

**CENTERS FOR MEDICARE AND MEDICAID SERVICES
TOWN HALL MEETING
The Effects of Coverage & Payment on Clinical Research Participation and Retention**

**September 20, 2007
12:00 pm CT**

Operator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode. During the question and answer session, press star-1 on your touchtone phone.

And now, I will turn today's conference over to Steve Phurrough. Thank you. You may begin.

Steve Phurrough: I'm Steve Phurrough. I'm the Director of the Coverage and Analysis Group here at CMS. Let me welcome you to the town hall meeting.

We, over the last several years, have been interested in clinical trials. And as you're aware, there has been a whole host of issues around clinical trials in the last year or so, particularly this summer.

One of the issues that's always a challenge for us is the issue of whether or - of how payer policies, whether it's Medicare or any other payer, affects the conduct of trial.

Do we pay too soon for something that prevents someone from then enrolling in the trial that's going to determine the benefit of that particular technology? Do our payment policies affect various trial design issues, such as randomization and blinding? What are the various issues around payer policies, again, whether CMS or other payers, that affect the conduct and outcome of clinical trials. So that's the focus of today's meeting.

We asked AHRQ to assist us in this meeting, and they have asked Duke Clinical Research Institute to assist us on that, and so they're going to be doing - leading out in this particular meeting today, working to make sure

things go smoothly today. And there are some other things that are occurring around this particular issue that they may want to discuss with you also.

There's one caveat before I introduce them. And let me make sure that you understand both here and on the phone that we are not discussing our clinical trial policy today. We will - we're not entertaining questions around the clinical trial policy, we're not answering questions around the clinical trial policy. If you want to talk to the - about the clinical trial policy, we'll ask you to - we'll ask the next person to - for their question.

Today's issue is solely focused on the effect of payer policies on the conduct and outcomes of clinical trials. I recognize many of you would like to know something about the clinical trial policy, and we have another process that's out there for doing that.

Well, let me introduce the facilitators today. We have two with us.

Amy Abernethy is the co-principal investigator for this particular project that we have underway. She's a practicing hematologist/oncologist, she's a health outcomes researcher and Associate - excuse me, Assistant Professor of Medicine at Duke. She's a senior fellow at the Duke Center for Clinical Health Policy and a faculty member at Duke Clinical Research Institute.

She has done a number of the technology assessments that we and other entities have contracted through AHRQ at the Duke Center to include some of the issues around (Compendia) that we had last year.

We also have Meenal Patwardhan, the other co-principal investigator. She's a health systems researcher at Duke, co-director of the Evidence Practice Center there, and also Assistant Professor of Medicine at Duke, and doing a broad range of things from finding evidence to working on implementing best evidence in practice, and has been working on a number of the issues that the Duke Center works on.

So with that, I will turn it over to Amy.

We want this to be a very interactive event. We have a series of speakers that will occur in groups, and then we'll have a time for questions and comments. This is mostly a listening session, so we're interested in your comments as to how you and your experience, feel that payer policies affect clinical trials.

Again, thank you for your attendance today and I'll turn it over to...

Amy Abernethy: I'm Amy Abernethy. I'm going to be moderating today. And first, Dr. Meenal Patwardhan is going to talk to us and introduce the project and tell us what we're here to do today.

Meenal Patwardhan: We've just had a little bit about the project, but to introduce to you again to the topic and the Duke Group that is conducting this under the Duke Evidence-based Practice Center which is housed in the Duke Center for Clinical Health Policy Research.

We are trying to understand the effect of coverage and payment on clinical research study part of the patient and retention, so part of the focus aspect of the coverage policy that CMS had.

In the Evidence-based Practice Center and OS researches all over the field, evidence-based practice depends on high-quality clinical trials to generate good-quality evidence.

And however you define it, good evidence should always be generalizable. And generalizable literally basically depends on a large number of patients participating in clinical trials.

Naturally, it is compromised if for any reason people do not have equal access to clinical trials. As you can imagine, many factors can influence a patient's decision to participate and to complete. Both of them are equally important at clinical trials.

One of the reasons could be, for non-participation or reduced participation or non-completion, could be because of third-party payment policies. Today, we are going to discuss this very possibility.

But could there be other reasons why patients are willing to participate in clinical trials?

Usually it's to gain access to a new treatment that is not available outside of the study. One of the most important reasons why patients participate in clinical trials are related to rare diseases or fatal diseases or so on. It could be to potentially improve their treatment outcome; and to contribute to the advancement of medical trials.

Of course, there are some downsides to participation too. Like we said, sometimes the study provides an opportunity to have the new treatment paid for, but sometimes it does not, and that's what we are discussing. And these new treatments could be costly.

Of course, the other side is that it's a randomized control trial, and although you participate in the trial, only half of the patients are going to get the treatment that we sort of hope for. That's the problem. And, of course, patients can't specify that they want to be in the treatment arm.

Health funders like Medicare or private insurance companies sometimes decide to cover treatment for patients who are not involved in the clinical trials and not to reimburse the patients who are on the trial after the study has begun. So, all those factors are important.

This change in payment policy could affect patient's willingness to enroll or to continue in the trial. And there is relative insufficient or non-representative participation in clinical trials that ultimately results in our inability to get some absolute indication of the benefit or harm of a new treatment. And how do they compare to standards of treatment to all the treatments? And that's the biggest problem that we are trying to understand.

Our entire project is based around today's meeting which is the town hall meeting in the center. Apart from that, we are also conducting a systematic literature search which we'll try to understand if there is anything in published literature about trials that have faced problems with recruitment or retention.

As you can expect, we do not think there is a lot in published literature about problems in trials. We generally really publish things about when trials have been really successful.

After this town hall meeting and sort of directed by the questions that arise during this meeting, we plan to talk to about 40 to 50 key informants on the field. And the entire summary of this process, the literature view, minutes of this meeting, and all our discussions that follow from this meeting, will be compiled into a report that we will be submitting to the agency for healthcare research and quality, and ultimately to CMS.

So as you can see, this is - this meeting is one of the most important components of our entire project plan.

I'll now turn this over to Amy, starting with the key questions and she'll now take over from this point.

Thank you.

Amy Abernethy: So, what do we hope to get out of this process?

We'd like to know the answers to the following things: how the payment policies set by CMS and other payment - other payers affect enrollment into

clinical trials; and certainly what we're looking for are examples of trials that have had problems and also trials that have not had problems -- what's really going on at the copay.

How do these payment policies affect randomization and blinding within clinical trials? In other words, are we able to conduct good, high-quality methodology trials?

What are the aggregate impacts of these effects if we find them? Does the timing of third-party payment in the clinical trial process impact the development of good evidence, and do differing payment structures within clinical trials affect the resulting evidence? Really ultimately getting the question of the evidence-based.

Today's forum and the goals.

What we'd like today - to do today is gather information on how payment policies affect real people who actually participate in clinical trials. We're really trying to gather data, looking for on-the-ground experiences and very diverse viewpoints.

Your input is important, input from people here in this room. We've got people coming in through the telephone system and certainly have had a lot of letters.

This is a public forum. For that reason, all members of the public including the lay, public, industry, government, research, health and non-health-related fields all should have equal opportunities to participate.

For times that there are questions for the public, and please bear with me for just a moment while I go through this to make sure we're all in the same place.

Questions for the public -- would you be willing to participate in the clinical trial if it were the only way to get a new and possibly more effective treatment?

Would you be willing to participate in a clinical trial if you would have to pay out of pocket for the drug procedure while on trial?

If you could receive reimbursement for it off trial, how would that influence your decision, and why or why not?

If you decided to enroll in the clinical trial comparing two treatments and one of the two treatments would cost more than the other, would you be willing to be randomly assigned to either treatment?

If you might be assigned to a study group where you do not receive a new drug or procedure but instead receive standard care, would you still be willing to participate in a clinical trial? Would your decision be different if you knew that you might get a new treatment for free by being in the trial?

If you've been involved in the conduct of a clinical trial, for example, as an investigator, coordinator, manager, or an administrator, have you felt that patient's decisions to enroll or continued participation in the trial were influenced by payment policy considerations.

And finally, if you rely on the outputs on clinical trials, to make decisions regarding healthcare. For example, as a part of everyday clinical practice or evidence-based clinical practice, have you felt that the output from clinical trials would be influenced by payment policy considerations?

Here's what we're going to do today. We're going to have three speakers -- Dr. Placido Grino, Dr. Cary Gross, and Dr. Lori Williams -- who will tell us about what are the issues around clinical trials enrollment, what is the (unintelligible) thus far, and what is it like on the ground trying to bring patients into trials?

We'll then have a question and answer session, followed by some real-life examples of clinical trials that are currently having problems by Dr. Lance Dworkin and Dr. Dan Martin. And then again, questions and answers.

And then finally, some special interest sections including disparities and speakers (unintelligible) Dr. Bressler, Dr. Walter Koroshetz, and Dr. Armin Weinberg. Again, followed by questions and answers and public comments.

I think we're all ready to get started. Let's go. A couple of process notes.

Each speaker has seven to ten minutes, and we'd like to have question and answer opportunities at the times I've nominated.

Discussions are going to be limited to seven minutes in person or in phone.

We are not here to specifically address the Medicare clinical trial policy, that's under reconsideration at this time, and I recognize that this is a hot issue, and so we'll need to make sure that we keep this in check.

Not all issues posed for discussion will be part of our report to CMS, but this will be recorded and be a part of the public record. If tangential topics are raised, therefore they'll be recorded, but we'll stop there.

Let's go.

The first person I'd like to introduce to you is Dr. Placido Grino.

Dr. Grino is here from Baylor College of Medicine where he had the Office of Clinical Research. He is Associate Dean of Clinical Research there. He is also Associate Professor of Endocrinology and is in the Department of Internal Medicine.

Prior to being at Baylor, he worked for 15 years in industry in research and development and medical affairs and he was in at least four major pharmaceutical companies at that time. So he has a lot of experience in the field, of industry as well.

Today, Dr. Grino will help us set the stage.

Dr. Placido Grino: Thank you so much.

Yes, indeed, I come from Baylor College of Medicine where the Office of Clinical Research has been running for slightly less than two years now.

So as to provide some context of the environment I come from, let me say at the outset that it's been a great success. We're supporting an ever-growing number of clinical trials across all specialties, many institutions across the Texas Medical Center.

And I think what's unique about our group which is relevant to the discussion today is that the way we have set it up is to provide a comprehensive package of services to investigate, meaning regulatory support, financial support, and very importantly, study enrollment strategies. We have dedicated people to try to enroll clinical trials.

And also we provide clinical research coordinators or nurses that move to the institution and next to the investigator where the study will take place. And they assume the logistics and the administrative responsibility of the study, again, focused on enrolling studies and making them happen.

So this is the context where I've come from. And what I wanted to do today is to provide you with some on-the-ground experience, personal and from our own unit, as to why things happen and why they happen.

We live and die, and this is quite of a bit of a flashback to my 15 years of experience in the clinical and in the pharmaceutical clinical development industry environment, we live and die by volunteering study subjects willing to participate in clinical research. They are the life blood of clinical research. Anything we do before we start the clinical trial is enabling activities. It is only when we initiate the study and we can put the volunteers in the study, be that healthy subjects or patients, that the study will actually take place, and the data will be produced.

Refusal to participate for anyone who has worked close with patients. Refusal to participate or to stay in a study is something that the patient very commonly decides on the basis of intangible factors and many times they will not communicate very ultimately to the study coordinator or to the principal investigator why it is that they decided to say no or yes or actually leave the study prematurely.

There is a combination of fear of retaliation, fear of disappointing the study coordinator, and just not wanting very openly to convey their feelings about the research opportunity.

I think that is the same that perception is reality, whatever the closest to reality that it could be, is when we speak about the perception that the patient may have about making a decision as a convenient decision to him or herself to participate or to remain in a clinical study.

And our own experience is that this is really based on the perception of easiness to participate. In other words, I think that patients can easily accept that there will be no benefit to them from an efficacy standpoint of participating in a clinical trial, and they are willing to accept even that there is a safety risk, that something could go wrong with the new treatment or the trial itself.

But what they are not willing to accept very easily is that the study will place an additional burden on their lives. And if that's the perception that they have, that there is some penalty to be paid by participating in a clinical trial, again, not very ultimately they will decline and not participate or actually leave the study.

So our approach really, and we practice that daily, is that short of inducement or coercion, we believe that it is the mission of anybody who is engaged in clinical and translational research to facilitate study participation.

But this has to be a combinatorial approach, you know, something from study coordinators and principal investigators of some of the institutions where the research is taking place, from sponsors funding agencies, and really anybody

who has anything to do with ensuring the ethical incorporation of volunteers into clinical studies.

So in our theory, and let me just convey to you some of the things that has thematic concerns are commonly found when you're facing the patient and you're trying to ascertain whether that will be a consenting patient or not.

Again, I wish to emphasize that what the patients perceive doesn't have to be true or correct, they only have to perceive it this way to be important.

Number one, for example, I could be refused benefits either from Medicare or from my insurance company if they find out that I am participating in a clinical trial, and therefore, the assumption is that at least for the period that I am in this study, my medical care is taken care of.

I get blood drawn. I get CT scans, I get ultrasounds, I see the doctor, I see the nurse. So I'm done. There should be no charges for my medical care to anybody else.

And based on that perception, many times what we get from patient is the following. "I have no insurance. I don't want you to know the name of my insurance company." Of course that's very difficult for a Medicare patient because we know they get Medicare based on their age. But that's the perception that's very common, the attitude that they display.

Another typical one. If something happens in this study, if something happens to me in the form of some adverse event, that actually I have read in the consent form that it would happen, so it's obviously a possibility, I may be refused treatment for that complication from my Medicare or insurance company because this will be interpreted as a direct consequence of an experimental treatment and therefore is not covered by regular healthcare payers. So, one more deterrent.

One that's happened in studies where the study actually provides some supplies but not others. A typical case would be a diabetes study where the patient is told, "We're going to give you a glucometer." So this is a study glucometer, you take it home, it's yours to keep. But we're not providing these things to check your blood glucose; this is just covered by insurance.

Many times the issue in the patient's head is, "Oh there we go. I'm going to request supply at this point but not all of them. So later on if I need to another glucometer because this one falls in the pool or something happens to it, then it'll be a refused coverage because I didn't request everything at once which is what's required."

So again, this is working inside of their head. And eventually, what comes out is a straight output, "No, thank you, I cannot participate."

Finally, obviously there is this sensation that some patients develop that based on a sort of almost religious mistrust of the system, especially in underprivileged populations where understanding of how government industry companies and the research enterprise work, they have this sort of mistrust that I am the ham in the sandwich.

So if these guys, these big guys, refuse to pay for whatever reason they may adduce, "I could get stuck with medical bills that I cannot afford. So I think I'm safe not participating in the clinical trial, I'm running the risk of being left in that situation."

And so those are all relatively typical and common concerns that many times patients will voice mostly to the study coordinators as a reason to either not participate or wanting clarification of what it means to them from that perspective to participate or not.

The missing link of course in all of these is that we don't have quantitative data. What I provided you with is testimonials, is anecdotes. I think it'd be very useful to actually have some statistics as to how prevalent this is and whether it's different in certain patient populations, certain diseases, or others and so on. But unfortunately, I don't know of any data that speaks to that issue.

And so at the risk of sounding inappropriate, let me say that our own perception would be that any final policy that relates to covering the cost of clinical trials should be easily applicable and unambiguous. I mean, everybody should understand what is that will be there for everybody including PIs, research staff, and so on when they need to communicate this to patients and patients themselves.

We believe it should be broadly communicated. It should be made publicly known so that there is no ideology about this, that there is no misconception -- it's clearly understood by the healthcare environment, and very importantly, by anybody who is engaged in clinical and translational research which then we'll have to communicate and educate the patients on a one-by-one basis.

And finally, we believe that if language in the consent form could be provided that's understandable as required by ethical guidelines that educates the patient, but most importantly, reassures the patient about what to expect when it comes to these concerns that they automatically have when they are asked to participate in the clinical trials, that could be a way of really ensuring that every single patient receives that information in a good way.

Thank you much.

Amy Abernethy: Thank you Dr. Grino.

Our next speaker is Dr. Cary Gross who is the Associate Professor at Yale University and Associate Director of the Robert Wood Johnson Clinical Scholars Program there at Yale.

He did his Chief Medical Residency at Memorial Sloan Kettering and is a General Internist working at Yale but focusing his research in cancer in vulnerable populations with a particular emphasis on clinical trial participation and the impact of chronic illness on cancer care and outcomes.

Dr. Gross is not here with us today and he is only able to participate via telephone, and so he will be speaking to us over the loud system.

Dr, Gross?

Dr. Cary Gross: Yes. Can you hear me?

Amy Abernethy: Yes, we can. Thank you for being with us.

Dr. Cary Gross: That's great. And are the slides all set up?

Amy Abernethy: We are ready to go.

Dr. Cary Gross: Okay.

Well, thank you very much for this invitation. This is a topic that is very near and dear to my heart. And I really consider it a privilege to participate in this project.

And thank you to Drs. Abernethy and Patwardhan for organizing.

So let's go on to Slide 2. This should -- is that working up there? You have overview slides?

Amy Abernethy: Yes, I've got it.

Dr. Cary Gross: Right. Okay.

So I want to, during my session, briefly to describe the background on paying for clinical trials, then provide some of our empiric analogies. Dr. Grino, you provided an excellent segue about data. There are some data that we have; that

is not in abundance. Then finally, a summary of the existing data pertaining to the impact of payer policies on trial enrollment.

Next slide.

So as we all know cancer trials enrollment is inadequate.

Next.

In this figure, if you look at the left-hand side, the Y-axis, these bars represents the percent of patients with cancer who are enrolled in NCI-sponsored cancer clinical trials.

So, on the far left, this group of bars represents all the patients and the tall bar is patients 30 to 64 years old with cancer. Only 3% of them are being enrolled in cancer trials. And as you see those smaller bars, all their patients are even less likely to be trial participants.

Now if you look at the right side of the graph, you'll also see there are important ethnic and racial disparities in trials enrollment.

Next slide.

And as Dr. Grino was pointing out, there are numerous barriers to trial enrollment. In addition to the patient factors such as age, race, mistrust, and other concerns, there are important clinician factors, researcher barriers.

And here today -- next slide -- we're mainly here to discuss health systems barriers to trials enrollment. As you see in the blue box here, these include access to cancer care overall obviously is a critical barrier to us, to cancer trials enrollment, access to a cancer research center where they have the resources to conduct trials.

And -- next slide -- the bottom here, focused now, is on the cost of trial enrollment and the degree to which that is a barrier.

So next slide, this should be Slide Number 8.

Amy Abernethy: Yes.

Dr. Cary Gross: And what I wanted to clarify is that we are speaking about the incremental costs associated with cancer trials enrollment. And what I mean by that is the patient care cost.

I'm not speaking about the cost of conducting the research or, you know, the researchers' salaries, or the investigational drug, or the databases. These are just the extra costs of patient care that are being incurred because the patient happens to be enrolled in a trial.

So when we're thinking about these incremental costs, two important questions come to mind. First, how much money are we talking about here? Secondly, who is paying these funds?

So, now from the perspective of the payer -- next Slide -- you can see on this figure, I've abstracted several studies from the literature. Now each pair of bars represents a single study where in that study the investigators paired trial participants with non-participants who were matched, they had the disease of interest and roughly the same age. And the height of the bar represents how much was the patient care cost.

And if you look across each of these studies, the heights of the bars are not that different. So what that means basically, the cost associated with caring for a trial participant, according to these five studies, suggests that it's not that different from the cost of caring for someone who's not enrolled in a trial.

Now - now in the early 90s -- let's move on to the question of who pays. Next slide. That should be Slide Number 10.

Now in the early 90s, there was a great deal of concern about the fact that most payers were following Medicare's lead and not paying for patient care cost associated with trial participation.

So in the -- well, actually up in - as late as 2000, the Clinton administration mandated that Medicare -- (this room) knows about this -- Medicare would reimburse for patient care cost. And also throughout the 1990s, an increasing number of states has their own mandate that private insurers within those states would have to pay for the patient care cost.

So what I'm going to do now is actually look at each of these two types of policy changes and will review their effect on the trials enrollment.

So first -- next slide -- did the enrollment of older persons in cancer trials increase proportionately after the Medicare policy changed?

Next slide.

Here is just a review this Medicare policy revision. Again, in June of 2000 was when Clinton ordered that Medicare reimburse for this patient care cost.

So here's what we did. Our approach is we identified participants in 23 NCI-sponsored clinical trials. And just to be clear, the reason why we picked 23 -- I mean the NCI had hundreds of trials -- was that we wanted to find trials that were recruiting patients both before and after this policy changed.

We also wanted to restrict our sample to studies that had - actually didn't exclude elderly as one of their criteria. And we included only lung, breast, colorectal and prostate cancer, just the four biggies as far as cancer deaths. And we looked at the percent of elderly, the percent of participants in these trials that were elderly both before and after June of 2000.

And another thing we did statistically was we accounted for the clustering, for the grouping of patients within each trial because, as you know, with different types of cancer, different types of research studies, the degree to which older people can participate could vary.

So what we did is by restricting our analysis to just these few trials and really also accounting for the - which trial each patient was in, we were able to obtain a valid comparison before and after.

So in our next slide, Number 13, this figure shows the pre-policy percent of trial participants who were over the age of 65 in these trials. And as you can see, roughly 40% of the participants were elderly.

Now -- next slide -- after the policy changed, it actually went down, down to about 35%. So this did not show that there was a substantial increase in trials enrollments after - of elderly after that policy changed.

Now, the next question we had, Slide 15, was this: was the state-mandated coverage associated with an increase in cancer trial enrollment? Now again, these are not Medicare patients, but it's the same idea, whether provide - ensuring that payers were providing these patient care costs, did that lead to an increase in enrollment.

Now here, before we switch to the next slide, let me set it up a little. We looked at Phase III studies first and then we looked - I'm going to show you the results of the earlier Phase II studies.

The reason why we analyzed these separately was because there was a concern that was raised by some of our advocacy partners that perhaps the early phase, the Phase II studies, were deemed by their payers to be more experimental and perhaps patients and their clinicians had a harder time -- before, these new state mandates had a harder time getting payers to reimburse for Phase II and for Phase III studies.

But okay, let's go on to Slide 16.

This figure shows the annual number of trial participants in the coverage and the non-coverage states in Phase III trials. And what I mean by coverage states are the - you could see how - the years at the bottom of this figure. So we selected a group of coverage states that mandated coverage in 1999, that's where you can see the vertical bar; and we had a control group of non-coverage states, so that's the dark bar. And the coverage the state mandates are the dotted line.

So as you can see, overall there was an increase in both coverage and non-coverage states as time went on. And this did coincide with a substantial increase in NIH and NCI funding. So the overall increase makes sense.

But the important thing from this figure is that there was not any real difference between groups. The states that mandated coverage did not have did not have a more rapid increase than those that didn't mandate coverage.

But things were different when we looked at Phase II.

Next slide.

Here, the sample size is a lot smaller. But again, the same - if you look at the dotted line, those were the states or the enrollment in states that mandated coverage. And after the mandate was enacted, you see there was an increase in enrollment in Phase II studies in those mandate states, whereas the big thick dark line after the mandates were enacted -- again these are the control state, so they did not have mandates enacted in those control states -- if you look at that big, thick dark line, the number of participants decreased.

So that did suggest that when states passed these mandates, there was not a huge increase in Phase III enrollment, but there did appear to be a significant change in Phase II enrollment.

Next slide.

So, in summary, the existing evidence does not support a major role of payer policy changes in enhancing enrollment in clinical trials.

Now, why is this? I want to show you the results of a recently published meta-analysis by another group.

Next slide.

And these investigators synthesized all of the literature that was available, and let me just lead you through this. At the very top, the number one concern cited by patients in all of these various studies when aggregated was quality of life. And again, this is something that Dr. Grino had alluded to, but they were concerned about the impact of how being in a trial could affect their quality of life.

More than 50%, if you follow the bar to the right, more than 50% of patients or prospective patients cited that as a concern that could hinder their trial enrollment. And on down, the possibility of getting a placebo, again cited by 50%; potential side effects, 45%. Keep going down the list. You have to go down pretty far. You see it's actually next to last where you get the cost or health insurance as a concern, only 15% of patients or prospective participants cited that as a concern.

So to me, the summary of our evidence, along with these findings, suggest that ensuring reimbursement of patient care cost is a necessary but not sufficient approach to significantly increase enrollment in clinical trials.

Next slide.

I just wanted to acknowledge our - some of our collaborators and our funders. And before I finish, I wanted to leave the group with a thought. And that is, payers benefit immensely from evidence about what treatments work best for their patients. So it's not just society or science that benefits or patients but the payers -- payers benefit as well. And they need to recognize this.

And any changes to the Medicare coverage policy need to reflect the data that we just showed, that there has not been adequate progress in enrolling older persons into research studies. So therefore, as Medicare is considering modifying their policy, things like paperwork, bureaucratic burden, clarity of the rules need to be streamlined and not made more of challenge.

Thank you very much again for the opportunity, and I look forward to questions and answers later.

Amy Abernethy: Thank you very much, Dr. Gross.

Great. We're ready to move on. And the next speaker is Dr. Lori Williams.

Dr. Williams is an instructor in the Department of Symptom Research at AMD Anderson Cancer Center, Houston. She's worked in oncology nursing for 24 years and has had on-the-ground experience in staff nursing, advanced practice nursing, as well as research, including functioning as a research nurse and administrator and now a nurse scientist. She's also the Chairperson of the

Scientific Advisory Board of National Patient Advocate Foundation. And she's here to talk to us about lessons learned in taking care of patients on the ground.

Amy Abernethy: ...Dr. Williams.

Dr. Lori Williams: Well, I'm very glad to be here with you and I think you'll hear some of the same things that you've heard from our first two speakers -- from me also -- so that - I actually think we do have some data. I do both qualitative and quantitative research, and I would call what we're doing today qualitative research.

You know, I struggled because I - my presentations are usually evidence-based and I really don't have any data for this. And then I thought, you know, "Experience is qualitative," so I would - I think we've got qualitative research here today.

I just wanted to tell you, I'm going to speak to you today from the perspective both of my experience as a research nurse and a nurse scientist in recruiting patient to clinical trials, but also from my perspective of working with the National Patient Advocate Foundation which is a non-profit organization that works to improve access to healthcare services through policy reforms.

And they have a sister organization called the Patient Advocate Foundation which works with patients by counseling them and providing case management to them to help them gain access to services.

In the last year, they had contacted 6.2 million patients. Twenty-five percent of these were Medicare beneficiaries and 78% were patients with cancer. I also have visited with their case managers who are talking to these patients who are having trouble with access on a regular basis.

And many of these patients do want to participate in clinical trials and there are cost issues that do prevent them from participating in clinical trials.

I think, you know, we all know the importance of clinical trials. They help us to advance our scientific knowledge so that we then can provide better care to improve treatment. Those of us who work in cancer are especially aware of this, because in the last ten years or so, because of research we are seeing more and more people live longer and longer with cancer.

And now also, because the area that I work in, we are getting to the point where there is more and more research now being done to relieve symptoms and toxicities of disease and treatment, so that when people live longer, they

also live better. And it is really important that we have patients in both types of clinical trials to gain answers to some of these questions.

The factors that I find that patients talk about when they talk about, you know, whether they're going to participate in a clinical trial or not, the first thing I think is their understanding of the importance of clinical trials. And usually, when I start to talk about - to a patient about participating in a clinical trial, I hear one of two things.

One thing is as soon as I say to them, "I'm here to talk to you about a research trial, they say, great, I'm all for a research, you know, I think it would be wonderful. I know you're going to tell me it may not help me, but it might help somebody in the future. And if it would help anybody" -- and, of course, I'm dealing with cancer patients, I say anybody with cancer, I want to do whatever I can to help.

And then there is the other group of people who are - have not bought into the importance of clinical trials and who say, you know, I really don't think that I want to be bothered with research again, the theme of it's going to influence, negatively possibly my life, it would be possibly a burden to me, and there's nothing you could tell me that would - that could induce me to participate.

So I think, you know, one of the first things we could possibly do to increase clinical trial participation is to have better education for the public on the importance of clinical trials.

I think the second thing that I hear that does influence patients' ability - willingness to participate in a clinical trial is whether they think that clinical trial might do anything for them or not. And even when we tell them we can guarantee you no benefit, if they have cancer and they have exhausted many of their options, they always hope that they might be the one who benefits from this new drug that's being tested even if we're not testing it for efficacy.

So I do think the patients' understanding of or their perception of -- a previous speaker pointed out -- of what that trial might do for them influences.

They also talked to me about what they think the side effects would be. And they do internally a risk-benefit analysis and they say, you know, I'm willing to accept the potential side effects or, you know, I'm not willing, I don't think it's going to do me enough good to accept the potential side effects.

And finally, there is the financial cost. They do worry about the extra cost, the burden of cost there might be on trial participation, whether it's medical cost or whether it's coming in for more appointments, whether it's - their caregiver might have to miss work.

I had been in situations where patients could only be admitted to a clinical trial. It could only get coverage for a treatment if they were admitted to a clinical trial.

The one instance in my practice that really sticks out for me is when we were doing autologous stem cell transplant for breast cancer and many, many women believed that they wanted to have this procedure and there were quite a few of the payers who decided that they would offer the procedure but only if that was in the context of a randomized clinical trial.

And I think this was done with the best of intentions. This trial was difficult to accrue to and the thought was as we offer patients the potential of having this treatment, if they participate in the clinical trial, we will increase accrual and we'll be able to answer the questions.

Unfortunately, I think there's a problem with that because I think that, to some extent, removes the voluntariness of the consent for the trial. And I think that raises an ethical issue for us. And so think that's something else that needs to be considered. I'm going to talk a little bit more about that in a minute.

Sometimes when there is only coverage available in the context of a clinical trial, then that treatment may not be available to all the patients. And I'll talk about that a little bit more later. Patients know when this happens.

If patients are only able to get a drug through a clinical trial, they may not report side effects because they may be afraid that they will be taken off the trial and they won't get the treatment any longer. And that is a big issue for a researcher.

And finally, age sometimes enters into this. And I'll discuss that a little bit more too.

The issue of if the randomized trial has a treatment in it that is only available for reimbursement in the context of that clinical trial, the voluntariness of the consent, I think, is definitely questionable in that case.

In the case of transplant for breast cancer, I saw patients withdraw from the trial as soon as they were randomized, and they got the arm that they did not want.

Most patients wanted the transplant arm, and so if they got the standard care arm, they withdrew. But there were a few patients the consented to the trial but didn't want a transplant and they also withdrew.

Some of the patients who really wanted a transplant went to another institution and tried to get randomized again in order to get the correct arm of the trial. And that has real implications for us as researchers in biasing our sample.

And so there are just, I think, many issues with tying reimbursement for a treatment through a clinical trial. And I would hate to see that happen again.

When treatment is not available to all patients, as our first speaker talked about, patients may not perceive the treatment is available to them in a research study even when it is.

They may - they said - I know at our institution, MD Anderson, patients sit in the waiting room and talk all the time. And, you know, if the patient next to them says, well, if they tell you so and so and want you to - put you on this trial, your insurance company isn't going to pay for it.

And even when we, you know, talk to them and say, well, yes, you have a different insurance, they're going to pay for it, they don't always - they always have that little doubt, and it's just like, you know, I don't need to do this research -- I'm just going to say no and then I'll be safe.

They made the client participate in a clinical trial for fear of losing coverage. That happens, in particular, in the type of trials that I deal with which are what we call ancillary trials. So it's not their primary treatment; but maybe we want to test a drug to prevent fatigue or nausea or vomiting. There are concerns, if their insurance company finds out they're in any kind of a clinical trial, that they'll quit paying for all of their treatments.

They may be concerned about fear of additional expenses such as things that the insurance company won't pay for. And I have had experience with patients where, once they were on a clinical trial, every time we ordered a CT scan or an MRI, the insurance company would make the comment, you know, well, we're not sure that this is part of standard care, we're not sure we're going to pay. And that became a hassle for the patient. And the patient might withdraw from the trial because of that.

Physicians may not offer treatment options to patients because they - either insurance coverage - they know insurance coverage isn't available or they may be afraid that it's not available or they may be afraid that they aren't sure of what is paid for and what isn't paid for and they might get into fraud and abuse issues, and so they just don't even offer the option to the patient.

Patients are often aware of therapies that are being investigated in the clinical trials. And they know when someone else also has gotten a treatment that they may really want.

I had a really unfortunate experience of having a patient's wife become upset in a clinical waiting room when her husband was not eligible for trial of transplant for multiple myeloma because he was on Medicare when younger patients were. She was screaming, "Why is my husband's life worth less than someone else's?" And so these are things that really get (at where people live).

As I've said previously, patients may not report side effects because they are afraid that they may be taken off of the study. We now have many new cancer therapies that are very effective, but they're also very expensive and they must be taken for a prolonged period of time. And patients do end up being on a trial and they don't want to lose their medication, so they may not report side effects, which again is a problem for us as researchers because we aren't getting accurate data.

And finally, the last thing that I wanted to speak about was patient age as a criteria for being on a clinical trial.

And in the past, we often have excluded people from clinical trials who are over 65 years of age because we thought that the trial might - the treatment might be too much for them.

And I know in my institution, we recently have gone to judging eligibility for a clinical trial not based on chronologic age but rather on functional status and comorbidities that may relate to the treatment. And therefore, this makes people of any age eligible as long as they meet the performance criteria.

And so I think that that's something that we need to consider when we're talking about recruitment to clinical trials, don't exclude people just because they are older.

Thank you very much.

Amy Abernethy: So we've had our first three speakers and I hope that we've set the stage.

With this, I'd like to move to the question and answer session and see whether or not we have any questions both from the audience here in the room as well as our telephone audience.

Anybody want to come to the microphone?

Thank you.

Man: I'd like to just make a comment and maybe Dr. Williams can also comment on it.

I'm from the University of Pittsburgh Cancer Center, and we're trying to instill in our physicians an attitude that clinical trial should be offered as an option to all patients.

What we're finding, however, is that physicians are reluctant to offer clinical trials to patients who have Medicare Advantage coverage since they know in advance that they won't be covered. And so that's a whole group of patients that are now falling out of our spectrum of coverage and participation. I wonder if others have experienced the same.

Dr. Lori Williams: I think you raised a good issue there. And that's similar to what I was saying, is when a physician knows that something is not going to be covered, he may just not even - he thinks, you know, I'm taking the time to talk to the patient about this clinical trial and chances are they're not going to want this. You - it does take additional time to explain to them what their coverage is going to be for that trial, that there may be - that there will be things that won't be covered, that it's going to cost them more out of pocket.

And so I think that's just another barrier to get people to offer clinical trials to patients. And I think any insurance that, you know, has special things like that and if it says, if you go on a trial, that it's going to change your coverage, that makes a difference to patients.

Amy Abernethy: Any other comments?

Sir?

Man: Yes. I would just like to reinforce that point, that we have a program trying to help physicians in disparity communities to enroll patients on clinical trials. And we are getting feedback from them that in disparity communities, the penetration of Medicare managed care is particularly high, and therefore, this is becoming a major, major problem for them in acquiring - encouraging patients from these disparity communities to participate in clinical trials disproportionately.

The second point I want to make is that in my previous life, I, you know, was a clinical researcher, and the ability to convince the patient to go on a clinical trial I think is directly proportional to how much time I was willing to invest in explaining to the patient what the trial was about and why it would benefit the patient.

And the other side of the coin is that if I have invested in a new technology which has already been approved by the FDA and is being paid for by CMS, especially if I'm getting paid more for using the technology compared to the previous technology, well, I have a very strong disincentive from encouraging the patient to participate in the clinical trial evaluating their technology.

So between the facts that as a physician I am able to influence the patient's decision to participate or not and having this incentive that a patient may not be aware of, where I get paid more by using Technology A or Technology B, I think this creates a really vicious cycle in terms of limiting my ability to encourage the patients to participate in research.

Amy Abernethy: Thank you.

Any comments?

Yes, sir.

You push the button to On.

Man: Yeah. You talked about the - a trial of mortality with stem cells in breast cancer patients. Now, I thought that that trial showed no benefit, is that right?

Dr. Lori Williams: Ultimately when it got - or when they got to enough accrual, it did show no benefit, but the, you know, I think the big issues there that I had with that one was that - was more the ethical issue of placing women in the position when they really want to - the therapy.

Man: Right.

Dr. Lori Williams: And I think if we at that point had done a better job of explaining to women that the reason we were doing the trial was we really did not know which, you know, arm was better. But...

Man: Right. But I think...

((Crosstalk))

Man: ...I would take exception to your point that, you know, if that treatment was available outside the trial, I think that the trial would never be done and thousands of women would have been having this procedure which eventually was shown not to be a benefit.

Dr. Lori Williams: I didn't mean to imply that the trial should have been avail - that the drug - the treatment should have been available outside of a trial. I think what the

problem was though it was available to some people, but in - there were some insurers that made it available only through a trial.

So I think if it was only available through a trial to everybody, that would - that probably would have solved the problem. The problem was when women were tried - they tried to force women into the trial, that was where the problem arose.

Amy Abernethy: We're going to take two more questions and comments at this point.

And I'd like to ask that each person introduce themselves so that we know who you are as you're making your comments and questions.

Thank you.

Suanna Bruinooge: Hi. My name is Suanna Bruinooge. I'm with the American Society of Clinical Oncology.

I wanted to add to the presentation by Dr. Gross. He had mentioned the one study of the before and after effects of the Medicare coverage policy.

And there was another study that was done by Joseph M. Unger et al and was published in the Journal of Clinical Oncology in January 2006. And this study actually did show that there was a positive impact on patient enrollment from the Medicare coverage policy.

Prior to adoption of the coverage policy, this was a study that was done in - related to a clinical trial that was offered by the Southwest Oncology Group, which is an NCI-sponsored research network. And they found that Medicare-age patients were significantly underrepresented in clinical trials prior to the Medicare policy. The Medicare patients count either only 25% of the overall accrual to the clinical trial whereas they compromised 63% of the population of all cancer patients.

After adoption of the Medicare policy in 2000, participation by Medicare patient increased from 25% to 38%. So they did show some positive impact. Particularly, the increase was most notable among those who had supplemental insurance coverage as well.

So I think that also shows that the, you know, the incremental or the - that really the coverage cost - the patient coverage cost associated with participation do have somewhat of an impact on patient ability to participate in the trials.

Dr. Cary Gross: Actually, I have some slides that might be helpful to respond to that. Thank you for bringing that up.

Dr. Abernethy, is it possible to open up my presentation again?

Amy Abernethy: Yes. Go ahead and start talking. I'll get...

Dr. Cary Gross: Okay.

So if you go to Slide Number 24, the - basically this - the study that you mentioned was kind of a big picture, global view of trial enrollment in one of the cooperative groups.

And please let me know when you have it up there because it'll make it easier for me.

But the - what the investigators did is they looked at, again, the percent of patients who were 65 years and over in the SWOG, one of the main cooperative oncology groups. And what they found, as you indicated, that there was an increase in the percent of elderly.

But just to say there's an increase in the elderly before versus after that policy changed doesn't fully take into account the complexity of the issue.

Do you have it up there or...

Amy Abernethy: The - yeah, Slide 24. There we go.

Dr. Cary Gross: There we go, okay.

So that's their data.

Okay, let's go on - that's the study we're just talking about.

So now go to Slide 25.

This is from our data. What I did is - this is just as an example just to show how it's a very complex issue. This is total enrollment again in our sample of all NCI cooperative trials. We took a larger sample, again both before and after the year 2000.

Now go on to Slide 26.

Here it is broken down by - instead of the total, now we broke them down into the four main cancer types. And you can see there's a huge variation across

cancer types. This compares the percent of elderly people in breast versus in prostate. And then also, within each cancer type, so again there was no significant trend one way or the other; that dark bar is before 2000 and the striped bar is after 2000.

So, if you don't take into account the fact that different types of cancer trials might have been ongoing, say, for instance, if you opened up three new prostate cancer trials after the year 2000 and closed down two breast trials, you can mistakenly assume that there is a huge increase in elderly patients as a result of your policy.

So I think it's important to really look at these issues very closely.

But I just want to summarize. I did not mean to imply that these - from our data or make the argument that these trial policies are not important. What I'm trying to convey is that they're not really getting us where we need to be. They're not leading to an increase in enrollment of elderly or minority groups. And I think that if we really have the specific goal in mind, which is to increase the overall enrollment as well as the diversity, the policies as written have not been effective.

Amy Abernethy: Thank you.

Any calls from the telephone lines? Any calls from the telephone lines?

Operator: Yes, thank you.

For questions on the phone, press star-1.

And we do have our first question from (Robert Reinhardt).

Your line is open.

(Robert Reinhardt): Thank you.

Yes. My name is (Robert Reinhardt) and I'm a member of the Community Advisory attached to the San Francisco Department of Public Health Research which conducts HIV prevention and treatment trials. And so that's the context to which I'm asking my question or providing a comment. And we especially advocate and represent on behalf of trial participants.

My first comment is, I think people in the room are generally aware that, you know, at the end of last year, FDA issued a proposed rule that - criteria for charging for investigational drugs. And without elaborating on the details of that proposal, which I actually personally thought was kind of vague and then

indeterminate, my comment is just that as you proceed in preparing this paper under the Duke auspices, that that kind of coordination or effect between CMS and that particular FDA policy might be something especially to highlight.

And then, my other comment about the presentation so far which were very helpful to me also is that I do think there's a lot of commonality in the problems of what were described as the burdens and the concerns of participants to join a trial.

But I guess I would also add that in - again, for purposes of the Duke paper, that although there are commonality among all kinds of clinical trials and all diseases, there are also, I think, a lot of differences in that some particular degrees or kinds of stigma or burden, for example in HIV trials, may not be precisely the kinds of experiences that cancer patients have. And so, again, when that study is, you know, unfolding, I think differentiating among different patient populations would be important.

And I do happen to know happen to know that for HIV trials, there have been a lot of data accumulated which, now that I - the beginning, I'm going to make it my business to try make sure that others, you know, provide you with other comments, you know, in due course.

That's it.

Amy Abernethy: Anything else? Any comments?

Neil Bressler: Neil Bressler. I just had one quick comment from the presentations.

I think Dr. Williams points out to us qualitatively we do recognize there must be some impact of these payment policies on participation. But it seems that we certainly have very limited data to know the magnitude of that impact. And even looking at these differences before and after 2000 don't tell us other factors. There's certainly other policies going on, community-based changes going on in not only reimbursements but, you know, people getting to these.

So certainly, it will help us in the future to collect this information. And it's very hard to collect because the decision to participate often is made before the consent process even starts. So the physician interaction with the patient and other people's interaction with the patient may not capture this data.

So as you forward to try and collect information on the magnitude, it will be very challenging, but I think it can be done, to figure out how to get that information early on in the process when the person is being evaluated by the health care providers.

Amy Abernethy: Thank you very much.

At this point, I'd like to go ahead and move on.

Yes, sir.

Neil Bressler: One more brief comment which has to do with what I think is a very strong bias towards cancer research in the discussion.

I think that as we collect data on the impact of these policies, we have to look at noncancer clinical research which constitutes a major component of all clinical research in the country.

Amy Abernethy: Thank you.

Operator: Excuse me, we do have two questions from the phone. Would you like to take those?

Amy Abernethy: Can we hold those questions until the next question and answer session? And we will have another question and session at that time.

Operator: Thank you.

Amy Abernethy: Okay? Thank you.

Next, we're going to move forward with Dr. Lance Dworkin, a Professor of Medicine and Vice Chairman of - for - of for Medicine for Research and Academic Affairs, as well as the Director of the Division of Kidney Research and Hypertension at the Alpert Medical School of Brown University in Providence.

He has laboratory researched in kidney failure as well as is a clinical specialist in hypertension and is Study Chair and senior leader for the CORAL trial. This is a study in renal artery stenosis and this study is pertinent to us in today's discussion.

Lance Dworkin: Thank you.

So I'm not an expert on health policy or funding for health policy. I'm an academic physician and a clinical trialist.

And I wanted to describe to you the experience of leading a trial which is currently ongoing and which is struggling to enroll patients and some of our thoughts about why that might be.

So, first of all, I think one of the points to make here is that it's very, very difficult to do clinical trials and there is in fact a paucity of clinical trials, particularly randomized clinical trials that are being done. And I think this is a major issue for medicine.

This is a slide recently published in one of the kidney journals looking at the percent of public studies that are randomized clinical trials in the literature. And the point is that it's a very small percentage of all published studies. And in my area, which is nephrology, only about 2% of all published studies are randomized clinical trials. So I think all physicians agree that this is exactly the best kind of evidence of what we're looking to do but somehow we're failing to succeed in this area.

So I just wanted to tell you a little bit about our study. And hopefully, that will shed some light on the question. And this is not a cancer trial, and it's not even really a drug trial. So maybe, it's a little bit different than what you've been hearing. We're comparing an intervention, which is a renal revascularization or angioplasty and stenting, to medical therapy.

And I think in designing and coming up with this clinical trial, there are a number of steps to this.

So first of all, pick a clinical problem. And renal artery stenosis is a common clinical problem. It affects 1% to 5% of all hypertensives, about 70% or 7% of all elderly patients, many patients with vascular disease in other beds.

Pick an area for which the best treatment is not known. In this particular area, there was an AHRQ review and I think - that's, you know, maybe not a definitive statement on this area. It was actually done after the trial was launched. But they've reviewed all the pertinent evidence for or against revascularization in this disease and concluded that the available evidence did not clearly support one treatment approach over another.

So here is an area where there's clinical (unintelligible) where there's really no evidence supporting one approach or another.

So then, the next step is to ask a clinically relevant question and designing randomized clinical trials. I think one of the pitfalls is to look at surrogate endpoints rather than hard patient outcomes. And that's something which we've tried not to do by looking at things like heart attacks and strokes in these patients rather than surrogate endpoints like blood pressure.

So this is the way our trial is designed. It's a randomized trial. Target enrollment is about 1100 with patients with about five years of follow-up. Our

primary endpoint is a composite which includes some hard clinical outcomes like death, stroke, myocardial infarction. And the way the study is designed, it has about 90% power to look at the primary endpoint.

And the way recruitment works is that we have a suspected patient, they sign consent, they undergo an imaging procedure that demonstrates the stenosis, and then they're randomly assigned to either receive the intervention or not. And then everybody gets an intensive medical regimen.

A big barrier to clinical research, of course, is funding. These trials are very expensive. I just mentioned this in passing. The cost of the CORAL trial to the NIH which is funding it is \$30 million unless we run over budget, which we may. This is equivalent to 80 to 120 individual RO1 grants. So, a big disincentive to doing this kind of research is the cost involved.

So this is, of course, the Achilles heel of most clinical research, is enrolling the subjects. Probably naively, we thought this would not be a problem in renal vascular disease, and we thought that all we had to do is find enough experienced centers because there were certainly enough procedures being done.

And this is some data looking at the number of renal revascularizations being done. This is a booming business in the United States. The number of procedures has been increasing progressively. Most recently, the estimate is about 35,000 per year in the United States. And remember, we're looking to accrue 1000 patients.

There is a significant payment. A lot of these are paid for by Medicare. And the average cost, not including everything, probably is somewhere in the \$2000 to \$6000 per procedure.

This just shows enrollment in the CORAL trial. The blue line was our projected enrollment when we applied for the grant; the yellow line is our revised; and the pink line is the actual enrollment. Between June 2006 and 2007, we enrolled 180 patients out of the 35,000 undergoing renal stenting in the United States. That's .5% or 1 out of 200 of all procedures.

And I just point to the fact that we had 456 reported screen failures. And these were patients who qualified by all other criteria, but failed to be enrolled either because of patient or physician preference.

And I would suggest to you that this number is a very, very gross underestimation of the number of patients that didn't enter the trial for this reason because oftentimes, patients or physicians wouldn't even consider a patient for a trial because of their individual preference so that they wouldn't

be entered in the screening log. But if the procedure was not available except through the study, you'll wonder how many of those patients would have - or physicians would have refused the entry for their patients.

So how do - how we try to stimulate enrollment in this trial? We've made a lot of modifications to the protocols to make it easier. Patients get free medications. We've increased reimbursement for the centers.

It's interesting, I participated back in July in a (MedCAC) meeting right here in this room, which was examining the state of evidence and the impact of coverage policies on reimbursement for renal artery stenting. And some of the topics that were discussed at that meeting were it only covered procedures for patients that were enrolled in approved clinical trials.

And I just want to talk about that and raise two issues related to that. And one has to do with registries versus randomized clinical trials.

So a lot of times, I think when coverage is limited to approved clinical trials, that includes not only randomized clinical trials but also registries. And there are important differences.

Registries collect information on patients undergoing a procedure or a therapy, but all of the patients entered in the registry actually receive that therapy. So they provide no useful information on the relative utility of the procedure or intervention versus no intervention.

And I think they can sometimes be useful after a randomized trial's demonstrated benefit to refine a clinical practice, but really shouldn't precede clinical trials.

And registries can undermine enrollment in clinical trials. Remember, all patients get the intervention - there's no untreated group. So if you or your patient, if you're the physician, believe in the procedure, then entry into the registry is preferred over entry into a randomized trial.

There's financial disincentives to randomization because if you're getting reimbursed \$6000 for the procedure and if you enter the patient in a registry, you get that 100% of the time. And if you enter the patient in a randomized trial, you get it 50% of the time. That's a significant difference.

And then there are also just, from the point of view of the conduct of clinical trials, big differences because oftentimes, the amount data being collected in a randomized trial is much greater than a registry. And so, participation in these trials is more burdensome both for the physicians and for the patients.

It's interesting to us that FDA is currently mandating registries for a device company seeking approval for a stent to be deployed in the renal artery. And the typical endpoint in these registries is the restenosis rate. So, a positive study would be one in which the stent was associated with a lower restenosis rate than historical controls and with an accessible complication rate.

But why do we care about restenosis if opening up the artery is of no benefit in the first place? So we believe that these registries really have no place until the randomized trial is done.

And if studies are not available, what about clinical practice guidelines?

So this is a big trend, I think, in medicine now. If you look at the available evidence and issue these clinical practice guidelines, and I think this is a laudable effort in - on the part of physicians to try to make sense out of data and make rational decisions. But there are problems with this process.

There is in fact a clinical practice guideline that's been written for renal artery intervention that was promulgated by an august body of societies. Many of them are in interventional societies who do these procedures.

And they make recommendations. Usually, they classify evidence A, B, C or D and then classify recommendations Class 1, 2 or 3. And Class 1 recommendations are recommendations for which there's strong support in this particular clinical practice guideline. A Class 1 recommendation was issued for renal artery interventions in certain settings. And that was based on conditions for which there is evidence and/or general agreement that a given procedure is beneficial.

And I would ask you, how do you reach general agreement if there's no evidence?

There is a cost to funding things based on clinical practice guidelines that they may be wrong. It contributes to a sense of complacency in the care of patients, it may increase cost without improving outcomes. And one example from my own field, in nephrology, we have clinical practice guidelines without evidence for treating bone disease and people with CKD. And in one hospital that takes care of about 500 dialysis patients, the cost of implementing these clinical practice guidelines was estimated at half million dollars per year. And again, remember there's absolutely no evidence that this improves patient outcome. And if you extrapolate that across the whole system, it has a huge impact.

There are other deleterious consequences to basing coverage on these clinical practice guidelines that are not supported by data. They serve as an

impediment to performing randomized clinical trials. Will I prove something that's already an accepted part of clinical practice?

And it becomes difficult for clinicians in IRBs to deal with randomized trials if one of the groups in the trial already violates an existing clinical practice guideline even if that guideline is not well supported.

And then, of course, when these things turn out to be wrong, which was the case recently in the nephrology with the erythropoietin therapy for anemia where, for many years, we've been treating patients through a certain hemoglobin target.

Finally, two randomized trials were published and both of them showed that that was associated with worse outcomes for patients and nobody knows what to do now. And there have been probably hundreds of articles written about this conundrum since those studies were published.

So, in conclusion, randomized trials are expensive, they're difficult to perform and they're uncommon, enrollment is a major barrier. Coverage policies, I think, do affect enrollment by altering the chances that an unproven therapy will be provided outside of the study.

Registries are not the same as randomized clinical trials and can substitute for them. Clinical practice guidelines based on observational data - data I think may increase cost without improving patient outcomes and also discourage enrollment.

And from our perspective, trying to get this particular trial done, we would like to see NIH, CMS and FDA kind of work together in order to encourage the completion of these types of randomized trials which, in the final analysis, were the only way that we'll ever really figure what's useful and what's not.

Thank you.

Amy Abernethy: Thank you very much.

That was interesting and is a nice - segues to the next talk by Dr. Dan Martin.

Dr. Dan Martin is a Professor of Ophthalmology in University of Atlanta. He's the Chair of the Comparisons of Age-Related Macular Degeneration Treatment Trial. It's another trial undergoing similar complications. And he's is going to tell us about this.

Of note, Dr. Dworkin and Dr. Martin have both been given 12 to 15 minutes for their presentation and hence they were each a little bit longer because these were trial-related presentations.

Dr. Martin?

Dr. Dan Martin: Thank you very much and thank you for your invitation to speak this afternoon.

What I'll do in the next 15 minutes is to give you a little background information on macular degeneration, the clinical trial that we've designed and why we're doing it, and then go through in greater detail what are the specific problems that we've encountered during the process - during the course of setting up this trial.

So age-related macular degeneration is a leading cause of vision loss in patients over the age of 65. There are 1.6 million people in United States already legally blind from this condition and another 9 million were thought to be at high risk progression to neovascular AMD.

The primary reason why people develop loss of vision in this condition is the development of neovascular or wet AMD. In this process, the neovascular vessels grow through the membranes beneath the retina into the subretinal space leading to bleeding and scarring and loss of central vision.

In the mid-1990s, we learned that a cytokine, VEGF, vascular endothelial growth factor, was an important contributor to that process. And since then, a number of drugs have been designed to inhibit VEGF. The most successful of these was a drug called Lucentis®.

In the mid-1990's, Genentech® was developing Avastin®, which is a monoclonal antibody against VEGF. They performed a series of now famous experiments that published in 1999 where they injected a monoclonal antibody, about 150 kilodaltons into an eye and looked to see where it went.

And what they concluded, on the right, was that the monoclonal antibody did not penetrate to the subretinal space which was the target tissue. If they took the monoclonal antibody, again shown on the right, and took off the two Fab fragments and tuned them up, and then injected those, as seen on the left, the drug penetrated into the subretinal space.

This modified these fragments to the monoclonal antibody, were then put through an affinity maturation process to increase the binding capacity, and that is what's known as Lucentis®. So Lucentis® is derived from a monoclonal antibody that's similar to Avastin®.

They then proceeded with two registration trials which demonstrated really an extraordinary therapeutic fact. This was one of the studies. The green line is, well, the standard of care therapy. At the time, as you can see, at one year, there was a substantial difference in visual outcomes with the average patient losing ten letters in the patient assigned to a treatment called photodynamic therapy versus a significant gain in vision of those who assigned to Lucentis®.

This slide is a summary of all of the efficacy data. And really, it shows you just how disruptive the technology was. Everything that preceded Lucentis® was much less effective, particularly when you look at the proportion of lines - of patients who had gained three lines of vision over 20, 40, or better, you can see the previous treatments, single digits were achieved. Whereas, with Lucentis®, which was given every four weeks injected into the eye for a period of two years, that treatment produced a - really a therapeutic effect we really had not seen before. We learned of these results in July of 2005.

The following paper at a meeting reported the clinical experience with intravitreal Avastin®. And it showed just in that one case report a therapeutic effect that looked like something we hadn't seen before. Avastin®, as many of you know, is approved for colorectal cancer in 2004 and was therefore available for off-label use. That single-case report stimulated a phenomenon which was really unprecedented in Ophthalmology.

Over the next six months, we estimate that more than 50,000 eyes were subsequently treated with Avastin® with no prospective randomized clinical trial data to support that use. What drove that was unmistakable efficacy that we really had not ever seen before.

There was a patient of mine who had failed photodynamic therapy who initially presented to me with neovascular AMD of 20/60 in February 2005. I treated him with a series of Macugen® injections. It's another anti-VEGF drug but was much less effective. After five injections, the patient's condition had continued to deteriorate, as seen in the upper right-hand portion of the slide. This is the cross-section of the retina.

A single injection of Avastin® one week later, she had significant vision improvement to 20/80; and two months later, she was 20/60; another month later she was 20/40 and she did not require another injection for more than a year, really remarkable result in the patient that's failed all treatments. So that's really why this phenomenon took place.

Well, it's obvious to many of us what the problems are going to be. Here was July 2005 and in early- 2006, 2006 we're accumulating this vast experience

with Avastin®, no clinical trial data to support it, and Lucentis® was to be FDA-approved -- it happened in June of 2006. The question would arise: which drug should we use?

There was also an enormous cost difference that has- that became very apparent once Lucentis® was approved. Lucentis® is \$2000 an injection, again given every four weeks for a total of two years. Avastin® is priced for cancer therapy and we need only a small volume of that, so .05 cc. The commercial cost of that stuff is \$50 per injection.

Because of the efficacy - the desire to understand efficacy, to understand really many aspects of this phenomenon, a group of us organized a study that's now known as the Comparison of AMD Treatment Trial. When we first met in the fall of 2005, our goal was to determine the efficacy and safety of Avastin® relative to Lucentis®.

The other design challenge was that Lucentis® had only been studied with six or every four-week dosing, whereas Avastin® had only been given on an as-needed basis.

And the anecdotal experience with that was quite favorable. We learned early on we probably didn't need to dose these eyes every four weeks. And we subsequently learned with Lucentis® that there were some populations of patients out there who also do not need as frequent a dosing, and yet the FDA approved a - the study that led to the FDA approval had only looked at every four-week dosing.

So we - it's clear that we need to understand whether this treatment strategy of dosing on a P.R.N. basis, or as needed, whether or not that would compromise long-term visual outcomes with this less frequent dosing.

So we designed the trials, submitted to the National Eye Institute, asked for and received expedited review. And on October of 2006, the Comparison AMD Treatment Trials, Lucentis®-Avastin® trial, was funded.

In this study, 1200 patients with newly-diagnosed neovascular AMD will be randomly assigned to Lucentis® given every four weeks versus Avastin® given every four weeks versus Lucentis® given on an as-needed basis as driven by visual acuity and a number of other parameters that we used to follow these patients, and then Avastin® also given on as needed basis.

The study was to be conducted at 47 centers in the US. It's a non-inferiority trial. Primary outcome measure is mean change in visual acuity. There's a whole bunch of other secondary outcome measures; I'm not going to go

through them. Just suffice it to say that we're looking really at all elements of the use of these drugs and how we can best optimize them to maximize visual outcomes. We'll be looking at genetics and pharmacokinetic modules and hope to report data within - in 2009.

The funding - the total cost of the study is \$50 million. The National Eye Institute granted us \$16.2 million over a four-year period to fund the infrastructure to the trial. The remaining \$34 million is patient care costs.

The majority of patients who developed AMD are 65 and older and therefore eligible for Medicare. So Medicare and its supplemental policies were only response for the standard patient care costs.

The question was, how would we handle the Lucentis® and Avastin®?

The cost of Avastin® in the study was about a million dollars when you consider the drug cost, the central compounding and the distribution. And we had money allocated to us from NEI to pay for that.

The cost of Lucentis® in this trial ranges from \$22 million to \$25 million depending on how we would up using in the as-needed dosing arms. Genentech has stated publicly many times, twice now on the Wall Street Journal, that they would not support this trial.

Given the percent of projects funded by the NIH is at an all-time low, I don't think it's reasonable to expect the NIH to cover the cost of Lucentis®, particularly when CMS is already responsible for care in majority of these patients.

Before this trial was funded, there was a lot of debate as to whether or not we should work out the potentially issues with CMS first or whether or not the trial should be funded first. At the end of the day, the NIH stepped forward first and funded the trial again in October of 2006.

We had our first face-to-face meeting with the Cambridge analysis groups, this group here, in July of 2006. We learned at that meeting a number of different things.

The first was that there was a question of whether or not even 80% of Lucentis® could be paid in a clinical trial without changes to the existing Medicare Clinical Trial Policy. This was a surprise to us particularly when Lucentis® was already FDA-approved and the existing policy stated that routine care in clinical trials covered with – with routine care defined as items or services that are typically provided absent the clinical trial.

Nonetheless, Lucentis® was deemed investigational, and this trial became an important stimulus for the revised Medicare Clinical Trial Policy. This was now no longer an issue. But it was an issue that didn't want the delaying the start of this trial.

The second issue had to do with masking. There was no payment mechanism in place that would allow simple masking of the identity of the drug. What we need to do in this study, do we need - first we need an initial outlay of \$25 million. It's not clear where that would come from. We need that to centrally purchase the drug. The drug would then be masked. We've arranged for Avastin® to be repackaged into smaller vials that looked - and then over-wrapped so they looked just like Lucentis® vials and we'll say, we have an IND for this, we've met all the CMT requirements for the FDA, we now have an 11 - we've established 11-month shelf life for Avastin®.

So the drug will then be masked centrally, but then sent to the clinics administered locally, and then billed in such a way since it somehow - it's billed locally but somehow the central purchaser has to recover that cost.

If you can work through that and if a DC must pay 80% of the drug cost, we also have the issue of the copay. And that is, the patients were, of course, responsible for 20% of their copay. In this case, the \$2000 - Lucentis®, which costs \$2000, the copay is \$400.

Avastin® is \$10. It's pretty easy to figure out which drug you've been assigned to if you're a patient receiving that bill.

Furthermore, that difference in cost could encourage differential dropouts. If you get past that, then the Medicare patient also receives the Medicare summary notice that would identify the drug billed which would also unmask the patient. Further, 85% of Medicare beneficiaries have a supplemental policy that also identified the drug and you now pay, thus unmasking the patient.

When we first met, we - of course, we were somewhat naïve and obviously wanted 100% of the allowable to be paid. What we had hoped that would happen was that a demonstration project would take place whereby CMS that - would adopt a payment method that would mimic a research grant award, that they would provide upfront payment to the study to purchase and distribute the study drugs.

This takes care of the money that has to be paid upfront. It also eliminates bills that never go to the patients. Central record-keeping of the drugs distributed in the trials. The patients who would receive no drugs, no bills for the specific drug injected.

And if this - this demonstration project would demonstrate that the benefit of giving the money to a trial organization with appropriate accounting safeguards in place to support a head-to-head comparison of covered drugs. These masking issues and copay issues are common to many trials we felt it'd be important to run a pilot project to see if this would work.

There are - the idea of, you know, asking for \$25 million we didn't think was so unreasonable because this project did not expand existing coverage. This was not going to be a net increase in dollars paid out by CMS. In fact, there was going to be enormous cost savings. For the 1200 patients participating in the study, when you've just considered that 80% of the drug costs, the savings to CMS is \$25 million, it's real simple math. It's not - these are not cooked numbers, it's pretty straightforward.

We learned that the project would, in essence, pay for the copays and, therefore, would take congressional authority to do so. And it was also it being a demonstration project, it was really not the appropriate mechanism for this circumstance. So we were encouraged to pursue legislative efforts to obtain funds, which we did for the next several months.

In November of 2006, it was determined that in fact the demonstration project may be an appropriate mechanism. Over the next three to four months, there were a number of different plans that were developed.

It was obvious to us during this process that there really was no precedent for doing this. And I don't mean this critically, it's just very clear. One project would be development - would be developed, would go up to or for legal review and would come back and say, no, that's not - that won't work. And then another would go and they go back and say, oh, (let me tell you) the changes -- do it the other way, do it that way before - it did the first time. This went back and forth. Meanwhile, months and months are going by and now, and mounting, frustration on our part.

At the end of the day, the project that was ultimately finalized was one where Lucentis® and Avastin® would be billed by clinics using a G code. So it was identified on the Medicare summary notice by the supplemental policies as Lucentis®-Avastin® study drug. The - Thus, the patient would not know specifically which drug they have been assigned to.

The price was the average cost of the two drugs plus a small margin that had been built it on the basis of the assumed imbalance in Lucentis®-Avastin® you should - in the as-needed dosing arms.

The National Eye Institute agreed to pay the balance of all the copays and it was determined it was legally permissible to do so after Medicare and supplemental policies had paid. The patient therefore would have no out-of-pocket expense and will remain fully masked which was the goal of our study.

The issue of the initial cash outlay and the financial liability remained unresolved, but we felt that we should - we've - we were - we could get the demonstration project finalized; we felt that we could work with that.

The project had full support by CMS staff. It's approved by - or redeemed approvable by the Office of the General Counsel within CMS. It was signed by the CMS Administrator May 2007, it was sent to HHS and OMB for its approval.

We had discussed with each of these offices and they had all expressed strong support for what we are trying to do. And three months went by. And out of the blue, at least to us, we learned that the Office of the General Counsel at HHS deemed the project as unapprovable.

And the only justification that sort of - and we still believe we don't have - we've not received a satisfactory answer on this. The justification provided was that "It was obvious that the demo project will improve the quality of the clinical trial with Medicare beneficiaries' participation in it that we did not need to do the project to prove it. I don't think any scientist would ever accept that argument as a valid argument.

So, where do we stand?

The CATT is fully funded and is ready to begin. The investigator meeting is slated for this coming Monday and Tuesday, we have 47 clinical sites in attendance. Medicare Clinical Trial Policy supports the Lucentis® use in the trial and Avastin® is covered by NEI funds, NEI will pay the copays since not covered by the supplemental policies.

Masking we've had to change. The masking will occur at the local level with maskers (unintelligible) examiners and masking of the treating physician. The patients will be unmasked.

This is not what we initially thought to do. We remain confident that we can do a clinical trial that can produce robust clinical data, but it is not optimal.

We have continued to work with CMS and they've been terrific in the last month in trying to develop an alternative plan that would allow for full masking.

However, we've been on the government's timeline for the last year and, as many of you know, it's not a good place to be. And we simply cannot wait any longer and have decided that unless can be worked out within the next few weeks or maybe a month, we may be able to utilize a different plan. But otherwise, we will simply have to move forward. The goal is to have the first patient enrolled by at the end of 2007.

So, in summary, my observations on this - on the problems that we've faced in this trial have been, first, well, the CMS folks that we've interacted with, they work very hard with these issues. The issue has been that it's been limited by an inflexible and inefficient system. There's really been no culture of communication with outside investigative groups, not so much with this group but the fact that these decisions by OGC were made unilaterally and there was never an opportunity to discuss them.

We - I would like to propose a program be established where the CMS could provide upfront funding for drugs in a clinical trials that's cost-neutral to CMS and CMS deems it's in the public's interest - best interest to do so.

The bottom line is we've been late for a year. This is an credibly important study. There are cost savings potentially of \$1 billion to \$3 billion per year, and every month that goes by is another month that patients with AMD still don't know what the optimal treatment for the disease is and the more money we spend.

Thank you.

Amy Abernethy: So now, we have more of the story. And with this, we'll invite more comments from the public both here in the room and from the telephone line. And let's start with the telephone line this time.

Operator: Great, thank you.

Once again, press star-1 for question.

And we do have a question from Patricia Farias.

Your line is open and please unmute your line.

Do we have Patricia Farias from Northwestern?

Your line is open.

Patricia Farias, your line is open.

Amy Abernethy: While we're waiting for somebody to come on the line, would anybody like to come to the microphone here in the room?

Are you there?

Okay. I'll go with Dr. Grino.

Placido Grino: Just to say that, in case it's helpful -- of the two major responsibilities that the research sponsor assumes which are study design and funding, it obviously creates a rift when there is funding that has to be covered by someone who does not play a sponsoring role for the study, because it had nothing to do with the design of the study. Just pointing this out, and it's food for thought.

Amy Abernethy: Is there a question on the line now?

Operator: Yes, thank you.

We do have Patricia Farias.

Your line is open.

Patricia Farias: Hello.

We were just wondering if any of the clinical trials is like the - getting paid for the administration charge?

Amy Abernethy: For the administration of the trial? Of the drug?

Patricia Farias: Of the drug.

Amy Abernethy: Administration charges of the drug?

Patricia Farias: Yes.

Amy Abernethy: Dr. Martin?

Dr. Dan Martin: The - in the file trial that I just described, there is a code that you bill for the intravitreal injection of the drug. And that is considered as a standard procedure and covered by routine care.

Patricia Farias: Oh, so it's part of the routine costs? Okay.

So that would be a covered service? Is that what were saying? If the medication is provided by the drug company and we are administering the

medication, are we allowed to get paid for the administration of the chemo drugs?

Amy Abernethy: I think we should move to our next question.

Operator: Thank you.

Next question. Catherine Hill, your line is open and please unmute your line.

Do we have Catherine Hill on the phone please?

Amy Abernethy: We have a speaker here in the room. Why don't we wait for - I have our next question here in the room while you're finding Ms. Hill.

Lee Ann Jensen: I'm Lee Ann Jensen from the National Cancer Institute, and I want to compliment you on a very nice talk and on your persistence.

I'm - I've been involved in lots of clinical trials and I can tell you that the problems that you've described are very common especially the issues between standard drugs that's payable and the one that's not and the cost and all of that.

And so my question is, what did the FDA have to say about the idea of not masking the patient? Would they - have you talked to them about that? We're they concerned? Have you resolved that?

Dr. Dan Martin: Yes, we've - yes and the - in an ideal world, we would obviously like to mask throughout or all across all arms of the study, the Lucentis® versus Avastin® fixed comparison.

Actually, masking is really not essential there because you're robotically injecting every four weeks. The physicians are not making treatment decisions.

Now, it might affect retention - patient retention, and so we do want to mask. But from a - in terms of how robust the data might be, that's not an area of concern for us.

I can't specifically speak for the FDA, but it hasn't been voiced as a concern. Some of the other comparisons become more important, but we have so far a green light to go.

Lee Ann Jensen: And basically, your outcomes measures are objective enough that masking isn't going to be an issue?

Dr. Dan Martin: I'm sorry. Repeat that?

Lee Ann Jensen: Your outcome measures...

Dr. Dan Martin: Uh-huh.

Lee Ann Jensen: ...they're unaffected by the lack of masking?

Dr. Dan Martin: Actually, we do have masking in place. We'll be - the primary outcome measure is visual acuity and we use mask visual acuity examiners.

The real issue is whether or not the treating physicians are biased into the study. Really, that's, well, the most important aspect of masking here. But again, the primary outcome measure, mask visual acuity which will take place independent of whether or not the patient knows.

Amy Abernethy: Is the question on the line available now?

Operator: We're actually showing we have no questions from the phone at this time.

Thank you.

Amy Abernethy: Thank you very much.

We have another question here on the floor.

(Harry Ridger): Hi, (Harry Ridger) from (Aberlay) Health. A question for Dr. Dworkin.

It seems like, you know, the CORAL trial, the issue isn't necessarily one of insurance payment given that, in this case, for most of the Medicare beneficiaries, there probably is the payment available either because the device is being done under an investigational device exemption, the regulation's in place to pay for that from Medicare and that generally is a covered service, at least currently.

You also - I guess my question really is, in your opinion, why has enrollment been so slow? You seemed to infer from your presentation that it had more to do with physician practice and the standard of care there coming from the clinical guidelines. I just wondered about your opinion there.

Lance Dworkin: Well, it's certainly true that the issue for us is not that patients are not covered. The issue is really the opposite, that they are. So, you know, this procedure is kind of being done indiscriminately. Well, that really is unfair, but it's being done based on, you know, the clinical practice and opinions of the physicians.

I mean, we have a lot of - and so, I do think physician behavior has a lot to do with enrollment and obviously, as already been mentioned, you know, physician beliefs and behavior impacts tremendously on what patients think and want. So, when a patient is being offered enrollment depending on how, you know, this is presented to them, you know, they may - are more or less enthusiastic.

So yeah, I mean, I think that the reimbursement policy here is basically permissive. It allows this procedure to go on, large numbers of them to be done despite the fact there isn't good evidence to support it. And it seems clear to us that if that was not available, that more patients would be enrolled in the study. So, it's kind of the other way around.

(Harry Ridger): Yeah.

Amy Abernethy: Any other questions?

Wonderful.

Well, let's take ourselves to the section of the day. And next, I would like to introduce Dr. Neil Bressler.

Dr. Bressler is the Chief from Retina Division at John Hopkins and is an endowed chair at the inaugural James P. Gills Professor of Ophthalmology. He is very interested in collaborative efforts and clinical trials of common retinal diseases, and he's the chair of the NIH-sponsored Diabetic Retinopathy Clinical Research Network. Today, he's going to talk to us about our topic.

Neil Bressler: So I want to really thank Dr. Abernethy and Dr. Patwardhan for taking this on, because I will share with you our experiences in retina disease in dealing with this topic so that perhaps it will give you some guidance in what we need to answer going forward.

I just want to make a few quick financial disclosures.

All the grants that come to the John Hopkins University are negotiated by that institution. I have no outside financial interests, but I do have numerous grants as principle investigator for the companies that are listed here over the past several years. And my wife, who also is an Ophthalmologist and clinical trialist, does receive consulting payments from Genentech®, for data and safety monitoring committee work, and NotalVision, which is an imaging group in ophthalmology.

I'd to then switch to what our experience with payment policies in clinical trials and how it may affect the conduct of those trials.

First, I want to talk about a trial that I served as a chair in the 1990s and in early 2000. And this was the Submacular Surgery Trial. It actually consisted of three different trials and it's relevant to a variety of payors.

The median age of a trial that was called Group H because it involves histoplasmosis effects on the retina was 48 years involving many payors that were not Medicare. But we had a group and trial in macular degeneration that Dr. Martin already eloquently described where the median age of entering this trial was 77. And even older in a Group B trial, which was large bladder hemorrhage from macular degeneration, the median age entering this trial with 79, spanning 57 to 94 years, involving many people who our dependent on Medicare for their payment.

Now, the design for this was to evaluate surgery versus observation. And we don't mask people to surgery in this trial.

The cost assumed that subject and their third-party payors would cover the cost of anything which is standard care, and surgery at the time for this condition was considered standard care and covered by third-party payors most of the time. And this would be for any standard of care that was simultaneous to a study visit for a procedure even though we were collecting that information. And it's important when we plan on collecting this information to be sure that the consent form indicates that the coordinating center with the data will be unmasked for the patient's identity in order to collect this information.

Now, that sounds great, but we don't want to exclude anyone with financial hardship from entering these trials. And that could include people with no insurance.

So how did we handle that?

Well, first of all, we couldn't find anything in the literature that described systematically how multicenter clinical trials handle subjects who do not have insurance when standard care costs are part of the clinical trial. So we devised our own guidelines and we said that subject without insurance for standard care, which is also part of research, that the individual investigator would manage this as is done with their financial hardship with any of their patients, which, in most cases, is to waive most or all those costs.

Now, we discussed ahead of time before the investigator started these trials that these waivers obviously constituted type a type of cost sharing between

the clinical center, which is getting intangible benefits by participating in the trial, and the National Eye Institute, and we're working with our colleagues and we try to come to an understanding about this.

So, this seems like a good system. Have the payers pay for the standard of care costs and don't exclude anyone with financial hardship because, of course, we're going to share in those costs.

There are many challenges to this, though.

First of all, there might be a center that had no problem handling one or two subjects out of 50 that did not have insurance, but all of the sudden, during the conduct of the trial, insurance will change for the other 48 people, and all of a sudden, they're hit with costs that they didn't expect because these insurance coverages changed where the person lost insurance.

And then it's not just the investigator who's doing the surgery or who's following the patient and giving the drug that's involved in the cost. There are other people that are going to be involved that are out of control of this trial. And this, for example, the people who are providing the anesthesia, or the facility costs to have the operating room.

And so we found out that you can't just get an agreement between the investigator and the central coordinating center, but that it was going to be difficult, if not impossible, to control all these costs.

So what we did was we created written guidelines and policies and that every problem that came up would go to the study chair and the principal investigator, the coordinating center to make a judgment whether there were other costs and other funds available that could be sent on a case-by-case basis. And as each case develops, we kept that case and that provides us the foundation for discussing the next case.

What we did not do and I would encourage you to consider is to make a plea and a guideline to multicenter clinical trials to see if they can come up with fairly uniform guidelines and begin to collect what those cases are and learn from the case-by-case management how to handle these financial hardship in the future.

So I want to end then with how it evolved to our next set of trials that I've been sharing. And this is the Diabetic Retinopathy Clinical Research Network. This is also funded by the NIH and it's dedicated to having a network to rapidly facilitate multiple trials that are going on for diabetic retinopathy. It was started in 2002 as a separate line item from Congress, so it fortunately did not involve pulling millions of dollars from all of our RO1 grants to be able to

develop the network. And the objective is to have this network ready to do multiple clinical trials in diabetic retinopathy.

Now, it involves community-based and university-based practices so that we see a variety of payment issues that come up all the time. And it was also designed to collaborate with industry to facilitate investigations because our investigators don't have a monopoly on all the ideas -- this is just an industry as well -- but it has to be within the network's dedication to academic integrity, complete control the data and optimal clinical trial performance.

So, we actually are able to get about 1/3 of all the retina sites in the country, including about 500 investigators and additional 1000 personnel. And since then, we've been able to rapidly run all these protocols that are listed here. I want to highlight two that are quite complex to tell you the lessons we've learned from having payment policies or having to develop them.

So what are the payment policies in the network?

Well, first of all, it applies to people across a variety of payers. In one trial, Protocol B, which is the intravitreal triamcinolone trial, about 45% were over the age of 65 where Medicare will be involved. But that means 55% had variety of commercial payers or no insurance.

In a more recent one, looking at ranibizumab which is Lucentis®, triamcinolone and steroid and comparing that with laser, again 45% are in the Medicare age group. And this involved a sham treatment versus true intravitreal injection. Now, by including a sham, because we thought that would be good for masking, that means we cannot charge the subject for their standard care injection because, as Dr. Martin alluded to, they're going to be aware of whether they got a bill for their standard care whether they're covered or not. And that would ruin the masking for that.

Now, we do call it masking, not blinding, in ophthalmology. And that is that we were looking into having this double mask between the subject, because they're the ones that we'll talk about the side effects and safety, and the outcome assessor, which is the visual acuity person, not the doctor who's injecting the drug.

But I would challenge whether we really have to do masking in most cases. And this is alluded to by the statement from the person from the National Cancer Institute.

There have been two (conference) systematic reviews that have been published, looking at 156 trials in a variety of medical conditions with controlled, randomly-assigned placebo or sham versus no treatment. And the

authors state that they were unable to detect a statistically significant overall effect of placebo intervention in trials with binary outcomes whether they were reported by the patient or observers, or in trials with continuous outcomes when they were reported by observers, like standardized visual acuity measurement through the continuous visual acuity letter score.

Now, they did see a modest difference for some trials that we've read about or been involved in with continuous outcomes that are purely subjective, reported by patient, such as patient-reported pain or phobias. But really, there was no evidence that for most of our trials, including our ophthalmic interventional trials that we discussed today, that placebo interventions in general have clinically important effect. And so this has to be considered as part of the formula when deciding do you really want to include it because it has a huge impact on your payment policy.

So how do we approach it? Again, there was no systematic review in the clinical trial literatures as to how people develop payment policies. And so, what we do is we create a list of each procedure at each visit, that it could be a visual acuity measurement. That's a study budget cost. It could be retinal imaging. Sometimes, that's standard care, sometimes it's a study budget. And we define it every single visit whether it's a standard care or a study budget. An eye exam could be a standard care or a study budget. Coordinator time and investigator time are only study budget. A laser treatment shouldn't be standard care. And the injection in this case, because we're masking people, had to be study budget.

There is also - that is - there's a variety of different combinations of therapy that are going on. Some subjects get laser and no injections, combination of monthly injections and laser, combination of injections that are three times a year or every month as in Dr. Martin's trial.

And so we have a variety of total costs that vary per subject. So in Year 1 for this trial, if you're assigned to sham, it's \$4300 to the study budget and \$2900 for standard care. Certain visit charges also are a part of standard care, such as laser or the visit itself.

But if it was a study drug that's given monthly plus laser, \$6900 for the study, \$2900, the same amount, for standard care. And what you can see down the line here is that those amounts can vary, but there's always a standard care amount that we are including as part of our payment policy that we explained.

And if there's financial hardship where the person cannot cover that, then we approach it in the same way in try and do a shared cost or a cost sharing with the investigators. Among 700 subjects, this gets to be millions of dollar and that's just Year 1. These trials go out to three years.

So, what have we seen about the impacts of payment policies in the ophthalmology trials that run across numerous centers?

Well, first of all, we would probably recommend that we now approach a systematic collection of what the problems are. But what you've seen is that with - these third-party payments are critical to the operation of our clinical trials, but we have no idea how many people don't enroll because of the policies, because we cannot collect that information prior to the consent process and the investigation going on.

In our anecdotal experience, it's actually fewer than 5% of the subjects that investigator calls in to the Study Chair to say, we need to discuss the problem that we have. And the investigator is otherwise able to handle those on their own, or those subjects never come to us in the first place. Many of these subjects are relevant to CMS, but they're also relevant to all third-party payors.

There is cost sharing that is going on with investigators. Even when you think that you have third-party payers covering this, they're not covering everything. There are investigators that are taking their own intangible discretionary fund to cover these costs.

It's clear that you'd have to have concise payment schedules that clearly say at the onset of the trial what is the investigator going to get paid through the study and what is standard care that will be covered at each and every visit for each and every procedure.

There is some central case management. We believe that's needed so that you have consistent application of guidelines of how to apply these payment policies and to create and revise policies. And I think they should be shared because the fact that this is ophthalmology is no different from what we've heard in renal artery stenosis surgery or in cancer as well.

Masking, though, should be used prudently. It raises study costs considerably and, in many cases, it really may not be needed to get the answers that we're talking about.

Thank you very much.

Amy Abernethy: Moving on to our last two speaker of the day.

Next we have Dr. Walter Dr. Walter Koroshetz. He is the Deputy Director of the National Institute of Neurological Disorders and Strokes and he is here to

talk to us more about our topic including the policies – policy-makers' viewpoint.

Dr. Walter Koroshetz: Thank you much. It's a great pleasure to be here and I very much enjoyed listening to the prior presentations.

And I think, you know, one of the things that comes out is, I think that the National Institute of Health is investing large amounts of the taxpayers' money to get answers to clinically important questions. And you can see the difficulties that, you know, really hardworking people are having trying to help the Institute to do this. So I think that the chance to come and talk with our colleagues in CMS and FDA is greatly appreciate and I suspect we'll need to do more and more of that.

So I'm going to basically repeat Dr. Dworkin's study, talking in a different fashion but the points still apply. He was talking about renal artery stenosis, and I'll be talking mostly about my experience in stroke, which is my field before I came to the NIH and NINDS which is the stroke (branch). So, I wanted to just kind of think from, you know, the big picture and go down.

And I think this is what we'd like to have in the best of all possible worlds, which is when medical hypotheses have been tested in preliminary studies, then going to randomized clinical trial has shown to be of benefit, and then this moves into clinical practice. But unfortunately, that's not the way it works all the time. And so that's - that was (perspective) of, you know, best of all possible worlds.

The patient's perspective has been talked and this is just the way I would, you know, schematized it.

The patient gets a medical diagnosis, you know, artery stenosis, right artery stenosis, and the patient at that point in time is thinking, how do I get rid of this problem and what are my treatment options? And the patient would like to make the problem go away.

So you show somebody with renal artery that's stenotic. They say, well, how do I get this to go away? And so they're thinking cure. And so the big arrow was towards cure. The patient wants to make their problem go away. And it's very typical for the patient to think about, you know, that consequences of doing that.

I was actually involved in the first testing for Huntington disease, a genetic testing. And the question was, you know, patients wanted to get rid of this diagnosis and unload it off of their minds. But in so doing, they were entering this 50/50 gamble of finding out exactly what they didn't want, and most of

them will go and try to say, I want to take the test because I want to, you know, get rid of the problem. But that's only 50/50. And it was really hard to get people to sit down and look hard at what the consequence of decisions are and that's the issue of risk.

So as you go towards partial treatment, people would come less and less interested. If you go towards conditions in which there's no available treatment, people get extremely nervous and they are really kind of become very risk - they become ignorant to the risks and it gets put down in their attempt to try and get rid of their problem.

Now, if you take that and then think of, all right, since this is an interaction between the patient and the doctor and I told you kind of what the patient is thinking, this is what the doctor is thinking, that, you know, here is the diagnosis, these are what - the things that I use to treat the patient. And what I have are my preferred treatment options and these are based on, you know, what I've done in the past, what I've read in the literature. But a lot of it is really based on the local standard of practice. And that is - a local standard, sometimes it's local in the area, but in fact, many times, it's local and what the department you're in.

So, if you go to the neurology department with a stroke and say this is what I, you know, this is what I have, what should I do, doc, you're going to get a completely different story. And if you go to a neurosurgeon with a same problem - and that's the real - realities that we have to understand and it certainly has a big effect on the clinical trials. And I think, you know, Dr. Dworkin was getting at that in his talk.

The neuro malpractice concerns that are going to influence what the doctor does, and then research protocols, unfortunately, are way down the list. And so people have talked today about you look at the numbers of people in cancer who are involved in research protocols. That's much better than stroke, for instance. That's actually probably the best of all fields. And so we have a real problem in enrollment and recruitment of patients into studies.

I just came from our council today, and one after another we were talking about how we're going to improve enrollment. The cost of these trials would double or triple as they - the enrollments close.

Enrollment in many clinical trials is not done in United States primarily anymore because we can't get patients. The enrollment is being done in Poland, in Romania, in Russia, in India, in South America. It's a real testament that we have to move our clinical trials for the American people out of the United States to get them done. So there is a crisis here. And the crisis comes in part because things can really go wrong. When - I talked about this

fact that the patient was - when met with a scary diagnosis really starts to ignore risk. They want their problem to go away.

The physician's treatment decision, unfortunately, can be affected by things that are related to the individual physician's success. So, finances. You know, I do - as was mentioned, I can go into a trial and I get paid for 50% of the patients, or I can go into a registry and get paid for 100% of the patients. Each procedure is \$5000 or \$10,000. That's a lot, lot of money.

Academic gain, politics within the university. One physician group now kind of taking over the turf that belonged to another group that's spanning its scope of practice. And even the sense of, you know, the physician's sense of - that this is what he can do, so he really needs to - for his own self-satisfaction, needs to continuously prove that his process is the correct one. And these things are real and they - and when you try to accrue patients, this is the kind of things you're dealing with.

And this becomes - these problems become really bad when the available medical evidence is not there to guide patients. When there's evidence, people will always go down the straight and narrow. They will not deviate from evidence for financial gain in most cases. But when the evidence is incomplete, then you - then things are open - more open to opinion as opposed - treatment based on opinion and where these individual issues come in more strongly.

Now I'm going to talk about a couple of examples.

This is an old example that has recently come up again. And this is extracranial-intracranial bypass where you've taken artery and you've put it into the brain and connect it to a brain artery for patients to have occlusion of the carotid artery. So, an extremely dangerous procedure.

But then when you think about, you know, the carotid artery is one of the major blood vessels to your brain, you know, it's not hard to convince them. But, you know, if this vessel's closed, you'll need more blood to your brain, we'll take this vessel and put it in.

And this operation was described in 1969. There were thousands of patient who had this surgery, and then people started to look at what this theory, this case here is and they really didn't see clear benefits. And that got to an NIH-funded trial which in 1985 showed no benefit. So for years, this procedure was going on, it had really no benefit in the patient population which was being used.

Then, in 1990, the Federal Register - Medicare withdrew coverage for this procedure because there wasn't available evidence. But this is really backward. You want, as you know, as Dr. Dworkin said, you want to make the payment approval based on the evidence and not vice versa. And it's really hard to do these kind of trials once they're being paid for.

Carotid endarterectomy was in a similar boat. We have a lot of knowledge about it now. And so that knowledge from randomized controlled trials does affect how treatment is occurring.

But there's another example of patent foramen ovale. So patent foramen ovale is an opening between the left and the right side of the heart, and there are certain circumstances with clot can come from the vein, cross that hole and go to the brain.

It's probably extremely rare, but it's possible. The trouble is, that there are 750,000 people with stroke every year in the United States, about 40% of those people we cannot find the cause of the stroke. But because patent foramen ovale is present in 28% of all patients, there's about 100,000 patients who are going to have a patent foramen ovale.

And so the question comes up, well, is that how I had my stroke? The doctors can't find anything else. Should I have it closed?

And it's clearly a great problem for a clinical trial. And there are clinical trials that are going on, but they can't recruit. And the reason they can't recruit is because there is a possibility for payment for patent foramen ovale closure through an exemption clause, Humanitarian Device Exemption clause.

But recently, because this - the problem was still prevalent, the FDA came in and basically took the exemption away because they were - they found that there 4000 patients a year in the United States who were getting their PFOs close and the trials were recruiting, you know, less than 100 a year. And, you know, it really created this example where, you know, the decision was made, okay, maybe this is not the right direction, let's take the approval away, get data and then we'll be able to revisit this.

Carotid artery stenting is in a similar situation now. It's a new procedure. A whole new physician group that's coming in to where previously it was only vascular surgeons and neurosurgeons. So, a tense political pressure to have carotid artery stenting done. It's one of the most common procedures - surgical procedures in the United States, is carotid endarterectomy.

And there's been lots and lots of juggling and pressure on CMS to approve carotid artery stenting, particularly asymptomatic patients, and without really

good evidence that's really going to help them. And again, courageous efforts by CMS to kind of hold off, try and get the data.

There's an NIH trial that's in process which is recruiting these patients. But it's been really slowed by this registry problem. We're trying to recruit 3000 patients and there might be 10,000, 12,000 a year who are getting stenting outside of the trial and these registries are really slowing things down.

And so, time and time again -- I think I'm running out of time - I have probably another 20 examples, but I probably can't get to them. But time and time again, I mean, the problem that Dr. Dworkin mentioned with renal artery stenosis, you know, it is repeated and repeated. So I think we can learn from our errors and try to get together, the FDA with CMS, NIH, to really think things out, get - it's basically a timing issue and - but it's - I don't think, if anything, it's not solvable.

So, it's a pleasure. Thanks very much.

Amy Abernethy: Thank you very much. Fantastic.

And moving on to our last talk and then we'll go back to our conversations with questions and answers.

Our last talk by Dr. Armin Dr. Armin Weinberg who is also at Baylor. He's a professor. And he's going to speak on Eliminating Disparities in Clinical Trials and also the impact that clinical trial payments has on that.

Dr. Armin Weinberg: Thank you very much.

Coming near the end, I'm going to try something a little different to keep myself on time. I'm watching the timekeeper there.

I'm going to do this in not so much a formal presentation, but in terms of some of the bullets here and just kind of give you some thoughts like I was a reporter or something.

I want to speak as the principal investigator of the project called EDICT, which is Eliminating Disparities in Clinical Trials. And it is funded by a grant from Genentech® and other sources including Federal support. So, that's disclosed.

The purpose of one arm of this is to really look at some of the opportunities for - affecting policy recommendations, policy change in eliminating disparities in clinical trials.

So, very quickly, with that in mind, I want you to know that we're looking at this as something that occurs not just to one area, but looks across public, private and nonprofit. And so today, I'm happy to be here talking to one part of that equation.

This slide is said to represent that finding of a year's work - a year and a half of research and interventions, discussions, interviews and so on. It really is the model with which are working, and that is the 3Rs as we call it.

First thing is that we found that there was a lot more known about recruitment into trials. The second thing we found is that there was a very a little known about retention or keeping people in trials, which I think is relevant to today's discussion. The third R is that there's even less known or even being done to return the benefits to the individuals and the communities where trials are done.

Now, in order to use this slide, I want to throw out here something for you to keep in mind. And as it relates to CMS in particular, you know, there are a lot of issues when it comes to underrepresented populations. I've heard a number of them talked about today. Those include, of course, the elderly and I'll mention again back on that but, you know, those with disabilities, those who have other special needs are often really excluded without even knowing. We have no concept of how many and what the impact truly is there.

Another element which is often overlooked is low literacy, which we've been seeing is more and more a problem and it is something we have start to address as a society and as a country. Why this slide to me is important today is because, when it comes to CMS, this should not be an issue, okay? Okay. This is very important I think for us to do.

This particular slide is courtesy of a colleague of ours who's in the audience here, Diane Delisi, and I wanted to say that one picture is worth a thousand words. So if we haven't already seen that there are disparities and there are underrepresented groups in clinical research, this slide should show you very clearly that there are.

This is based on the data that they looked at Phase I through III treatment studies from January 1, '03 to June 30, 2005. On the left, you see rate, and you can, of course, see that the - by the way, if you haven't been able to tell, the picture - the visual is - the light blue is white, 88.6%, and on the right of the circle is not - is ethnicity, and that's 94.4% Latino or Hispanic.

Okay. So, when we looked at these issues, obviously there's lots of other things to consider.

One is - and again for CMS, I would like the case that in terms of the science, there is a need for us to keep pushing forward, if nothing else, in the understanding of what it means to be more inclusive of those who are over 65. There are far too few people over 65 who are routinely excluded because someone just in the design stage went with the more traditional view of making it easy not to have anybody with comorbidities. And it just makes life easy. Those comorbidities may or may not be relevant to the study, but they're just there. It's almost like you get a form and you just sort of put people down and it's done.

And since -- myself included -- many of us are aging, I'd like to be given the opportunity to know that when the drugs that are developed on people under 65 used on over 65, I might get actually, you know - after the fact.

Okay. The next point is that this project is all about really trying to use a new sort of, you know, approach to developing these policy recommendations. So what I'm going to share quickly is the fact that this is our sort of simplified methodology, if you will.

But really what we've done is we've looked at bringing together the public, private and nonprofit leaders, advocates, survivors, community researchers, academic researchers, pharmaceutical, biotech companies, federal liaisons and so on, to try and figure out where there might be areas that we could indeed look at policy opportunities for making a change.

As a result of a policy roundtable, we hosted - a year ago, September, we identified nine such areas. And I'm just going to let you take a look at some of these. I'm not going to go into it because of time, but you can see we have one OT2 that's focusing on assuring health care coverage in clinical trials. I think that's may be one of the reasons that I'm here today.

I will say, though, that the findings of that particular group and the work they're doing have already heard the need for transferring some of this into a more comprehensive look at the issue because education of the health professional including the physician, education of the research including the design, are all part of the equation.

We have five other themes, and you can see these go all the way through to regulatory oversight and enforcement.

Now, very quickly on this slide, the bottom line, the punch line is, if you look at that middle one, 60% of participants surveyed, you know, fear insurance denial is a major reason for not participating.

So even if there is data that says maybe coverage isn't such an issue, you have conflicting data sometimes. Well, there may be some reasons for this. We could debate, discuss -- I hope we can at some point -- what this really means, what the real answer is.

I can tell you that some people, especially in those underserved communities I just had a few slides back, never had insurance, or felt they had insurance that was going to give them much of a chance to get into the system to begin with. Now, when you get into sort of the CMS area, post 65, so is there some baggage, I guess, is the point. There are some things that we don't really fully understand, that we may not have fully accounted for that may be playing out here.

I can also tell you many who have insurance don't know what their benefits are when it comes to clinical trials. And that, too, is a problem.

And I'll tell you one other thing.

Having reviewed a few articles on this subject, many physicians who are participants in guiding patients into trials don't really understand the trial. That could also be a little (unintelligible).

Okay. So I really - again, we - one of the things that we did do is we did look at what are the - some of the recommendations and revisions that are coming forward here as far as the CMS program, and we did submit recommendations to the Centers for Medicare and Medicaid Services.

The recommendation that we see here actually, I think, makes a lot of sense from our point of view. Now, you know, we're obviously concerned about improving and increasing participation of underserved and underrepresented groups in clinical trials.

Well, the reason that we've put this out there is that, you know, there was an NIH Revitalization Act of 1993 that really requires that minorities and women have to be included in clinical studies. That's one of the reasons, as investigators, we now have these forms and tables we have to fill out. The problem is this makes perfect sense.

We also should, by the way, to make sure that this group not only has enrolled but that they're retained, again to my earlier point. And unfortunately, the data that we have come across is that, you know, initially, in looking at this kind of recommendation, people think this is going to cause a lot more work. And quite honestly, it could cause some work, but it is the kind of work that probably should be done anyway if we're doing the work that we said we're originally going to do, which is to design a table, that this is our target, this is

who we expect to recruit, and this is why if we don't get it, we don't, or if we need to do a better job, we address that.

So I think in this particular slide, one can say the Federal initiatives today have not necessarily prevailed or prevented widespread disparities in clinical trials, going back now some 13 and 14 years.

I think it's also important, real quickly as we come to the end of my time, to point out -- the second bullet here -- 80% of the trials, as Dr. Williams pointed is not all about cancers, are industry funded.

So when we looked at some of the data that is out there that is shared, it's often very good. It tells us a lot. Think of that visual that my colleague afforded us that show how, you know, how the disparity is there. That was with sponsor's funds, from NIH, okay? So think of what it might tell us if we knew what there was from the bigger picture of the - all these studies.

There's another point here that I think is very important for today's discussion. And that is one that says it's difficult to see how CMS can see a return on investment if retention isn't known. And I think that's very important, again going back to those recommendations. It's not just enough to have a plan for improvement but a plan for retention. If you don't have these populations well included and retained, it will begin to start to take a toll.

Now, in summary, I guess what I'm going to end up on a couple of quick slides here. And it's goes like this. It's something from the EDICT, and again this is sort of coalition, if you will, of minds, okay? Again, public, private, nonprofit, advocates, scientists, researchers, center directors, and so on.

I think this is important discussion because there's a science case. We know we need to have a better science discussion about what is a good sample, how are these studies being designed and who should really be on them. Is the burden of disease being really properly assessed? Is the catchment area or service area being considered? I think those are things that we would want in any good study.

Business case. I think we know we need to have a good return on investment. Everybody does -- the NIH does, private industry does. Community, however, offer those. Social justice obviously means something to many people, and it's time for us not to leave that out of the equation.

So, when I come to the end of my remarks, I thought I'd share with you a couple of things.

Number one, I heard before if we had, again, people who - a question of coverage. I wouldn't posit that people - when you look at the question of whether coverage makes a difference, many people don't know if they have coverage. So - or the systems are not there to know if the, you know, if the coverage has made a difference.

I can probably find one-on-one examples, and I think we heard some today, where you've been able to put in place a system that makes a difference. You can also find one probably where they don't. Where at a stage where we need to separate out and not necessarily look at the aggregate as much as we sometimes need to look at the best examples we have going forward.

I think it's also important for us to know that we have an opportunity to deal with something that came up in the (DOMA) Report. My time is up which is good because I'm coming to the end.

The (DOMA) Report, you may recall, one of the individuals who was a - very much a part of it, a signatory, was a woman named Dorothy Height. Dr. Dorothy Height was a distinguished leader in the African-American community.

After - when she participated in the decision about whether the IRB and whether or not, you know, there was not only science but equity as a part of the recommendations for Human Subjects Protection and Inclusion, you know, she specifically said, "Absolutely, equity was important."

There was a great deal of misperception. When she went to the prison, it was assumed that the Black prisoners would be those who were being used as guinea pigs. She said, "Quite the opposite as the case."

What happened was, when we went to prison, we found that Blacks were being excluded from the studies, many times to the advantage of the White population of prisoners. And so, you know, it's easy to make assumptions, but it's hard to find the evidence sometimes. We have to make sure we are working on the evidence.

So my closing thought on this is I think we must remember two things.

Cost was not supposed to be a barrier in the NIH Reauthorization Act. And for CMS to play a role in making it a barrier I think would be an excuse that we should really not do. We must not become part of the contributor to a barrier to providing quality access to clinical trials.

Now, I'll stop with the saying that my father who is a 95-year-old ophthalmologist (unintelligible) ophthalmologists here, taught me a long time

ago that one of the real important lessons of life is do not let what you cannot do interfere with what you can do.

Thank you for that.

Amy Abernethy: Thank you.

I would like to give some applause to all of our speakers today.

And with this, what we will do is we'll go into 20 minutes of questions and discussions followed by a very brief wrap-up and a bidding of adieu.

So, do we have any questions?

One person coming to the podium.

And if you want to get the telephone lines ready?

(Charles Carrington): Hi. My name is (Charles Carrington) of Duke University. And today I'm representing the American College of Emergency Physicians, which takes care of many underrepresented patients and clearly needs substantial evidence basis to its practice.

One issue that I haven't heard about, and I'd like just for a comment, potentially from Dr. Bressler, is the impact of trying to ascertain standard care, usual care versus experimental care and the challenge that presents to the institution, and specifically a number of trials in emergency and acute care sponsored by industry and because of this difficulty in trying to ascertain which services are paid for by third-party payers including CMS versus those covered by the study, that this is done on a manual case-by-case basis.

It's encouraged a huge cost to the institution; and frankly, some institutions like mine have now put that back on the investigators. So, you mentioned that there are a number of indirect costs, and now they've become quite real to investigation.

Operator: For questions on the phone, press star-1 please.

Neil Bressler: ...which is the same way we approach the study design. That is, we have a steering committee that we hope represent various investigators, coordinator, statisticians, et cetera, that help design the study.

That same committee then sits down with the proposed study budget and goes through line by line what are we going to consider standard care and what are

we going to consider study-related costs so that it's not decided by a study chair or the coordinating center, it's decided by a committee.

We then vet that to the entire study group that plans to participate in the protocol, and that usually takes care of about 95% of the issues. And then there's that other 5% that people recognize afterwards, and we try to address those before we actually start.

There will always be some disagreement. But we try and get (those to as smallest) possible so that there's fairly - a fairly good likelihood that we'll have consensus as to what we finally decide in that grid is going to be standard care costs and study costs. So that's an approach and it seems to work most of the time.

(Charles Carrington): A follow-up question, if I may.

However, from the institution standpoint, not only for that trial but for every other trial that's done, there has to be a system in place to assure that the study costs and the usual costs are covered. That itself becomes a burden and becomes very challenging in terms of cost structures.

And I mentioned in my first question, that's now being asked to be borne by the investigator or potentially by the investigators division or department when it comes to trials such as industry trials where an awful lot of the innovative interventions are being generated.

Neil Bressler: I agree with you and their details, I think, will be on the scope of discussing it here. But certainly, I think we should share how we're approaching this.

(Charles Carrington): One possible solution might be in the automation of some of these cost structures, particularly by agencies involved like CMS, so we can't get away from this manual, case by case basis and potentially start to look at this either at a more automated, retrospective potential and not try to do it prospectively individual by individual.

Amy Abernethy: I'd like us to move on. And in follow-up, I'd like to ask one quick question to Dr. Bressler.

A lot of this requires a lot of fiscal literacy on the point of view of the physician. And I'm wondering whether or not you've seen that fiscal literacy change and whether or not you see a differential across the community versus an academia.

Neil Bressler: So, for the first part, we are learning a lot more than we were taught in medical school, but it goes along with we're learning more about clinical trials

and what are the appropriate fiscal approaches, et cetera. So yeah, it is part of the - I believe, management have to make sure they're fiscally up to date.

I would say that we see the whole spectrum, you know, community-based and university-based where there are people in the community-based ones that are way up to date on exactly what's going on and point out things and some they don't get it. And the same is true in the university-based centers. A wide spectrum.

And the same is true when we monitor. We must monitor to be sure they're following the study-related costs versus the standard care costs. And we find some university-based centers get it, some don't and some community-based centers as well. So, we haven't found that it can split in one or the other.

Amy Abernethy: Thank you.

Yes, sir.

Bhadrasain Vikram: Yeah. Hi. Bhadrasain Vikram from the National Cancer Institute.

A number of the speakers pointed out the differences in the level of evidence required by the FDA, CMS and what NIH and CDC might regard as appropriate levels of evidence and also said, you know, these agencies of the, you know, Health and Human Services need to work together to try and resolve these discrepancies.

But the question is, how do you go about it and whether the panel feels that it should be done on a disease by disease or a specialty by specialty basis. Or is it more global approach that needs to be taken? I'd be interested to hear your comments on that.

Amy Abernethy: Dr. Bressler? And then, I'll see if anybody else has a comment.

Neil Bressler: There are different roles among the agencies even though they're all under the Department of Health and Human Services. So the FDA is, you know, making a decision of what can I do to allow an industry to market across state lines. And that requires a certain competence that might be far higher than what a physician requires to decide, that's enough evidence for me to recommend this to the next patient that came in based on the clinical trials.

Nevertheless, I agree with you that having forums like this -- and there have been several and more recently in years -- is important so that where there can be harmonious statements made across the agencies, it will make our design of the clinical trials much easier.

Amy Abernethy: Any other comments on this question? Dr. Armin Weinberg? Oh, Dr. Walter Koroshetz.

Dr. Walter Koroshetz: Just a thought perhaps.

If this is about, you know, the case of an NIH-funded research versus CMS statement for standard of care, if this is about sharing cost by two Federal agencies, the question is, can this burden be removed from the research enterprise and managed at the agency level?

In other words, can CMS reimburse the NIH for the budgeting process rather than placing the burden of having to determine study-by-study what's covered by one agency versus the other and possibly Dr. Armin Weinberg was pointing out, you know, impeding the research enterprise.

Amy Abernethy: Other questions?

Man: I'll just say that there are, you know, some - there are liaisons and regular discussions that the NIH is having with the FDA and CMS. And I think I've only been there a short time. My - what I've been told is that this is occurring on an increasingly frequent basis. So - and I think that's the way you can - a lot of these things are just common sense discussions that can help prevent problems.

In terms of the finances, I don't actually know there were clear stipulations when Congress puts money into Federal agencies. They did it for a purpose and that moving that money to another agency requires a clear legal agreement. And those are hard to come by.

Amy Abernethy: We go to a telephone call next, and then we'll go to the next question on the podium.

Are there any questions from the telephone system?

Operator: Yes, thank you.

We have (George Silverman).

Your line is open.

(George Silverman): (Hi). It's (George Silverman) of the Cancer Policy Group.

Amy Abernethy: Can you speak up please?

(George Silverman): Sure.

(George Silverman), Cancer Policy Group.

There's been an implicit and understandable kind of concern about the implications of coverage for CMS' clinical trial costs. But I don't want to, you know, have the meeting close without understanding the opportunities that exist here. Particularly in terms of these institutions have patients involved in trials that are paid for by CMS, then Medicare has the ability to compare outcomes for patients in the controlled arms of those trials with outcomes in the general population of that institution as a mechanism for possibly determining generalizability in the trial population vis a vis the general population.

(I know it's a pharmacological) point but, you know, this is an opportunity here that hasn't existed before.

Amy Abernethy: Any comments from any of our guests?

No? Okay.

Anybody else - any other questions from the telephone system?

Operator: And we're showing no questions from the phone.

Amy Abernethy: One more, sir. Yes.

Okay, we have somebody at the podium.

(John McGinnis): Yeah, just a follow-up on your presentation, Dr. Martin.

I was just curious. With respect to the issue that was identified by the General Council, can you elaborate on that a little bit as to what they were concerned with or what...

Woman: I don't know.

Dr. Dan Martin: I don't know.

Woman: Can you tell us who you are, sir?

(John McGinnis): Oh, (John McGinnis) (unintelligible) Reporter.

Dr. Dan Martin: Yeah, I don't know. I don't. I mean, that's why the closing - in my closing comment, I said there was a lack of culture of communication.

Decisions seem sometimes to be made unilaterally with no discussion. At least, the investigator group that had brought issue to the table are not allowed to participate in order to discuss with the individual, and it seems to be the decision-maker in this process completely excluded from that. And that doesn't seem to be a very constructive way to move forward.

(John McGinnis): There were several point that you had identified as that there being a precedent for. And I guess you've answered that there wasn't, you know, a particular aspect of some of those new processes that you had develop for the purpose of this trial, that they were - that they found to be, you know, inconsistent with the statutes.

Dr. Dan Martin: I'm not aware. Certainly on our view of the - what we understand about or what demonstration project was supposed to do and certainly what's written, if you review that and look at what was proposed, I don't see what the problem was. And neither does anyone else that I know, at least externally who's looked at this could see either. So, it's not clear to me why the decision was made.

(John McCann): Okay, thanks.

Amy Abernethy: Any other question? Any questions from our panel?

With this, I'd like to - do you have a question?

Man: Only for the other group.

Because the one that we didn't mention about the impact of payment policy is the management of complications from being in the trial. And I just wonder, there was a comment from the other group as to how they word the management of complications from the cost thereof. Let's say the complication had occurred because of a study procedure and the costs related to that.

Amy Abernethy: Mr. Dworkin, do you have any comments?

Lance Dworkin: Well, for us, our procedure is a covered procedure. And actually, it's usually paid for by third-party payors, either CMS or somebody else. So, just to where a - complication related to that, that presumably would be covered and handled as in clinical expense.

In our institutional consent form, we always include the statement that the institution is responsible for adverse events that are directly attributable to the experimental procedure. That's part of the study.

But I think, you know, where the rubber hits the road is when you get to what is directly attributable, which is oftentimes difficult to determine and - since most of the events that patients have that are adverse events in clinical trials are the same types of adverse events that they have outside of clinical trials. So I think that becomes a very thorny issue for institutions in determining how to assign liability in situations like that.

Man: So you may want to look into that issue to be - well, see, they're comfortable entering the trial and having all those costs covered and that's, well, been defined. But they may hesitate joining -- and, of course, it would take a very sophisticated person, but they exist as they're reading through this -- for fear that, well, maybe my complication as the result of joining will not be covered, and if I just have it outside of the trial, it may be. So it's another tiny twist on the issue, but still I think relevant.

I know in Japan, for many of their trials, if you enter a trial, the way they've covered it -- and this is the extreme -- is that they insist that the sponsor, whoever that may be, often industry, covers anything that comes out medically over the next several years while the person is on a trial. Obviously, that's an extreme approach to it, not necessarily one I'm advocating.

Amy Abernethy: Thank you.

(Tracy): I am (Tracy) with the Coalition of Cancer Cooperative Groups. I wanted to go back to the studies that were mentioned earlier and make two points.

One is for the cooperative groups between 1997 and 2003, there was a 30% increase in patient participation in clinical trials. So that data is available - excuse me.

Secondly, just saying for the record, with Dr. Unger's study, so it might be wise for the Duke team to go back and check the methodology with Dr. Unger because I think that it may have been unclear -- excuse me -- in the slides that were presented.

Thank you.

Amy Abernethy: Thank you.

Dr. Dworkin.

Lance Dworkin: I want to come back to one issue that came up earlier.

There was this notion that in situations where the benefits of the procedure or medication are unknown, that it's some - there's an ethical issue with

restricting coverage to patients that enter - and only to patients that would enter into clinical trial because it creates, I guess, the possibility that there could be some coercion that's involved.

But I have a problem with that conceptually because it seems to me that to cover something for which there is no benefit also, you know, creates the possibility, the usual or potentially even harmful procedure will propagate throughout the population. So there's risk on that side also. I'm not sure exactly how to resolve that ethically. And I don't know whether other people have thought about that.

I've always thought that it was okay to not cover things that or not to provide things for which there's no known benefit. And then, if somebody wants to possibly get that therapy in the context of the clinical trial where they sign a consent form, that clearly states that they're going to be randomized because there is an evidence that one approach is better than another, which is the basis of all randomized clinical trials. That's not really an ethical problem.

Amy Abernethy: Thank you.

Man: I'd just like to comment on that (unintelligible) and I apologize, you may have already made the comment, but there have actually been, over the last 18 months, two separate ethical publications about this very issue that talk about whether it is ethical to require clinical trial - this patient in clinical trial is a condition for coverage. And both of those particular organizations who went through this discussion, one being NIH, agreed that, you know, there was not an ethical issue with that.

Amy Abernethy: Thank you.

With that, I think that it's appropriate and a good time to conclude.

I'd first like to thank all of you here and all of the people on the telephone lines and in the public who have been willing to participate in this forum today.

I'd also want to thank Dr. Phurrough, Dr. Matchar who's the Director of the center where we work, Mr. Julian Irvine who has really helped to get all these organized and together with Michelle Atkinson here, Dr. Leslye Fitterman who's also been critical to making this project happen here at CMS. Ms. Jane Miller and Ms. Mary Havert have been our project officers on the ground making this project happen. And Dr. Patwardhan is going to close.

Patwardhan: It's time to close the forum. And once again, I thank all the speakers who for traveling and bringing up this interesting issue here in this forum.

Our audience is really important for bringing up all the questions that you raised. And we will make the part of our report.

And for the speakers, of course, we are going to be in touch with you in the coming few months. So, it's not over.

Thank you all.

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