three protocols for those categories.

DR. FRIEDMAN: Paul?

AUDIENCE PARTICIPANT: In terms of patient selection, obviously, when dealing with MIGS, often we do cataract surgery together. So, perhaps in terms of patient selection, I'm sure, obviously, there are studies which are for combined cataract with MIGS and others just for MIGS. And sometimes we have patients clinically which appear with uncontrolled pressures, and they have a clear lens.

So, let's say you try to enroll that 40-year-old patient with the clear lens, and you said, well, there's great trial with this device and, then, I'll do phaco with the MIGS. And then, they happen to be -7.00D myope, and they develop a retinal detachment.

So, perhaps also including a Lox scale for grading of cataract severity could be included

in the combined studies.

DR. FRIEDMAN: Yes, please, Malik.

DR. KAHOOK: So, Husam, you know, we spent three-and-a-half years on the ANSI standards, and you're refractory/non-refractory out from the stage.

(Laughter.)

DR. ANSARI: I wasn't on that committee for three-and-a-half years.

DR. KAHOOK: Right.

DR. ANSARI: I came in; it was almost already written. So, I'm not taking this blame.

DR. VARMA: And actually, you'll see, if you read through all the minutes, there was a lot of discussion on this. And it's why it was actually said "Let's put this in the appendix."

DR. KAHOOK: Right.

DR. VARMA: Because there is so much disagreement on all of this.

DR. KAHOOK: No, we lost years off our lives, I think, in that.

But my question is, I have been involved in planning a lot of the workshops and participating, both as a speaker and from the audience. And one thing that I would love to come out with from this meeting is actionable items, things that we can really take and build upon.

So, we're throwing in some new variables, some of which are very controversial, like ocular hypertension. But the other one that is pretty controversial that we're not talking about too much is the introduction of OCT as a metric for defining disease. And I'm wondering if somebody from the FDA can actually comment on how can we incorporate OCT as

a metric for defining disease when it has really been used for any clinical or surgical trials. I don't know if anybody from the FDA can do that.

DR. FRIEDMAN: Malvina?

DR. EYDELMAN: Thanks, Malik.

So, I want to reiterate, actually, what Malik said, which is very important, that our hope for this panel discussion is to help tune in rather than create a bigger space to define in the following two sessions.

DR. FRIEDMAN: Okay.

DR. EYDELMAN: So, just to bring back everybody's attention to the fact that the current two MIGS devices on the market are intended for IOP lowering in patients with glaucoma.

There's certainly an option for somebody to design a device for OHT, but whether that should be the discussion for the rest of today's panels I think is going to really make it very complicated because I believe, then, the rest of the discussions will have to deal with what the expected safety and effectiveness for OHT versus for the patients with actual glaucoma.

So, while we are discussing this, I would like very much to make sure that the following two panels are very clear about the patient population for which they are discussing the safety and effectiveness. And that's my sort of bringing it back.

DR. FRIEDMAN: Okay. But in terms of the question that was asked about OCT --

DR. EYDELMAN: I will get to it.

DR. FRIEDMAN: Okay.

DR. EYDELMAN: I have a very long-winded way. So, for those of you who,

and many of you were at our OCT workshop about a year-and-a-half ago, and as we said previously, there's no OCT that's cleared for glaucoma specifically.

So, while you can make recommendations for particular thickness or thinness or particular measurements, I don't think it is viable to make a general statement that glaucoma as detected by OCT.

DR. FRIEDMAN: Okay.

DR. EYDELMAN: Did that clarify?

DR. FRIEDMAN: Yes. So, now I think what the FDA would like -- and I'll do this briefly because I don't think we need to spend a lot of time this -- but clarify from the panel in terms of the definitions of glaucoma that Rohit put forth, do people feel that others should be used? If they have other ones, can they state them and say whether they would prefer them and what they would rank the order of defining glaucoma.

So, Brian, I'll let you start. Basically, what he proposed, a mild, moderate, severe that is already out there and people are using. Are there other ones that you would propose or do you think that that would be how you would define glaucoma in most of these studies?

DR. FLOWERS: Frankly, I would need to give that more thought before I give an answer that I would be proud of.

(Laughter.)

DR. BUDENZ: I can start. I can start. I can start.

So, the mild category right now, as it exists, is something that we would call pre-perimetric glaucoma. There's no white-on-white defect, but you in your heart of hearts knows this patient has glaucoma. Either you have seen a SWAP defect or a change in the optic nerve or something that you definitely feel that is glaucoma. So, that is not an ocular

hypertension patient.

DR. FRIEDMAN: Right.

DR. BUDENZ: So, that I think is a reasonable definition.

I'm not so sure that the definition of moderate and severe is tight enough in that classification, and it could use some work, I think.

DR. FRIEDMAN: Okay. Henry?

DR. JAMPEL: Well, I was kind of worrying about giving my own talk or speaking.

(Laughter.)

But I would argue that, if one is going to say someone has glaucoma, that it should be more than just you looking at the patient. I mean, I know that, clearly, there's pre-perimetric glaucoma, but whether there's really OCT glaucoma, I mean, I would have to see that.

DR. FRIEDMAN: Yes, go ahead.

DR. LEWIS: Yes, I thought Rohit's classification is very valuable and it kind of incorporates a way for us to use this for FDA trials. It doesn't, though, incorporate some of the other risk factors that someone could have who is -- it's such a high risk to get glaucoma, the patient who has a family history over the thin cornea, and perhaps has pressures of 17-18 that might fall out of that criteria, and yet, is perhaps predestined to get glaucoma isn't really addressed in the classifications.

DR. ANSARI: I said it before. I actually very much support the classification that Rohit has outlined. I think that it makes a lot of sense. You know, the severe patient, however you want to define -- as Henry defined it I think is excellent -- who needs a very low pressure could be one class. And then, the patient who has less severe damage, but also

needs a low pressure is another class. And then, the patient with mild damage which needs lower pressure is the --

DR. FRIEDMAN: So, let me put a specific question to the panel because it gets into this OCT question. We all feel that there are people who don't have documented field loss of early glaucoma. I mean, that's come across.

Are these people to be in studies of new surgical devices or not? Do we think that there should be a way that that kind of definition should be included in these studies? And if so, why do you think so?

DR. FLOWERS: Well, I believe it already is. I mean, I think everyone in the trials does not have to have visual field loss.

I can't recall off the top of my head the specific criteria that has to be met, but they have to have documented glaucoma, which can be by optic nerve exam. I'm not sure if OCT is a specific criteria or not. But those patients are already allowed in a study without field loss.

DR. JAMPEL: I mean, at least in one of the ongoing trials, the patient cannot have an MD that is positive. That's it.

DR. FLOWERS: Right.

DR. JAMPEL: An MD of minus .05 would be okay if the investigator thought there were characteristics of optic nerve --

DR. FRIEDMAN: And you would want to see something tighter on that?

DR. JAMPEL: Yes, I think so. I mean, it's not that hard to have abnormal OCT. It really isn't.

(Laughter.)

DR. FRIEDMAN: I guess it comes back to what -- I mean, we're down to like

maybe 10 minutes left. What is it that we're actually trying to accomplish? I mean, I think we're trying to, I think, make it easier to get new treatments to our patients that are safe and effective, right?

And so, I think putting up increasing roadblocks to that is probably not the direction we want to go in. And so, when I think about the things that, at least for me, it would be nice to walk away from, I think the standardization thing is quite important. I mean, just looking at the different trials that I'm in, you would be surprised at how different all the protocols are for even randomization schedules.

Two of the trials I'm doing randomized 3-to-1; one of them is 2-to-1. Why is that difference? These are sort of silly differences. Some of them have same-day pressure checks, the same day as the surgery pressure checks; some don't.

So, if we could sort of address those things, I think it would be important. And I do think trying to get the trials through, I think there's a lot of good reasons to try to get the trials through in a year versus two years or even longer.

DR. FRIEDMAN: That's not really on our agenda.

DR. FLOWERS: I know. You're right.

DR. FRIEDMAN: Yes.

Do you have some suggestions, Rohit, for us, though, quickly, about what you think should be the definition? It's, you know, the threshold definition to be in a study at this point.

DR. VARMA: Okay. I think if they have --

DR. FRIEDMAN: For glaucoma. For glaucoma.

DR. VARMA: Right. If they have evidence of optic nerve, of characteristic optic nerve damage, they have glaucoma. Now I'm not saying it has to be purely OCT-based.

I think that there needs to be a little more careful, if you will, identification of maybe loss of a neural rim or RNFL seen on other imaging, the waves, and so on and so forth.

But, once you believe that the patient has evidence of damage, they are glaucoma. You don't have to wait for the visual field, white-on-white, and so on.

In fact, I think all of us would agree with that, although I think Henry is feeling a little uncomfortable.

(Laughter.)

DR. JAMPEL: Oh, yes, sure I am. Visual field is normal. OCT is normal. Pressure is 16. And you say they have an optic nerve that looks like glaucoma.

(Laughter.)

DR. VARMA: I didn't say glaucoma. I didn't say OCT --

DR. FLOWERS: But, Henry, that's not the real world. These are not the patients that are in these studies. I mean, the people aren't that way.

DR. JAMPEL: Right.

DR. FRIEDMAN: But we can define that.

DR. JAMPEL: Yes.

DR. FRIEDMAN: Like we can say you have to have a photo graded by two, by a grading center, or you have to have one of these three things satisfied to prove the nerve --

DR. JAMPEL: Yes, if you throw out the eye pressure criteria, which I don't have a problem with, then you had better have something else, or else you will have people who are totally normal.

DR. FRIEDMAN: I mean, I got someone referred to me with astigmatism of zero. So, you have to be cautious.

But, anyway, what were you going to --

DR. VARMA: No, I was just saying, I said they have to have evidence of optic nerve damage.

DR. JAMPEL: Let's make that objective. We can do that.

DR. FRIEDMAN: Objective, that is.

DR. VARMA: Yes. Now pick how you're going to define objective, you know, but fine.

DR. FRIEDMAN: But something more than one person looking at the --

DR. VARMA: Fine, but, okay, two subjective assessments. Okay, all right, fine.

(Laughter.)

But all I'm saying and trying to do is that, once you have made that determination purely on a structural basis, you're fine then. Then, go ahead, enroll them and treat them, because you are going to do that in your practice anyway.

DR. FLOWERS: There's more danger in going the other way because I think, if you're talking about washing-out these patients, I would rather wash out someone with pre-perimetric glaucoma with clear OCT damage.

I've looked at, obviously, lots of optic nerves. I can tell when it is damaged or not. I would rather have that person be washed-out than someone with clear field loss who is going to go through a 30-day washout, whose pressure may go wherever.

DR. FRIEDMAN: Reay?

DR. BROWN: There's another important aspect of patient selection, and it's a little bit off this; it's actually a lot off this topic.

(Laughter.)

And that is pseudoexfoliation and pigmentary glaucoma. These are huge problems in recruitment for these studies because we can't include them. And I understand the arguments, but I wonder if the panel could give an "amen" to including them.

DR. FRIEDMAN: Rick?

DR. LEWIS: Well, I mean, this gets back to my original point, that it is all about pressure reduction here.

DR. BROWN: Yes, we don't care what the angle looks like.

DR. LEWIS: I agree entirely with you here.

DR. BROWN: It is just that they should all be in there.

DR. LEWIS: Pseudoexfoliation patients who have sort of an accelerated open-angle glaucoma natural history should be included. It is unfortunate.

Again, our goal is to show these devices lower pressure and are safe. And the criteria for enrollment we have been fighting about, and I actually agree with Henry. But the fact is that we need to show that we can get these pressures down.

Some of these people with pseudoexfoliation have very high pressures. You know what the natural history is, and we can't put them in these trials.

DR. FRIEDMAN: So, would that be the sense of the panel? Because that would be nice to communicate that to FDA, if that were the consensus.

DR. ANSARI: Whereas I agree that the devices are intended to lower pressure, and that is the primary endpoint, I am concerned that implanting a device in a patient with one of those conditions, the device might be compromised by that disease state. And then, we wouldn't necessarily know -- I don't know.

DR. LEWIS: But we need to know that.

DR. ANSARI: Yes, we do need to know.

DR. LEWIS: That needs to come out in a trial rather than to come out anecdotally once it gets approved. Wouldn't it be better to have that as part of the subset of the trial? Right now, they're excluded.

DR. FRIEDMAN: So, does anybody feel strongly they should be excluded?

(No response.)

Okay. So, the panel is giving you support.

Angelo?

DR. TANNA: So, Rohit used the phrase "evidence of structural damage" or something along those lines. Well, evidence is probably not enough, depending on how you define evidence.

But, for these pre-perimetric cases, which I think are an important subpopulation of people to tap into for recruitment into these clinical trials, I think you want documented evidence of structural progression, either OCT or photographic, that could be looked at by a reading center and somebody can say in an objective fashion that there is structural change.

DR. FRIEDMAN: So, progression is a much higher standard because you might only have seen somebody for a shorter period of time. I wouldn't require -- I mean, I know what you're saying is sort of a pure definition of glaucoma.

DR. TANNA: It's a way to be sure the patient has glaucoma. You know, as Henry said, these patients with structurally-suspicious-looking discs, you know, where some of us may categorize them as abnormal in a glaucomatous fashion and others may not, those are probably not the best patients to be enrolling into a clinical trial to determine if an

investigational device is effective and safe.

DR. VARMA: If you think it is hard now to enroll, you just --

(Laughter.)

I mean, it would be absolutely impossible to show structural progression over time, but, yes, it's important. But I would argue you have notch. You have RNFL loss, in fact, in that area. How many other things could that be? Or other similar issues which, in fact, are very clearly stated, in fact, which is you have a disc hemorrhage and a notch in that area. You have, you know, things of that sort, in fact.

DR. FRIEDMAN: All right. For the last word, we'll let Joe, and then, I'll summarize briefly.

DR. CAPRIOLI: I find myself agreeing with Rohit again. This is unusual.

(Laughter.)

Clearly, you can have patients who have very strong structural evidence of glaucoma that we can all agree on. There's another group where it's a lot more fuzzy to get cup-to-disc ratio. If you have a notch in the right place, you have a disc hemorrhage, it's glaucoma. And I think we can all agree on a definition of glaucoma that would allow those patients in with pre-perimetric damage.

DR. FRIEDMAN: So, I think to give back to FDA some of the summaries of what we found, I think we all like the idea of this kind of mild, moderate, severe, and there may be some ability to tighten up those definitions slightly in some of those areas. There are published publications discussing the way those are defined. So, we could use those for now.

People feel, at least some -- and I would say it's a consensus -- that some objective measure of the optic nerve, not just one person in a room saying, "I think the nerve looks

funny," if you're not going to have definite field loss, would be a requirement to enter these studies.

As a total aside, in the outside glaucoma group, people feel that there is a little bit of discomfort with completely excluding everybody who doesn't have glaucoma from every study ever.

And the last thing I would say that came up is this refractory/non-refractory is really not understood by clinicians. It is not really something we use clinically. The thinking, over time, you want to think a little bit more along the lines of what Rohit has proposed, which is more pressure lowering needed clinically, less pressure lowering needed clinically. Those are the ways we think typically.

DR. EYDELMAN: So, if I can just ask one clarification? I know you have three minutes. How much of an optic -- you said any optic nerve damage, but how much assurance of optic nerve damage do you feel is needed before somebody enters a trial? As we said, is it a reading center? Is it just two people?

DR. FRIEDMAN: I'll put it to the panel.

DR. LEWIS: Well, I think if we start getting into reading centers for optic disc evaluation, it adds a tremendous amount of cost and time and expense. You know, the spectrum of optic nerve change in glaucoma is huge, from end-stage to disc hemorrhages. There are so many other changes.

It seems like if we're looking for a truly objective way and we're not going to go the way of the reading center, we have to look back at an OCT and somehow define agreed-up criteria of what an OCT change would be for this study.

DR. VARMA: I mean, I think one approach -- and I've not given this all that

much thought -- but one approach may very well be to have two independent measures, if you will, of optic nerve damage.

So, an assessment of the disc, whether clinically or with a photograph, plus an additional maybe OCT or other things, so that you have some additional independent validation of the fact that there is damage. That may be one approach to that.

DR. EYDELMAN: So, just the last comment. Coming back to Malik's earlier comment about OCTs, would the panel care to comment on what on OCT would you like to see as evidence of the optic nerve damage and whether you believe one OCT evaluation is sufficient or do you believe it needs to be a repeat OCT? And I promise that's my last question.

DR. FLOWERS: I guess that whole topic makes me uncomfortable because I just see what looks like unnecessary roadblocks being thrust in front of recruiting patients, in some ways ahead of clinical judgment.

As everyone has pointed out, sort of defining optic nerve damage is so varied. You would have to have a lot of different criteria, OCT being one and disc hemorrhages and the like, notches.

I think having two OCTs is unnecessary. I think most of us can look at an OCT and tell if it showed optic nerve damage or not. And so, only one OCT with -- I think we could come up with criteria, if it were just inferior pole damage or total RNFL loss below a certain number, 80 perhaps.

DR. VARMA: Brian, here, in fact, it's only that group which is pre-perimetric.

DR. FLOWERS: Correct.

DR. VARMA: It's not the group --

DR. FLOWERS: Correct.

DR. VARMA: -- where you have some evidence of optic nerve change and visual field loss. No, that is --

DR. FLOWERS: There are plenty of people who have significant loss on OCT who have no field loss.

DR. FRIEDMAN: So, we want somebody who has the real loss on OCT and not just all green totally normal --

DR. FLOWERS: Right, right.

DR. FRIEDMAN: And you say it looks like glaucoma.

(Laughter.)

DR. FLOWERS: Right. Exactly. Right. Well, I don't think that happens.

DR. SINGH: So, that one, it's probably worth asking everyone on the panel.

DR. FRIEDMAN: Yes, I was going to do that. I was going to march along, yes. Yes.

Don?

DR. BUDENZ: Yes, I think we could develop, you know, a system whereby the clinician certifies that this is a glaucomatous optic disc and there's some abnormality on OCT, which we can debate whether it's a 5-percent of 1-percent level and reproducible. You can get two scans in one succession, and it's not like visual field where you have to wait a week. You just have to get two OCTs back-to-back and just make sure there's something reproducible there.

DR. FRIEDMAN: Henry?

DR. JAMPEL: So, I'm sticking with what was on my slide, which was --

DR. FRIEDMAN: Nothing moves him.

(Laughter.)

DR. JAMPEL: -- visual field abnormality. You don't even need to look at the disc. If the visual field is normal, what I just threw out there was statistical significance, either for the overall RNFL or a sector or a segment at the P 1 percent level. And that's open to debate.

DR. VARMA: One or two? One test or two?

DR. JAMPEL: Oh, do it twice.

DR. FRIEDMAN: Yes, I like the idea. So, I would agree with Henry. I think twice, you can just boom, boom, and that way, it is not an artifact; it's something real. And you show that it's the same thing, the same location. And I like that.

DR. LEWIS: But cataract by itself can cause depression or loss of visual field. And so, there are so many artifacts that you're going to throw into this.

You know, the OCT seems to be in many ways more reliable and reproducible than a visual field. We could come up with some basic criteria that is straightforward and much easier for the companies and the investigators to work with.

DR. LEWIS: But, I mean, we are all taking care of these patients and recommending them for a study because we think they have glaucoma. And this is just saying it's not just your gut feeling, but they have field loss or they have something that is -- anyway, Rohit, I assume you're okay?

Husam?

DR. ANSARI: Yes, I agree with Henry.

DR. FRIEDMAN: Okay. Did we give you what you wanted to know,

Malvina?

(Laughter.)

Okay. All right. Thank you, panel. Thank you very much.

(Applause.)

DR. SINGH: We'll reconvene at 3:40.

(Whereupon, the foregoing matter went off the record at 3:25 p.m. and went back on the record at 3:45 p.m.)

DR. SINGH: Somebody asked whether these slides might be available. And after the workshop, these slides will be available on the FDA website. There will also be an enduring piece, a manuscript, that will be relay the proceedings of this workshop.

So, the second panel session is in safety endpoints and adverse outcomes. And I'm going to ask Rich Parrish to come up and introduce his fellow co-moderator and his fellow panelists.

DR. PARRISH: Thank you very much, Kuldev.

In the spirit of being in Washington, we're going to run this as though we were Sam Rayburn or Tip O'Neill and try to stay on focus and to point.

My Co-Chair is Dr. Jeff Liebmann. The speakers in this session will be Greg Skuta, speaking on hypotony as an adverse outcome; Doug Rhee, on substantial increase of IOP versus baseline, and then, Dr. Leon Herndon, on substantial visual field loss.

The specific questions that I am going to ask each member of the panel to address are included in your pamphlet. And at the bottom are the specific issues the FDA has requested that they have feedback on.

With respect to this section, it reads, "For the following safety concerns, what are the

definitions or relevant clinical findings that should be present to classify them as adverse outcomes? What is the threshold percentage of a study population that could have this outcome with respect to hypotony, substantial increase in IOP compared to baseline measures, and, lastly, substantial visual field loss?"

So, those are the issues. And the other questions are listed above for the other corresponding session.

Our first speaker is Dr. Greg Skuta, addressing the issue of hypotony as an adverse outcome of MIGS.

DR. SKUTA: Thanks, Rich.

With regards to disclosure, I am on some committees for the Ophthalmic Mutual Insurance Company, but, otherwise, have no disclosures to declare.

Well, with regard to a definition of hypotony, some would define this as intra-ocular pressure below a certain level, say 6 millimeters of mercury. In two textbooks, Jonathan Pederson defined statistical hypotony as IOP of less than 6.5 millimeters of mercury, which is more than three standard deviations below the mean. Others, including Pederson again, would define clinically-significant hypotony as an IOP below which an eye does not function normally.

In two important papers from Bascom Palmer, hypotony was defined as IOP of less than or equal to 5 millimeters of mercury and TVT -- this was on two consecutive visits -- after three months.

We have heard this afternoon already that many of the manifestations of hypotony -- and I would just emphasize here this includes hypotony maculopathy, which is characterized by decreased visual acuity, optic nerve and retinal edema, and macular folds.

It's really important, I think, from the outset to understand that some eyes with statistical or numerical hypotony experience none of the above; whereas, some eyes without numerical hypotony experience some or all of the above.

This is an eye with profound hypotony maculopathy, disc edema, macular folds, vascular tortuosity, that we have all, unfortunately, seen in our practices.

In a landmark paper in 2003, investigators from Bascom Palmer looked at risk factors for hypotony maculopathy in 228 eyes from their practice, 81 of which actually had hypotony maculopathy and 147 of which had hypotony without maculopathy.

They determined that risk factors for hypotony maculopathy included younger age, the average of 50 in this study, male gender, and also myopia, again with an average of -3.00 diopters. Interestingly, a history of diabetes and cardial effusion were associated with a decreased risk for hypotony maculopathy.

In the trabeculectomy study, Dr. Gedde and colleagues, with five years of follow-up, did establish a criterion for failure, whereby IOPs were less or equal to 5 millimeters of mercury, this was considered, again, failure.

In the trabeculectomy group, we know that their rates were higher. But if you look at this broken own in more detail, about a third of the failures with the trabeculectomy group, in fact, were related to persistent hypotony, three in the two group. Of those 16 eyes, three actually had stable vision, 13 had some decline in vision, although that was variable decline.

What about the Collaborative Initial Glaucoma Treatment Study? Well, interestingly, hypotony was not systemically defined or recorded as a postoperative complication on the post-trabeculectomy follow-up form. Investigators, though, could record this under other problems, and there were four eyes, just under 1 percent, noted to have hypotony or

prolonged low intraocular pressure.

Let's focus now on the MIGS procedure, first, trabecular micro-bypass stents. One of these includes the Hydrus, about which we have limited data to date in terms of published literature. Another is the trabecular micro-bypass stent known as iStent.

Tom Samuelson and colleagues published a paper in Ophthalmology in 2011 looking at a randomized controlled clinical trial in which 111 patients underwent iStent with cataract surgery and 122 patients underwent cataract surgery alone. One eye -- the group was not specified here -- experienced transient hypotony at five to seven hours that was resolved by one day postoperatively.

What about ab interno suprachoroidal stents? Again, one about which we have limited literature to date is the iStent Supra, but you can see here from this diagram that it is placed into the suprachoroidal space, but intraoperatively.

With regard to the CyPass, we do have a series published in JCRS last year in which 184 patients in a prospective case series underwent a cataract surgery and placement of a suprachoroidal micro-stent.

The most common complication in this study was transient early hypotony with around 14 percent of the patients experiencing an IOP of less than 6 millimeters of mercury. But hypotony resolved in all but one patient by one month and in all cases by six months.

Could we go back one slide here? Well, something here got hidden, I guess, but that's fine.

Transient hypotony was attributed in this case to micro-stent placement and creation of small cyclodialysis clefts. And I had a picture of a standard traumatic cleft here a moment ago.

But, particularly, in early postoperative course, the cleft was felt to possibly extend beyond the implant's external diameter. And this was felt to explain some of the hypotony with resolution of these small clefts over time.

Let's look now at subconjunctival-based transferral filtration devices. One is the AqueSys, described very nicely by Steve Sarkisian earlier this afternoon. So, I will not go into detail here again. But, as Steve pointed out, there are no peer-reviewed applications to date on this particular device.

What about the InnFocus MicroShunt? This is shown diagramatically in the lower right side of your side. But this is a filtering device made from the polymer shown in the slide here and placed by an ab externo approach. The procedure involves creation of a fornix-based conjunctival flap and the use of intraoperative mitomycin. And once again, there are no peer-reviewed publications to date on this particular device.

Both of these devices control flow and minimize hypotony by applying Poiseuille's law of laminar flow to create a tube that is sufficiently long and narrow. But they do both involve diversion of aqueous to the subconjunctival space with creation of a filtering bleb, and for these reasons, and in addition to that, the MicroShunt associated with the use of intraoperative mitomycin.

So, as filtering procedures, it would be important, I believe, to determine the incidence of transient and long-term hypotony and any impacts on vision.

In summary, then, it would be helpful and appropriate to establish a consistent definition of hypotony. Documentation of transient and longer-term hypotony would be particularly relevant for minimally-invasive surgical procedures that involve placement of the device into the suprachoroidal space or that involve subconjunctival filtration.

And finally, it's extremely important, I believe, to document visual impact, if any, and differentiate postoperative statistical hypotony from clinically-significant hypotony.

Thank you very much.

(Applause.)

DR. PARRISH: Thank you, Greg.

Our next speaker, Dr. Douglas Rhee, will present substantial increase in IOP versus baseline as a serious adverse outcome.

DR. RHEE: Thank you very much.

So, I have the pleasure of presenting the opposite of Greg.

And these are my disclosures. It's up to you and my future psychiatrist to determine how conflicted I am.

(Laughter.)

So, in outline, I am just going to go over some definitions and, then, give some examples.

This is the older version. Is there a new version of the talk that I uploaded a couple of hours ago? No? Okay, we'll go off of this one. That's fine.

So, what is needed? We do need to evaluate this as an outcome measure, and a significant high IOP is likely to have been a causative factor in the immediate, intermediate, or late postoperative period, for a number of different serious issues. So, acute optic nerve injury or snuff-out or wipeout, retinal occlusive events, and corneal endothelial damage. And all of these have been reported, and in the updated version there were more references; that's all.

But, in terms of how do you define it, and I think that's what one of the purposes here,

was to try to get some clarity. And I'll try to do my best, but I'll give some explanations as to why it's hard to do that.

Colloquially, first of all, let's learn to call it the same thing, which I think IOP spike is a reasonable thing. That is what we colloquially call it, and it would be nice just to be able to search for it in literature, to just use that definition.

It's difficult to singularly define, as it is with many things that we have already talked about in these sessions, because it is very individualized for optic nerve susceptibility, in that there could be a patient where you could have a 30-millimeter-of-mercury elevation for a day or two, and it has absolutely zero significance, but it seems like a really bad thing. And then, there will be a patient where you will have a 10-millimeter elevation for a few hours and it can have a devastating effect.

And there is no way to know preoperatively or postoperatively which one of those patients, at least with our current understanding of the disease in terms of optic nerve susceptibility. Some patients will have more or less optic nerve susceptibility.

And also, what you call an IOP spike depends on the baseline IOP of where the patient sits. This has nothing to do with IOP spikes from surgical devices, but this is something that Marlene Moster and I did a while ago with steroid-induced, but we used multiple definitions.

And you would like to see, if everything worked out right, as you increased the severity of the IOP spike, you would just have concentric rings, but there would be no discontinuity. But, in fact, what you see, this has to do with IOP elevations after intravitreal triamcinolone. So, just a steroid-induced elevation. But, even when you use multiple definitions within the same population, there is some overlap, but there's also areas of discontinuity.

My advice that was in another version is that we should actually use multiple

definitions. And then, in terms of cataract extraction, and with trabeculectomy, is that I was just trying to point out that the IOP spikes occur with our existing technologies. It is not that our existing technologies are devoid of this adverse event. In fact, they happen fairly significantly.

There was an article that I had tried to show that was just from The European Journal of Ophthalmology that looked at a couple hundred cases of phacoemulsification in glaucoma patients. And the way they defined a pressure spike was greater than 50-percent increase from the baseline. So, if the baseline was 10, then 5 was it. If the baseline was 30, then 15 was it. But they divided by a percentage, and it was roughly about 17 percent.

And trabeculectomy, interestingly, the rates of IOP spikes, no matter how you define it, is roughly in the single digits. It's usually 2 and 6 percent. So, I'm just trying to point out that it does occur.

And in this, oh, my goodness, I need a refraction. This is too small even for me to read.

But it's roughly about 2.3 percent with cataract plus Trabectome. And I'm just trying to give some examples of where MIGS actually is helpful. In this case series, it is actually lower. And then, when compared directly -- this is another series by Brian Francis -- when you compare combined trabeculectomy versus phaco/Trabectome in this case, it's 4 percent versus 17 percent.

And if I got the numbers wrong, I'm sorry. I'm actually having trouble seeing it because they are small. But there's a statistically-significant difference.

And so, what I think we're seeing -- and this was just my own data -- where for cataract, or for combined trabeculectomy, depending on the definition we use, I actually

experienced much higher rates of IOP spikes, but the new technology was helpful.

And the point that I'm trying to make with that is not to say that necessarily these technologies are particularly helpful, but I think it's important, rather than just looking at a case series and trying to compare it historically against another case series, you would really like to see a comparative study. And that's how we should all be evaluating it. I know most of us that design study trials here already know that, but I think it is important to point that out.

And this is the Phase 3 cataract versus iStent. And there was not much, with one iStent, there actually wasn't that much of a difference in terms of the IOP spike with having the device.

And then, there's a slide that I had inserted where in Europe -- and again, it was off-label use, and we never do that here in this country -- so, of course, it's European. But in that study where they did off-label two iStent devices, there was actually a small benefit to IOP spikes. So, again, it is nice to have that in comparison.

And in the control arm, the rates of IOP spikes were actually vastly different. And that just has to do with, it is an artifact of the fact that we keep using different definitions.

And here's an example from Ivantis. These are corporate slides that they presented to me. These are not published, and these are their slides. They generated them.

But what it did show is that there is a difference between phacoemulsification in the pre-op and one-day postop versus -- this was a study randomizing phacoemulsification versus phacoemulsification plus the Hydrus device, which we saw a great introduction earlier.

And there is a much improved or protected effect of the Hydrus device. And you can look at it versus numbers, versus percentages. But it's nice to have that by comparison.

So, in conclusion, I think we absolutely need to collect -- and it's the consensus of this

panel, I think, that we need to collect -- data on IOP spikes. Multiple definitions should be used and reported, so that studies can be compared against each other.

And then, TM bypass procedures do pretty well.

Thank you.

(Applause.)

DR. PARRISH: Thank you very much.

I'll ask each member of the panel to address the question posed by the FDA with, first, respect to hypotony. Each member will respond. We will, then, go to their response on the substantial increase in IOP and, then, lastly, to address the issues posed, the questions posed by them with respect to substantial visual field loss.

Our last presenter is Dr. Leon Herndon, who will address the substantial visual field loss as a serious adverse outcome of MIGS surgery.

DR. HERNDON: Thank you, Rich, and I'm happy to be here.

My disclosures are not relevant for this talk.

So, I am starting out very basic. As we know, the visual field is an island and has been described as an island of vision surrounded by a sea of blindness. And when you map the island of vision, we know that the higher sensitivity is consistent with the fovea; that eye contours around this island consist of points of equal light sensitivity. We know that both eyes were together in the visual field, and the middle is served by both eyes. To the far extremes, one eye just covers the visual field. And we know also that the opposite retina is consistent with the opposite visual field.

That's very important when you start looking at the automated static perimetry. We know in this case of a paracentral defect, that the retina area is served by that is the opposite to

the area of the defect; also, with arched, webbed, and nasal defects.

We need to say a word about global indices. When we're trying to talk about progression of visual fields, we know that the mean defect is the mean deviation from normal age-adjusted values expressed in decibels, and the p-value is significant. The pattern of standard deviation is significant for variability of deviation and is sensitive to a regular hill of vision. Increased values suggest focal deficits.

This is a real-life patient who presented with a mean defect of his right eye of minus 2 (-2.00D) and of his left eye of a minus 4 (-4.00D). And he presented, as you see, to significant loss, minus 13 (-13.00D) in the right eye and minus 12 (-12.00D) in the left.

The thing that was different about this patient is this occurred over just a six-month period of time. So, these were some surgical interventions and mishaps between that period of time that led to the significant visual field loss.

So, why should we bother with visual fields? We know that glaucoma affects the peripheral vision well before the central vision. And the central vision acuity is a poor test for glaucoma in the field or in a clinic. Visual fields deal best as functional status of the visual status, and they assist in diagnosis and following of glaucoma.

A word about severity. We have already talked a little bit about this. But the vision field can be used to address the severity of functional damage to the optic nerve. Severity can be used to set target intraocular pressure once a diagnosis is made.

Although the ocular visualization is important for future comparison to detect change, the large differences between individuals makes grading of the severity of glaucoma impossible based on optic nerve cupping.

Another way to look at different severities of glaucoma based on the visual fields uses

a the Hodapp, Parrish, and Anderson Scale, where early deficits were noted to be mean deviations up to minus 6 decibels, and there are no points adjacent to fixation with a sensitivity less than 10 decibels.

Moderate deficits were patients who had mean deviations between minus 6 and minus 12 decibels, and no point adjacent to fixation with a sensitivity of less than or equal to zero decibels.

Severe defects were defined as mean deviation of worse than minus 12 decibels; any point adjacent to fixation less or equal to zero decibels, and both hemi-fields contain points less than 5 decibels adjacent to fixation. So, another way of looking at different categories of severity of disease.

Why should we look for early or subtle progression? We are all aware of the data from Olmstead County in Minnesota where patients who were treated over the years by good doctors doing the right things, over 20 years, as you see, those who start out with treated ocular hypertension, after 20 years, 14 percent of them presented with unilateral blindness. After 20 years, 4 percent of these patients who were well-treated over the period of time presented with bilateral blindness.

Those patients in the study who started out with treated glaucoma, 54 percent of them over 20 years developed unilateral blindness compared to 22 percent over 20 years who developed by bilateral blindness.

I do want to say a word about quality-of-life measures. The Los Angeles Latino Eye Survey, of which Dr. Varma was the key author, was a survey of over 6,000 subjects in Los Angeles. Of those, 213 were patients who were diagnosed with glaucoma. These patients underwent SITA 24-2 standard testing. The mean defect was used to assess the severity of

glaucoma.

Also, they employed the short Form 12 NEI-VFQ-25 measures to assess health-related quality of life. We saw a trend towards worse NEI-VFQ-25 scores with worsening of visual field loss. So, for discussion, we need to also consider quality-of-life measures.

It's already been mentioned, the iStent trial. And I won't go into it, but just to say that first-year results, they did not really follow visual fields. The study was carried out to two years, and this was published by Craven, et al.

And they found that -- let's go back; let's go back two slides, please; thank you -- the average mean defect in this study was minus 3.77 decibel. In the iStent group before, minus 3.22 decibels in the stent group at two years compared to the control group, those who just had cataract surgery, where the baseline mean defect was minus 3.94 in the control group before and minus 3.16 decibels in the control group at two years. So, over two years, in this population of patients that we're talking about today, there is no progression based on visual field indices.

But what about the Early Manifest Glaucoma Trial? As you know, this is sponsored by the NEI. The question was, should patients with newly-diagnosed glaucoma be treated with pressure-lowering therapy? 30-2 visual field testing was performed every three months, and the median mean defect was minus 4 decibels.

The Advanced Glaucoma Intervention Study, 789 eyes were studied over eight years. And we saw that the mean defect was worse, as you would imagine -- these are more advanced disease -- minus 11, and a different schema among Black patients versus minus 9 or so among the White patients.

And finally, CIGTS had a question in patients with newly-diagnosed glaucoma: is

initial surgical therapy preferable to medical therapy? The average mean defect at baseline in these groups was minus 5.7 in the surgery arm versus minus 5.2 in the medicine arm.

We saw over a period of five to eight years there's very little change in mean defect over time. But, if you look at what they categorized as significant progression, minus 3 decibels or worse, we found that over five to eight years a significant number of patients in both groups progressed.

They also show that those with more advanced disease benefitted more from surgery than from medicine.

I want to skip ahead to state that there are different scenarios and analyses. But, in the absence of a criterion standard, it is difficult to assess which of these measures is better trying to determine progression.

These findings make it difficult to identify one method as having clear validity over the others. So, what constitutes clinically-significant visual field progression? Well, I'm not sure.

(Laughter.)

So, the question we have for the panel upfront, my last slide, is, how often should visual fields be performed in clinical trials utilizing MIGS? What level of progression should constitute an adverse outcome? Should we look at mean defect or should we look at pattern of standard deviation? And finally, should quality-of-life measures be included?

Thank you.

(Applause.)

DR. PARRISH: Thank you very much.

I would like the five panel members to come up to the stage, if you would: Dr. George Spaeth, Dr. Dale Heuer, Dr. Cynthia Mattox, Dr. James Brandt, and Greg will be here.

The speakers can have a seat out in the audience, if you would.

And as we start to think about the specific questions posed, I would like to add a preamble. And that is, should we differentiate a very low intraocular pressure, aka hypotony, as a failure to achieve a desired intra-ocular pressure level versus a low intraocular pressure with specific associated adverse outcomes, to keep that in mind? And I'm going to pose that same kind of question as we go through the other two issues.

The first respondent, George, your thoughts on the issue of hypotony. And then, we'll move down the line.

DR. SPAETH: Oh, thank you, Rich.

First of all, just a general worry about "safe". That's one of those really dangerous words. There's nothing that's really safe, of course. What we mean is adequately safe, and I think we have to remember that when we're using the word.

Specifically, your question, we have to do it both ways. It's not an "either/or". You can have a person whose pressure goes from 22 to 15 and they end up with hypotony maculopathy. A person whose pressure goes from 25 to zero, and they have 20/20 vision; they have no maculopathy; they have no problem whatsoever.

But, on the other hand, we know that when patients go from a relatively-high pressure to a pressure that's really, quote, "low" -- let's say 5 or 6 -- that they are at risk for developing problems such as suprachoroidal explosive hemorrhages.

So, just the lower pressure by itself I think you have to know about that. And so, I would encourage collection of data that says what's the pressure, and putting a figure on it arbitrarily. But, then, you also have to include data that is going to define hypotony in terms of its clinical findings. Is there macular edema? Are there corneal folds, suprachoroidal

hemorrhages, suprachoroidal effusions?

And I think that would really do the thing, taking into account both within the clinical definition of hypotony, which is not based on a figure, and then, just the fact that low pressures below 6 -- or pick a figure; I don't think it matters really -- patients with those low pressures are predisposed to getting the sort of problems that appear clinically.

DR. PARRISH: Dr. Heuer? Dale?

DR. HEUER: Yes.

(Laughter.)

No, seriously, I think one of the problems with it we have is whether we're looking at an endpoint, in which case it's the numeric, or we're looking at an adverse event. And as I understand, our charge is to look at adverse events.

So, in the realm of adverse events, it really is the consequence of the finding of low pressure. I actually totally agree with what George said, although I couldn't repeat it now, if I had to do.

But I do think that the other issue that comes into play, even more in the realm of elevated intraocular pressure, is the timing. When are we looking at this? Because if a patient has a pressure of 5 on the first postop day, and from then on it's 12.3 because that's what you want your pressure to be, it doesn't really have any clinical significance. And so, I think we need to define timing and outcome influence.

DR. PARRISH: All right, thank you.

Dr. Brandt?

DR. BRANDT: Two comments. One, as one of the TVT investigators, I would say that I was arguing with my fellow investigators a long time about defining hypotony

as a number below which the person was felt to have hypotony. I think everybody on the panel shares the experience of having patients whose pressures are consistently 3 or 4 who are seen really well and have been stable for years. Those folks have not had a bad outcome from their surgery. We hit it out of the park for those patients. And yet, by choosing strict criteria, we actually, I think, give ourselves a bad rap for having achieved such a low pressure and done so very well.

And partnering with that, many of you in this audience know that I have spent a lot of my career thinking about ways of measuring intraocular pressure. And I would caution our colleagues from the FDA of locking into these numbers because over my career I have become more and more skeptical of our ability to measure intraocular pressure accurately.

And I would say that accuracy of our P measurements in the single-digit range is really poor. And so, you have this enormous wide confidence interval around these IOP measurements of 6 or 7 or 5. So, to set strict numeric criteria I think is a big mistake, and in doing so, you're overestimating your ability to accurately even measure that outcome. So, I would caution you from choosing numbers like that.

DR. LIEBMANN: Just to echo Jamie's comments, I would like for us not to think about it in terms of absolute numbers as well, but, rather, in terms of cause, duration, and effect. So, in these surgeries, most of which involve angle configuration and angle anatomy, we may be more predisposed to things like cyclodialysis cleft and transient low pressure and its sequelae.

There are ways we can look at those structures relatively easily. OCT could allow us to look at macular folds, OCT biometry, anterior segments, and we could really determine whether people are actually having sequelae from the surgery itself, rather than look at the

specific number.

DR. PARRISH: Dr. Skuta?

DR. SKUTA: Well, I think George said it particularly well, but everyone has said it already. And in my presentation, my message I think was simply that we do need to measure the pressures and maybe divine some criterion for a 5 or a 6 or somewhere in that range potentially, but, more importantly, determine the effect on the eye in terms of vision, in terms of choroidal detachment, and so on and so forth. And so, I believe those are really important.

As I said earlier also, I think in the MIGS procedure it seems particularly relevant to the suprachoroidal stents and to the filtration procedures.

So, a little to add to what's been said already.

DR. PARRISH: Dr. Mattox?

DR. MATTOX: I agree with what everyone is saying along the panel already. But I'll give you a good segue into the next section, which is that I think that the consequences of hypotony are what define some of our actual complications. And rather than counting hypotony as a separate complication, independent of those other consequences, you could consider grouping those particular complications related to hypotony as a group. So, if that helps?

DR. PARRISH: Would you care to offer those most common complications that you think are causally related to persistent postoperative hypotony?

DR. MATTOX: Sure. I think hypotony maculopathy is the obvious one, choroidal effusions, and, again, the duration of those events is critically important as well. More devastating would be suprachoroidal hemorrhage or a snuff-out related to hypotony,

which either of those may have devastating consequences, but are unlikely to happen in this population perhaps and unlikely to happen in this type of procedure.

DR. PARRISH: The second part of the question that we were asked to address is if we could suggest a threshold percentage of the studied population that could have this outcome. Based on the discussion in the last session, it seems that there is a spectrum, those who have more advanced disease, those who have less advanced disease. Perhaps we could start talking about those that have real glaucoma, but it would fall on the less serious spectrum.

George, could you offer any numeric range in which the kind of complications that Dr. Mattox just described would be acceptable?

DR. SPAETH: No. I really think that she hit it on the head. Just do away with the phrase "hypotony". Don't use it at all. Just say hypotony maculopathy, choroidal detachment associated with low pressure or suprachoroidal hemorrhage, whatever. Just talk about the things. Why have the figure at all?

DR. PARRISH: I guess the question was not a number of intraocular pressure, but, rather, the percent or proportion of patients who have relatively-mild but real glaucomatous disease who undergo either one of the current or to-be-defined MIGS procedures, a procedure which presumably has relatively low risk. What percentage threshold would you accept for any of those kinds of complications that Dr. Mattox just described, 5 percent, 1 percent, half a percent? Just any suggestions on what tolerance you would have?

DR. SPAETH: Excuse me, Rich. I misunderstood your question. When a person is going blind from glaucoma, and they are rapidly progressing to total visual loss, we

would be willing to accept very high percentage of patients who have something like hypotony maculopathy because they're going to go blind anyhow. What, 25 percent, 50 percent maybe even? Who knows? A patient who has no visual loss and whom you do not know they're even going to get worse, zero.

DR. PARRISH: Dr. Heuer?

DR. HEUER: Well, let me back up and add one to Cindy's list that I think is the most common and vexing problem that I see with patients with what I might call borderline hypotony, and that's variable vision, people that can't quite -- you know, some days they're good; some hours they're good; some times of the day they're good. That's actually perhaps preclinical or subthreshold macular hypotony, but I think it also can come from the cornea.

So, having added that, I wouldn't look at this from the direction you just did: are we starting with someone with mild glaucoma, medium, or moderate? It really is device-specific.

And I think I would use kind of Tom's approach, Tom Samuelson's approach earlier. I think the ones to the canal, hypotony should be less than 1 percent because the only way you're going to get it, as Jeff pointed out, if dinking around in the angle, you cause an inadvertent cyclodialysis cleft. Otherwise, you just can't get there from here, to use a phrase, because you're going into episcleral venous pressure.

So, I would think in those devices that intend to bypass trabecular resistance, it should be 1 percent or less. And those may be the ones that would use, would seem more of a place in most of the milder patients. But some of the milder patients may have had that and it wasn't effective or their pressure is really high and you need more reduction.

And so, if I had to put a number on it, if you start doing transconjuctival or translimbal approaches into the conjunctiva, you know, you may have 5 or 10 percent. It also depends,

back to my previous comment, are we talking about somebody that has a choroidal effusion in the first week, but it's gone after that? That's going to be perhaps a higher number, if we're doing a translimbal approach.

And in the cyclodialysis space, I just don't know that we know enough to know what to expect in that group.

DR. PARRISH: I think there's a comment from Dr. Singh.

DR. SINGH: Yes. I was just going to say that, you know, one way to phrase that question, George gave the two extremes. Someone who has severe visual loss, you would probably accept very high rates of maculopathy. Those who had no vision loss, you would accept zero.

And one of the purposes of the first panel was to define what's mild, what's moderate. In some ways, it might be worth asking that question for mild glaucoma versus moderate-to-severe glaucoma. What would be considered acceptable for a MIGS procedure being used in different subgroups of patients where you have different IOP goals.

But it's your call. I just thought that might be better, another way to approach the question.

DR. PARRISH: All right. The Chair is happy to accept that recommendation.

Jamie, why don't you answer Kuldev's point?

DR. BRANDT: I agree with you, Kuldev. I mean, you have spoken quite eloquently at a variety of meetings of each millimeter additional lowering is always a balancing of risk, and that there's always, the lower you want to go, the higher risk of doing harm.

And I think you have already heard from the panel that somebody with advanced disease, you're going to be willing to accept a higher risk of overshooting. We need the data,

just continuous data, to see what sort of target we're going to be able to achieve on average with a given procedure and what the spillover, and then, adjust the risk as appropriate for a given patient or assess the risk and decide on the treatment.

I'm not sure if I have much to add to what's been said so well.

DR. PARRISH: Speaking of the prerogative, if I were sitting at the Chair of the FDA, I would say, "Gee, now I want to have a uniform application that I can apply. I don't want to have to consider which way the next generation of devices, MIGS or FIGS, or whatever they will be called" -- (laughter) -- "will work."

We could all come to some agreement. I agree with what everybody is saying, but, from an administrative standpoint, thinking about future applications, it would be very difficult, I would think, to have a separate listing for all the potential ways we might be able to get aqueous out of the eye. That's just an editorial comment.

DR. PARRISH: Go ahead.

DR. LIEBMANN: So, in a way, it depends upon what the goal is. As George mentioned, if we're talking about an iStent versus cataract surgery, we are only going for a couple of millimeters, maybe get the patient on a medication or two, we can't afford hypotony for those patients.

On the other hand, if we develop a procedure that lowers it 7 or 8 millimeters in a trabeculectomy, we are going to have a different set of criteria, and we will accept 2 percent in one group and 5 percent in the other group as a difference.

So, I think it depends upon what our goal is and what the procedure is offering us.

DR. PARRISH: Dr. Skuta? And then, Dr. Mattox.

DR. SKUTA: Just, I mean, you know, I think that some discussions earlier

today related to greater than or equal to two lines of vision change, and so on and so forth. That's a reasonable thing.

You know, I actually looked -- I think Don Budenz may be in the room still -- but I looked at the hypotony maculopathy paper from Bascom Palmer from 2003. And interestingly, if you look at some of the charts there, if I remember correctly, the vision in the control group, if you will, those without maculopathy, went from a median of around 20/50, I believe, to 20/70. I think those who were actually in the maculopathy group went from a median of 20/40 to 20/80. So, there's a little difference there, but not a lot.

And so, is Don still in the room? I'm not sure if he is right now or not.

But, you know, it is very important, I think, to really assess the level of change of vision, whatever criteria you might have, greater than or equal to 2 or maybe 4, and so on, in terms of determining success from a visual standpoint.

DR. PARRISH: Dr. Mattox?

DR. MATTOX: I agree with assessing it on a visual functional level. But I also wondered, do we have to define it a priori what the acceptable rate of these events are? Isn't that something that happens at the end of a trial or are we talking about in the period during a trial design here now? Or are we talking about an approval process?

DR. PARRISH: I believe we're talking about an approval process and a criteria established before you test the newest device in order to ascertain whether or not it has an unacceptable incidence of adverse outcomes.

DR. MATTOX: Okay. In that event, I would have to qualify it based on the effectiveness of the device. I think it's really critical. You know, that determines everything, how effective it is.

DR. HEUER: Rich, could I add, expand on what Cindy said?

DR. PARRISH: Malvina has a comment. Let me go ahead and get to her.

DR. HEUER: Go ahead.

DR. EYDELMAN: It's dead (referring to microphone). Oh, no, it's not. Okay.

So, yes, every clinical trial needs to be designed with some predefined safety endpoints. So, this is what we're trying to get at: what would be the acceptable safety profile that we can say would be a success for a clinical trial of a brand-new device?

Ultimately, at the end of the day, each PMA, as Dr. Kiang addressed, all of these would be coming in through a PMA. And each PMA stands on its own, and we do evaluate its profile. But we need to define the parameters, the endpoints, for any successful clinical trial.

And with that, if I can just echo what Kuldev said earlier, I think it would be very helpful if we could once again hear for the low and the high end, well, for the mild and severe glaucoma. If that's how you want to structure the rest of the questions, I think that would be very helpful, since the first group left the definition pretty wide.

DR. SPAETH: I didn't get the sense after the first meeting that there was a general consensus as to the definitions of mild, moderate, or severe, especially mild.

(Laughter.)

And I think that is what you have to get at first. Because if you're defining mild as no visual field loss whatsoever, and you're thinking in terms of pressures or disc asymmetries, or something, I don't see how you can accept any visual decrease as acceptable. It's got to be zero.

If, on the other hand, you know, we save 5 decibels of field loss, well, then, I think that

puts you in a different category, and maybe you can accept a very low rate of hypotony.

DR. PARRISH: Dr. Heuer?

DR. HEUER: I've lost track of what the question is. But I'm not quite as strident as George. I think if you are going to do surgery, there is going to be some risk anytime we enter the eye.

And what I wanted to expand on in Cindy's point is that we, as glaucoma specialists, have very selective memory about how frequently we get complications. And there have been criticisms of many of the studies that I have been involved in. When we gather information systematically and prospectively, the rates of our complications are much higher than any of us think they are, even though we think we're doing world-class perfect surgery.

And so, I think if we were to sit up here and pontificate about some arbitrary percentages, we may, in fact, be doing the FDA and our glaucoma public a huge disservice, except to speak somewhat qualitatively.

And so, to try to answer Malvina's question, in a patient with mild glaucoma -- and I guess I'm a little bit in George's camp; I'm a little uncomfortable if somebody's got a pressure of 18 and you just kind of physically know they're going to get glaucoma. That is a patient that could wait until your trial is done to figure out if they need that implant, rather than putting that patient in a study. But I'll take that editorial comment off the table now.

If somebody has got bone fide mild disease, I think in terms of the risk of hypotony, it ought to be certainly less than 5 percent at anytime during the course of follow-up.

DR. PARRISH: Dr. Brandt, any comments?

DR. BRANDT: I would simply add that calculating or trying to determine a priori a low-end acceptable rate also requires you to know something about how well the

procedure performs overall. I'm going to accept the higher rate of hypotony if overall I have a 90-percent success rate in the procedure. If it works 90 percent of the time, and I know that I can get them down below a certain number, most of the time I am going to accept a higher hypotony rate. But if the procedure does nothing for 20 or 30 percent, I am going to be much less accepting of hypotony at the other end. So, you need both ends of the spectrum to decide an acceptable downside.

DR. PARRISH: Maybe I could go to Dr. Mattox. We could go to the second issue, and that was with respect to a substantial increase or, as Dr. Rhee termed it, an IOP spike compared to baseline. How high? How long? What consequence should we be providing the information to the FDA on? And in how many patients could we live with that, an acceptable threshold?

DR. MATTOX: So, to me, IOP spikes in our glaucoma world are less concerning than hypotony and the consequences of hypotony. We live with them all the time. They rarely have severe consequences over days or weeks or hours for the most part. And in these types of procedures that we're talking about, I think that that is still going to be the case for what we experience.

So, I don't think it is as concerning an issue, and I think it is something that we can manage medically in the clinic as we need to. And part of the beauty of the MIGS devices and operating on patients who are in the mild-to-moderate stage of their disease is that it is unlikely that we are going to severely harm them in the short-term with pressure spikes.

So, that is a qualitative answer. I know you're going for the more numerical answer, but I'm going to decline to give that. How about that?

DR. PARRISH: All right. Dr. Skuta?

DR. SKUTA: Well, again, you know, I think this is, in my view -- and it has been said already this afternoon -- you want very vigorous data collection. And I think that it's really only after you collect the data that you can sometimes make some judgments as to how significant that is.

And I think with the spikes, it is the same thing here. I mean, you want to develop certain levels of recording the data, evaluating the data, than determining what that means in terms of the visual field performance later on, and so on and so forth. And so, I tend to kind of echo what Cindy has said here, you know, in terms of the overall meaning of the IOP spikes.

DR. PARRISH: Jeffrey?

DR. LIEBMANN: I agree. I think that the visual outcome, whether it is acuity or field, is much more important than the actual transient nature of the spike.

DR. PARRISH: Dr. Brandt?

DR. BRANDT: My only addition to what's already been said is, in this era of electronic medical record and capturing multiple datapoints, particularly on the first postop day, what IOP constitutes a spike? If you capture three or four IOPs on the first day, in the clinical trials I have been involved in, the case report forms are really inadequate for capturing the nuances of a high IOP. Then, you burp some Healon out of the eye. The pressure drops, and so on. And what data are you going to be using in your analysis? I think a lot of thought needs to be applied to how data is collected, especially in the early postop period, for generating these AEs.

DR. PARRISH: Dr. Heuer?

DR. HEUER: So, are we still talking about mild now?

DR. PARRISH: As you wish.

DR. HEUER: This time I'm actually serious. Because if we're not talking about mild, if we are talking about moderate or severe glaucoma, particularly if we are talking about devices that are going to be used in combination with phacoemulsification, while I'm the last person in the world who wants to add more of a burden, the reality is the pressure spike occurred yesterday, somewhere between the time you're seeing them on the first postop day and when they left the operating room.

And so, if we really want to know what the pressure spike is with or without a device in that cataract space, we may have to structure the studies so that those cases are done early in the day, and they have a four-to-six-hour pressure reading for the advanced glaucomas, where it might make a difference.

Otherwise, I totally agree with what Cindy said. Most of the time it doesn't matter. I mean, I probably have pressure spikes, depending on how you define them, in 33 to 50 percent of my trabeculectomies because I purposely tie my flaps really tight because it's a lot easier to loosen a flap than to tighten it.

DR. PARRISH: Dr. Spaeth?

DR. SPAETH: I hadn't planned on anything except I think, as the study is being designed, if you're going to look for pressure spikes, I'm a little more concerned about it than Cindy is. And maybe it is because the patients that I see are, well, they are very similar, I am sure, to hers.

But you're going to have to work into your study that the patients have their pressure checked shortly after the procedure. I check the pressure two hours after every time I do a trabeculectomy because I stitch my things very tightly, too.

But, more importantly, I just want to take this opportunity. This is a great, wonderful

session. And all the people who are responsible for putting this group together and having so many people come, I think it is just fantastic and a great tribute to both the FDA and to the American Glaucoma Society.

DR. PARRISH: Thank you.

Let's move to our last question, since I was unsuccessful in getting any quantitative information for the FDA on any of the specific questions I was asked to address.

(Laughter.)

Our Speakers of the House have done much better than me in the past, I assure you.

So, the last issue relates to the so-called substantial visual field loss. I guess the issues are, how do we differentiate visual field loss as a natural progression of disease, as an untreated progression versus a rapid deterioration, which I think is the issue that is being addressed here with the severe adverse outcome?

Cynthia, what are your thoughts on guidance for defining substantial visual field loss? How much loss? Where? And I guess we should introduce what Leon had brought to the question, the issue of using a functional measure of visual acuity; i.e., one of the short Form 12 or the VFQ-25.

DR. MATTOX: So, in this population I would not collect visual field information at all.

DR. PARRISH: Uh-hum.

DR. MATTOX: It's short-term. We're not going to see a change. You saw the preliminary data from the MIGS devices that we do have. The mean deviation doesn't change over two years. I mean, I just don't think we're going to see it. I don't think it's necessary.

DR. PARRISH: We would by central visual acuity as a surrogate for severe visual field loss. I mean, if someone had a snuff-out, you would be able to determine that simply by measuring their acuity centrally. If they were 20/40 and now they're 3/200 eccentrically --

DR. MATTOX: You know, I mean, I think the incidence of that is going to be so rare that, sure, I'd take that.

DR. PARRISH: Admittedly.

Greg?

DR. SKUTA: I would do visual fields. I think there is value here in collecting the data. Again, I'm not sure I can establish a criterion, which I know you want, Rich, and Malvina wants and others here.

But Dale hasn't spoken yet. Whatever Dale is going to say, I agree with.

(Laughter.)

DR. HEUER: Wow, I've just been given carte blanche.

(Laughter.)

DR. LIEBMANN: I agree with Cindy; it is not going to be a useful outcome measure. But I think in terms of enrollment and, then, just safety, you need to do them.

DR. PARRISH: I actually agree with Cindy that I think it's of very, very little value. And I point out the fact that, even in the Ocular Hypertension Treatment Study, you had to be a really good test-taker to get into the study. There was incredible variability.

And I think you would harm recruitment by requiring people to be able to do reliable visual fields. Is the patient who can't do reliable visual fields often because of their significant disease? And then, another question comes. When it's combined with cataract surgery, are

you going to re-baseline them after their cataract surgery and have to get two or three repeat visual fields? That's the only way you're going to get any meaningful statistical analysis of the visual field. And I don't think you're going to get much out of it in pivotal trials that involve a few hundred patients.

DR. MATTOX: Rich, I want to qualify my answer. I would include visual fields as entry criteria because I think you need to know who's mild, moderate, and severe. But it's the progression that I think is unnecessary.

DR. PARRISH: Yes.

DR. HEUER: Hey, I'm a glaucoma specialist. I'm going to do visual fields.

(Laughter.)

Which reminds me of the old joke about the three specialists going to ARVO, and I won't do the joke now; I'll do it later.

(Laughter.)

The only visual field changes you're going to see consistently are people that had a choroidal hemorrhage or some other catastrophic event, which may or may not be related to the procedure, unless you see those particular catastrophic events lining up more frequently with that procedure than the control, if you're doing a controlled study.

So, I'm going to do visual fields, in part, to characterize the glaucoma at the beginning, and just because I have to do them anyway on the patients. But this is not the setting to be doing a glaucoma natural history or altered natural history study.

DR. SPAETH: I agree, except for the fact that you said you're not going to see any visual field changes. You're going to see all kinds of visual field changes. Unfortunately, I think they just won't be real.

(Laughter.)

DR. PARRISH: There's a comment from the audience. Dr. Reay Brown from Atlanta.

DR. BROWN: Thank you, Rich.

There's another important issue in safety that's not on the program at all. And that's whether follow-up should be one year or two years.

And I just finished the CyPass trial. And as I put my last patient in the trial, since all the patients have to be followed for two years, and then, it is probably one year to go through the approval process, if it becomes approved, it is going to be three years before I can actually use that device.

And so, I am wondering if we could get a discussion going about whether one year or two years is appropriate. It seems to me one year is enough. And I just would like the panel to comment on that.

DR. PARRISH: I think the issue is here, and we have to be careful. It may be more adequately discussed in the next session on efficacy. I mean efficacy at one year, efficacy at two years, whatever. Efficacy is defined as a floor and a ceiling of intraocular pressure.

I think it's fundamentally different than dealing with serious adverse outcomes. And as we sit here and think --

DR. SPAETH: I disagree with that, Rich. I think Reay's right on target, especially with anything that's going in the suprachoroidal space.

Many years ago this was a commonly-done procedure, cyclodialysis. I did hundreds and hundreds of them, maybe thousands. And they can do very well for a year or two even,

and then, all of a sudden, that closes down.

So, if you're going to talk about adverse events with something going on in the suprachoroidal space, you're going to have to follow them for a pretty good long period of time. I would certainly favor two years, too.

DR. BROWN: My point would be that one year would be enough. I'm on the one-year team.

(Laughter.)

So, you know, I just wonder, you know, at some point, it became -- it was one year, and then, suddenly, it was two years. And it's a huge burden both for the companies supporting the test.

And then, also, as I say, for me, if I'm using something that I find to be helpful, and others would as well, it seems in a blinding and curable disease, to have to wait three years before you can use it again seems like a long time. And I guess I'm not getting resonance with the panel here, but this seems to me a really important issue. And it may be efficacy as well as safety, but I think it should be addressed at some point.

DR. PARRISH: Perhaps the FDA could answer the question, which is better, one or two?

(Laughter.)

DR. EYDELMAN: Well, I'm not going to say which is better, one or two. But I would like to clarify that, during the review of the FDA, there's nothing that precludes the company and the sponsor to continue implanting patients that need that particular device. We have something called continued access IDE.

So, if the question is that you finished the study and it's being approved -- and by the

way, we try to approve within a year these days; that's a sidebar -- you can continue to provide the patients with the needed device.

But I am very interested in hearing, since there was obvious discrepancy between your comment and the panelist's comment, about appropriate duration for assessment of safety, whether it's one or two. So, it's back to you.

DR. BROWN: Let me just make a follow-up comment to yours. And I don't really understand the program of continued use. I mean, like it would be one or two patients, right? I mean, it wouldn't be -- I mean, it's not open season.

The thing I'm talking about is, if something is helpful, that I think we ought to have access to it as soon as possible and not have to wait three years after it was implanted the last time.

DR. KIANG: Hi. Dr. Tina Kiang.

It's not open season, but a company, a sponsor can ask for a number, you know, whether it be 50 or 100, while the data is under review. So, it's not open season like you can continue implanting forever, but you can specify a number under the same criteria as under the clinical trial.

DR. BROWN: And that would be at the end of the follow-up period or through the whole --

DR. KIANG: Yes.

DR. BROWN: They can just continue --

DR. KIANG: If you --

DR. BROWN: I mean, I'm not actually for any company. So, anybody from industry --

DR. KIANG: Yes. If you fill the enrollment for the trial, you have your cohort for the trial, then you can have an additional cohort of continued access.

DR. BROWN: Right. Okay. I mean, I just think it's something that should be discussed because the difference between one year and two years in terms of the cost to the company and the delay in achieving approval, I mean, it's a significant problem.

DR. PARRISH: Maybe I could just briefly ask, starting with Greg, then Cindy, and the other members, if they think one year would be adequate for most of the severe adverse outcomes that we have been talking about up until now.

DR. SKUTA: For adverse outcomes and safety, I think absolutely yes. And I think, if you're looking at efficacy data, I mean, you obviously want longer-term data potentially. But I think in terms of safety issues -- are you referring to safety issues mainly, Reay?

DR. BROWN: Yes.

DR. SKUTA: For a safety issue, for example, I think a year probably is adequate.

DR. PARRISH: Cindy?

DR. MATTOX: I agree, a year for safety.

DR. PARRISH: Jeffrey?

DR. LIEBMANN: I agree, a year for safety.

DR. PARRISH: Jamie?

DR. BRANDT: A year for safety, yes.

DR. PARRISH: Dale?

DR. HEUER: A year for safety; a lifetime for efficacy.

(Laughter.)

DR. PARRISH: Dr. Spaeth?

DR. SPAETH: I think the overwhelming majority of complications are going to occur promptly. So, yes, I think a year is enough.

DR. PARRISH: Well, on that note of relative consensus, thank you all for being here.

The next session will begin in about two minutes.

(Applause.)

DR. SINGH: Thank you, Rich.

I'm going to ask Joe Caprioli, who is going to be chairing the effectiveness endpoint session, I'm going to ask Joe to introduce his panelists.

We're getting tight. We're not going to have any more breaks. We're just going to power through.

DR. CAPRIOLI: Okay. Hello. On behalf of Ron Fellman and myself, welcome to the effectiveness endpoints part of the program, which I think is an important part.

One note, Dave Epstein, who was to be one of the panelists, couldn't make it because of a flight cancellation. So, I have asked Murray Johnstone to take his place on the panel.

And, Paul, why don't we actually, after all, have all the panelists come up? I think there's room.

So, anticipating a great deal of discussion about this, let's launch into the program straightaway.

And we have asked Murray to provide us some comments upon the anatomical and physiological basis for outflow surgery, and what can we expect, based on those

considerations?

DR. JOHNSTONE: So, the title, the anatomic and physiologic basis for outflow surgery effectiveness: what can we expect?

Financial disclosures.

When we talk about physiologic mechanisms/endpoints, we really need to talk about flow through the conventional outflow pathways. And we will have to ask, how can we recognize clinically-normal flow? And particularly, how can we recognize restoration of normal flow after MIGS procedures?

Scanning electron microscopy, illustrating the pathways; conjunctival sclera, trabecular meshwork; the anterior chamber. And we can see Schlemm's canal, collector channel ostia, which on a flat view will look like a round circle, but, however, very convoluted in fact. The aqueous passes, of course, through the trabecular meshwork into Schlemm's canal, then through these collector channel ostia, ultimately, into intrasclera collector vessels, then into the aqueous veins in the episclera as well as those in the conjunctiva.

We can focus briefly on the area of the collector channel region. And we see here there are frequently flaps present at the collector channel ostia. It has been reported for many years. And these flaps are hinged are their base, and there are attachments between the flap-like structures and cylindrical structures spanning Schlemm's canal which are widely described as well by a number of investigators.

If we look at intraocular pressure, we face an intraocular pulse solution of about 3 millimeters of mercury. Eye motion and blinking is about 10 millimeters. So, we have a really extensive oscillatory flow.

And Schlemm's canal itself actually is a reservoir. This is normal pressure and this is

low pressure, illustrating how much -- this is two eyes of the same primate -- how much the canal of Schlemm can vary in dimensions. It's highly-flexible or compliant.

And we can look here at the pulse infusions to demonstrate this spontaneous trabecular meshwork motion with a pulse wave induced, but also there is recoil, which is of most interest because we have induced the pressure outward, which is really dependent on compliance of the trabecular meshwork. But of interest is the recoil, which is the tissue itself which responds to these pressure changes. And this, of course, is what presumably is occurring physiologically in the eye.

We can look at changes in the trabecular meshwork height, in this case in a series of situations, about 9 microns. And we can also look at the duration it takes for this recoil to occur, this spontaneous elastic recoil, about .5 seconds, 500 milliseconds, which is within the range of what occurs with a cardiac pulse.

We can ask how much flow we should anticipate with each heartbeat, and that's about .03 microliters per minute if the structure is actually inducing pulsatile flow. And that only requires about 2.7 microns of motion of the trabecular meshwork if we consider normal TM and Schlemm's canal geometry.

So, all of this seems to induce pulsatile flow. It is widely recognized, very well documented, that aqueous outflow is pulsatile and it involves the aqueous entering up sclera vessels where diastole the blood is prevented from moving, and then, systole it moves outward.

And we can see this is the conjunctiva with the blood entering the episclera emissary during diastole and entering systole, being swept outward.

Where are the aqueous veins that we should look for, if we're looking for physiologic phenomena? It turns out flow is highly asymmetric. It's not at all uniform around the canal.

There are typically zero to five aqueous veins, but, in reality, usually one to two is more typical. It only requires two aqueous veins to take care of all aqueous outflow.

And where are we going to find them? It turns out 87 percent are in the inferior quadrant and 56 percent, just over half of them, are in the inferior nasal quadrant. This is from the work of de Vries in over 200 patients.

And what does aqueous venous flow really look like? It turns out that during systole there's a pulse wave of aqueous that enters the aqueous veins. And then, during diastole, episclera blood enters those same vessels. So, there is a constant oscillatory phenomenon that is associated with these changes.

And we can see this propagating from the image on your right all the way across to the left in the upper area. We see aqueous entering the aqueous vein, moving into an aqueous venous channel. During diastole, blood enters the aqueous vein, swept away to the next systole. We see laminar flow in the aqueous vein as the wave propagates, and we see trilaminar flow, all the phenomena.

So, how do we recognize the aqueous veins? They are really not something people are trained to look for. It turns out often they're partially filled with blood. They're hard to identify. And some of them are completely clear.

But, by putting a little bit of pressure through the lower lid, just very gentle pressure, it raises the pressure. We got a bolus of aqueous entering the aqueous vein. It makes them immediately recognizable.

Then, when we release, actually, blood comes into the aqueous vein and you see this oscillatory phenomenon. It works particularly well with clear aqueous veins. You press a little bit, draw below the homoeostatic pressure, and then, what happens is that blood will flow

in the aqueous vein that was otherwise clear.

Well, what about trabecular meshwork resistance? We have been informed by Morton Grant's work that 75 percent of the resistance is in the trabecular meshwork. So, we can make a hole in the trabecular meshwork and anticipate that we're going to remove 75 percent of the resistance.

Well, in fact, that's really not the case. And you really need to read the fine print because Morton Grant showed that only 6.3 percent of resistance is eliminated by a simple opening in the Schlemm's canal.

And there's an arithmetic increase as we go around the circumference of Schlemm's canal, and it takes an entire 360 degrees to remove 75 percent of the resistance. And the reason, by a number of studies, seems to be that the meshwork is almost in apposition to the external wall, elasticity and compliance constantly maintaining an appropriate relationship, which is perhaps lost in glaucoma.

And so, we can't anticipate simply passing a single opening in the canal restoring flow. So, somewhere we have to target where we are going to look if we want to establish that.

And this is a beautiful video by Ron Fellman that kind of tells us whether we have reached an intraoperative and short-term postoperative endpoint. This is with a Trabectome with the same phenomenon that we can anticipate occurring with a MIGS procedure.

And you are going to see here -- this is in his Journal of Glaucoma paper -- with either infusion of balanced salt solution or in this case with a phaco tip, just increasing the pressure, we see the aqueous vein flow occurring. So, that's an endpoint. That tells us that we have created a communication with the aqueous vein that is functioning.

And can this occur long-term? Can we see it? And this is from, actually, a

viscocanalostomy procedure, but it illustrates what can occur. And perhaps what we should be looking for is an endpoint late, if we're really establishing persistent flow.

This is a viscocanalostomy flap that I did. And this is an oscillatory flow in an aqueous vein. What you see here is pulsatile. This for five years that I followed this lady, her pressure was normalized without meds, and you could see at every cardiac pulse wave this oscillatory flow and the trilaminar flow in this aqueous vein. So, we have reestablished flow somehow into the aqueous veins by a surgical procedure. And, of course, if we're talking about conventional flow, that's what should occur.

Also, with simply a blink in your eye movement in the same patient, a big bolus of aqueous enters the aqueous vein system every time she looks down, a very striking phenomenon, and you can induce it by digital pressure as well, which I actually did here.

We can look at other ways of looking at this issue of trabecular meshwork motion. We recently developed an OCT system which really is good at looking at this issue. We are going to compare CM with OCT. The ciliary muscle, trabecular meshwork, Schlemm's canal, a collector channel, a septum spanning between the collector channel and the trabecular meshwork. And this is right at, basically, a collector channel entrance.

And we can look at collagenous structures, which I mentioned, which span between the trabecular meshwork and this collector channel ostia, which are very frequent phenomena. And we can look at, with this high-resolution OCT system, we can literally look at motion of the collector channel ostia in response to pulse-induced trabecular meshwork motion. So, we see that collector channel ostia are very important to this situation as well.

In summary, we have some physiologic endpoints. Certainly, intraocular pressure is one. But if we are really asking restoration of normal flow, then we should look at pulse

physiologic mechanisms. And the challenge is to identify MIGS that maintain this trabecular meshwork motion as a mechanism of restoring normal function.

And acknowledgments.

Thank you.

(Applause.)

DR. CAPRIOLI: Thanks, Murray.

Before we go to the next talk, I thought we would have just a short discussion of Murray's beautiful presentation. Remarkable videos, Murray.

And then, after the next two talks, we'll specifically address the questions that were posed to us.

So, Murray, what would you expect, from knowing what you do about outer wall resistance and the amount of meshwork you can bypass with some of these procedures, what kind of pressures would you expect?

DR. JOHNSTONE: Well, I think it has been repeatedly mentioned that we do have a baseline of episcleral venous pressure. And in some normals, especially young people, and actually in some population, the Mores and some others, pressures are down around 8 to 10 in the normal. And one might assume that, if you could optimize pulsatile flow, you might, at least in some patients, achieve these very low pressures.

DR. CAPRIOLI: Okay. Maybe I would like to just ask the panel about that question. Concerns about the outer wall with Schlemm's canal which may actually have more resistance than we thought initially? So, we have episcleral venous pressure, but you also have outer wall resistance.

So, Paul, would you like to give us your opinion about that?

DR. HARASYMOVYCZ: We have been using some of these things in Canada for four years. And what you realize is that it takes many years to become proficient at actually using the devices and knowing what they do.

I think that trying to target that fluidway that Ronald Fellman showed intraoperatively -- so, for instance, if we use one type of stent, we put it in and we evaluate for flow, and we don't see it. And then, we explant it and re-implant it in another quadrant.

So, I think we can generalize, but if we don't have a way to measure what we're actually doing, this way, indirectly, through that kind of flow, that may directly influence the success or the effectiveness of the surgery.

So, surgeon experience and, also, having maybe these kind of endpoints during surgery are important.

DR. CAPRIOLI: Tom?

DR. SAMUELSON: I think Murray's work just shows us what we don't know. I mean, Murray has enlightened us in so many ways on the meshwork function.

And I have always been partial to retaining the structure of the inner wall. I like the concept of stenting rather than the ablative procedures that occur on an ab interno approach.

But I think we don't know, to tell you the truth, what influence does phacoemulsification have on Murray's motility and is that involved in the mechanism of pressure reduction with phaco? And if we can harness that and make that better with some of these plus procedures that we're doing -- we're just learning, and that's what is the greatest thing about this new era.

DR. CAPRIOLI: Jay?

DR. KATZ: Well, thanks to Murray, we understand that Schlemm's canal is

not a pipe. It is kind of a working tissue.

But I guess what's amazing is that we are reexamining the whole concept of what's at issue with open angle glaucoma. Is the resistance to outflow just in the inner wall? Is it downstream in some patients? The collector channels, are they abnormal to some extent? Is there elevated episcleral venous pressure in other patients that has been unrecognized?

And I think we're still learning, but I think with the devices that we're talking about, most of the devices today, anyway, with MIGS, I think they're all limited by episcleral venous pressure.

DR. CAPRIOLI: Yes, I think that is a good point, Jay. We have to remember that Schlemm's canal, in evaluating existing procedures and developing new ones, that Schlemm's canal is not a pipe. I like the way you put that.

Ron, any thoughts about this?

DR. FELLMAN: Yes, a couple. You know, one is Murray mentioned restoring outflow. So, should we have a different set of effectiveness endpoints when we try to restore normal outflow for a patient versus making a hole in their eye? That's something we have to think about because, traditionally, we don't think that way.

But, now that we are back in outflow land and collectors and channels, we have to, I think, consider everything differently. So, when we are restoring normal, when we are trying to restore or improve outflow, should we have a different set of effectiveness endpoints? I think that is an important point we all should be thinking about.

The other point I want to make quickly is, you know, it took us a long time to modulate wound healing with a filter, and we certainly have gotten better at it. Right now, our modulation of wound healing in the canal is probably where trab was a long time ago. So, I

think to all of the clinician scientists out there who know a lot more about that than I do, I urge you to try to study wound healing in the canal, so we can improve our results.

DR. KAHOOK: So, I will be touching on some of the effectiveness endpoints in the next talk. So, I will reserve that for the slide deck.

What I will say, though, is I have definitely noticed a difference between one device versus two devices with the iStent with a bypass procedure. And I think our Canadian colleagues have identified that very well in the literature.

And the other part to that -- and it's --

DR. CAPRIOLI: Let me interrupt. When you say "a difference," what do you mean by "a difference"?

DR. KAHOOK: So, the IOP lowering with two devices or three devices appears to be consistently better than one device. And that is --

DR. CAPRIOLI: With the iStent?

DR. KAHOOK: With the iStent, right.

DR. CAPRIOLI: With the iStent.

DR. KAHOOK: The other part of this I think that we have discussed and a common theme to the whole discussion today is that our patients are very different. One versus the next is going to be very different.

So, in some patients we might have more TM resistance and removing more of the TM might make a difference in that particular patient. In other patients, some of their resistance, or maybe the majority of their resistance, is past the TM. So, that's what complicates a lot of our data interpretation and our study planning.

And I think we really need to understand that process. What are the differences and

how can we gauge which patients might benefit from which device?

DR. CAPRIOLI: It looks like we're back to outflow research then.

(Laughter.)

Robert?

DR. NOECKER: I'll just reiterate what Malik said. I think we see that our patients are very heterogeneous, especially in their facility of outflow and the level of the outflow. I think in some ways that may explain with the iStent. I recognize, too, that with whatever version of the iStent, if you put in two, you're more likely than not to have a lower eye pressure. The question is, are we just increasing our probability that we're hitting the sweet spot, as maybe Paul is suggesting? Or is it the fact that we're opening up more of the entire area of primary resistance?

So, the second thing I think we'll learn, too, is perfecting our techniques for a lot of these devices. I mean, a lot of times we just focus on getting them in. And I think many of these things may be a little bit more technique-dependent, and I think we'll get a little smarter with that as well.

DR. CAPRIOLI: Murray, do you want to comment on the continuity of Schlemm's canal apropos of two working better than one, and maybe three working better than two, and so forth?

DR. JOHNSTONE: Yes. I think there is very, very good evidence that there's very little circumferential flow in the canal and it acts as though there is a series of little sort of chambers, and that if you open in place, you can't anticipate getting a 75-percent increase in reduction of resistance.

But I think a couple of things here. It seems, at least in some cases, you really can

target the aqueous veins. And I've got some beautiful videos that Ike Ahmed shared with me where basically he puts an iStent in one location and he has identified an aqueous vein. He tries to stent it, and nothing happens. And then, he moves a millimeter and a half away, and then, there's dramatic improvement in the outflow.

So, it looks like, at least in some patients, there's a possibility of using a pretty systematic clinical approach to identifying the aqueous veins and targeting them. Now it is not going to work in everybody because in everybody you can't see aqueous veins. But I think, given the fact that we have got a series of collectors around the eye, but most of them don't seem to be functioning most of the time. It is a highly asymmetric thing. Nonetheless, obviously, if you could hit more aqueous or if you hit more collectors, you are more likely to get an improvement in outflow. So, it seems pretty obvious that two is better than one.

DR. CAPRIOLI: All right. Thank you.

So, we would like to invite Malik to come up and talk about the selection of effectiveness endpoints and targets.

DR. KAHOOK: So, we're going to solve this issue in five minutes right now. So, take notes.

(Laughter.)

Selection of effectiveness endpoints and targets: what do we need to show?

These are my disclosures. I work with several of the MIGS companies. I am also a consultant to the FDA.

I'm going to use three sources for the talk, and a lot of these slides are actually word-for-word from some of these documents.

The first document you have heard from, Eva Rorer, the implantable glaucoma devices

document from the ANSI Standards 2013.

The second document is the World Glaucoma Association, "Glaucoma Surgical Trials" document from 2009.

And the third part is just my clinical and surgical experience.

We have seen this before, but it's worth repeating. Refractory glaucoma has been traditionally treated with trabs and tubes. Surgery for non-refractory glaucoma, traditionally treated with drops and laser, has introduced new questions for industry, for physicians, and for the FDA alike.

Efficacy endpoint concepts from the MIGS experience includes washout period. We have heard this before today. The washout period is necessary because the modest IOP lowering with MIGS devices could be augmented or masked by topical medications. The washout period can be done before the baseline visit or before or at the visit window for assessing the primary endpoint.

Another concept is limiting surgeon and center bias. There are now set minimum and maximum numbers for both study and control devices.

The title, again, is selection of effectiveness endpoints and targets: what do we need to show? And I think there is little debate over what we need to show. We need to show sustained IOP lowering that is significant. The major question is not what; it's when and for how long and in what percent of patients.

The ANSI endpoints document recommends 24 months of follow-up for safety and efficacy endpoints. The same document also states that, "Shorter study durations may be justified and longer study durations may be necessary, based upon the risk analysis or emergent safety issues."

So, risk analysis is a major factor in determining study duration, but we don't have a great amount of insight into risk/benefit analyses for MIGS devices. The current recommendations appear at first glance to treat all devices equally, regardless of method of implantation, location of implantation, and historical perspective available; for example, some of the devices that already exist on the market.

So, from the clinician's perspective, each anatomical space is unique. Risk profile for a Schlemm's canal device, in my opinion, is different from a suprachoroidal device. A full thickness procedure might present more, in fact, does present more risk than some of the other devices we're talking about today.

Historical data can drive decision-making for study duration, and we have heard about this a lot today. Have other devices been approved that occupy the same anatomical space that can help drive the study duration? Are there any patterns in the first 12 months of data that present a red flag? Can we perform a risk/benefit analysis based on one-year results if the safety profile proves clear and the efficacy is measurable? And is there room to adopt guidance set forth by the least-burdensome provisions of the FDA Modernization Act that advocates for using post-marketing information to ensure timely public access to beneficial new products?

The efficacy and benefit post-MIGS-device implantation can be masked when concentrating on statistical means. A discussion of means, especially when the downside of implanting a device is minimal, disregards a significant subset of patients that had more robust IOP lowering.

And that's the question I ask above: how many patients need to benefit to justify using a device that has a negligible downside in those where it does not work?

We need to maximize our efforts to decrease uncertainty. Uncertainty leads to less funding, less innovation, lost opportunities for novel and advanced treatments, and subsequently, to fewer options to enhance outcomes for glaucoma patients.

There are significant deficits in how clinicians define glaucoma. I think we have seen that today. We can't even agree on what "significant" is. Are we talking about clinical or statistical significance? If the experts can't agree, why would we expect the FDA to take definitive actions on endpoints?

So, here are my suggestion steps:

Professional organizations, AGS, the Academy, can provide guidance for risk/benefit analyses in each MIGS space. And I'm talking about anatomical space in this case. We can get input from the physicians, from the FDA, and, of course, from industry.

Use the risk/benefit analyses to help dictate duration of pivotal trials. How much do we really learn about safety after one year? I think we almost got consensus that we don't learn much after one year. If the answer is minimal, then MIGS device efficacy can likely be measured at one year and allow for quicker access to newer technologies.

We can maximize the use of post-marketing information, like registries that we have been hearing a lot about, to expedite approval of devices that have a low-risk profile and fill a large unmet need for patients with mild-to-moderate primary open angle glaucoma, which represents the majority of our patients.

There should be a push for less concentration on statistical means and more discussion about the upside for some patients with little to no downside for all patients.

The final documents can serve as a regulatory guide for MIGS devices and support innovation by addressing uncertainties.

Thank you very much.

(Applause.)

DR. CAPRIOLI: Thank you, Malik.

I might be correct -- correct me if I'm wrong -- but I thought the consensus was that a year was long enough to determine safety from the last --

DR. KAHOOK: Right. That's right. That's what I'm saying, that a year is long enough.

DR. CAPRIOLI: I thought you said the opposite.

DR. KAHOOK: I would never disagree with the panel here.

(Laughter.)

DR. CAPRIOLI: Okay. Good. Then, my mistake.

Jay?

It's my pleasure to introduce Jay Katz, who is going to talk about the composite endpoints of safety and effectiveness.

DR. KATZ: Thanks, Joe and Ron, and good afternoon/good evening, everyone.

You have heard some fairly spirited discussions about eligibility for the trials evaluating MIGS, and you have also continued on to kind of spirited, lively discussions about endpoints in terms of efficacy and safety and how we agree on that. And there's a lot of room for improvement.

This has been kind of a wonderful discussion, and I congratulate everybody for organizing this meeting.

I am going to talk about composite endpoints. So now, we are going to take all the

uncertainty and put them into an equation with even more uncertainty, I think, in talking about composite endpoints.

Here are my disclosures and your brochures.

So, some of the issues I want you to think about is, do composite endpoints benefit the patient, industry, clinicians, scientists, the FDA process? Is this going to be a legitimate score? Is it going to be believable? Does glaucoma as a disease lend itself to this process? Could there be drawbacks to the system? And specifically, should MIGS at this point be exposed to kind of this novel grading process?

Composite endpoints consist of a number of endpoints that have been merged. And they can be either efficacy or safety endpoints. And so, the composite endpoint occurs when either one of the endpoints occurs. And the result, the desired result, is that you increase the event rate, decrease the same size, and therefore, have a more rapid and less-costly trial. That's the ideal.

So, this is going to be dependent on the clinical question you ask, the outcomes that have been chosen, and the analysis that has been undertaken.

Here's just a quick sample of a theoretical situation where you're looking at a control versus a device, looking at the particular event rate, looking at efficacy, and comparing the two and coming up with a ratio, and with power calculations, coming up with a sample size of, let's say, 1100-some patients.

If you choose wisely and getting a composite score, adding a safety variable, you can come up with a sample size of 330. But if you don't choose wisely, you can now increase the sample size instead of decreasing it.

There are advantages that have been made very clear in other studies outside of

ophthalmology where you can decrease the sample size. You can have a net clinical benefit, kind of merging safety and efficacy, and you avoid using a single primary endpoint.

And many of us think that that is great if you can do that, but there are some disadvantages. The interpretation can be difficult when the endpoints are really not of equal importance. And it is going to be very difficult, I think, for a lot of us to equate importance both on the efficacy and safety side. It is difficult even agreeing on just what's equal importance on the efficacy side, let alone both.

And, of course, as you have probably gathered from the discussions we have had, getting sponsors, patients, investigators, the IRB, the FDA to agree is going to be quite difficult at this point.

And then, having individual claims for product labeling is also going to be, I think, very difficult to interpret.

So, again, you can merge efficacy outcomes. You can merge safety outcomes. And I think what we're talking about today is trying to get a mixture of efficacy and safety parameters to come up with a so-called composite endpoint surgical success score. And can we do this?

So, where's the benefit here? Is it really going to benefit industry to have cheaper trials? Are patients going to look at these scores, which will be public, and have some meaningful interpretation on their end? Will physicians be able to interpret this, once devices are approved with a surgical success score? And is it really going to streamline things for the FDA and make it a more effective way of evaluating products?

So, there are some concerns I am going to share with you. You know, traditionally, efficacy and safety have been separate inquiries, and balancing the risk versus benefit has been done for years now. And so, if you merge those two, you actually may mask very important

issues, both on the efficacy and safety side.

Another concern is that, when you have a composite endpoint of efficacy, you may be low, even though you might have an outstanding single parameter, but low in other outcome measures. So, there may be a device that lowers pressure 25 percent consistently, but it doesn't really discontinue medications and it doesn't give you a low target pressure.

Also, when you are comparing devices is another concern. If you have a surgical success rate and product labeling, can you really compare different devices based on that surgical success score? Most of us would argue that you still need a randomized prospective trial to do that.

Another concern is that, if you have a very effective device, but with some serious side effects perhaps, should that device be given a low score and not be approved, for example, or should that device be available in the right clinical circumstance?

And if you have -- again, this is public information for patients. Will they be kind of inquiring whether their surgeons should have used a device with a higher surgical success score?

So, in short, the question for all of you to think about really is, is glaucoma too complex to utilize at this point a composite endpoint score, to really have some useful meaning for our discussions in evaluating MIGS devices?

We have all heard that glaucoma is really a group of disorders, all with different kind of outcomes with surgery, and the disease has different stages, rapidity, progression, and all the other factors that we use in making clinical decision making. Is that really going to minimize the impact of a composite score of devices?

So, I would suggest that simpler is not always better. And I would suggest that at this

point in time, until we have better really unification on endpoints, both in terms of efficacy and in safety, I think it is premature to get composite endpoint scores at this point for evaluating MIGS devices.

Thank you.

(Applause.)

DR. CAPRIOLI: Thank you, Jay.

Before we launch into our discussion, I would like to make a plea. I know how difficult it is for glaucoma docs to talk about numbers or to be very specific or to agree with each other.

(Laughter.)

But I am going to beg you to just do just that. Go out on a limb. Be specific. And let's talk about numbers. We have to have a place to start.

I mean, we're in a unique position here to help ourselves by helping the FDA make decisions about surgical innovations we want to provide to our patients. So, it doesn't help for us to do a lot of hand-waving and saying, "Well, I don't know." Well, I think we do know more than we admit to, and we have to have a start, a concrete start. So, try to be specific whenever possible.

With that, the first question we were asked to visit was: what should be the primary endpoint of the trial and how long should the trial be?

Robert, why don't we start with you?

DR. NOECKER: So, I mean, in terms of measuring efficacy, there has to be some degree of IOP lowering. And once again, I think if you're thinking in terms of on-label -- you know, say we're targeting the mild-to-moderate glaucoma population -- there

does have to be a bar. I mean, I think precedent has been set with maybe at least a 3-millimeter reduction from baseline. I think you could do it in percent reduction, in that order. And I would say that maybe the bar that we need to use.

I think maybe not a bad historical comparison, as what we did with the SLT trial, and, you know, how we did with that. And that was one of the endpoints that was measured, was percentage of patients having at least a 3-millimeter reduction from baseline.

That was totally different. The patients on medications failed with prior laser trabeculoplasty. But I think that is a reasonable starting point in terms of saying this is what the bar should be in terms of measuring efficacy from baseline, change from baseline.

That was concrete.

DR. KAHOOK: That was concrete. That's right.

So, I agree with what Rob said. And I think probably the secondary efficacy endpoints are the longer and more heated discussion here.

One thing that we don't talk about a lot when it comes to MIGS devices is the fact that, when we implant them, many patients do benefit from the surgical procedure. And those who do not benefit, rarely do they suffer any type of complication that would cause us to pause about recommending the surgery for that specific patient population.

So, in the mild-to-moderate glaucoma category, what I would propose is that a secondary endpoint would be an analysis of that risk/benefit. How many patients are getting significant IOP lowering in the face of not having minimal to no complications within a given trial? And I think that will help us also dictate how we use it in clinic.

DR. CAPRIOLI: Ron?

DR. FELLMAN: Yes, I think the concept that Rob said of having another

canal-based procedure or trabecular procedure, like SLT, that's a pretty good way to compare something else that you might be doing to the outflow system where you're modifying the meshwork or the collector system, the canal.

So, I think many people are trying to relate outflow surgery or canal surgery to trabeculectomy, and that is why I was saying, should our effectiveness endpoints be different when you're trying to restore somebody's outflow system versus either putting a tube in the eye and shunting fluid to the equator or shunting fluid underneath their conjunctiva? I mean, can we really equate those?

So, I think the idea of equating or at least thinking about efficacy as far as collector surgery, canal surgery, to SLT or laser, certainly, it is very different, probably radical thinking for some people. One's incisional surgery; one's laser surgery.

But I still think that is a very smart way to think about things because they are totally different. And we know now that -- you know, 50 years ago, when people were looking at collector channel surgery and they found out it worked great in kids but didn't work as well in adults, and it got abandoned for so long, and nobody looked at the canal anymore because all the aqueous went under the conjunctiva with the trab, luckily, we have people now, we have doctors, investigators, scientists that are really looking into outflow. And we are trying to learn more about it because our surgery now is so much better for that.

And I think that that's the way that I tend to think about it, just in the grand scheme of things.

DR. CAPRIOLI: That wasn't very specific, Ron.

(Laughter.)

DR. FELLMAN: Oh, okay.

DR. CAPRIOLI: We'll come back to you. Think about this a little bit.

Okay. Murray?

DR. JOHNSTONE: Well, I think one issue here is, are you defining this with washout or without washout? Because it changes --

DR. CAPRIOLI: Yes. Let's say after washout.

DR. JOHNSTONE: After washout? Okay. So, if we're doing it with washout, I would say maybe a small reduction -- I mean, without washout, maybe a small reduction. But, with washout, 3 millimeters you might argue is good. But we have really got a situation where it really depends on the starting point. If you start with somebody who has got a pressure of 30, you drop them to 27, that doesn't really do a lot for them. On the other hand, if they're 21 and you drop them 18, maybe that is pretty important.

So, I think specific numbers are not so good because of the fact that you've got the variability of where the starting point is. So, then, do you want an absolute value? And that is something we have dealt with in the past? Do you want everybody under 21, under 18, et cetera, et cetera? It would be nice to say everyone under 15 or so, but, you know, that is maybe not a rational option.

And then, the third possibility, trying to deal with the issue that we've got varying pressures we're starting from, would be the percent reduction. And I have been told in some studies it is pretty hard to tell reductions under about 15 percent because the noise factor is pretty high. So, maybe a 20-percent reduction versus typically 30 percent is what we like to see in our surgical procedures, but in this setting perhaps a 20-percent reduction might be a consideration at least.

DR. CAPRIOLI: Okay. Good.

Jay?

DR. KATZ: All right. I'll keep the ball rolling here.

I think that, assuming that the people that we're talking about with MIGS devices are going to be kind of early-to-moderate disease, I think a very reasonable goal should be 20-percent reduction off of medications, below baseline, off of medications.

DR. CAPRIOLI: Okay. Great.

Tom?

DR. SAMUELSON: So, I agree with that. I think canal-based procedures based on how safe they are, a 20-percent reduction or a 2-millimeter drop, 2-to-3-millimeter drop I think is fine. For everything else, because we haven't really established safety, it's more difficult, but my hunch is the efficacy needs to be more.

DR. CAPRIOLI: Okay. Paul?

DR. HARASYMOVYCZ: So, on Jay's talk, I thought that was very interesting. And when one compares what has been done in cardiology for many years, so we are always following cardiology, it seems, they do have composite endpoints, such as MACE, Major Adverse Cardiac Events, where they have pluses and minuses.

And I think we could do something similar with intraocular pressure. I'm talking about they stayed on their meds; they weren't washed out.

But let's say I haven't lowered their pressure, but they are on three less medications. Then, that composite number, that would be a great benefit, even if we had some kind of quality of life, like the picture that Reay showed us. They are much more comfortable without their medications. So, that could also go into that composite number.

Visual acuity could be in the composite number, which would encompass the pluses

and minuses. Maybe they gained vision, removing the cataracts. Maybe they lost vision if someone had hypotony.

And then, finally, as we said visual field, I don't think in one or two years probably we would be able to tell a difference, but eventually we can look at five-year outcomes. So, I think looking at composite numbers could be quite interesting.

DR. CAPRIOLI: Okay. Thank you.

Oh, Malvina? Thank you. I didn't see you over there.

DR. EYDELMAN: Sorry. Sorry. If I just ask for clarification?

Thank you for very interesting comments. I just want to make sure I understand what I heard so far.

I heard either absolute, which is something around 3 millimeters after the washout, versus 20 percent, around 20 percent for mild to moderate. I didn't hear the discussion at which timepoint we're talking. Are we talking about at one year? Are we talking about at 24 months?

And before I sit down, I actually was wondering if the rest of the panel would like to comment on what Malik proposed, that in addition to the primary, there is an additional endpoint for a percentage of patients with a particular amount of drop, in addition to the mean delta.

DR. CAPRIOLI: Okay. Thank you. We're getting to that, Malvina, believe it or not.

Now we have heard 20-percent reduction. That takes into account the starting point, which is important. And let's say we define early as pre-perimetric, but no glaucoma, no damage, however we define that, early damage. Moderate would be field loss, and one,

heavy field but not threatening fixation. And then, severe would be both on the field and threatening fixation.

Would you accept the same 20 percent in each of those three categories or would you demand more in one compared to the other?

Paul, why don't we start with you, just quickly?

DR. HARASYMOVYCZ: Well, in that case, maybe we don't have to wash out. Maybe we can just take the real number of their IOP, because I don't think I would be comfortable washing out in end-stage glaucoma. What's their real IOP? And then, how many less medications are they on? But maybe we could wash out the mild ones.

DR. SAMUELSON: Joe, I would probably demand more as a standalone procedure, but I think as a combined procedure, I would still accept that modest reduction because I'm going there anyway, and I'll take whatever I can get.

So, you know, it depends a little bit on the scenario, and we haven't really discussed, is this a standalone procedure or a combined procedure? Because if it is combined, I think we typically know we can expect a little bit more.

DR. CAPRIOLI: Okay. Okay.

DR. KATZ: I agree with Tom.

DR. CAPRIOLI: Okay. Murray?

DR. JOHNSTONE: Yes, I think Rick Lewis kept bringing us back to the issue of what question are we really trying to answer here. And the answer we're trying to answer is how much pressure reduction are we getting. I think you want to stick with some sort of a set of criteria that allows you to answer your central question.

DR. CAPRIOLI: Okay. Very good.

DR. FELLMAN: Are we to answer the one-year part of when your pressure --

DR. CAPRIOLI: We are going to do that later.

DR. FELLMAN: Okay. You know, I think the 20 percent is a reasonable number. Clearly, when you do a washout and the pressure is 30, it is not unusual to see the pressure come down into the teens. So, certainly, the higher the pressure is, you can get more of a percentage.

But I like Paul's idea of including some of the secondary measurements, like, for example, the fact that the patient may have moderate damage if you do a phaco-MIGS device. And on postop day one, the pressure spike is usually minimal. And that, to me, is certainly reassuring, knowing how high pressure can go and how scary that can get sometimes. Agreed, it doesn't hurt most people, but there is a group of patients that I think it is important.

As eligibility criteria expand in the future for certain studies and patients with more advanced disease are entered into them, the fact that the IOP spike is blunted may become more significant.

DR. CAPRIOLI: We will talk more about that when we talk about composite endpoints as well.

Malik, the same criteria across all severities?

DR. KAHOOK: So, just a very difficult question to answer, I think, in view of everything that we brought up. So, I think 20 percent is a nice round number, but we really have to bring in those secondary efficacy endpoints, which I will hold off on.

DR. CAPRIOLI: Okay.

DR. KAHOOK: It sounds like you want to discuss that later.

DR. CAPRIOLI: Okay. Robert?

DR. NOECKER: Yes, I think 20 percent is good. And just so I get it out there before I forget, I mean, I think one other measure is maybe in terms of predictability of response, some measure of standard deviation or standard error. Because I think it has been alluded to here, you know, all the lack of like getting it low enough.

I mean, the thing that bothers me, pressure spikes, I agree with Ron, they don't happen that much. But what scares me the first day is really low pressure, surprise low pressures, which happens with almost every other procedure we do. And those are the really bad days. Those are when you cancel your weekend plans.

DR. CAPRIOLI: Okay. All right. So, we have pretty good consensus that 20 percent, regardless of the severity of glaucoma.

Now just a one-word answer, one or two years? We'll start with you.

DR. NOECKER: I think one is enough, looking critically at the data. I think it is rare to see much movement between one and two years.

DR. CAPRIOLI: Okay. That was more than one word, but it's okay.

(Laughter.)

DR. KAHOOK: One.

(Laughter.)

DR. CAPRIOLI: One. I would say one.

DR. KATZ: One.

DR. JOHNSTONE: One.

DR. HARASYMOVYCZ: One.

DR. CAPRIOLI: Okay. All right. Great. So, we're getting there.

DR. KAHOOK: I'm starting to get scared with the consensus up here, right?

(Laughter.)

DR. CAPRIOLI: The idea about secondary measures, and you proposed, Malik, I think something like some proportion of patients that are reaching some more profound pressure reduction should be given some late --

DR. KAHOOK: Can I give a scenario, I guess to clarify that?

DR. CAPRIOLI: Please. Go ahead.

DR. KAHOOK: So, we're talking a lot about washout pressures, and this is something that was introduced with the MIGS devices, at least emphasized with the MIGS devices.

So, a scenario would be, if you do a trial and you do the washout pressure, the endpoint for the study, and you've got a subset of patients, let's say 30 percent of the patients have IOP lowering of five points or more. But if you look at the mean IOP lowering, it might be 10 percent, given that some of the other pressures danced around the mean a little bit.

To me, that's a conversation I would love to have with a patient, that there is a 30-percent chance that you would get a five-point IOP lowering with this device and there is minimal risk, minimal to no risk with this device. So, that kind of endpoint to me, as a glaucoma specialist, with mild to moderate would be a great conversation to have.

DR. CAPRIOLI: Okay. So, what would you propose? Let's assume that it is very minimal risk for a procedure, and the average is not going to reach our 20-percent threshold. I mean, could this be an "either/or" hurdle?

DR. KAHOOK: So, I think, unfortunately, I know you would like me to be a little bit simpler with the answer. But this brings in the specific space that we are targeting.

So, if we were are looking at Schlemm's canal versus suprachoroidal, versus a

full-thickness procedure that involves a bleb, the conversation is much different. So, to answer the specific secondary endpoint for percentage of success, washed-out responder success, what that amount is, I think you need to put four people from the AGS side, four people from the FDA side into a room and hammer it out.

(Laughter.)

It's not going to happen in a room like this because there are specific details you need to work through. Just getting consensus that a secondary endpoint of washed-out responders is meaningful to a glaucoma specialist, and even more important, meaningful to our patient, hallelujah.

DR. CAPRIOLI: At the end of one year.

But let's make an assumption. I am asking you to make the assumptions it doesn't matter if it's in the suprachoroidal space, which is likely to be more risky, or just in the Schlemm's canal. Let's make the assumption that this is a safe procedure, however you want to define it; minimal risk, as we like to talk about --

DR. KAHOOK: Adequately safe.

DR. CAPRIOLI: Adequately safe, as we talk about with MIGS. Let's make that assumption for this particular Procedure X.

So, what proportion would need to have a reduction of 30 percent or 40 percent to have the FDA approve it, even if the mean doesn't reach 20 percent?

DR. JOHNSTONE: Could you define that? Could you define that as to whether they are doing a cataract surgery along with it, so they're not being subjected to an extra procedure? Because that is a very big part of the question.

DR. CAPRIOLI: That gets even more complicated. We're not going to be

able to --

DR. KAHOOK: Yes. Well, you could make it --

DR. CAPRIOLI: Let's just try to --

DR. KAHOOK: Yes, you could make it very simple, actually, and just say, yes, it involves cataract surgery, just like all of the MIGS categories, for the most part all of the MIGS devices involve cataract surgery. So, you're in there anyway, which, Murray, I think is your point.

DR. CAPRIOLI: Okay. Let's assume it involves cataract surgery.

DR. KAHOOK: So, if you have -- I'm going to give you some solid numbers here, Joe. Okay?

DR. CAPRIOLI: Excellent.

DR. KAHOOK: So, if you have 20 percent of the washed-out patients classified as responders -- so, we can say four to five points lower from baseline -- then, to me, that is intriguing. And those are just some basic numbers that can start a conversation.

And we're introducing the concept that a washed-out responder becomes very important for a MIGS device approval.

DR. NOECKER: Malik, is that above and beyond the phaco effect or is that total effect?

DR. KAHOOK: Why did you have to say that?

(Laughter.)

Let's say it's above and beyond the phaco effect.

DR. SINGH: Yes, that's a key.

Joe, I'm in your blind spot here.

But I think that's the key. You're talking about a delta of 20 percent. You're not talking about a total of 20 percent. You're talking about a delta over a cataract alone.

DR. KAHOOK: Well, we're talking about a controlled study that has phaco as the control group, right? So, we're not going to call a washed-out responder a responder if they didn't respond beyond the control, right?

DR. CAPRIOLI: All right. So, restate that.

(Laughter.)

DR. KAHOOK: Wow, I don't think I can.

DR. CAPRIOLI: Let's see if you can say the same thing twice.

DR. KAHOOK: So, let's say we have 20 percent of the washed-out patients are classified as responders. Am I good so far? Is that what I was saying?

(Laughter.)

Who have responded by 4 to 5 millimeters of mercury above and beyond what the control group responded with phaco alone.

DR. CAPRIOLI: Okay. Can everybody on the panel live with that? Any dissenters?

(No response.)

And this would be the "either/or" criteria for FDA approval?

DR. KAHOOK: If we don't get any dissenters, I'm leaving AGS right now. This is like freaky, right?

(Laughter.)

DR. NOECKER: So, you're saying only a 20-percent response rate? You know, that is 20 percent of the patients --

DR. FELLMAN: Had 4 to 5 millimeters of mercury?

DR. NOECKER: Right. So, this is --

DR. FELLMAN: Only 20 percent? I would say 50 percent.

DR. NOECKER: So, you would say 50 percent?

DR. FELLMAN: My number is 50.

DR. CAPRIOLI: Okay. How about your number?

(Laughter.)

DR. CAPRIOLI: So, the proportion of patients who get a robust response in a procedure that's safe and done with cataract surgery, Procedure X. How many patients, what proportion of patients would need to --

DR. FELLMAN: Washed-out. I'm going to go 30.

(Laughter.)

DR. CAPRIOLI: Okay. Pick a number.

DR. JOHNSTONE: Well, if there's no downside, and I was a patient with very serious glaucoma, it would only require a very small percentage.

DR. CAPRIOLI: Okay. So, you're more like 20? Okay.

DR. KATZ: I'm going to go with Ron and go 30 percent.

DR. CAPRIOLI: All right. Go with Ron.

DR. SAMUELSON: I'm fine with 20 to 25 percent, for the reasons Murray mentioned, and I'm ready for qualitative comment, whenever we're allowed.

(Laughter.)

DR. CAPRIOLI: So, now it's all up to Canada, right?

(Laughter.)

DR. HARASYMOVYCZ: I agree with Tom.

DR. CAPRIOLI: Okay. So, we're talking about this theoretical procedure, something like if a third of the patients -- can I just rephrase that? A third of the patients have a robust response, but don't meet, on the average, the 20-percent reduction. That might be also a consideration for approval. And that was at the end of one year.

I would like to get into the combined efficacy endpoints.

DR. KATZ: Joe, what about reduced --

DR. CAPRIOLI: Oh, sorry, yes.

DR. KATZ: -- drug burden for the patients as an endpoint?

DR. CAPRIOLI: I think we're talking about that when --

DR. KATZ: Okay.

DR. CAPRIOLI: -- we talk about your topic.

Rohit, did you want to --

AUDIENCE PARTICIPANT: Joe, I just wanted to, in fact, ask everybody whether this is one IOP done on a day or if it is multiple IOPs done, because that has a huge patient burden issue. And as it stands now in the ANSI, I guess there it is multiple measures done on the same day at 8:00, 12:00, and 4:00, or so. So, you have to have an effect over the good course of a day.

And I'm just interested in knowing whether everybody feels that that is important or not.

DR. CAPRIOLI: Let me answer for the panel, but, dissenters, please feel free to speak up.

I would say it has to be an average of several pressures measured before and after.

Obviously, it has to be sustained and above the variability of pressure measurement.

Okay. Jay, you brought up some interesting points about the composite measures and there are difficulties in glaucoma, in particular, because of the complexity of the disease and the variation of severity and the variation of starting points.

But could you imagine having some sort of sliding scale with respect to starting points or severity of disease, and weighting endpoints differently? So, dysesthesia would count less than endophthalmitis.

DR. KATZ: Yes, I think, you know, in the perfect world, Joe, I think we could come up with a sliding scale of severity and weight things. But I am waiting to see that being done. It hasn't been done traditionally, and most of the surgical outcomes, the papers that are published in our peer-reviewed journals don't really weight them. And so, some of the papers you look at that are current don't do it currently.

So, if you give me that sliding scale and we agree on them, I think it would be fantastic. That would be great to put that in.

DR. CAPRIOLI: It is hard enough to agree on non-sliding scales.

But, Paul, comments about that?

DR. HARASYMOVYCZ: The other thing we didn't mention was re-intervention rate. So, that could also be a part of it, meaning we do all this and, then, anyway, the patient has to go on and have a trabeculectomy. And, you know, it's a burden to them, to society. There's additional cost. So, we should consider that as well.

DR. CAPRIOLI: All right. Well, that would be a failure of the MIGS procedure, I think.

DR. HARASYMOVYCZ: Yes.

DR. CAPRIOLI: Tom?

DR. SAMUELSON: In terms of the sliding-scale-type thing?

DR. CAPRIOLI: Composite. No, just --

DR. SAMUELSON: You know, composite --

DR. CAPRIOLI: -- coming up with some kind of a composite.

DR. SAMUELSON: It seems like my window to say something qualitative. In my experience, patients value safety over everything. It's amazing, when I have my conversation. "This procedure is less effective. You're more likely to be on medications, but it's extremely safe. This procedure, you're more likely to be on medicines. We're more likely to get a marked pressure reduction, but it carries more risk." They almost every time go to the safe procedure.

So, I think composite endpoints are important, but I want it separated out as well. I would love to see the composite score. I think it is really important. But I want to know what's the chance that something catastrophic can happen.

DR. KATZ: Well, I just to want to just emphasize again that I think -- and correct me from the FDA if I'm wrong -- but I think there is a need to kind of merge efficacy and safety into a composite score.

What's the advantage currently, you know, of merging them as opposed to keeping them separate? You know, if you merge them, you may mask one or the other. And so, I think that is the danger, is that we currently are evaluating them, and I just don't see that a composite score is going to help us.

DR. JOHNSTONE: One issue here I think is that there is no way to quantitate these. These are all really value judgments. For instance, if you do a suprachoroidal

procedure, and you get one patient with hypotony maculopathy, how many patients have to be a success before you decide that it is worthwhile? So, there is no way to quantitate it. It is very much a value judgment, and I think a difficult thing to ever come to.

DR. CAPRIOLI: Okay. Ron?

DR. FELLMAN: I agree. I think it is still best to separate it. I agree with Tom.

DR. KAHOOK: I think in our discussion we're not separating them. We're talking about the two hand-in-hand. So, I think it would be good to work towards getting to the level of a composite. We're certainly not there yet, like Jay said, but I think that's where we are headed.

DR. NOECKER: I think, you know, in terms of severity of side effects, I think we need to think about, I guess, the patients, more of people. And I think a good measure is kind of looking at morbidity or return to normalcy.

You know, because you say, oh, dry eye is not a bad side effect, but I have had patients that that ruined their lives, you know. And endophthalmitis, well, you've got some, but you bounce back.

So, I think one measure is thinking about kind of return to normalcy. And in the real world that's kind of why use our one eye stent patients, because I figure I'm not going to screw anything up.

DR. CAPRIOLI: So, it sounds like composite scores are a good idea. We probably need to know about more how to weight the various variables that go into the score and probably not a place to start, but maybe a place to work toward. Is that agreeable to everybody? Okay. Great.

If there are any questions from the audience, I think at this point we would be happy to entertain them.

But, while we are waiting for that, the last question here is: what are the appropriate targets for overall study success? So, that sounds like a composite answer that has to have certain efficacy and a certain safety.

But any -- go ahead.

DR. KATZ: Well, Joe, I just want to get back. You know, Reay Brown showed that picture earlier of his patient with drug in one eye and the pressure was controlled, but the patient was absolutely miserable.

And all the issues of confines and cost and side effects for patients, I think that one of the endpoints really should be the ability to get patients off medications for all those reasons. I think that's pretty important.

DR. CAPRIOLI: So, that sort of brings us back to risk/benefit considerations. And one benefit, of course, both financially and in terms of quality of life, would be to get patients off medications. And that needs to go into any sort of risk/benefit analysis.

I think that probably comes after approval of a device. Yes or no? Comments?

Another chance for you to say something qualitative, Tom.

(Laughter.)

DR. SAMUELSON: I think the primary FDA role is to ensure safety. I think to make sure the well-being of the population is covered. And then, as physicians, let us use different procedures and devices, based on efficacy, where we think it fits in.

I just had an iStent denied. The pressure was 14. The letter I got back said the pressure was adequately controlled. What this insurance agent didn't notice was that they

were on four medicines and their corneal thickness was 460 microns. I mean, they were getting worse.

But I think it's up to us to figure out what situation to use different modalities, and FDA's primary role is to ensure safety.

DR. CAPRIOLI: Great.

DR. KATZ: We don't use quality-of-life measures, either, much so far. Should we be using quality-of-life instruments?

DR. CAPRIOLI: All right. We will come to that.

Malvina?

DR. EYDELMAN: Just to clarify, in light of the comment that was just made, as Tina summarized in her slides earlier today, these devices come to us through a PMA. And the statute requires us to assure safety and effectiveness before we approve.

DR. SAMUELSON: Yes, and I don't argue with that in any way, shape, or form. I think effectiveness is important, but I think in terms of weighting different safety or efficacy, I think the safety is really the important, and efficacy is important, too, but every little bit helps in glaucoma management.

I mean, you know, when they say, "No, this patient is too advanced to use that procedure," well, okay, then, I'm going to put him on bromonidine? I mean, give me a break.

DR. KAHOOK: So, Tom had a second comment, though, that I think is really important. And I don't know if the FDA wants to comment about this.

The idea of going for a year with safety and efficacy data, but, then, using post-market surveillance, post-marketing information that is -- we're all talking about this in AGS and Academy registry is getting that information.

How does that weigh into the PMA track? There's no reason that you're married to two years if you can use post-marketing information. Is that correct? Do we understand that the right way?

DR. EYDELMAN: So, we actually have a lot of efforts in the registry world, as you are well aware of. And we are looking in every -- we are taking every opportunity where we can utilize post-market data in lieu of pre-market. Having said that, there is some basic safety and effectiveness that we need to get assurance of prior to approval.

But all of your comments are definitely going to be taken and weighed very significantly before we put it in writing in our guidance as to what is the minimum pre-market data that we need to see.

DR. CAPRIOLI: Okay. Now, with respect to the appropriate targets, should our targets for the overall study success include some measurement of quality of life, which is the question that Jay brought up?

Robert, do you want to start?

DR. NOECKER: Say that question one more time?

DR. CAPRIOLI: Should quality of life be one of our success targets?

DR. NOECKER: Yes.

DR. CAPRIOLI: Okay.

DR. NOECKER: I mean, my position is, I guess to be self-critical, is we need to start thinking more like cataract and refractive surgeons, and I think we need to look at our patients' quality of life more than probably what we do now.

DR. KAHOOK: So, if we thought like cataract surgeons, we would be on the beach instead of snowing here in D.C., right?

(Laughter.)

Right. I think quality of life, there is an argument that that should be, you know, one or two on our list as far as importance. We are treating the patient. If the patient is happier and doing better, you know, and we have decreased the pressure and we have had no significant side effects, I mean, that's what we're all striving for. So, quality of life should be a part of it.

DR. FELLMAN: Yes, I totally agree. I guess the question is, how do we incorporate that into the study? And what instrument do we use to determine quality of life?

DR. CAPRIOLI: Yes, I'm certainly not a quality-of-life person.

Rohit, are you still here?

(Laughter.)

Do you have any comments about quality-of-life measures in a MIGS study and how it should be used?

DR. VARMA: You know, I think it is going to be important. As Ron just said, which particular instrument you choose. Because the standard ones which haven't been used are geared more towards central visual acuity loss. Whereas, here what we are trying to assess is whether or not the individual is happy, is functioning in terms of how they've gotten back to where they were prior to this particular operation which was done.

And so, I think that there's a need to develop an instrument which potentially is geared directly to the Boards which can be used for this purpose. And the FDA has some very well-laid-out guidance on that which says how to go about development.

DR. CAPRIOLI: George?

DR. SPAETH: I just want to add to that because I think that's on target.

Personally, I don't think you ought to include quality of life because there isn't any way to measure it accurately, until they develop something that's going to do well, because this has got to be so focused.

DR. TARVER: So, I'm Michelle Tarver at the FDA. Sorry.

So, my comment is that we are currently asking all device companies that come in and want to measure something that potentially is based on the patient's report to develop these types of instruments. And I think Dr. Varma has already alluded to our guidance document that spells out what has to be submitted, and it has to be done prior to the pivotal trial being conducted.

We're having a workshop on March 28th. I don't know how many of you have signed up for it. But we are going to be discussing this topic, in particular, which is PROs and the importance of them.

And the agency itself has specified this as being a priority for us to capture this in our studies.

DR. CAPRIOLI: Any other comments from this side?

DR. SAMUELSON: I was going to say it's the No. 1 job we have, as physicians in the lane; it's difficult to capture in a study. And so, if you're able to find a way to do it, I think it's great. I do think it's our No. 1 job, but it is difficult to figure out how to weigh in a study. So, I hope you are successful with that.

AUDIENCE PARTICIPANT: Dr. Caprioli, one comment about that. With the effectiveness of these surgeries, we're looking at pressure reduction; we are sort of banking on other studies that have proven that reducing pressure helps preserve vision in glaucoma, right? We're not trying to reproduce that endpoint with every study.

I'm wondering if quality of life in these procedures is the same, because they are intraocular devices. We are not creating any eye irritation by doing the procedure. We think we are relieving it.

So, if there are studies that prove that getting off of medications with something inside the eye improves their quality of life, do you have to, then, do that for every procedure that uses essentially the same mechanism, just to reduce the cumbersome stuff you have to do for the studies?

DR. CAPRIOLI: One of the values of these procedures is to reduce the medication burden and to remove some of the compliance issues.

But, to that question, any comments?

(No response.)

Well, I think we probably all agree that quality of life in some measure, as imperfect as they are, should be included. It may catch some of the improvement of the patient's quality by relieving the burden of medications.

But let me summarize briefly before I ask for any final comments.

We agreed that, after a washout, the procedure should have on the average a 20-percent reduction.

Approval should also be entertained for those procedures who in the minority of patients may have a robust reduction of pressure; let's say 5 millimeters of mercury, even if they don't reach the threshold of the mean of 20 percent.

Composite measures are desirable, but yet to be developed. And because of the nature of our patients, the variability of severity, and their starting points, and so forth, it is a fairly-complex issue.

And then, finally, quality-of-life measures should be routinely included in any such study.

Any other comments, questions from the audience or the panel?

(No response.)

We called that; we're five minutes early.

(Laughter.)

DR. SINGH: So, I'll come on up.

This was a terrific session. The whole day, the whole afternoon was fantastic.

I want to thank Joe for just really doing a great job of getting things out of people and just forcing them to take a stand.

(Laughter.)

Because that's what this is about. I think he put it perfectly when he said, you know, in our field we always are afraid to really say something definitive because we're worried about the consequences. But I think he handled it perfectly.

And it has been a great day. I want to thank the FDA for being great partners in this project. And hopefully, this is the beginning of -- well, it's not the beginning; we had one more previously -- but, hopefully, we will continue these discussions and, hopefully, we will do more of these, certainly when we are in D.C., but even outside of D.C.

The other thing I want to do is remind the faculty to not leave right away. Anyone who is in the audience that participated, come forward because we are going to do a group photo before everybody leaves.

And Malvina is going to have the last word, which she always does anyway, right?

(Laughter.)

DR. EYDELMAN: I wanted to thank the Committee and all of AGS and code of superb leadership for a truly, truly outstanding day. I feel that we have done an enormous task. We have gotten a lot of you to agree on many concepts. And as Kuldev said, this is quite -- it's actually Malik said, I think, this is quite an amazing accomplishment.

And we were listening very carefully. We heard all your comments, and we are going to translate that.

And as I mentioned at the beginning of this fantastic day, we hope to put together the first leapfrog guidance and help this emerging technology reach the market.

Thank you all.

(Applause.)

(Whereupon, at 5:59 p.m., the meeting was adjourned.)