PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

BOARD OF GOVERNORS MEETING

Monday, May 8, 2017

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Washington, DC 20005

[Transcribed from PCORI teleconference.]

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AGENDA

AGENDA [Continued]

P R O C E E D I N G S

[10:08 a.m.]

CHAIRMAN NORQUIST: Welcome to the May 8 meeting of the PCORI Board of Governors. I'm Gray Norquist, Chair of the Board. Welcome to those of you who are joining us for today's Board meeting, which is being held in Washington, D.C., and via teleconference and webinar.

Thanks to everyone who has joined us in person, online, or by phone. As a reminder, instructions for logging in or calling in are available at our Web site, PCORI.org/events.

All Board members are present with the following exceptions - Allen Douma and Christine Goertz, who are on the phone with us today.

I want to remind everyone that disclosures of conflicts of interest for members of the Board are publicly available on our Web site, and are required to be updated annually. Members of the Board are also reminded to update your conflicts of interest disclosures if the information has changed, and you can do this by contacting your staff

representative.

If the Board deliberates or takes action on a matter that presents a conflict of interest for you today, please inform me in advance or at the time so we can discuss how to address the issue.

If you have questions about conflicts of interest or disclosures or recusals relating to you or others, please contact your staff representative.

All materials presented to the Board for consideration today will be available during the webinar and then after it will be posted on our Web site at PCORI.org. The webinar is being recorded and the archive will be posted within a week or so.

We have a scheduled public comment period today from 3:00 to 3:30 p.m. Eastern Daylight Time. If you are interested in registering to provide public comment, please go to our event page for the instructions, or you can always e-mail us at info@PCORI.org, or provide input through our Web site.

A final reminder, we are live tweeting today's activities on Twitter, and you can join the

conversation with @PCORI.

The first item is the Consent Agenda. It includes the minutes of our March Board meeting and revisions to the committee and advisory panel charters.

Are there any edits or comments on the minutes or questions about the revisions to the committee and advisory panel charters?

[No response.]

CHAIRMAN NORQUIST: If not, I think we can do just a simple voice vote to approve the Consent Agenda. All those in favor?

[Chorus of ayes.]

CHAIRMAN NORQUIST: Anybody opposed?

[No response.]

CHAIRMAN NORQUIST: Anybody abstain?

[No response.]

CHAIRMAN NORQUIST: Great. I say we are going to be on time, Joe. The first session is our Joint Methodology Committee and Board Session, which is titled “PCORI’s Role in Evaluating Precision Medicine Treatments.” I’m going to turn it over now

to Joe.

DR. SELBY: I'll just make a few opening and explanatory remarks about how this came to pass, and I'll turn it over to Robin, and I believe Evelyn before Robin.

Good morning, everyone. I want to welcome the Methodology Committee here. They are here to make another presentation. You will recall the wonderful presentation we had on value that was led by the Methodology Committee last year. We said please come back, and they have come back with maybe an even more interesting topic.

You may know that in our legislation, we are told to attend to differences in treatment effectiveness by patient characteristics, including age, gender, race and ethnicity, socioeconomic status, and genetic and molecular subtypes. We were pointed to precision medicine at a time before the phrase "precision medicine" had been coined, I think.

Precision medicine is beginning to be practiced in a number of areas, nowhere more than in

oncology where tumor markers, and sometimes constitutional markers as well, but more frequently tumor markers are identified that have links to particular therapies that predict whether a person and their tumor will respond to a particular medication.

From time to time, we get applications that are in this area of precision medicine. It's obviously not a set of treatments whose efficacy has been well established. It is a set of diagnostic tests and treatments that are beginning to be practiced, and you can hear them advertised a lot.

It's complex. The readings show -- Naomi's publication that was in our background reading shows the area of precision medicine, targeted therapies with diagnostic tests is complicated, it requires a real causal model because there are multiple steps. How one envisions that and how one instructs applicants to put proposals together in this area is a subject for us this morning.

Beyond that, precision medicine means a lot more than genetics, even the precision medicine

initiative, socioeconomic, race and ethnicity, cultural, language, kinds of characteristics of patients can influence treatments.

How to get the right treatment to the right person. That's a very patient-centered approach. Precision medicine is a discipline that is being invested in mightily and beginning to show up in practice.

We're very grateful to the Methodology Committee for putting their thoughts together on this. I will turn it over to Evelyn.

CHAIRMAN NORQUIST: Just one second. They told me the microphones are not very sensitive, so you have to talk very close to the microphones.

DR. WHITLOCK: How is that? Is that close enough? No? Thank you. I just want to make a couple of comments to frame the discussion, and then we are going to hear from several of the Methodology Committee members about some of the more technical aspects and deeper considerations around precision medicine.

We wanted to start with a definition of

"precision medicine." This begins to frame the fact that this issue -- it depends on what you're talking about. NIH's definition of precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability, genes, environment, and lifestyle for each person.

It reflects what was talked about by Joe. It is something that brings genetics into a broader set of variables that try to target treatments. Others have picked up the term "precision medicine" or even altered the term to mean either the same or different things.

There was an article last week in the New England Journal of Medicine about precision directed initiatives, talking about perhaps it will take us too long to get to the genetic kind of informed things we should be doing, some other activities at the learning health system level, personalized medicine, genomic medicine, and even in the articles that were provided for you, the range of applications as shown, as people are thinking about

adding biological data into EHR data, thinking about learning health systems, and even thinking about clinical pharmacokinetics, and making sure dosages provided to patients are actually therapeutic.

What we want to do today is recognize that PCORI can make a contribution in this area. We'd like to talk about both the breadth and the depth, and get a sense through the discussion today of where the most fruitful areas are for us to focus on in the near future.

Joe alluded to some of this, the challenges we have faced thus far in comparative effectiveness research vis-à-vis precision medicine. When you think about precision medicine, particularly related to genetics and genomics, it's a relatively young field, early in its development, and there's rapidly changing knowledge in genetics, genomics, and molecular diagnostics.

When we start looking in these areas of genomics and genetics, many of the studies are primarily early phased, which can make it challenging, when we apply the usual definition we

have had for comparative effectiveness, which is that you are comparing two or more applications to widely available comparators. It also can create challenges for us when we do emerging technologies because they often don't have insurance coverage, and we rely on widely available coverage to cover the costs of the interventions we are comparing.

There is also an issue around durability and timeliness of evidence, given the rapid evolution of the field.

Nonetheless, and Naomi's paper makes a great analogy to this, to other kinds of technologies that have diffused rapidly in the past. There is a diffusion, and stakeholders are interested and concerned about whether and how these types of developments can contribute to patient-centered care.

We think there are not just challenges but opportunities for PCORI in precision medicine. Because it is inherently patient-centered and aligns with our overall goals, as Joe referred to, we would love to focus on about what we can do in the short

run and make sure we're thinking about it in the right perspective.

We already support methodologic research that has been used to enhance both understanding and appropriate use of methods for looking at variation and treatment effects, both benefits and harms.

Issues around predictive analytics and that sort of activity, getting a heterogeneity of treatment effect, are areas where with or without genetic information, we can more effectively target treatment.

We can also look at some of the important patient-centered issues that will become important as more and more targeted treatments hit the market, so how best to incorporate patients' perspectives and engage patients in decision making around genomic and non-genomic targeted treatments.

We could potentially set up surveillance and partnerships with other agencies to identify early focus topics that are ready for patient-centered CER.

Another example is we could have a way to

monitor the diffusion of these precision medicine technologies through PCORnet to see which ones are reaching the critical mass in wide enough use that are appropriate for CER. These are just a few examples, and I am hoping the discussion will lead to others.

We do believe PCORI is an important contributor in this space, and NIH and others are committing substantial resources. PCORI can invest in ways that complement and perhaps expand others' investments.

We believe that having a clearer framework for those projects and that scope of investment in our research agenda will help us more effectively identify areas and respond to investigator initiated ideas.

Given the rapid evolution of this field, we believe that whatever we discuss today will probably require revisiting in the not too distant future because this is such a rapidly changing and important area.

With that, I'm going to turn it over to

Robin, and she will introduce the Methodology Committee Panel that will be talking about this from several Methodology Committee members' perspectives.

DR. NEWHOUSE: Thank you, Evelyn. We will start with Dr. Steve Goodman, and move to Dr. Naomi Aronson, and I will close with some additional comments before we open for discussion.

Steve?

DR. GOODMAN: I'll just make a few comments. I think I'll surely make more as the conversation proceeds, and just make a few observations.

Many of the points I would have made are actually made extraordinarily eloquently in the background readings, so I'm not going to rehash a lot of that material, but hopefully the relevant stuff will surface.

I just want to say a few things. First of all, and this underscores one point that Joe said, if we're going to be thinking about this in any meaningful way, we certainly want to get off the genome mix wagon, which Evelyn also pointed out is

critical.

As soon as we identify precision medicine dominantly with genomics, in some ways we are betraying the very values of what PCORI is about, and a lot of what PCORI was built for and what we do best is a form of precision medicine, if we start defining medicine in all its broad form, which is not just efficacy, almost all the dialogue right now is about efficacy, not about tolerance, not about side effects, not about picking the medicine that best suits the lifestyle, the preferences, and the entire life experience of the person getting it.

In many ways, that's what PCORI is trying to do. That is a form of precision medicine as well. That can only be practiced at the bedside with informed practitioners with patients as partners.

Let's not lose sight of what in a sense real precision medicine is, which is matching the needs of the patient with their own preferences on how they want to go forward. That language is almost completely absent from most of the writings

on this, and again, it focuses a lot on efficacy.

Another thing I'll say, getting back to the genotyping, we have to be very careful. The reason there has been some nominal success in cancer is because the target that has the genomic lesion is the tissue itself. It is the diseased tissue. It's very, very easy to slide over, again, Joe sort of alluded to this, to the germ line genome that we all have, and that may or may not be subject to change, even if we know it leads to certain overall risks.

Trotting out cancer all the time as an example of potential for success doesn't apply to the vast majority of multifactorial diseases where we don't necessarily have a tissue or a single lesion, a tissue that has differentiated itself from the germ line. Cancer is almost unique in that sense.

I want to bring up a theme that Naomi does in her article, and hopefully this will not undermine what she is just about to say, which is the notion that many of the pressures that we feel in this area are in a sense technology driven. It's

very, very easy to come up with predictors these days, predictive analytics. Genes are part of that, but they certainly are not the only thing.

The problem is people start making money very, very quickly off these analytics, and very, very rarely -- there is no pathway for approval of the analytics that are akin to the drugs or biologics, so they are out there being used with no confirmation that their use leads to better health.

We don't have to subject them to the same levels of proof. In fact, there is quite a lot of evidence, and this was covered in the background article as well, that they can drive up costs quite a lot, particularly if the tests themselves are expensive or mistakes are very, very expensive. We have to make sure that we understand how harmful those mistakes can be, both economically and to people.

One role we can have is to put these technologies to the test, which they rarely go through, and the problem is they often get, I think, vetted in practice way before we can test them, and

certainly the gene expression tests for cancer are a very, very good example, and those have a better evidence base than about 95 percent of the other tests that are out there, and only now are the results beginning to come in.

One role that we can play is actually requiring or funding the testing of any of these predictive technologies in a way that there doesn't seem to be a market for other motivation right now.

I think that's all I'll say for now. I think there is going to be a lot of other things that come up. I think figuring out PCORI's role here is going to be very interesting and very challenging. It could be that if a lot of what we do already falls under this rubric, which I think was my first point, and if there are things that we might be doing that are not being done by other agencies and that fall within our sweet spot, I think that will be the goals of the subsequent conversation.

CHAIRMAN NORQUIST: Do you want to take questions now? How do you want to handle this? You

want to wait? Okay.

DR. GOODMAN: I think I'm passing it off to Naomi next. I hope I didn't say what you were going to say.

DR. ARONSON: No, you didn't. You anticipated it nicely, thank you. My thoughts are divided into two main things. One is some concrete examples of emerging genetic tests, one which may be very close to camera ready for us. I'll talk about some of the opportunities.

The second connects to the effectiveness, it's not just tests, it's the delivery of the tests.

My first set of examples is in what I would call emerging technologies that are about to be established based on really compelling rationale, but in the absence of empirical evidence. Actually, this is probably why comparative effectiveness exists.

We talk about a comparison to an established technology. The first technology I want to draw your attention to, and obviously my focus is influenced by what we have been doing in the

clinical effectiveness area at Blue Cross and Blue Shield Association -- the emergence of expanded carrier screening or reproductive decision making, both pregnancy planning and pregnancy.

As you are aware, the convention has been targeted carrier screening, classically, specific ethnic groups, and classically, an example would be say Tay-Sachs area screening in Ashkenazi Jews. There are only two conditions of which I'm aware for which there are universal screening, and that is cystic fibrosis and spinal muscular atrophy. As far as the rest of testing, it is done on a targeted ethnic basis.

We now have several companies that have developed a large screening. That is they could screen for all conditions. We really don't know the implications of that. Not only would they screen for all conditions, some of the things they would screen for are actually now in the area of what we would call "newborn screening." This is completely changing the framework and perspective of what is an enormously impactful public health practice.

I just wanted to speak to what I think some of the opportunities are in this area. The big opportunity would be a very large trial showing the outcomes of targeted screening, which is the convention now, versus expanded carrier testing.

That is huge. I think you would want to engage multiple companies out there. I think there are a handful. I'm aware of three. Maybe there are others. I don't think they could even do it themselves if they wanted to. They may not be motivated to.

ACOG has just come out with a statement that has moved pass neutrality in expanded carrier screening, if potential parents are interested, that explains the risks and benefits. It's very hard to explain the risks and benefits when you actually don't know the algorithms and outcomes here.

The huge opportunity would be to conduct this trial. Short of that, here are some other opportunities I see. One would be to try to model the implications of this, understanding that we are now going into various ethnic groups.

You can argue that we are in a post-ethnic society. I will think of my own family, my brother is Ashkenazi Jew, he is married to an Italy born Italian. Their sons have both married Asian women. His grandchildren are half Chinese, one quarter Italian, and one quarter Ashkenazi Jew. So, maybe all this ethnic stuff doesn't matter anymore, but I'm not so sure that's true.

In addition to not knowing the prevalence of these conditions in other ethnic groups, we don't actually know how severe they are. I think there is excitement with a certain naiveté in saying we can find out everything, because we really don't know the consequences.

Another opportunity would be to try to model this, taking into account the tests, what is known about the tests, what is known about the prevalence in other ethnic groups, what is known about the expression and severity in other groups, and try to model what the consequences would be.

At least we would be getting to some kind of informed consent here because as much as the ACOG

recommendations say counsel, I don't know that you have enough information to make informed consent or to counsel on.

I will add another dimension which I think is right up some of our classic patient-centered outcomes and concerns, and that is how were the conditions that are being tested for in these expanded panels selected.

The one I'm most familiar with basically ran a survey through a panel of 15 physicians asking them to rate the severity of certain conditions. The lack of patient-centeredness aside, it's hardly a rigorous or valid model.

Another opportunity here is to actually understand the testing, and what are the tradeoffs they are willing to make, and whether it is worth being tested or not. For some people, avoiding any risk of a congenital condition might be worth it, for others, not. At this point, there is no information.

I am particularly concerned that we see a shifting of categories from carrier screening to

incorporating newborn screening into these tests, many of which are remediable diseases if you catch them early enough. It's an entire shift in the public health focus.

Finally, there is a question again of counsel the patient, get informed consent, but is there really enough information to give it.

I've outlined a couple of sub-questions that I really think could be refined into a research agenda for us.

My next one is the so-called "personalized cancer treatment." I know I'm taking some time, so I'm not going to dwell on it. I am going to make one remark, and that is most cancer centers now are advertising the tumor profiling that Steve spoke about, which is the idea that if you have a genetic marker in your tumor and there is a corresponding targeted therapy, that you could use it off label, but frankly, its success has been limited to targeted therapies themselves.

There are probably a couple of dozen of these, maybe 30 of these, a lot of overlap. What

they target, so it is not as many diseases as the number of therapies, but the success and actually generalizing them off label has been fairly limited.

First of all, the theory that the marker would be unique to the tumor is apparently not true because now studies show you can find these markers in normal tissue. There is the whole question of if you find the marker, is it actually relevant to the tumor, much less will there be a response.

There have been some histories of failure in an attempt to expand the labeling of these targeted therapies to other cancers because really some mutations are drivers, some mutations are passengers or bystanders, and we really don't have that sorted out.

I think what is very compelling from a PCORI point of view and our commitment to open science is the fact that this has been now a feature of every cancer center. You have to say we do personalized cancer therapy. These studies are being done internally. They are not being shared.

These are all open science principles, and

as a consequence, patients are being subjected again and again, unknowingly, not deliberately, but unknowingly, and this is the open science issue to therapies that are futile. They have failed in other settings with other patients. The information is not out there.

There is actually a portfolio of trials and studies, studies in progress. Friends of Cancer Research is a major partner in one of them. On lung cancer predictors. A particularly interesting one is actually a registry type study being sponsored by ASCO. I'm normally not a big fan of registry type studies for efficacy, but what is really unique here and I think is incredibly important is the fact that they have established futility criteria.

They will quickly eliminate those targets and therapies which are shown not to work, and it really only takes a dozen or so cases to do that. Success is knowing what works or getting a signal of what works in this case, and also knowing what doesn't work, because there is huge opportunity here, for patients and for the health care system.

I won't say more about that, but I really did want to emphasize the intersection between the open science issues and this practice of taking a compelling therapy without evidence, not contributing to and perpetuating a state where we are subjecting patients to futile therapies. I suspect in some cases we are also offering successful ones, but we can't sort it out.

I want to go on now to my second set of issues. Am I way over time? I can stop any time you want.

Let me highlight three effectiveness issues that I think -- I haven't got it formulated, but I bet we could develop something. One is we know better but we all believe the test results or the results of a test are real, but there is accumulating evidence now in the area of what's called "next generation sequencing," that is the ability to do simultaneously multiple markers, that there is actually not that high agreement either in concordance of finding the variance or concordance of interpreting the variance.

Meaning the result you get and the action you take has a substantial element in it of where did you have your test and who read it, not what is the actual underlying condition.

Now, we all know tests are like that, but I think this is supposed to be precision medicine, and we are dealing with multiple variables and there is great faith being put in it, and its disseminating rapidly. I think that needs closer looking at, how do you in fact get to some consistency and concordance.

Actually, even farther down the line, which is very little paid attention to, is actually what happens to the specimen before it gets to the laboratory. Carolyn Thompson, who used to run the NCI Bio Repository Program, has done a lot of work on that.

The samples that are actually getting to the labs may have been handled in very different ways. Somebody may have taken a coffee break between the surgery and pathology. We have specialized labs, so there is a shipping quality

issue.

We actually need to understand more in how to intervene better, as to how to assure the quality of the specimens as well as the quality of the labs.

Third, there is the issue both for clinicians and for patients as to the understanding, interpretation, and application of these results. There is a huge shortage of genetic counselors. That is exacerbated by the fact that they are now being snapped up and employed by genetic testing companies, and also by utilization review companies. That's a less independent workforce.

Irrespective of that, not enough of that information going on. What are some remedies for this? There are some alternate ways for employment decisions. We need to think about this in the context of not only all the genetic tests that are out there clinically but there will be increasing direct to consumer tests.

The issue again of informed consent, what do patients actually understand. I think this is a constellation of issues that are really about

effectiveness and where we might find opportunity.

Finally, I will just mention one that is emerging in the area of genetic therapies. There are some diseases that can be eliminated by a gene transfer. There is already one approved and available in Europe and Italy for combined and immunodeficiency disorder. I think about 16 individuals have been treated, but it is curative.

One open question on these therapies is durability, are they truly cured, how long do they last. In some of these diseases, if you have four/five/six years and there is that data there, that in itself is remarkable.

Emerging on that pipeline probably next are in hemophilia. That is actually going to be quite accessible, I think, because the costs of treating hemophilia are huge. Even if you have $1 million therapy, the return on the initial investment is probably fairly rapid, so it’s a little less daunting than some of the others emerging.

I think next in line might be beta thalassemia, sickle cell disease, but there is a

huge pipeline of disorders, and they will become more common disorders, and the overall question is how do you manage the financing of a therapy where maybe the initiation is maybe $1 million, maybe only $600,000.

I know that companies are actually working hard to increase some of their efficiencies in production, but you still have a very extensive initial outlay here.

This is what we actually looked at in terms of Hepatitis C. There you are looking at a 70,000 to $100,000 therapy. Now we have multiples of that. The question will be how will the financing be managed. It's not something that I think payers have really actuarially incorporated. I think it's going to be very, very challenging.

There are notions out there. There are a group of economists at MIT who are using a financing scheme where you can actually put your baby's gene transfer on your credit card, just like you did your mortgage, your car, or interest loan, and pay it off over a lifetime, so that parents will have the

choice to do this for their children. We also know where the mortgage crisis had gotten us and the college loan crisis, and I myself would question some of the feasibility and social impact of that with respect to disparities and so on.

I think this is not so much a question of value or efficacy, but actually a question of health care system and disparity as to how these will be managed.

Those are my thoughts.

CHAIRMAN NORQUIST: Robin, I'll let you run the session. It's up to you how you want to do it.

DR. NEWHOUSE: I'm just going to make a couple of comments just about the role of the health system because I think that is one of the things we haven't addressed at this point, just a couple brief things.

First of all, health systems are already imagining a day where precision medicine is considered part of routine care. For example, when patients are admitted within the health system, medications and dosing and treatment decisions would

be made on their personal characteristics or phenotype.

Building the health care infrastructure for precision medicine will require a number of innovations and transformations in informatics technology to enhance communication across setting, building teams of clinicians and support for patient care, creating decision support tools to inform clinical and patient decision making, and also developing a health care workforce that Naomi mentioned across disciplines.

Precision medicine needs to be available across the continuum of care. Right now, the expertise is really in academic health centers. Across the continuum, which includes primary care, community health, and acute care and other places.

When we think about precision medicine, we also have to think about the opportunities and support needed in health systems as well. Some of the questions related to the development of health systems, for example, would be how will sensors, self-monitoring devices, and other sources of

personal data be incorporated into precision medicine.

How will electronic medical records and predictive analytics enhance identification of people that can benefit from precision medicine, and how will we engage patients in designing these health systems of care to deliver precision medicine.

Some questions related to the provision of care may include what are the benefits and risks associated with precision medicine for individual patients. What are the characteristics of teams and workforce needed to deliver precision medicine, and what designs, methods, and analytic approaches are needed to advance precision medicine.

When we think of health systems, I think the broad spectrum ranges from the individual genotype and a person to some broader philosophical and scientific questions, but also bigger. In order to sustain and enable and really be able to scale up precision medicine, we're going to have to partner with health systems and make sure we build

infrastructure, and think about the approaches to individuals and populations as well.

I'll close with that comment. I know we have a number of tent cards up. Ellen, you had your tent card up. Bob. Ellen, Bob, and then Barbara.

DR. SIGAL: Thank you for the presentation. I don't think I've ever been so violently in agreement with PCORI as this opportunity. I think this is incredible. It's an area that we work in and have a very, very high level of frustration because we published something recently, a survey that we did with treating physicians and hospitals, where there were two FDA approved tests in lung cancer, EGFK and ALK. We were shocked by the survey results because I think in one case 70 percent and in another case 60 -- I don't remember the data -- did not use the FDA approved test.

Does it mean that the other tests in the community setting are not right? We don't know, but the point is we were shocked that there was an FDA approved test. When you go now to where we are going with NextGen and these tests, every single

sector has their own tests. You go to Memorial Sloan Kettering, you go to MD Anderson, Dana-Farber, Mass General, and they are all different. Do they work? Maybe? There are standards, CLIA or CAP. It's a manufacturing standard, but not necessarily for efficacy.

We have been working very closely with the FDA on trying to get some ability to have some standards, some concordance or some accelerated pathway to see if in fact these tests really work as they should, because you are making treatment decisions on them.

It's been an area of enormous frustration. I do know with MATCH, they did concordance testing. They spent a lot of time on it. I think initially it was close to 90 percent, it wasn't 100 percent. However, other surveys or other tests that I've seen show lower, like 70 percent, 60 percent. So, there is a huge gap.

Having said that, if you're going to really use these tests, as we all believe these treatments are in fact going to be really important for

patients, and it certainly takes away a certain population that are likely not to respond, the tests need to be accurate.

I think there is a lot we can do to at least see if there is some concordance or some standards or some ability to really inform people in the community that these tests may not be accurate. Again, another factor that we have seen which was very troubling initially, and I know from our own experiences, when we initially were doing the tests, and we do have a test that now is going to FDA approval, a lot of the investigators did not want to give the results to the patients.

We were shocked, very upset about it, however, when we went through the IRB, the IRB basically said this is coercion, and in fact, the patients need to know, which I think is really very important.

Having said all of this, I think there are huge opportunities for PCORI to really come in here, see what's working, what isn't working, to look at this. Also, I think that maybe some PCORnet and

maybe there is data now because we do have enough data from a lot of these tests, a lot of these trials, where one may be able to look at some economic data, but I think it's the future.

I think if this is true comparative effectiveness, if you are going to be using tests to determine your treatment, those tests need to be accurate, and figuring out a way forward that isn't too burdensome for the academics or others, but to see if these work, to do some education, is incredible.

We were so shocked at our results when we did our survey, and we did publish the sample size. Again, what we could not determine was whether in fact these other tests that were not FDA approved were accurate or not, and we don't know.

Patients have no idea. When they are given a test and they go to an institution, they have no idea of what questions to ask.

The other issue is that many of these academic institutions are using these tests, and they will do a panel, research panel on patients,

and they'll start treatment. In one case, somebody called me on it. I said did you ask them why they started treatment, because it could take a month to get these results, and patients often will be starting treatment. They said, well, it's only research purposes, it doesn't matter.

Well, it really does matter. It's a big deal, and I hope we can figure out a way to do something on it.

[Audio malfunction.]

CHAIRMAN NORQUIST: I think we're back on, Bob. When you pull your microphone toward you, watch and make sure you don't unplug the back of it.

UNIDENTIFIED SPEAKER: Looking at those through EDIC glasses, maybe the best way to inform is through health policy. As a lot of the bio comments have been made, some of the comparative effectiveness issues will actually inform health policy in the future, and especially in the current climate of is health care going to look like.

I guess I'll throw out the question, this is not an original thought, somebody said it, but it

was a publicly uttered comment which means to me it is now open source, but are your genes a preexisting condition. Is your zip code a preexisting condition. These, I think, are some of the things that health policy is going to need to be looking at.

Particularly when we start talking about who is going to pay for it, and I will tell you this, Federal Blue Cross/Blue Shield does not cover the cost of sequencing, either tumor or host. They will cover the cost of looking at specific markers, approved markers, I guess, but not for sequencing.

I think there are two lessons out of that. One is if we are going to build an informational base that actually will allow our big data resources to harvest information, then the ability to pay for this really becomes a public policy issue, but if it doesn't, then we will then have an inherent inequity in health care delivery that only those who can afford to pay for that sequencing can get the targeted precision therapies. I think that is a real important policy issue, right, both from the

broader big data perspective but also specifically for the very real patient perspective.

The other piece, and I will end with this, is that it is very easy -- my research career has been in cardiac biomarkers. Every talk I ever gave on the subject always ended with the same slide. It's very easy to show a prediction, it's very hard to show predictive value.

That's crucial because every piece of information can inform but does it change the pathway, does it change how we are going to treat patients. We really need to be looking at predictive value in everything that we do.

Just to wrap it up, I think the work that we can specifically design and support through PCORI can inform health policy, might scare some people in the discussion we have about reauthorization, unlike in Europe where they talk about comparative effectiveness also including costs, which some people equate with value, I don't, a very different thing.

Let's look at where the gaps in evidence

are, where crucial health policy decisions will be being made, and really think about how our funding and research capabilities might inform that. That makes the EDIC's job a whole lot easier. Thanks.

DR. NEWHOUSE: Barbara?

DR. McNEIL: I enjoyed these comments. I have really only two. The first is that I think that when we are talking about precision medicine, all the principles we have for comparative effectiveness research apply. So, there should be nothing really new. I think this is basically what Steve was saying. We shouldn't be reinventing the wheel for work we do in the field.

I'm not sure if I disagree with Ellen or not, but I don't think it's our job to look at the correlation between home brew tests and FDA tests. I think that is the purview of either the home brew makers or the FDA makers or somebody else. I'm not sure that's a comparative effectiveness mandate.

Basically, I think we are talking about doing what we have always done with a very specific emphasis, whatever the definition of "precision

medicine" is. Steve was making it very broad. Naomi was talking about some very specific examples.

I was trying to find a slide which I can't seem to find now in looking through the documents. It worried me a little bit. Maybe, Steve, you could comment on it. I thought it said, but I could be imagining this, that we would look at PCORnet to see the fusion of precision medicine, and I thought it was largely talking about genomic, but it could have been broader than that, techniques -- oh, it's your slide. There it is. No wonder I didn't see it.

There it is, number four. To try to relate that sort of ad hoc utilization with outcome. I wanted to ask Steve whether he thought there was any way on earth that you could risk a guess with patients who got those tests with those who didn't.

DR. WHITLOCK: Can I just clarify that what that meant to say was when you have a lot of different tests and a lot of different treatments, if you're asked a question do you get better outcomes with genomically targeted treatments in cancer or not, it's a hard question to focus, so

this was really about are there opportunities for us to figure out which precision medicine technologies, which tests, are sort of out there and in common enough use that there were searchable targets.

This is not about using PCORnet to determine whether or not the treatments are effective. It's really just about identifying targets.

DR. McNEIL: I misunderstood, sorry. That's fine.

DR. GOODMAN: Thank you for not having to answer that question.

DR. McNEIL: You couldn't have answered it, right?

DR. NEWHOUSE: Russell, Sharon, and Joe.

DR. HOWERTON: As a representative from a health system, I would emphasize that the implications of precision medicine occupy a great deal of thinking and support the importance of this question that everyone is highlighting here, simply archiving the information that comes from this in our data warehouses alone is a challenge.

I do have a concern from a PCORI point of view, and if I'm not mistaken, we don't fund actual care, so in an environment where the testing and the treatments are expensive, and the interactions between payers and these things are complex today, I have a concern that aggregate use of PCORI resources in the time horizon that we have known to us, that we will be greatly challenged to make an investment of the magnitude to bring knowledge to this complex field.

If we somehow transposed ourselves in time and moved our authorizing legislation to today and had a 10-year window, or this problem were in 2009/2010, it would appear to me to be a perfect place for us to work with the investments of the magnitudes needed to answer the profound questions that are going to arise here.

I wonder if there will be investments of the volume we can commit to now that will be material in this field during our time of ensuring that we are demonstrating maximum outcome for our investments.

Not to diminish any of this, I agree with almost every sentiment expressed here, but it is a big elephant to chew.

DR. NEWHOUSE: Thank you, Russell. Sharon?

UNIDENTIFIED SPEAKER: I agree with what Russell just said with the exception of listening to what Naomi was describing, if you think of precision medicine much more broadly than genomics, there is opportunity within a broader definition of "precision medicine," just another way of talking about patient-centered, patient-targeted, think about a contribution we can make in the time we have left.

The other comment is to continue the thought that I think we are going to see a collision of public policy around the affordability of health care with the avid enthusiasm for things like 21st century cures and genomics. There is the will and the interest in funding the shiny new things, and at the same time a growing resistance to paying for the costs of that research.

I think we see this blast of money for NIH

finally, enhanced funding for NIH, as enthusiasm for 21st century cures and what we are seeing play out now with anywhere between 600 and $800 billion targeted out of the total expenditure in health care through at least the House version of the AHCA.

These are both legitimate concerns. This isn't about putting PCORI in a position of taking a policy position between these two things but just saying as a country, we are of two minds. I think Bob's point is really on target, that we are potentially going to exacerbate the gap between what we can do and what we can afford to do.

DR. NEWHOUSE: Thank you, Sharon. We have Joe, Mark, Steve, and Leah.

DR. SELBY: Thank you, Robin, and thanks to everybody for this presentation. I wanted to respond to Russ and Sharon a bit, and then ask Steve a question.

Russ, Evelyn had put in one of her slides this challenge, which is to fund studies in this area, we have always had it as a requirement that the applicants describe to us where and how the

treatments are going to be funded because PCORI has never funded new costly treatments, particularly treatments that weren't -- we don't fund treatments period, but certainly we don't fund treatments in situations where plans are not covering them yet.

It's a real dilemma for what Sharon is talking about, which is the overall question -- certainly when PCORI was being planned, when CER was being first sort of examined and looked at, some people thought that CER was going to be a way to kind of in a relatively rapid fashion assign these new therapies to the people who could benefit and pretty much establish that there is large fractions for whom some of these new therapies won't be of benefit, so getting the right therapies to the right people would be a way of managing the costs even while you were rapidly improving the outcomes for people.

In practice, how as a funder of CER you look for or shape the kind of CER studies that can help is part of the dilemma that we face every day and part of the discussion we are bringing to you.

Steve, you mentioned a couple of times that many of these are still efficacy testing, I just wanted to see if I could push you to elaborate a bit.

It has seemed to us that one of the challenges here is that these are multi-step processes. There is a step of testing, and then there is the step of making decisions about treatments on the basis of the tests.

You have some uncertainty about the validity of the tests, particularly as Ellen points out, when the tests are provided by multiple, and then you have some uncertainty remaining about in general populations, does applying these tests to the allocation of therapies really improve outcome, so the effectiveness of that, maybe even the efficacy of that is still unknown.

I wondered what exactly you were implying when you said these are still efficacy tests and whether that gives you pause about creating a CER study where you say tests as to therapy versus traditional approach to therapy with clinical

outcomes as the outcomes, and whether you are saying it is too early to do that or whether you're implying that the uncertainty about the underlying efficacy of these two steps means it's too early to do a CER study.

DR. GOODMAN: I'll offer a very brief answer. I never think that it's inappropriate to do a formal study that looks at patient outcomes, just define them broadly.

What I was focusing on was that most of the rhetoric and most of the methods are all about ascertaining differential efficacy, not looking for the most part, certainly in the same study, differential adverse effects for tolerability or all those things.

A lot of it is finding the drug that works the best in given populations. That efficacy may correlate with, for example, if it correlates with dose or increased susceptibility to adverse effects, or it may be in people who may for some reason or another not tolerate those adverse effects well.

If you're looking at broadly defined

patient outcomes, which includes adverse effects and function and those things, absolutely. In fact, that is what I think is one of the problems, we're not doing that enough. We are just looking at the efficacy equation, often through modeling.

MS. WHITLOCK: Can I maybe add in? I know I'm jumping the cue. I think the issue that Joe was trying to express, I would express maybe a little differently going back to the analytic validity, clinical validity, clinical utility kind of situation.

If someone asks a question that appears to focus on clinical utility but we haven't really established analytic validity and clinical validity, that's where we are running into trouble, I think. It goes back to what Ellen was talking about.

I think in some ways as we are talking about these things, just talking about efficacy versus not doesn't appear to really get at it because we have these issues of analytic validity, variation in the marketplace that is not covered by any regulatory purpose, not necessarily knowing

clinical validity.

Sometimes people are talking about multiple targets matched up to multiple treatments that may or may not have been shown to be efficacious. It's hard to think through in a way to make sure you can mount a valid study that also gets you to health outcomes.

I think maybe that helps the discussion a little bit, to think about it in those tiers.

DR. NEWHOUSE: Mark?

DR. HELFAND: I was going to begin by saying what Evelyn just said in a different way. When Barb or others say not much has changed, I think another way to say that is a lot of what we think of now as the framework for evaluating diagnostic tests was developed in the 1970s and 1980s, what I studied when I was a Fellow.

These terms, I'm not sure everybody knows what they mean, "analytic validity" and so on. Maybe it's worth stopping for a second. Analytic validity, another way to say that is just you do the test and it measures what it is supposed to measure.

As Naomi mentioned, it's not as valid if you are a minute late getting it to the lab and it doesn't measure that any more and it's not as valid if you measure it twice and get very different results, and if it doesn't have that, why go on.

That first tier is there may be 50 of these on the market for a particular application and only four or five of them have demonstrated if you think PCORI would work with those.

The clinical validity, other people have said it here in a different way, does it have an impact on diagnosis or impact on treatment. The clinical utility is whether it has an impact on outcomes and on society, whether it has societal impacts.

With that in mind, I wanted to say a positive story about the VA study, which is just being started on pharmacogenomic testing for depression, initial depression.

I think it is a short but good story. In 2014, there were press releases saying that the VA had approved for use -- I don't know how widespread

-- one of the pharmacogenomic tests to guide initial therapy in depression.

A couple years later, 2016, they asked us to do a systematic review. As people have pointed out, there's probably a ton of them out there. There were only three that had any real evidence. One of them was the one the VA had approved, but of the three, that's the one that had shown it failed to demonstrate any efficacy. The other two -- by "efficacy" here, what we mean is there was an effect on remission rates within the study period. If it was a 12-week study, there was one more remission for every 10 people compared with the usual care.

The usual care aspect of this particular story is very relevant to PCORI. I'll say why in a minute. Essentially, Steve is right. They focused on some form of that efficacy for remission rate.

If you ask people why should you use these tests? They are thinking about it. People will try three or four antidepressants before they find one that actually is tolerable or they take long enough to have a therapeutic effect. The studies didn't

really look at that, the few studies that were out there.

The information gaps that the systematic review pointed out were along those lines that said none of the studies looked at the number of failed attempts to treatment, the therapeutic impact. Whether that was reduced compared to not using these tests. None of them looked at whether changes in medication were actually implemented based on the results, versus usual care, and here's what happens.

All these things were not studied, and then nobody really looked at time to remission, just at the remission rates, and the most ironic aspect, I think, of these studies is while focusing on something precise, these genetic tests, which are supposed to differentiate people, none of them had looked at demographics, psychiatric or medical comorbidities, symptomatology, anything else that might have helped you figure out which treatment.

Even in an usual care study if properly designed, you can measure those things. If you're not looking at the test in isolation but along with

other things that might help you choose treatment.

The nice thing about this story is the prime study is 20 sites, focuses on the information gaps identified in that systemic review that we did. It's one of those studies where you get the results of the test immediately. Looking at these intermediate things that you mentioned, diagnostic impacts, therapeutic impacts, and the ones I mentioned.

I think it's a good case study. I would just say one more thing about these frameworks. Most of this stuff about the framework, the analytic validity, clinical, was worked out in the 1980s. I think the biggest contribution in the last 10 years is heading to those and when you need a randomized trial. That is the body of work that is something to consider.

DR. NEWHOUSE: Thank you, Mark. Steve, Leah.

DR. GOODMAN: I would say first of all right off the bat about 95 percent of these tests fail. When you partition out where and why they

fail, even if they can get through the first several levels of analytic validity and all these things, performance, in the most extreme cases, versus normal, almost all the rest are cleared out when you say how does this add to what you could learn from just a few questions.

Usually, the amount of information that even the most sophisticated tests adds is almost zero.

CHAIRMAN NORQUIST: Are you the one that's scaring off all the investment bankers?

DR. GOODMAN: I try to when they ask. They can look halfway okay, but they no longer look halfway okay when you consider everything else. That wasn't a comment I planned to make but Mark made it irresistible.

The other thing I just want to point out -- and I read the New England Journal piece while we were talking, thank you for pointing that out, I hadn't seen it. Is this the one where they were proposing the precision delivery initiative? Yes. They made this point pretty clearly, which is that

we don't have an infrastructure, and I think it was mentioned here, to deliver the information at the time it's needed at the point of care.

We know that already just from evidence-based medicine. We know that a huge number of people are not -- as much as we derive the over generalizability of clinical trials, maybe not over generalizability but they don't differentiate between heterogeneity, the fact is we do better if we treat according to the results of clinical trials over not, and we don't do that very well right now at all. That is really simple information, pretty simple information.

We are now talking about highly, much more textured, much more granular information of uncertain reliability, and we have already demonstrated that the system is not set up at multiple levels to ensure the best evidence-based treatment defined in the crudest terms.

We need to pay very serious attention whether that same system can deliver on the promise of something that requires a far more complex

infrastructure to deliver the information no less to act on it. I think that is no minor thing. We should look at our history of being able to act on the information that we have when it's delivered in a very simple way, and that question is a question not just of therapies and evidence but of an entire system that is configured to handle that evidence.

I think that is a huge challenge for us.

DR. NEWHOUSE: Thank you, Steve. Leah?

MS. HOLE-MARSHALL: I think most of the points I was going to make are already made, so I will keep it brief. I do agree that focus on the adding value, we already have a lot of determinants of health, and I don't think we're being precise in precision medicine, what we mean by that here, so I think one of the things PCORI could do is help define at least what we mean by that, so a lot of the comments around determinants as well as in the context of what is the genetic test adding, which is the primary way that word gets used, that it would be really helpful in framing any questions or research we do.

I like Mark's suggestion about finding a case study, whether it is the VA one or another, that we could use as a framework. I was wondering what our question is related to this. I find it a really fascinating topic.

Is it that we are wanting to remove some of the current PCORI criteria that are making some of these proposed studies not get funded. I think I heard that as a comment, well, they are so new they are not paid for, and therefore, we can't study them because they're not paid for. Maybe we should consider funding them, which gives me a lot of heartburn, to be honest, but maybe if it's done in the right framework.

I'm not sure what the question is for PCORI as a funder. Are we saying there are certain criteria we have in place that are not allowing us to study this generic term, and therefore, we need to waive some of those criteria. At least for me, that would be a good next step out of this conversation, to understand that.

Just to put a from the ground viewpoint on

it, we recently changed some of our payment policies after discovering we had been billed between 2 and $10,000 for patients for genetic testing related to opioid or their potential for opioid addiction, because they do multiple panels of a multiple base, so it's not just the single test is $800, it is often multiple panels over multiple times, with pretty much no evidence that it actually adds anything in the current system.

To the earlier point about what we could learn, what we know of those predictors for addiction as well as what we know about whether that is the appropriate treatment at all for that patient.

Really, the questions in that area were completely off base. I would encourage us maybe along the lines of Naomi, there are areas because it's such a huge proliferation, where there seems to be promise over other areas, maybe it is appropriate for us to take a few of those and then use a case study about here's some frameworks, kind of use that for research in areas we think there might be the

promise of actual information.

UNIDENTIFIED SPEAKER: If I could just respond, I don't think we are looking for any change in criteria, absolutely not looking for sort of permission to cover the cost of a therapy, definitely not.

If anything, there may be a little curiosity about the criteria that is sometimes used in merit review panels and afterwards that we either fund treatments that are already shown to be effective and then we compare them to each other, or we fund treatments that are already in kind of expanding use, despite evidence of effectiveness.

Those are kind of the two things. There is variation out there in the community, something has taken hold without good evidence of effectiveness, so we have seen ourselves as appropriately funding those kinds of studies, but never paying the cost of it.

This kind of linking of a test with a new treatment, with the choice of treatment, is one where certainly the effectiveness of that hasn't

been shown in broad populations yet. It does seem to be taking hold in some places, and that was the question.

UNIDENTIFIED SPEAKER: The other point is making sure that we get as you were saying kind of the appropriate definition for the kind of work that PCORI will do, and similarly, some of the frame working we were talking about, making sure if we are doing some of these studies, the things that are rapidly diffusing, do we have a stable enough situation in terms of analytic validity and clinical validity in order to actually do the outcome studies.

It's all of that. Just getting all of people's perspectives and thinking so we take the opportunity, as Russ said. We don't pretend that we know what we are going to do beyond 2019. We have lots we would like to do, but we take the opportunity we have now and try to make a contribution in this area.

DR. NEWHOUSE: Thank you. We have about 14 more minutes. We will spend about two minutes on

each question or comment.

CHAIRMAN NORQUIST: We should allow Allen and Christine on the phone, just double check with them see if they have anything.

DR. NEWHOUSE: Allen and Christine, we will ask if you have any questions right after Freda. We have Bob Jesse, Bob Zwolak, Ellen, and Freda.

DR. JESSE: I'll try to be quick. I know that's hard sometimes. I just want to remind everybody that every piece of information has a fourth dimension that we rarely talk about, which is time. Information decays over time. DYNO (phonetic) has tried to build a business model by closing the gap between wanting to know and knowing, and they just forgot one of the other key pieces about accuracy and reproducibility, some of those other things that are important that we kind of kick back and forth on both sides of the table here.

Another thing, which I'm not saying to brag, but I was just given this award from the Biomarkers Society, a Lifetime Achievement Award, they called it. What is remarkable is neither the

Society nor the award actually exists. It was a recitation of 25 years of what they called "Bobisms." You heard one of them today, which was the whole idea of the difference between showing a prediction and predictive value.

The other one that made the top 10 list, I've continuously said there is no such thing as standard care, it's a euphemism for random care.

So, comparing anything to standard care in my mind is relatively useless, if you can't codify what that actually means, and from a methodology perspective. I think it is something important we pay attention to.

DR. NEWHOUSE: Thank you, Bob. Bob Zwolak.

DR. ZWOLAK: This has been a great discussion. When I think about this over the last couple of years, I really think PCORI has found its sweet spot in terms of our studies by thinking of issues with the greatest public health benefit impact, things like pain, fatigue, depression, insomnia, opioid abuse, which you will see this afternoon when we introduce the two targeted PFAs of

opioid abuse in pregnant women and symptom management in people with really advanced illnesses. Both have enormous public health implications.

I think the feeling is pretty good about funding those. When we talk about precision medicine, it seems to me the way we look at this should be through the PCORI lens, how do we look for the greatest public health benefit.

A lot of the comments around the table, this is so individualized, it will be a little bit challenging to actually accomplish that.

DR. NEWHOUSE: Thank you, Bob. Ellen?

DR. SIGAL: First of all, I agree with almost all of what has been said. I want to say a few things. The train has already left the station on this. This is happening, in fact, today. I think there is a huge role for PCORI. I agree with Bob, we don't necessarily have to say this is our gold standard, but I think our mission is comparative effectiveness, but to see if certain tests work is well within our mission, and to look at these standards that are really important.

I would say also recently there is a lot of published work on CDL1 assays, using it without a lot of discretion. We know for 80 percent of patients, it does not work. However, the assay doesn't work. There is a huge amount of lack of concordance among basic assays for whether it works or not.

I think we have a big contribution, but I do also want to go to what Leah said. I think we have to find exactly what it is we are talking about, what specifically should we be doing in this space that would add value. I don't think we can determine that today in this room. To suggest that we can't add some coherence to a very interesting and somewhat Wild West environment out there would be wrong, and I think even from some of the stuff we have in PCORnet, retrospective data, we may be able to see some interesting patterns develop.

I hope we can figure out what we should be doing. I don't think it's too late, and I don't think it's too early. I think there are some low hanging opportunities right now for us to do

something that would add really to the field.

DR. NEWHOUSE: Thank you, Ellen. Freda?

DR. LEWIS-HALL: Actually, Ellen just touched on one of the points I wanted to make. I had three. First of all, I think there is a clear opportunity for us to do something meaningful. I'll come back to Mark and Naomi's examples, that we don't have to go in all the places, it's unclear and we're not sure. There are a few places where we have greater kind of focus, more science to support the work, and we may be able to get some early clarity around a couple of key health issues, to Bob's point, if we start now and start there.

I think that would be important and that would also meet kind of Leah's question about what is precision really.

The second is around timing. This is not new. If you think about our rotational time, by the time we actually began to do work in this space, we will be a little bit behind the curve, frankly, for some of the work that's necessary. I would encourage us to seek out ways to move quickly.

The third is actually Steve was compelled to say something to Mark's comment, and I'm compelled to say something to his, which is yes, it is complex, and this is an added level of complexity. Many of you have heard me say we are delivering Star Wars intervention in medicine into the Flintstones' health care system. The question is whether or not we want to be kind of satisfied and dumb down the therapies that we are putting into this environment, just because the system can't handle it, or whether or not we have an opportunity to maybe refine some of the things the system is capable of, that they can accept these in a better way, because they are missed opportunities to get the right people, the right treatments, at the right time, integrating all of the information that we have available to us, new and old.

DR. NEWHOUSE: Thank you, Freda. Allen and Christine, I promised to take a pause and see if you have a question or comment.

DR. GOERTZ: The advantage to being on the phone is you get to listen to everyone else ask your

questions, so I don't have anything to add.

DR. NEWHOUSE: Thank you, Christine.

DR. DOUMA: I'm in concordance with that.

DR. NEWHOUSE: Thank you. Naomi, last comment, and we will just have some concluding thoughts.

DR. ARONSON: I just wanted to make some assumptions about analytic validity because we don't have concordance among the labs, so we are learning new tests. I don't want to come to the premise that it lacks validity and we can't get started.

DR. NEWHOUSE: Thank you, Naomi. Gray, concluding thoughts?

CHAIRMAN NORQUIST: Thank you, Robin, Steve, and the Methodology Committee. I know a number of the members are here as well, and Naomi. I think the key thing is we go back to what Leah, Ellen, and others have said, where do we go with this. It's been a great discussion. Where do we go at this point, what is the process now.

We have agreed that we will have discussions, but we need something concrete out of

what we are going to do. I think it is a very important topic, an area we need to be in.

Joe, I'm going to put it on you and Evelyn now at this point, what do you hear from this and where do you think you want to go with this and what is the next stage in the process? We don't want to have a discussion and then it just drops and we don't do anything.

DR. WHITLOCK: Well, it seems to me that we have opportunities. There are some case studies we can look at. There are some examples that people have brought to the table here. I think we need a clear set of definitions and some sense of a minimal framework around which we can look at these studies, if they are investigator initiated, or select targets for us to put out more focused funding.

I suspect we would be most effective in this if we put together a small working group from the Methodology Committee, even if there are some Board members that would like to join, and have us work forward on this in a pretty focused manner. I think that would get us there more quickly than a

lot of going off and coming back and going off and coming back. That would be my suggestion, and we bring back the results of that process if people are willing, to a future Board meeting.

CHAIRMAN NORQUIST: I would suggest that you do that, and do it in conjunction with the SOC, right, Bob? Maybe to some degree, the RTC. If you do that in conjunction with them and come back with some kind of more concrete kind of proposal about what you would like us as a Board in general to decide.

UNIDENTIFIED SPEAKER: I agree, I think that is an excellent suggestion. I also think it would be great to invite Board members who wish to join, because there is expertise around the table, encourage them to join this working ad hoc group.

Ellen, if you don't want to volunteer to join, I suggest we draft you, because I think it is really important to be able to look at this from the point of view of acute urgent disease as well as from the point of view that perhaps I, Bob, and others are more familiar with in terms of chronic

disease.

DR. WHITLOCK: I'm recruited.

CHAIRMAN NORQUIST: Always. I just want to remind people that whenever we pick a topic, that doesn't exclude anybody from the Board who wants to participate on something. Always, anyone is welcome, those of you on the phone, too. We never want to forget that.

DR. NEWHOUSE: I just want to make sure that we don't leave out the Methodology Committee because they have made a huge contribution here and there may be individuals who want to join. I think the correction you made, too, Gray, the SOC will be kind of overseeing this. Is that correct?

DR. SELBY: This is the second year in a row where you have really brought us topics that were causing us quite a bit of discussion inside PCORI, and that I as the Executive Director was running into everywhere I go, you brought it to the entire Board.

I am constantly invited to talk on precision medicine. I actually say I think

comparative effectiveness research and precision medicine are extremely complimentary disciplines in many ways. We look for treatment heterogeneity. Precision medicine comes along, and its effectiveness has to be evaluated. I think Evelyn's suggestion of an ongoing work group really fits with both the mood of the Board and the Methodology Committee here and with our needs.

CHAIRMAN NORQUIST: Okay. The next part, Robin, I think you and David are going to bring up some revised standards for the Methodology Committee report.

DR. NEWHOUSE: Come on up, David. Emily Evans is back there, too, who has been just incredible support for the Methodology Committee, our partners, and PCORI staff. We are very thankful for them.

I think what we will need is the slides up for the Methodology Committee presentation and report.

What we will be reviewing and asking for at this point, we have a set of approved standards by

the Methodology Committee, and what we are coming to you to ask you is to adopt those new standards so they can be posted. I'm just going to keep on talking. Again, these are a list of our Methodology Committee members, many of which of us are here to join in the presentation of the Methodology Report, and the new methodology standards.

Just as a brief review, the methodology standards were part of the authorizing legislation for PCORI. They were required for the Methodology Committee. That was our main job, to develop minimal standards for the design, conduct, and reporting of comparative effectiveness in patient-centered outcomes research.

These standards provide guidance for researchers and those who intend to use the research results. They reflect best practices, so minimal standards. They are used within PCORI to assess the scientific rigor of funding applications and to monitor the conduct of research awards.

Our first job was in May 2012 to deliver the first set of methodology standards, which began

in 2013 by people who submitted proposals to PCORI. Now we are coming to you with a revised set of standards and one new set of standards for your adoption.

Since 2012, a lot has changed. We certainly have learned a lot about PCOR and comparative effectiveness and how standards can be used. We used a very systematic process to review, revise, and update the original 47 methodology standards that were used -- that were presented in 2012 and adopted in 2013. We created one new category of standards which were research design using clusters, very relevant for the kinds of proposals that PCORI is funding.

We posted the methodology standards that were revised for public comment between February and April. We received public comments. We incorporated those public comments back into the methodology standards, and we as the Methodology Committee approved these new standards on March 20 of this year, 2017.

In terms of the summary of the changes, we

have now 48 standards and 12 categories, one new cross-cutting standard, and that is a standard for causal inference methods, and five new standards for research design using clusters.

The general rationale for these changes were we streamline and clarify the language, we ensured alignment of the standards among all standards, and then reflected on the advances that we have used in methods for patient-centered outcomes research and comparative effectiveness as well.

Just in terms of high level changes, these are just a couple of the changes. Research question, developing a formal study protocol. You will see in the new revised standards the required elements of the protocol and there is also documentation of amendments.

In terms of patient-centeredness standard 4, the standard supports dissemination and implementation of a study. You will see the standard now includes the study results need to be made publicly available and presented with lay

language summaries.

In the data network standard 1, the requirements for design and features of data networks, there is additional expectations for privacy protections. Data networks 2, selection and use of data networks. We added ensuring appropriateness of the data network for the specific research question that is being asked.

Standards for studies of medical tests, you will see it was previously called standards for study of diagnostic tests, but really these standards apply to studies of any test used to inform medical decision making. This will give you some idea of what those changes were in the standards that you received.

In addition to updating the methodology standards and creating new methodology standards, the Methodology Report was also revised. There are a number of changes. We also used a systematic process, and once again appreciate Emily and David's leadership in helping us with these revisions.

The purpose was to reflect advances in the

methods that we have learned since it was published in 2013, the references of the scientific literature, and to incorporate additional public comments that we have received, as well as improve security in the general guidance and discussion section.

In terms of summary of the changes, Section 1 through 4 were updated and streamlined, and background rationale section, Section 3, were updated to reflect current standards.

In terms of our next step, we are recommending adoption of the updated methodology standards today for use, recommend implementation of the updated methodology standards in Cycle 2 2017 funding cycle, and that is the applications that would be due October 25, 2017. We will also need to update our training material and resources for use of the methodology standards that are available.

In terms of our next step, yesterday we spent most of our time talking about the development of new standards in a number of areas, and those are standards on complex interventions, data management,

data quality, individual participant data and network meta-analysis, and qualitative methods.

With that, I will close the report of the Methodology Committee and give a great thanks to the Methodology Committee for all of their work and also David and Emily for all their help and support. Without them, we couldn't get this work done.

We would refer to Gray for a motion.

CHAIRMAN NORQUIST: Thanks, Robin, and thanks to your committee. We need to first have a discussion and then we will do the motion. Gail?

MS. HUNT: Could you summarize a little bit of the public comments that were made that you incorporated, particularly, if there were patients and caregiver comments. Thank you.

DR. HICKAM: We did receive public comments from patients and caregivers, and they largely had to do with clarifying wording, to make sure it reflected the broad range of stakeholder input that was relevant to clinical research projects. It did inform changes -- the Methodology Committee actually spent a lot of time working on the wording of the

standards, as was mentioned. The standards were thoroughly reviewed.

Those comments that were made by members of the public tracked straight through to changes that were made by the committee in getting the wording right.

MS. HUNT: I guess I assumed that a lot of the public comment would be from other stakeholders and that is what was incorporated into the methodology standards. That is why I was asking about patients and caregivers.

DR. HICKAM: I can assure you we received input from both scientists and members of the general public. One thing I should say is we are releasing a full report that basically gives details on every public comment we received and how it influenced the revisions.

CHAIRMAN NORQUIST: Thanks. Allen or Christine, do you have any questions?

DR. GOERTZ: No, none. Thank you.

DR. DOUMA: I don't either.

CHAIRMAN NORQUIST: I need a motion to

approve the updated methodology standards and accept the revised Methodology Report.

UNIDENTIFIED SPEAKER: So moved.

CHAIRMAN NORQUIST: Second?

UNIDENTIFIED SPEAKER: Second.

CHAIRMAN NORQUIST: Thank you. In the room, we don't obviously have to go around, all those in favor, just raise your hand.

[Show of hands.]

CHAIRMAN NORQUIST: Is anybody opposed?

[No response.]

CHAIRMAN NORQUIST: Anybody abstain?

[No response.]

CHAIRMAN NORQUIST: Allen, I need your vote.

DR. DOUMAS: I'm in favor.

CHAIRMAN NORQUIST: Christine?

DR. GOERTZ: In favor.

CHAIRMAN NORQUIST: I can't hear them. Christine, what did you say?

DR. GOERTZ: I said yes.

CHAIRMAN NORQUIST: Allen?

DR. DOUMAS: Yes.

CHAIRMAN NORQUIST: Thanks. Rick Kuntz and Harlan Krumholz are also not here. It's approved. That's it. Joe, did you want to say something before we break?

DR. SELBY: Yes. I just wanted to ask, Robin, with these changes, we have done a fair amount of work to disseminate the methodology standards. I know we have a curriculum online, and we also have a CME course online. Is this going to take updating of those? Does this create some dissemination needs?

DR. NEWHOUSE: I would say there are going to be some updates required, not to everything, but to some of the portions as a result.

CHAIRMAN NORQUIST: On your slide, you showed there would be updating of training. Okay. We are going to break now for lunch. For those of you on the phone, we will return at 1:15 Eastern Daylight Time and restart.

[Whereupon, at 11:57 a.m. a luncheon recess was taken.]

A F T E R N O O N S E S S I O N

[1:15 p.m.]

CHAIRMAN NORQUIST: Welcome back, everyone. We are restarting. The first session of this afternoon here is Joe Selby will do his Executive Director's Report and the Dashboard Review.

Let me just double check. Allen, are you back on?

DR. DOUMA: I am, indeed. Thank you.

CHAIRMAN NORQUIST: Thanks, Allen. Christine?

DR. GOERTZ: Yes, I am.

CHAIRMAN NORQUIST: Anyone else on the line?

[No response.]

CHAIRMAN NORQUIST: Thanks. Joe?

DR. SELBY: Good afternoon, everyone. A little bit out of order, obviously, because we had the Methodology Committee with us this morning for their great discussion on precision medicine.

I want to take a moment to officially declare that the era of results at PCORI is now

open. Starting at the beginning of this year, we begun seeing in our weekly reports on publications increasing numbers of actual CER studies, and by a pretty rigorous definition of what is and isn't CER, we count 27 studies from about 21 research projects.

These are all from the broad awards, from the very first cycles of the broad. Most of them are in either the clinical effectiveness area, assessing prevention, diagnosis, and treatment options, or communications and dissemination research areas. There is a small representation already from addressing disparities and improving health systems.

I want to say I am impressed by the distribution of journals in which these articles have appeared. Yes, we have seven in so-called "high impact journals," but the vast majority of them are in the very next tier of journals, Pediatrics, JAMA Internal Medicine, JAMA Surgery, to name a few.

A very good showing, and I will say we have really been heartened on the staff at the relevance

of many of these articles. They really do speak to doing research differently, to asking questions that matter, and especially they speak to outcomes relevant to patients.

Even in the broad's, which we have had some concern about, the early returns suggest when researchers and stakeholders get together and go through the merit review process that we have, they can come up with some pretty relevant research, some of which is in fact likely to have an influence on practice.

The early research is in a wide range of areas. In cardiovascular disease, we have studies of precision tools for patients with chest pain in the emergency department helping to decide whether to stay overnight and have studies done the next day or whether this can be managed as an outpatient.

Two studies in prostate cancer that appeared -- I'll get to them in a minute -- about patient reported outcomes in prostate cancer. Three papers, as I think you're familiar with, on discharge treatment for children who have been

hospitalized with severe bacterial infections, in each case showing these children do at least as well at home on oral antibiotics as they do with intravenous or a PIC line, and have many fewer complications.

In the addressing disparities and improving health systems, a very interesting randomized trial of pure health navigation in patients with severe mental illness. That is schizophrenia. These pure health navigators help patients blend their physical and mental health needs.

A very nice study involving patients, hospitalized patients and their families, in reporting errors and adverse events, showing families are new and somewhat unique, that is they add to the detection of significant adverse events and errors over and above an employee reporting system.

The last one is on management at the system level of patients with high dose chronic opioid therapies.

A very nice mix of studies, just as you

would expect from the broad's.

I also want to take a minute to say not surprisingly, our third annual meeting is going to focus very clearly and directly and just about exclusively on delivering results. Now that you have results, how do you communicate them to audiences that have patients and caregivers and clinicians who aren't researchers, so you can inform choices.

That is the theme. The dates are October 31 to November 2, adjacent to the all PCORI Board meeting, and really a nice note, one of the keynote speakers will be Alan Alda, who has distinguished himself and won many awards personally, not for his distinguished acting career, but as an advocate for improving communication and the public's understanding of scientific results. He has a foundation that is dedicated to that. He actually was pulled into a PCORI award as well.
Alan Alda will be with us, and will be actually working with us to help shape the agenda, he and his foundation.

To the Dashboard, your trained eyes will detect one yellow band, and that is in the upper left corner, and that is the funds that we have committed to research. This is one of Bob Zwolak's major reasons for living, to get those funds committed.

Although you will see there is a shortfall after two quarters, that just made the cut of a 15 percent deficit, so we have turned it yellow.

There are a lot of promising funding announcements that are in the late stages of review. There is still a chance that we will achieve this highest ever commitment goal by the end of 2017.

Project performance continues to be very high, well above 90 percent. This is the proportion of projects that at the most recent assessment were either green or yellow. Your background materials show you that the vast majority of those are green, on schedule. It does have a recruitment measure in it for those studies that do recruiting.

We have a theme each quarter, and our next quarter will be about recruitment, with the third

quarter Dashboard, we will give you a presentation on recruitment data in our studies. We have been looking at this a lot, working to improve the assessments of recruitment. We will have that to show you next quarter.

The budget is right on target, and later today you will have the mid-year financial report presented by Regina.

Draft final research reports are coming in very nicely. You see in the most recent quarter, 27 out of 29 anticipated draft final reports were received on time. That is really incredible. The ones that are not on there do eventually make it in, and that data is in your background materials, too.

The next four are gray. The first two, it is just because it's a little too early to tell. The one in the very middle of the Dashboard is about a percent of projects in which the peer review -- once the draft final report was submitted and sent out for peer review, the proportion that gets peer review done in five months. We only have one. It didn't make it. It was 5.5 months.

I just got told a minute ago that we have a second one that has just been approved, but I'm not sure exactly where it made it. We now have two approved, and they will now be posted on our Web site after translation within 90 days.

Next quarter, I anticipate having many more. This is something we are going to watch with you very closely, are we doing the right intensity of peer review, are we getting it done in a timely way. Part of the aim of peer reviewing is so that we can post information in a timely way for other researchers. This is not the same as a journal. This is just peer review to get the project report on the Web site. We will see how we have done after we have 10 or 12 projects.

Next is the public release of research findings. This just holds PCORI accountable for getting abstracts posted, translated abstracts posted within 90 days of the approval of the final report, both a lay and professional version. No data there yet. We are not 90 days out from approval.

At the bottom, you see the growing numbers in proportion of publications that are in fact CER results. In the middle, you will see numbers of publications from PCORI that are in the top five percent of altmetric scores. I am going to go into altmetrics. We are going to keep showing you altmetrics, so you will all get to know them.

This is an index of the very early attention to a study. It could be bad attention, so it is attention positive or negative, but it is early attention. We do very well, in fact. You can see we have a large number of projects/publications in the top five percent of research.

In part, that is because our research is intended to catch the public eye. It is not aimed just at other researchers. We are looking for ways to come up with a better benchmark to compare ourselves against, something in the area of clinical research.

The last one, and we are going to talk a lot about PCORnet in the remaining part of this presentation, this is the once a year attention to

PCORnet on the Dashboard, you see the number of projects that are funded, including externally funded projects, gradually increasing. I think you will see a continued increase in these and continued increase in the externally funded projects over the next six months.

Three examples of studies that really in our view hit the mark, are exemplar studies. Here are two studies that appeared back to back in JAMA about a month ago. Both of them are in cohorts of men who have been treated for localized prostate cancer.

They both present patient reported outcomes of patients who have undergone modern, up to date treatments. In the case of prostate surgery, it is largely robotic surgery. In the case of radiation, it is largely intensity modulated radiotherapy.

There are randomized trials that have already suggested that there is a group of patients with prostate cancer that do equivalently in terms of clinical outcomes regardless of which of these three treatments, radical prostatectomy, radiation

therapy, or active surveillance that they choose.

These are two studies that informed those patients when they are at a point of choosing, and they have been told that in terms of clinical outcomes, it is pretty much a wash, the choice is up to you, and this shows both studies remarkably consistent, prostate surgery is associated with somewhat more urinary incontinence and sexual dysfunction, radiation therapy is associated with other urinary symptoms such as obstruction and discomfort, and also with some lower bowel GI symptoms, gastrointestinal symptoms, from the radiation therapy. Of course, active surveillance is not without its down side, too, because this means getting a biopsy every six months at this point.

This information really rounds out to be an update of the information needed by men making these controversial choices.

This is another study. You will see also these are very high altmetric scores, and I'll show you in a minute. Anything above -- what is it,

Michelle, 20? Big time, is in the upper five percent. These are well above 20.

This is another study from the PROSPER study of patients with atrial fibrillations had an acute ischemic stroke, and it really shows two dramatic findings. The first is outpatients with AF who had a stroke, 84 percent were not receiving guideline recommended therapeutic anticoagulation. Thirty percent were not taking any kind of antithrombotic, not even an aspirin, at all.

There was not a comparator group here to know what people with AF across the country are doing, but one would suspect they are doing better than this, so the message being the occurrence of stroke in patients with atrial fibrillation, a good part of the reason is just inadequate anticoagulation.

The second finding, also in bold, in the last paragraph, is among these patients who had a stroke, those who were taking Warfarin, anticoagulants, or even antiplatelet therapy, had much less severe strokes and lower in-hospital

mortality than patients who were not.

Again, that is a comparative study there, and shows better outcomes if you are taking the anticoagulant.

There is actually a very interesting question. We don't know yet whether it was not prescribed, whether it was prescribed and refused, whether it was taken for a while and then adherence failed.

We were actually talking with the American Heart Association about just that complex set of possible explanations, and probably it is some of each of those. It is certainly a target for interventions that aim to increase the rates of anticoagulation.

This is a very nice example. This is the second journal now which has really come out and said on the basis of what PCORI has shown us, we want to see a change in the manuscripts submitted to us for publication. In this case, this is the Journal, SLEEP. They attended a conference that was funded by an engagement award, a Eugene Washington

Engagement Award. After this meeting, they were so impressed that they wrote an editorial and changed the policy of SLEEP. It is the journal of research on sleep disorders. Requiring that these articles be written or at least a people-centered language summary be provided.

Their quote was “The establishment of PCORI in 2010 ushered in a new era of patient professional partnerships in medical research and health care. PCORI has made overt what was actually true all along, that meaningful medical research is a collaborative effort.”

Back to the altmetrics. Altmetric scores are based on the amount of attention that an article is receiving in news articles, on social media, and in blogs. You see the colors are related to the sources. Red comes from news. Blue comes from social media. Gold is blogs.

You can see here is six of ours with high scores. Most of them are CER results, one isn’t. One of them is a research letter. Again, this kind of research, I think, is meant to capture the public

attention, and it is a very good sign that it is, whether we're doing a better job than others, projects that look like ours but weren't funded by PCORI, we will try to show you in the coming quarters.

Now, we switch to PCORnet. I just want to show you briefly two examples of studies that have attracted external funding that came to PCORnet. The first is our first NIH funded study to be precise within PCORnet. This is the INVESTED trial. In some ways, it is built on the infrastructure that we put together for ADAPTABLE. There are seven clinical data research networks involved in this. This, like ADAPTABLE, it's a comparative study of two doses of something. ADAPTABLE is a baby aspirin and an adult aspirin. This is one dose of influenza vaccine versus a double dose in patients with congestive heart failure or post-myocardial infarction.

It is a study that aims to have 9,000 patients eventually. They have been through a pilot stage. PCORnet stood out as being more efficient

than the other sites, thanks to the SMART IRB. Early results from the INVESTED pilot study showed that the SMART IRB approach yielded an efficiency boost during startup, and for shadows, the improvements we anticipate as we implement SMART IRB across all of our PCORnet studies.

A very nice study. I think we have recruited 450 out of the 9,000, and next year we are aiming to recruit 3,000 of the 9,000. This was a startup year this year.

UNIDENTIFIED SPEAKER: Could I just ask one question? I was intrigued by this. What generated the interest in this particular study? I didn't understand the logic. I'm sure it's there. Mike?

UNIDENTIFIED SPEAKER: A couple of things. There is literature to show that influenza is itself an independent predictor of bad cardiovascular outcomes, and the second is there has been some observational literature suggesting that people that got the higher dose vaccine had lower risk of cardiovascular events.

DR. SELBY: Actually, dosing studies are

among -- in different populations and sub-populations, are among the kinds of practical questions that often don't get addressed elsewhere, so I wouldn't be surprised to see more of them in PCORI.

This is our first study funded by the Agency for Health Care Research and Quality. It involves two of our CDRNs, both in pediatrics, both focused on pediatrics. One about a linkage between dental treatment and prevention of dental disease, and the second, about the safe and judicious use of antipsychotics in children and adults. It involves two dental plans. Actually, two CDRNs, OneFlorida is one, and the second one is PEDSnet, Medicaid and CHIP administrators, and managed care organizations. They are testing the feasibility and usability of two performance measurement sets.

One of the things that makes research goes faster, that is intended to make research go faster in things like PCORnet is the existence of data sharing agreements between institutions. We have 117 institutions that needed to have these, and all

but two have signed them as of about a month ago. The target is to get the last two by June 1. My understanding is they are on track to do that.

I'll also say the institutions have subsequently been working a lot on a DSA version 2.0, which is even more acceptable. Some of them signed the first one holding their nose a bit. There was just some things they still weren't comfortable with. The second one has moved along very nicely, and I think by the fall, we will have version 2.0 signed off. That just means a higher level of institutional endorsement and hopefully use.

SMART IRB, I mentioned. This is a templated IRB. This was really developed, to my understanding, that it really got its start in the CTSAs, and we have adopted it. We aim to work closely with the CTSAs to complement each other and collaborate as much as possible.

Hi, Harlan.

DR. KRUMHOLZ: Hi, Joe. If you could remind us or talk about the strategy to ensure that

this becomes part of the research infrastructure in the country and maybe beyond, in the sense that are there toolkits for others who want to follow?

There are lots of people who are needing to do data use agreements. We just spent years and lots of time, lawyers and smart people, convening consensus around these documents. Can we post all these template documents? Can we share them broadly? Are there going to be toolkits so if somebody wants to do this, they can say we are following the PCORI standard, and then can we publicize it? I fear that lots of people are spinning their wheels, spending a lot of time when they could just take advantage of the work that has been done already.

DR. SELBY: Yes. That's my second next slide. I will just jump to it for a minute. This is something that I must say that I have only become familiar with in the last few weeks, something that has been done by the PCORnet Coordinating Center, and particularly this project was led by Genetic Alliance. It is called the "PCORNet Commons."

It was a part when we funded phase two. They have built a rather beautiful Web site that is open to anybody that is called the "PCORNet Commons." Its aim is exactly as you say, to increase collaboration, efficiency, people-centeredness, clinical research, across the country. You can join conversations and you can also look at materials, materials around engagement, materials around data, and materials around research.

I can't say, Harlan, that I've actually seen it, but I would bet a nickel that all this stuff about SMART IRBs is on this.

DR. KRUMHOLZ: I just want to make one further and just a point of clarification. Is this a PCORI site or will this be a PCRF site?

DR. SELBY: Right now, it's a PCORnet site.

DR. KRUMHOLZ: We should be able to continue to promote and distribute these things, I'm sure they will be fine with it. I was just thinking also this might be an opportunity for you to pull together a group of ARHQ, NIH, Gates, a bunch of foundations who might actually coalesce around a

central resource.

GitHub. Coders use a GitHub to exchange programs and codes. We need a GitHub for these sort of more technical administrative functions within a trial that could be contributed to by everyone so people aren't jumping around.

DR. SELBY: That's a brilliant idea.

DR. KRUMHOLZ: I bet they would really like to do that.

DR. SELBY: That's a brilliant idea. Bill is not here. I know Bill is pretty aware of this, but I think the idea of getting other agencies to talk about how we can expand it and use it is a really good one.

DR. KRUMHOLZ: Someone from NIH here, that person could help, too.

DR. SELBY: This is the last slide on PCORnet. This just says that the Front Door is now completely open. We opened it last fall to network members and collaborators, colleagues of network members across the country. We opened it to public queries in April of 2017.

I understand there were some public sponsors that were really pounding on the door and might have gotten a toe in a little bit before April of 2017.

At any rate, we are working with 65 total requests now submitted through the Front Door. Some of them are manageable by queries, some of them are more continued development of research proposals.

We are talking about the foundation as much as anybody. Events are being convened throughout the year with key audiences. We had one at Health Datapalooza, and there will be another one at AcademyHealth. These are just user sessions for people who would like to learn more about using PCORnet. Disseminating the availability of PCORnet and making folks familiar with it is front burner now.

MS. HOLE-MARSHALL: Joe, one question. I think it would continue to enhance people's ability to understand how to use PCORnet, and also our transparency to publish what those queries or what those questions are, once we agree we're going to do

them, and then of course, similar for results as well.

DR. SELBY: Excellent. I'm pretty certain, Leah, that is the intent, and I think some of them may already be published. I will double check on that.

PCRF has been around long enough to have a mission. It sounds a lot like the kind of work we aspire to do and what we hope to see in a PCORnet or PCRF.

This is the time line. Right now, they have been spending time comprising the board and launching the program office. I will show you how that is progressing in just a minute. Beginning to get the business development underway.

The summer of 2017 is going to be a crucial time when the foundation and PCORnet and its member networks set down to forge their relationship. There are some outstanding questions about what that relationship is going to look like, will PCORnet continue beyond say 2018 or will PCRF be the replacement for PCORnet. I think that is a very

open question now.

PCORnet is very large, has a very broad scope of activities. The question is whether PCRF is going to embrace all or some of those, and whether some of the others should live on or not. That is a question for a future date. It's going to be a very interesting summer as PCRF and PCORnet sit down to discuss the future.

I think this is the end of that. Let's just see if there are any other questions. I'm just about out of time.

CHAIRMAN NORQUIST: Harlan?

DR. KRUMHOLZ: I want to ask one thing about PCORnet. When we met in February, we talked about developing these rapid cycle projects that might be able to funnel into the funding that had been set up for them. I know I missed the morning. Are we starting that?

DR. SELBY: They are on track and in fact, the first three, one of which came from PCORI's staff, working with the stakeholders, one of which came from a collaborative research group and from

PCORI staff and stakeholders, and the third one came really from a discussion between PCORI staff and PCORI Board members, were submitted. They went through a feasibility assessment, and the feasibility assessments are being turned over to -- we have a subcommittee of two members of the SOC and two members of the RTC, and I think you're an alternate, in fact, who will review these and turn them around in a week.

These are projects that may cost as much as 400,000 to $500,000, but they have been judged to be both useful demonstrations of PCORnet's utility and also perhaps opportunities to expand PCORnet's capacity, while answering questions relatively rapidly.

DR. KRUMHOLZ: In the next six to eight weeks, you think those will cycle through?

DR. SELBY: Those are through. They are at the door, in the inbox or almost to hit the inbox of the subcommittee members.

DR. KRUMHOLZ: Great. Thank you.

CHAIRMAN NORQUIST: Allen or Christine?

DR. DOUMA: Yes, I have a question. Joe, in your time line for the PCRF, full ops and launch is summer/fall. That's a pretty broad window. Are you going to get more specific some time soon so you can focus on it a little bit better?

DR. SELBY: I think the summer is this process, which is going to take a while, Allen, of negotiating out the governance of PCRF, and the relationships of 33 networks, not to mention several health plans and potentially new members to PCRF.

I think it is legitimate to give that some time. I didn't quite understand what you said that I said would be ready in the fall or summer/fall.

DR. DOUMA: I think it says "launch and full operations."

DR. SELBY: It says launch the program office and do business development. That is in the spring of this year.

DR. DOUMA: Go back, it says "launch and full operations" on my slide.

DR. SELBY: Oh, it's the small print. That means exactly in late September. I can't speak any

more to that. This is a figure that we took from the foundation, obviously. I think they mean by the fall, they will have their business development working, they will have their contracts ironed out with the networks so they can field studies.

DR. DOUMA: That makes sense, if they just designated that time frame as “fall” or even better, end of September, it is better guidance, a better tool to use than having a six-month window. I hear what you are saying about there is a lot of work that is going to be going on during the summer in preparation for that. The chart doesn’t indicate that very well.

DR. SELBY: Okay.

CHAIRMAN NORQUIST: Bob?

UNIDENTIFIED SPEAKER: Joe, are you taking questions only PCORnet or --

CHAIRMAN NORQUIST: Anything he has presented.

DR. SELBY: Or anything else.

UNIDENTIFIED SPEAKER: Nice job, thanks very much. If I could just take this opportunity

again to ask about the awards process. For the first cycle, we have something like 82 applications and three awardees, or 82 letters of intent and three awardees.

If you start all the way back at the letter of intent level, it is only a 3.6 or 3.7 percent success rate for applicants. We do certainly have an ambitious goal, if we are now considering PCORnet, which I think we are hoping to award $360 million or so during fiscal 2017. With what we have done so far, that leaves about $290 million yet to award. One award date, I think, is in August. It's going to be an enormously busy summer for your staff and the Selection Committee. I'm not sure how close we will get to that goal.

The question I have is we had this application enhancement work group now about a year and a half ago, two years ago, we thought we made some real strong suggestions for improvement. It may be in fact we are doing our very, very best at finding meritorious research comparative effectiveness projects, and we certainly wouldn't

want to fund projects that weren't meritorious, but it looks like it will be a challenge again this year.

I was wondering if from the process that we did finish and that we announced now I guess a couple of months ago, were there lessons learned, are there additional points we can consider in application enhancement as we go forward.

DR. SELBY: I'm going to turn this over to my colleague and Chief Science Officer, who also works closely with you, and who I understand you have an under the table bet with about whether we will make it this year.

[Laughter.]

DR. SELBY: I know Evelyn has thought a lot about this. It's a great question. I'm glad she is here to answer it.

DR. WHITLOCK: Let me see if I can summarize the question. The question is I think you were looking at the three funded. That was from quarter two, right? Just sort of the angst about us being where we are in terms of awarding and the

large amount. I will say two things.

One, I do believe looking at the letter of intent for the PCFs -- I don't have the data to show you but I have shown them previously, there was a down turn in numbers of letters, and then the number of good applications for one of the PCF cycles that have since shown an increased backup.

I think you were seeing the results of that down turn, and that should not be seen again if the upturn in LOIs and then what appears to be up turn in more meritorious pragmatic clinical study applications is as we think it will be.

That's the answer, I think, to the first question. The second question really had to do with timing, which is something you have been bringing our attention to and that we have been working on since last year, and that is it used to be that in the first funding cycle, we had relatively few opportunities, and then in the second cycle, we had a few more, and then we had a lot of opportunities in the third cycle.

We are trying to spread them out more and

increase the number of opportunities under your leadership, but it hasn't quite hit yet because it takes a while for those to get in play.

You will see a broader range of funding opportunities through this year, which will affect the awards next year.

The final piece is what will be coming at us and you, all of you in the summer. We had seven merit review panels to deal with the bolus of what we are dealing with, so it took us repeated meetings over a period of a month to get through that, and we are now preparing slates.

We have asked the Selection Committee to meet twice because we don't think that the Selection Committee can get through it in one setting. We are going to bring it to the Board in two separate groupings. We will bring one grouping in August and the second grouping in September, both in time for the end of the fiscal year 2017, and I still am hopeful, depending on how you respond to various opportunities, that if you respond positively to some opportunities to perhaps allocate more dollars

in a certain area than we thought initially, I'm still very optimistic that we are going to do quite well this year.

Does that answer your question?

UNIDENTIFIED SPEAKER: Yes.

UNIDENTIFIED SPEAKER: Thank you. I wanted to along these lines add a query that may or may not be for Evelyn. I continue to be amazed at how many specialist physicians and good investigators I interact with who have never heard of PCORI. I know I've been saying this since the second month I was on the Board, which I think is now several years. I know everyone on PCORI staff is working very hard to bring PCORI to the attention of specialist physicians.

I'm wondering if there is any update about any innovative methods that people have tried or are planning to try in order to achieve this?

CHAIRMAN NORQUIST: I'm just curious, when you're saying that, are you talking about physicians who are in research or people who are just in practice?

UNIDENTIFIED SPEAKER: Yes, for example, three weeks ago, at UCSF, we had ground rounds from a hepatologist based at one of our main campuses. The person presented some excellent research. At the end of the research, both I and Neil Powe, who is on the Methodology Committee, spoke with the young investigator and said this is patient-centered research, this is a perfect PCORI project. The response was what's PCORI.

I believe UCSF has quite a number of PCORI grants. This is within the Department of Medicine. Nonetheless, this is still the response. I just think we need to tell people often and in many different ways, and I know it must be unbelievably frustrating to the staff to hear me say this, please know I'm not doing anything except saying I think we need to continue to work on this, and if there is a way in which the Board can be helpful, please put it back on us.

I remain really impressed.

CHAIRMAN NORQUIST: It's a legitimate question.

DR. SELBY: It's a legitimate question. One thing that comes to my mind, and I think Evelyn may want to say something and Jean may want to say something, too, it suggests to me in some ways the lesion is actually on the campus and maybe in the Office of Clinical Research.

CHAIRMAN NORQUIST: I've heard similar comments. I was just curious about yours. I've had a similar experience. Let's not blame it all on UCSF.

DR. SELBY: Oh, no.

UNIDENTIFIED SPEAKER: The number one NIH funded Department of Medicine in the country, let's agree they don't do a good job at disseminating research opportunities. It still creates the issue from PCORI's perspective about how can we bypass those episodes that are not working well.

DR. SELBY: I think we can assume your Department of Clinical Research probably does a better job than others because you UCSF does have a lot of awards. It does suggest that a conversation with a AAMC might be a chance to get in front again,

although we have done this some with Deans, particularly Deans for research, would be one strategy. That is just one thing that it suggests.

I will say another thing, which is we are going to visit with the AMA very shortly, within a couple of weeks. I think that is another place to talk about reaching specialty societies more uniformly, although we annually have a large gathering where 50 or so clinical specialty societies are represented.

UNIDENTIFIED SPEAKER: I actually think that one of the best ways to get at specialists is probably through the CTSAs. Many of them are really large. Your entryway doesn't always permeate throughout the whole subculture of the CTSA, but we have been doing a fair amount of work with them, mostly around PCORnet, but your point is well taken.

I think penetrating into the departments, particularly in the fellowship programs, is really challenging. You bringing it to our attention is really good. I've heard it as well. Times when I've gone down to speak to universities, the number

of people who are early in their career that attended some specialties is really high, and they are really eager, but they don't have the support structure at their institutions to help them. So, it's a good reminder.

CHAIRMAN NORQUIST: A lot of places don't have CTSAs, so let's not forget there are others. One of the other things is who the mentors are of the junior people, if they don't know, then it doesn't get kind of passed on.

Bob, is your card back up?

DR. JESSE: Let me tell the other side of that story. I was driving up yesterday and got a call from a colleague, a cardiologist, who is an electrophysiologist. He said what are you doing. I'm driving up to the PCORI Board meeting. Oh, yeah, PCORI, we have a grant. I said, oh, who is your patient partner. There were several mileposts on 95 that clicked by in silence. We were only going about five miles an hour.

[Laughter.]

DR. JESSE: He said what the hell are you

talking about. I explain this whole idea of patient driven research, and to get a PCORI grant, you had to demonstrate that from conception through submission that you had a patient partnership that was driving the question. Didn't really understand that.

For the particular grant they were asking for, I said look, if you want to put in a grant for developing patient-based criteria for the implantation of defibrillators, probably have an ample base because that's what patients always want to know, do I really need this. I said you of all people should know this because you put in my dad's, and on the table before you started, he was lying there saying do I really need this. The fact that I was in the room saying yes, which was gratuitous, because he fibrillated on the table. That was proof enough.

I don't think the research community really understands that part of PCORI, and it may be the message we need to get out, and maybe we need to talk to U.S. News and World Reports, as they are

lining up how they rank medical schools, which only really looks at NIH overhead as much as anything. We need to get to junior folk. We really need to get that word out, you are doing patient-centered research. They probably understand patient-centered care better. It's a chance to do it differently.

Given that opportunity, they also realize they are closing down their competitor base if they can do that well.

CHAIRMAN NORQUIST: We are going to need to wrap up. You have another presentation.

UNIDENTIFIED SPEAKER: If people are gambling over there, do we have any PCORI grants on gambling addiction? Maybe we could get you enrolled.

UNIDENTIFIED SPEAKER: I didn't know if Debra Barksdale wanted to talk. The VCU kind of symposium that was there recently, do you think that's a good model for the kind of things that will help investigators really know what PCORI offers in a way that would be constructive? I know some folks from Dissemination came down. You hosted them.

DR. BARKSDALE: It hasn't occurred yet. It is later this week. I can report afterwards.

UNIDENTIFIED SPEAKER: We do pre-announcements. We are trying to get those out every time. If we have some way that we could figure out how to get a better targeted list, and I don't know what that is, we would be happy to add that in when we do our targeted announcements.

CHAIRMAN NORQUIST: Freda.

DR. LEWIS-HALL: I think we had the discussion with the American Heart Association. The idea would be to reach those not yet reached, like those that are out of our redundant circles. We may be able to connect to see if they were any more successful, which I think they were, in reaching the unexpected potential.

CHAIRMAN NORQUIST: We will leave it as an action item, Jean, for your group to think about coming back with some kind of plan or something and see where we are.

We are going to move on to the next topic, which are two actual considerations for approval for

these targeted PFAs, one on medication assisted treatment for pregnant women with substance abuse disorders, actually opioid use disorders, and then symptom management for patients with advanced illness.

What we will do is we will split the two. Evelyn and Bob, if you want to present on the opioid use disorder with pregnant women first, and then we will take questions, and make a decision, and then we will go to the second.

DR. ZWOLAK: Thank you. My comments will be very brief. I think you will see in these two topics a real focus based on what the Board of Governors has indicated over the last year or two in dealing with major public health problems, dealing with hugely important issues, opioid abuse and treatment that will help a large number of people if we can sponsor some high quality comparative effectiveness research.

It's very difficult for me to think about the horrible problem of an opioid addicted pregnant woman. I can't imagine being in that situation if I

were the woman and the impact on the child is enormous.

I think this is a compelling funding opportunity, and the staff has gone through all the right review of background material. I think it's ready for a positive vote by the Board. With that, I think Evelyn will make the presentation.

DR. WHITLOCK: Thank you, Bob. On behalf of the Science team who helped to develop this, I want to present to you the funding opportunity that we are bringing you to do another targeted funding announcement focusing on opioid use disorder in pregnant women.

As you are well aware, PCORI has already released two opioid specific targeted PFAs. We released those in Cycle 3 of 2015, as the clinical strategies for managing and reducing long term opioid use for chronic pain. That was reissued in Cycle 3 of 2016.

There was a sequential targeted funding announcement that was to look at preventing unsafe opioid prescribing in primary care among patients

with acute or chronic non-cancer pain. That was released in Cycle 3 of 2016, and that is one of the group of new awards that will be coming to you in the summer that we will be referring to.

When we look at these previous targeted funding announcements and we look at our current portfolio, we note we don't have anything that focuses on pregnant women, and one of the top priorities for the Medicaid Medical Directors Network in 2016 was in pregnant women with a focus on pregnant women who are on opioids, looking at effective options, approaches and treatment options.

I want to thank Greg Martin for sharing that information with us. He's worked carefully with the Medicaid Medical Directors. I was able to talk to them recently, and this is a very, very important area for them. In some states, Medicaid is the largest payer for all births. These types of opioid addicted women in pregnancy has been on the increase.

Just to tell you where we are, this would be considered a sequential targeted funding

announcement. It's additional in the series of opioid disorder announcements, but focused on this special population.

As I mentioned, it was originally identified by the Medicaid Medical Directors Network and prioritized quite highly by them. We have discussed this at various multi-stakeholder meetings, at advisory panels, and the SOC approved this, and it is coming to you today for approval. You can see there have been a range of inputs from various stakeholders.

Why is this important? Well, as I alluded to, the prevalence of opioid use by pregnant women has increased dramatically, and as you are not surprised, associated with this are really serious maternal, fetal, and neonatal risks, and there are evidence-based effective treatments available.

The most strongly recommended by the World Health Organization and others is medication assisted treatment. What that means is that pregnant women are given maintenance therapy with an opioid agonist, so either Methadone or

Buprenorphine, and that medication assistance is combined with psychosocial services and of course, prenatal care, and in that context, you can improve outcomes for the mother and the baby.

You see better adherence to prenatal care. You see better maternal weight gain, higher neonatal birth weights, decreasing opioid use and reducing criminal activity.

Of the two medications that are used in this context, Buprenorphine -- both of them are agonists but Buprenorphine is safer than Methadone, so fewer of the infants go through what is called “neonatal abstinence” or “withdrawal issues.” The birth outcomes are better on Buprenorphine than Methadone.

There are many reasons that women don’t receive medication assisted treatments, although many women are motivated, there are barriers to getting treatment, including stigma as to where treatments are available, lack of access altogether, and concern about legal consequences.

Because of the Drug Addiction Treatment

Act, which made Buprenorphine more readily available through any clinician's office, it is possible that women could access treatment more easily, but it's not common that clinicians are qualified and certified to give the Buprenorphine treatment in their offices. Fewer than half of counties in the U.S. have Office-Based Opioid Treatment available, and the percentage of qualified clinicians vary, but it is very low in OB-GYN, about one percent, and about 22 percent of family medicine.

There are concerns that providers have about getting qualified and providing this treatment, including their concerns about being an expert even once they are qualified, the inadequacy of support, and access to mental health providers, and the unfamiliarity with managing some of these kinds of issues, but we feel both the patient and provider barriers offer an important opportunity to compare successful models so that more good treatment options for pregnant women and their babies can be made available.

When you look at different models, and some

of these have come from the states that are the most strongly afflicted by this increasing prevalence in pregnancy, so New Hampshire, New Mexico, and Oregon have experimented with a model that looks at integration of prenatal care, Office-Based Opioid Treatment, addiction medicine treatment, and psychosocial services.

West Virginia, another highly affected state, has looked at co-locating services, so making sure at least the Office-Based Opioid Treatment and prenatal care are co-located, but just collaborating and referring to community psychosocial services, and other places will provide prenatal care in one place and then refer for opioid use disorder treatment, which may or may not include maintenance therapy. I am sure it includes psychosocial services.

These are different models, some of which are being implemented at fairly wide levels. The importance of understanding how these models might be most effective and feasible could be really important for addressing this problem.

Similarly, some of the models involve elements that address some of the most challenging parts of this, and those have to do with the expertise and also getting women on treatment.

The hub and spoke model looks at making at the hub addiction specialists in this disorder are available to the clinics that are aligned with the center hub by spokes, so people can do the work in their communities that have access to more intensive support, and this can include things like providing a centralized resource for induction of treatment and stabilization.

There is a time for both of these medications where women have to be -- it has to be timed to the right point for them in terms of their previous drug use. They have to then have their doses be done and escalated to a point where they are in a stable situation. One of these models is to do that in a more centralized way as opposed to supporting people doing it in a more dispersed way.

Also, the way the psychosocial services are supported is another variant in terms of how the

additional support is provided.

We have proposed two research questions to offer the opportunity to look at these various models of treatment and help inform those on the front line of this problem about what are the best ways for them to organize this effective care.

The first is what is the comparative effectiveness of alternative models for comprehensive opioid use disorder treatment delivery on maternal and neonatal outcomes in pregnant and post-partum women with different levels of addiction severity?

Comprehensive care must include prenatal care, medication assisted treatment with either Buprenorphine or Methadone, and psychosocial care.

The second question is what is the comparative effectiveness of remotely supported opioid use disorder treatment delivery to pregnant women that includes more versus less resource-intense approaches to induction and psychosocial support for Office-Based Opioid Therapy in terms of the impact on maternal and neonatal outcomes?

If you want to go into a bit more of the outline of what we would be asking for in a targeted funding announcement, we are looking at ensuring that we have outcomes that relate both to the pregnancy and to the opioid use disorder, so the addiction specific or opioid use specific outcomes are related to illicit drug use in general, to relapse, to treatment entry and retention, and to patient quality of life, anxiety and depression.

Related to the pregnancy, the interest is in birth outcomes, including pre-term birth, pregnancy complications, birth weight, neonatal complications, and issues around neonatal withdrawal.

We will be looking at repeated assessments to measure maternal and neonatal outcomes during pregnancy as well as into the three-month post-partum period.

Eligible women are those with opioid use disorder and their infants, and they will be in Medicaid and private insurance kinds of settings, and we are interested in looking at a heterogeneity

of treatment effects among subgroups as defined by addiction severity, income, or other disadvantages.

As I said, there are different models that can be compared, and I've been through these. The integrated, the co-located, the usual kind of dispersed care through various places, and the availability of remote support in order to help clinicians, particularly in rural or settings without a strong addiction treatment clinic environment, to be able to provide these services.

We would like to commit up to $16 million in total costs. We estimate we could fund three to four studies with this amount of money, at a total direct cost of about $3 million per study, and we also think we could complete these in a project period of three to four years because the time period of pregnancy is relatively short, so assuming adequate ability to recruit, we should be able to get to patient important outcomes within three to four years.

I will stop there and see if there are any comments or questions. We are at the point where

the SOC has endorsed this. We are bringing it to you for a vote. Should you approve it, we will release a pre-announcement and the targeted funding announcement would be in the public domain by June 23. I will stop there.

CHAIRMAN NORQUIST: Okay. Let's open it up for any questions. Harlan?

DR. KRUMHOLZ: I just want to make sure I understand. This is randomized?

DR. WHITLOCK: It doesn't have to be. It could be a natural experiment. I think there are some, we know from some of the preliminary literature that there are in certain states say Medicaid adopted policies that might vary in these dimensions, so there could be a natural experiment. It wouldn't have to be randomized design.

DR. KRUMHOLZ: I guess the question is whether we are going to encourage that. The second thing is I just think it's important in these kind of studies to be clear that we are asking for interventions at scale that are pseudo-diagnostic, it can be tailored and refined, but it is of

greatest use if this can scale broadly. It doesn't have to scale to everybody because that may not be possible. It needs to at least be inherent that these are complex interventions, so the applications need to acknowledge that these are complex interventions, which mean they interact with sites.

We need to be able to understand how what we are testing is not in a special place where there are a lot more resources that are being brought to bear that are producing results that are unlikely to be achieved without the trial around it.

As they put in these applications, it seems to me they both have to understand the interaction with site and the degree to which they are really testing some real-world application.

I'm in favor of this, I'm just saying as we go out. The issue about heterogeneity is an interesting one. By saying that, you're implying we're going to fund to have adequately powered subgroups that are going to represent distinct hypotheses for which P values are going to have to be adjusted for in the overarching study design.

I think that is fine, but I think we need to be purposeful about that. It's not just about we're interested in heterogeneity so we expect you to have subgroup analysis, but if we really are interested in heterogeneity, that needs to be one of the principal aims, not a descriptive feature of hypothesis generating for the future.

We could back off that, but I'm just saying if you are going to actually assert heterogeneity is important, then these need to be built to test heterogeneity in ways that are robust, or else we should just say heterogeneity is just going to be purely secondary and descriptive and hypothesis generating for the next study. I think we need to decide about that.

It matters for the $16 million whether or not you are going to super fund one that has the power to look at heterogeneity or whether you will fund them for the main effect and then everything else is just for potential hypothesis generation for the future.

Of the three things I just mentioned, the

second one around the complex intervention and notion of scalability and there would be tools and toolkits and the means by which this can spread as a dissemination, if successful, seems to me would be an important feature to be embedded in the call for proposals.

CHAIRMAN NORQUIST: Bob Zwolak?

DR. ZWOLAK: I think those are very much cogent and important observations. To some extent, the key comparator here is care given in a Methadone clinic, which could well have obvious stigma for a pregnant woman versus a physician's office which requires that physicians buy into the training and willingness to prescribe the Buprenorphine.

That may or may not be scaled. One of the things I think it will test is whether the Buprenorphine Office-Based prescription is a scalable --

DR. KRUMHOLZ: You are describing a feasibility study, not a comparative effectiveness study, which could be fine, but then we just need to be precise about whether we are saying can it be

done, can you implement it, will they do it, is it better than a comparator.

DR. ZWOLAK: It certainly depends on what part of the country you are in whether this is comparative effectiveness, where there is availability of that approach, or feasibility, where there may be less of that. I think part of this is in fact a view. You are right. I think it varies across the country.

CHAIRMAN NORQUIST: Yes. I noticed you had Medicaid, and not all these people are going to have Medicaid. There will be a fair number of uninsured. If they have a child or something, they should have Medicaid, but some people go into jail and then they come out, they lose their Medicaid.

I think it is going to have to be a very diverse group, but I think we are calling for that. We will have to see what we get, right? Then we will have an opportunity to look at what applications look like when they come in.

DR. KRUMHOLZ: Are there Medicaid Directors who are going to be on our study section?

DR. WHITLOCK: I think they would be willing. This is one of their highest priorities.

DR. KRUMHOLZ: I think we need to know from Leah and others like this is evidence that would lead to some policy action, but let me just say I'm in favor of the topic, don't mistake what I'm saying, but I want to make sure this size investment is returning knowledge that is likely to -- there are two things that could be happening.

One is there are some policy decisions that are going to be made, and they need evidence to make those policies. It's not clear to me that is the question or if the question is whether or not the effort to deliver it in this setting is worth it because you either expand the scope of people being treated or it is actually better, it turns out to be better if you can treat more people even if you treat it at the same level of efficacy.

I'm just saying this could be quicksand unless there is a great deal of clarity around what are the specific questions. You could go out with the call for proposals and say we would be

interested in answering any of these 10 questions and see what comes in. I just think the specificity by which we articulate the questions and know who the customers of those answers are is going to be important to whether or not this turns out to be a good investment for us.

CHAIRMAN NORQUIST: I would just add not just the Medicaid Directors but mental health/substance abuse agencies in the states. Often times, they are the ones overseeing these programs.

Leah?

MS. HOLE-MARSHALL: We struggled with this a little bit, at least I did in terms of this topic, coming here, and I also strongly support this as a very important topic. It is really just a question of how to get the notice and request out. Medicaid is responsible for about 50 percent of the births in the nation, so I had proposed perhaps a special emphasis on Medicaid, but I also understand this is not necessarily a Medicaid alone.

UNIDENTIFIED SPEAKER: [Inaudible.]

MS. HOLE-MARSHALL: Fifty percent of births are paid for by Medicaid in the nation.

CHAIRMAN NORQUIST: In some states, it actually may be higher than that.

MS. HOLE-MARSHALL: Yes, absolutely, that is a national statistic. Definitely don't want to increase the stigma that this proportionately affects low income people because that is certainly not the case. We struggled with that a little bit in the committee, and ultimately settled upon kind of these are the populations of interest, but I think your point is well taken, Harlan.

While we require dissemination or implementation plans in all of our studies, it would be particularly critical in this one, especially if there is a focus on a particular subgroup, that special attention or focus paid to how this might actually proliferate outside of the study. That is actually the key policy issue right now for the Medicaid agencies that I work most closely with, where to invest funds and how to make it the most value for the most number of patients.

CHAIRMAN NORQUIST: Perhaps one of the key things is their partner in this should not only be patient groups but the Medicaid Directors and their relevant areas or mental health and substance abuse agencies.

UNIDENTIFIED SPEAKER: In the PFA, that they need to demonstrate those specific stakeholder partnerships. I think that is a really good point. I think we can take some of the points that Harlan made and write them into the PFA about the importance of the real-world test and scalability. I think that will also help us focus, get the kind of comparative models that I think Medicaid in some states are being forced to but don't really know if this is the best way to go.

It will help us get in that direction. The other thing we could do potentially is talk about scalable treatments or scalable approaches as you are talking about, or smaller studies that address any of the barriers.

For example, clarifying the barriers around how much you can get the penetration of

Buprenorphine and Office-Based Opioid Treatment, disseminated.

We could also do it that way, too, so that we look at the bigger picture but also maybe even some of the component steps.

CHAIRMAN NORQUIST: Sharon?

DR. LEVINE: Depending on the power of the study, you may be able to also look at whether the payment model in Medicaid makes a difference in terms of the success of the work. Medicaid managed care versus traditional Medicaid fee-for-service.

UNIDENTIFIED SPEAKER: I wanted to say to Harlan, if I could, I think we almost always call the subgroups out in this way, but I think you make an important point that we are still talking about internally in the programs, how much do we require that something be powered for hypothesis testing.

I would say in the context of this literature, it is my understanding, and I'm not an expert, the more there are other kinds of barriers, the more unlikely. That is just almost common sense. I'm not sure we need to demonstrate that.

That probably is going to be most important for us to address effective systems or effective components of systems and that heterogeneity at this point will be something we would look at in an exploratory way rather than a hypothesis testing kind of way.

CHAIRMAN NORQUIST: I need a motion to approve.

DR. LEVINE: So moved.

CHAIRMAN NORQUIST: Second?

UNIDENTIFIED SPEAKER: Second.

CHAIRMAN NORQUIST: All those in favor, just raise your hand.

[Show of hands.]

CHAIRMAN NORQUIST: Anybody opposed?

[No response.]

CHAIRMAN NORQUIST: Anybody abstaining?

[No response.]

CHAIRMAN NORQUIST: Allen?

DR. DOUMA: Yes.

CHAIRMAN NORQUIST: I think Christine dropped off. Christine, are you back?

[No response.]

CHAIRMAN NORQUIST: It passes. We are behind a little bit, but that is okay. Evelyn, the next one, symptom management for patients with advanced illness. Bob, did you want to say anything?

DR. ZWOLAK: Only briefly. Again, this is a response, I think, to the Board's desire that we aim for the largest impact on public health with common problems, and this one is really important.

DR. WHITLOCK: I'm going to try to talk a little more quickly through this recommendation for a targeted funding announcement in symptom management for patients with advanced illness.

Again, this is building on our previous announcements that we have done in palliative care. These also were done in Cycle 3 of 2016, and will be coming to the Board this summer, looking both at advanced care planning as well as models of delivery.

We did have a pretty broad-based workshop with stakeholders around advanced illnesses and care giving in 2016. From that work, as well as many

other recent reports from various either blue ribbon panels or alliances in this country and in other countries, there has been a lot of call for symptom management, particularly in advanced illness, as a very important area for further research.

You can see those outlined here and the range of folks that have called for it. In particular, there has been a call for -- if you go down to the almost bottom bullet, need for research outside of cancer populations, consideration of caregiver outcomes, and maybe not on this page but on another side -- it's in the middle -- especially for children, not having much evidence at all for children.

The background, we have presented to you before, palliative care approaches can improve patient well-being in those with serious illness, and there have been a number of systematic reviews which show there are a wide range of beneficial patient outcomes with palliative care services, clinically meaningful improvements in quality of life, symptom burden, caregiver distress, reduced

hospitalization.

But as you look at research in this field, there have been some areas where there were deficits in the research knowledge about how best to support patients and families. These have included models of care delivery, advanced care planning, and symptom management is a third major area. Under that, you see all the reports that have recently called attention to this issue.

We have put out two previous targeted funding announcements, as I mentioned. This would be the third funding announcement looking at the comparative effectiveness of treatment options for relief of common symptoms across multiple advanced illnesses. The kinds of symptoms such as pain, fatigue, difficulty breathing, insomnia.

If this is approved, then it would be released in June of 2017 for potential awards in May of 2018.

The rationale as we have put it together is this is the remaining top priority for research in this area. There have been previous studies on

symptom management in patients with advanced illness. They have been more focused as the previous slide said in areas maybe mostly cancer oriented or particular populations of patients. There have not been very many head to head trials, and most of the studies have been quite small and unable to look at any kind of treatment variation.

The proposed question that would be in this funding announcement is what is the comparative effectiveness of two or more interventions, including at least one pharmacologic intervention, for symptom management of patients with serious advanced illness.

We have focused on the symptoms that have been most commonly reported as problematic and needing research across a variety of publications and in both adults and children.

The most common symptoms are pain, fatigue -- they are not surprising to anyone, I don't think -- pain, fatigue, dyspnea, insomnia, anorexia-cachexia, nausea/vomiting, and depression/anxiety.

We would like the study to examine more

than one symptom and certainly be attentive to any impact that might make one symptom worse when it is trying to improve another.

The population would be patients with advanced life limiting illness and their caregivers. Conditions could include but are not limited to things such as advanced heart failure, where there is not much research, advanced cancer, COPD, end stage liver or kidney disease, and advanced neurodegenerative diseases.

We have decided that in order to encourage research in younger patients, that we would call it as a special interest, but you can discuss if that seems right to you. I think that is what the SOC suggested, we just mention not make any special funding separation, but just say we are particularly interested.

The interventions and comparators, we thought it would make sense to have at least one pharmacologic intervention since these are commonly used in these situations, but that comparator could be another commonly used pharmacologic intervention

or a non-pharmacologic comparator, and any of the proposed interventions and comparators would need to have at least moderate evidence of efficacy and/or be in widespread use, and be capable of delivery in a standardized format, and it would address actual clinical choices by patients and their caregivers and clinicians in specific practice settings. They can't be asking about things that would not be available.

The outcomes and timing, we have called out there should be patient-centered outcomes such as quality of life. We haven't specified it any further than that. Certainly, there need to be caregiver outcomes as well. There need to be symptom outcomes, and there needs to be attention to any unintended effects of symptom treatment, including exacerbating other symptoms and/or patient or caregiver experience. An example here is delirium, which can be made worse by some treatments.

We have specified at least a six-month duration of follow-up.

The total commitment we recommended for this targeted funding announcement would be up to $25 million in total costs, we believe we could get 8 to 10 studies done for this amount, and we also believe that the total costs of the study would not need to be extremely high, and the maximum project period could generally be three years, because of the nature of the question and the time to get to patient important outcomes.

At the advice of the SOC, for studies of uncommon conditions where it might take longer to recruit a sample size, PCORI would consider funding larger or longer studies with a strong rationale.

Let me open it for comments or questions and discussion.

UNIDENTIFIED SPEAKER: Evelyn, that was a lovely summary. Bob, I can't remember, did we discuss whether hospice patients were in or not in the study? I don't think we did. Is that something we should raise now? The time of this is six months, so presumably, that would be appropriate for a lot of hospice patients. It would be a vehicle

for getting a lot of them to enter the system rapidly, we could identify residential or home hospice based patients. It has just occurred to me now.

DR. WHITLOCK: I don't think we discussed that. I think we were assuming it would be people more like folks -- the general rule of thumb was six months or something, although people think folks should be getting hospice earlier, but I think the idea was more people with more like a three-year projected life span, so thinking less about hospice and more about earlier interventions.

UNIDENTIFIED SPEAKER: We may need to be a little more specific.

DR. WHITLOCK: We probably do. Thank you for bringing that up. What would you recommend?

UNIDENTIFIED SPEAKER: I actually don't know. I hadn't thought about it at all until I just looked at that. It strikes me this might be really terrific for some hospice patients where six months might be 100 percent of your life.

DR. ZWOLAK: I would agree, hospice is not

what it used to be. I think people are being much more thoughtful about hospice and only getting involved earlier in their stage of disease. I think hospice patients would be potentially superb candidates.

CHAIRMAN NORQUIST: I think, Bob, you are absolutely right. It's not the six months. I've seen people with a year. Gail, you are next.

MS. HUNT: The average length of stay in hospice is two weeks. This is really about palliative care, so you are right, three years, two years, congestive heart failure, things like that, rather than end of life, six months' diagnosis, that you actually get in in two weeks. I think it would be important to be sure this is focused on palliative care, even though it might be easier to recruit people out of hospice because they are like the captive population.

UNIDENTIFIED SPEAKER: You are saying two weeks in hospice?

MS. HUNT: Two weeks in hospice is the average amount of time, the average stay in hospice.

DR. ZWOLAK: I'm not sure we need to micromanage this at the table, but I think potentially we could build in some life expectancy metrics rather than yea or nay to hospice itself.

CHAIRMAN NORQUIST: Other questions or comments? Allen, do you have anything?

DR. DOUMA: No, I don't.

CHAIRMAN NORQUIST: Christine, are you back?

[No response.]

CHAIRMAN NORQUIST: I need a motion to approve this targeted funding announcement.

DR. McNEIL: So move.

CHAIRMAN NORQUIST: Second?

MR. BARNETT: Second.

CHAIRMAN NORQUIST: Put your hand up if you're in favor.

[Show of hands.]

CHAIRMAN NORQUIST: Against?

[No response.]

CHAIRMAN NORQUIST: Anybody abstaining?

[No response.]

CHAIRMAN NORQUIST: Allen, what is your vote?

DR. DOUMA: I approve.

CHAIRMAN NORQUIST: Okay. It's approved. Thanks, Bob, Evelyn and team. The next one is the mid-year financial review, but I do have to check. We have the public comment period which starts at 3:00. If you want to get started, I may interrupt you.

DR. SELBY: I will just say Regina and her team as usual have done a great job, and this has been carefully overseen and reviewed already by the FAC, so I think it looks like Larry has some opening comments, and then Regina.

MR. BECKER: Thanks to my fellow FAC members, Bob, Kerry, Christine on the phone. We went through this a couple of weeks ago. The mid-year financial review, we will give you a comparison between PCORI's budget and actual expenses for the first two quarters, and what you will find is that we are within five percent of budget, not-withstanding Bob's comments about 20 minutes ago.

It looks like we are right on budget, and if you have been here for a few years, that's Herculean work, because we have been well off by halfway into the year, so we are getting there, and beginning to understand and being able to execute a whole lot better.

I'd also like to inform you that at our monthly meetings, the FAC is continuing regular reviews of investment reports. You remember, we took on the cash, the financial report, the operational Dashboards which tracks the overall operational performance against its goals.

My thanks to Regina, the whole financial team, the FAC, I'm going to give this to Regina to take you through all the details.

MS. YAN: Thank you, Larry. I would like to go over with you how we are doing mid-year with our expenditures compared to our budget.

Our fiscal year 2017 approved budget is $423 million, and our budget for the first six months is $196 million. Our actual expenditures are $186 million, so we are really coming very, very

close, at five percent. Last year at this time, our budget versus actual variance was 18 percent. We are on track with all our activities and expenditures.

Right now, we are expecting that the second half of the year will be more or less the same. I know previously there were some concerns about our award invoices coming in slowly, but I think we have caught up right now. We are just slightly behind the last quarter mainly because we have improved our functionality and have made some changes on online invoicing.

If we take a look at the proportions of our budget, for the first six months, our budget is $196 million, of which 89 percent is in program expenditures, 4 percent in program support, and 7 percent in administrative support, and our actual is following pretty closely to that breakdown.

Our total revenues through 2019 is $3.3 billion, and we have done a projection for all of our expenditures through 2024, and it is more or less the same, program expense is about 91 percent.

This is more or less going to be the breakdown in the ratio you will be seeing in all our expenditures.

That is our mid-year review. Any questions?

[No response.]

CHAIRMAN NORQUIST: Allen, did you have any questions?

[No response.]

CHAIRMAN NORQUIST: All right. Thanks, Regina. I am just checking to see if we are going to have a public comment period. No. If no one is present or waiting on the line, we will not be initiating our public comment period.

[No response.]

CHAIRMAN NORQUIST: Joe, did you want to make some final comments?

DR. SELBY: Extremely briefly. I think this morning's precision medicine discussion has already led to the formation of a work group to get moving quickly on this, and to look for a model of the kind of study that would make sense for us to

fund, and then hopefully find one and fund it, either through targeted announcements or by recognizing the right pragmatic study.

This afternoon in the Director's report and Dashboard report, I think one of the things we certainly continue to have our eyes on is commitments, and we will see in the fourth quarter when all those commitments are projected to happen how close we come. We will also report to you on recruitment.

With respect to PCORnet, and particularly the PCORnet Commons, just to take a close look to make sure we are really getting all the learnings from PCORnet onto the Commons, and also to look for ways, maybe with other agencies, to exploit the Commons or to share our input on other Web sites like the Commons, so that together we can change research in a more timely fashion.

We approved both of those funding announcements with good suggestions from a number of investigators that I wrote down, and I think Evelyn and her staff got them, too. I won't repeat them.

Thanks for a good day today. Back to you.

CHAIRMAN NORQUIST: Does anybody want to make any other comments or have questions?

[No response.]

CHAIRMAN NORQUIST: Okay. Thanks. Thanks to everyone who joined us in person or by webinar or teleconference, and a reminder that all materials presented will soon be available on our Web site at PCORI.org. Today's webinar was recorded, and that archive will be posted within a week. We always welcome your feedback at info@pcori.org or on our Web site.

Thanks, and good afternoon or morning, wherever you are. Thanks.

[Whereupon, at 2:50 p.m., the meeting was adjourned.]