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Health Technology Clinical Committee Public Meeting
November 18, 2016

Chris Standaert: Well, good morning. We're going to call our meeting to order. So, I'm Chris Standaert. I'm the Chair of our committee. This is the meeting of the Washington State Health Care Authority's Health Technology Clinical Committee on November 18, 2016. We are here to address two particular topics today, negative pressure wound therapy and fecal microbiotic transplantation. The first of those will be in the morning. Just to review our process a bit, we have several new people here, and this is our first meeting where our clinical expert is a member of our committee for the day. Dr. Quigley is here serving in that role, and we appreciate that. Again, that's a new role for our committee. So, we will work through this. We are an evidence-based committee, and we have a statute from the state of how we do things, and we look at the evidence, and we try to decide on what to do with the topics presented to us based on efficacy, cost, and safety. Those are our concerns. We rely on our evidence vendors for our data, and we discuss our data and our perspectives on it, and we're all clinicians and that's a deliberate thing to have clinicians making these decisions, which I think is important. So, we will work through these things today, and I think that's it. So, I will let Josh review our status at the moment.

Josh Morse: OK. This will be brief, just a couple updates about today's meeting and the next meetings in the next few months. So, today's topics are the negative pressure wound therapy for home use topic this morning. Then, after this topic is fecal microbiotic transplantation. In January, a mere two months away, surprisingly fast we're going through the end of this year, we'll have the pharmacogenetic testing topic and a rereview of artificial disk replacement. In March, we have one topic scheduled, and that's extracorporeal shockwave therapy. Then, in May, we have treatment for chronic migraine and chronic tension-type headaches and varicose veins. Currently scheduled for July 14th is the follow-up to the May meeting to conclude meeting business, and that's been conducted by phone, as you know, the past few years.

And this just goes through essentially the topics that were selected last year and where we are moving ahead through these topics. So, what we haven't scheduled yet, you'll see at the bottom there, are skin substitutes and the computer-aided detection that's an adjunct to mammography, and we will be scheduling those soon, likely for the fall of 2017. Does anybody have any questions for me before we move on? OK.

- Chris Standaert: Alright. Our next order of business is to approve our minutes or review our minutes from our meeting in July. So, normally most meetings we will have our prior meeting's decision that we will then finalize our vote on that decision. So, at the end of today, we will come up with a coverage determination for these two topics. We will decide upon that. We'll agree. We'll vote, and the majority sort of moves on with what that decision is. That decision goes out for public comment. Then, at our next meeting, we will vote to approve that or otherwise do what we want and do what we think we need to do with it and finalize that decision. So, for today, our last meeting, which reviewed evidence and topics, was in the spring, and we, over the summer, voted on that at a meeting, a separate meeting just for that purpose. So, today we don't have any topic or decision to approve. Normally, we would. So, today, we have meeting minutes, which are not terribly extensive from the phone call we had, the phone meeting we had in July. So, people have had a chance to review the minutes. If there are any questions or comments, please let me know or corrections somebody thinks needs to be made. Otherwise, I just need a motion to approve them.
- Gregory Brown: Approve.
- Chris Standaert: Second somewhere?
- Seth Schwartz: Second.
- Chris Standaert: Thank you. So, all approved, all vote to approve the minutes? So, if you were on the phone call you can vote. If you weren't on the phone call, you can't.
- Josh Morse: Six to approve.
- Chris Standaert: That's what we need. Yeah. OK. So, we will move on. So, our first topic is negative pressure wound therapy, and we hear from three separate sort of consistencies in a way. The State Agencies will present their perspective on this and tell us about their views on a topic and the evidence that they have and that we all have. Then, there is a time for open public comment, and we have a sign-in sheet for people who come in who know they want to speak and can sign in, and then we can run through that. We'll open the phones to make sure there's anybody who is on the phone listening to the meeting who wants to address the committee can do so, and if there are people in the audience who at the last minute, as we're going through that, decide they want to address the committee, they can do that, as well. That is the opportunity to tell us your perspective. There is a defined time for that and however we are dealing with time, we will open up somewhere in that space for people on the phone or otherwise planning to talk during that time. So, with that, we'll start.
- Shana Johnson: Well, hello and good morning, everyone. I'm Shana Johnson, and I'll be presenting the agency medical directors' presentation on negative pressure wound therapy.

Briefly, negative pressure wound therapy is the application of negative pressure to the surface of a wound and this modality is thought to promote an ideal healing environment and aid in wound healing.

For this technology review, we're focusing on the clinical effectiveness, as well as safety, of negative pressure wound therapy in the home or outpatient setting, which is where we identified most of this care is taking place. The specific wound classes that the technology looked at include diabetic foot ulcers, venous and arterial ulcers, pressure ulcers, mixed etiology chronic wounds, and surgical wounds.

The agency medical directors' concerns regarding this topic for safety medium, cost medium, and efficacy medium to high.

So, I'll start just by going through some data. We identified that the majority of this care is taking place in the home or office or outpatient setting with a relatively smaller percent being taken place in facilities, such as skilled nursing facilities.

Moving to the diagnoses that we see this most commonly used across agencies, you see Labor and Industries, Medicaid and PEBB along the bottom line and the number of patients in the vertical axis, and nonhealing surgical wounds was the most common diagnosis identified. Pressure ulcers were also very common. Overall, the coding was fairly nonspecific, however, and there was a lot of nonspecific coding.

Next, looking at the average daily use per patient by year and by program, overall it appears that Medicaid and Medicare have a much greater average use, as compared to Labor and Industries and PEBB, just looking at the associated codes with the ulcer that's appeared to possibly be a severity of illness effect. The brackets noted are arrow bars, which demonstrate a variation year to year within a particular agency was significant.

Next, we'll take a closer look at utilization in particular agencies to take a look at what degree of outlier effect is present. So, here we show PEBB data. The hash mark you see at the one month is the time at which 50% of people have completed therapy. Other things of note on this graph is 82% of these patients completed treatment by month two and 91% completed treatment by month three.

When we look at Medicaid fee for service data, we see that 51% completed treatment by month two. By month three, in contrast to 90% having completed treatment, only 63% had completed treatment. So, it appears their level of outliers is quite more substantial. Some people receiving the negative pressure wound therapy for up to five years.

Lastly, we'll just take a brief look at costs. In PEBB, you see the cost rates and unique patients per year is relatively flat with a cost being between 220 and 240,000 per year.

Shifting to the Medicaid data is harder to follow, because there is... during this time period, there is a shift of 90% of Medicaid clients into managed care programs, and the Medicaid managed care money is a shadow amount, as it's a capitated program. So, an algorithm is used to calculate the costs. So, you can look at it for what it's worth, I guess.

So, reviewing our current state agency policy, PEBB, we have been told, does cover negative pressure wound therapy but we were not able to identify a published policy. Medicaid fee for service and Labor and Industry covers it with conditions via prior authorization process, and Department of Corrections covers it.

Briefly looking at the coverage policies of Labor and Industry and Medicaid, Labor and Industry covers negative pressure wound therapy in those that are not responsive to standard treatments or those who are at high risk of failing treatment, and the majority of what they cover are the wound types that we'll be talking about in the technology review today.

Medicaid fee for service covers it for Stage 3 or 4 pressure wounds that have tried and failed standard therapy after at least 30 days and complications of a surgically created wound that have tried and failed standard therapy after six weeks. All other diagnoses are considered on a case-by-case basis.

Noridian does have a coverage policy for negative pressure wound therapy. A complete wound therapy program must have been tried or considered prior to the application of negative pressure wound therapy, and they also have discontinuation criteria with the requirement that there has to be a measureable degree of wound healing for a total of four months.

AETNA has a coverage policy that mostly parallels Noridian policy with similar discontinuation criteria. Of note, with AETNA's policy is, they mention in the background section of the policy that the body of evidence is weak or insufficient in many of the areas. So, they cover it, but in their background section, they don't... they acknowledge that they feel the evidence is not strong.

Hayes is going to go into great detail regarding the evidence report. So, I'm just going to briefly summarize kind of the key findings and some of the key articles just to help bring you to how we came to our recommendation.

So, diabetic foot ulcers favor negative pressure wound therapy, key article being Blume 2008, a randomized control trial, quality fair, greater proportion achieved wound closure in the negative pressure group, 43% versus 28% in the active treatment phase, but they also noted fewer secondary amputations in the negative pressure wound therapy group, which I thought was a pertinent clinical outcome. As we shift to arterial and venous ulcers, the key article that they were quoting was a 2012 article; however, this was a retrospective chart review and so, it did show that it favored negative pressure wound therapy, but not the

typical type of article that I feels meet muster for determining whether an intervention is efficacious compared to standard care. When you look at pressure ulcers, there is the Ford 2002 article. This was a randomized control trial, but it only had 22 patients. It was only six weeks long. It showed there was decreased ulcer volume, but they also noted, after the study, that 15 of the cases had underlying osteomyelitis, which would compromise wound healing in any patient. So, I don't know that any good conclusions can be drawn from that study. Then, the retrospective chart review from 2012 showed a trend that wasn't statistically significant. Moving to the next ulcer population, a perspective cohort found that it favored negative pressure wound therapy, and with surgical wounds, there was either no difference or favored negative pressure wound therapy, depending on the condition. The strongest article being the Armstrong 2005, a randomized control trial that was in favor of using it for partial diabetic foot amputations. There was one study on pilonidal cysts, which showed no difference in time to complete healing and very small studies on perivascular wounds.

So, after reviewing the evidence report, three key findings came up. There was some indication that negative pressure wound therapy may improve wound healing. A fair trial for diabetic foot ulcers, but overall very low quality for the other ulcer types; however, the use of this modality is very common and diffuse across community practice, but the body of evidence available is insufficient to clearly prove an additional clinical benefit of negative pressure wound therapy, and these three key points are what the agency grappled with upon making a recommendation.

So, with that in mind, our current recommendation was as follows: The agency recommends to cover with conditions following appropriate step therapy, and by appropriate step therapy, the first step would be general and optimized wound care measures, as well as doing appropriate care for the conditions surrounding the etiology of the ulcer. What I mean by that is, like for a diabetic or neuropathic ulcer, their diabetes management should be optimized. If the ulcer is on the plantar aspect of the foot, there should be appropriate offloading. With pressure ulcers, appropriate offloading of that ulcer with position turns or appropriate mattress, no underlying osteo should be evaluated.

We would also recommend that there be discontinuation criteria and contraindication criteria. Discontinuation criteria would be if there is no evidence of wound healing with the therapy. We could also consider a time limit of four months with a case by case review needed for longer therapy. Contraindications, typical to what is currently recommended, the wound should be adequately debrided. It is not ideal if there is underlying osteo, malignancy in the wound, or fistulas or exposed open organs. And that wraps up this presentation. Any questions?

Chris Standaert: Questions for Dr. Johnson? Yes, Carson?

Carson Odegard: Yes. So, I have one question on... from just a kind of historical perspective, especially on data collection, what data were you collecting that would raise

concerns about safety, as far as medium concern of safety. I was just wondering what... I can see that cost issue in the...

Shana Johnson: Sure.

Carson Odegard: ...in the managed care sector, but.

Shana Johnson: Well, you know, I'll be honest that this topic was picked prior to my employment at the agency. So, I can only kind of make an assumption in that, any time we do a technology review, safety is of utmost concern. I guess there have been cases, well, like, you know how there's contraindications for negative pressure wound therapy? I think that highlights that there is potential safety concerns with it, um, like, if there's coagulopathy, and I think there was also some sort of FDA message that came out warning against not using it in certain indications. Someone else might remember those off the top of their head, like our clinical expert.

Chris Standaert: That was in the evidence report, mentioned the FDA report. So, I suppose if the evidence vendor feels comfortable discussing that they could do that.

Shana Johnson: Yeah.

Chris Standaert: If they answer that question. Do you guys... did you guys review that FDA warning as part of your report? You certain put it... referenced it in a?

Candi Wines: OK. Yes. We did read two alerts issued by the FDA, one in 2009 and a follow-up in 2011. There will be some details in my presentation if you want to wait until that point.

Chris Standaert: OK. Yeah. That is part of the... two separate alerts brought out by the FDA for safety concerns reported. It looks like outside of the literature to the FDA in their own reporting mechanisms that triggered them.

Seth Schwartz: I guess I would, I would have a follow-up question about cost and... in the sense that I'm trying to understand the cost of this treatment relative to the cost of alternative treatment.

Shana Johnson: Oh, yeah. So, I will, I mean, I think Hayes has more information about that, but, that's a little bit challenging, because I believe all the studies on cost were industry funded, and... so, she'll go more into that and give some conclusions. Well, were you talking about cost-effectiveness or just...oh yeah. Cost compared to usual therapy. So, Hayes will go into this in more detail. My recollection from their presentation that they presented was they compared it to usual cost of regular therapy requiring a nurse to come into the home and do the wound care. When I was in practice, my patients didn't necessarily need a nurse to come in and do their wound care. So, I don't know that it was a fair comparison.

- Seth Schwartz: I guess I'm asking more about the data that we have for the State of Washington, not the published data. In other words, do we have any sense of what it costs to care for patients with the same diagnosis who do not use...
- Shana Johnson: No.
- Seth Schwartz: ...negative pressure wound therapy?
- Shana Johnson: I don't believe we have that data. Kris, can you comment?
- Kris Urv-Wong: We didn't do the cut via the diagnoses. They were very diverse, and as Dr. Johnson said, they were very nonspecific. So, it was hard to look at apples and apples most of the time and to look at length of the diagnosis beforehand, as well, to make sure that we were really doing a match.
- Seth Schwartz: OK.
- Chris Standaert: I think some of his last question is that there are numerous ways that people treat these wounds of various sorts, wounds and ulcers, and reading the literature they're sort of all over the place, and some of which are commercial products, some of which are not commercial products. Some of which are probably fairly expensive. Some of which are probably not, um, and I guess I would wonder, probably close to what Seth was wondering, is there some other standardized protocol that was already approved by state agencies for use of these ulcers at home, product, commercial products are the things that we might be able to wrap our heads around in terms of costs, but if that's not available... I was wondering the same sort of thing.
- Kris Urv-Wong: That is a really great question, um, I don't think we have that data.
- Chris Standaert: Dr. Quigley, do you have a...
- Terence Quigley: If I may, I, I actually...
- Kris Urv-Wong: Yeah, please.
- Terence Quigley: ...tried to look this up prior to coming here today, because cost is always at the top of everybody's mind, and although I don't have the resources that the Hayes people have, and I would defer to them, the fact is that there's costs, there's costs, and there's costs. So, there's the cost of the therapy. That's one thing, and there's the cost of alternative therapies. That's another thing, but then there is the costs over the length of a wound. So, if you're going to cut the time for treatment in half, those costs, although more expensive per treatment, may, in fact, be less expensive for that patient's episode, and those data, at least I tried to look for that, I could not find that data, but that would be the data that the committee should really look at is the cost of therapy per episode of care, regardless of what you do.

- Shana Johnson: Absolutely.
- Gregory Brown: I have two questions. If I heard you correctly, you said the number one use in the state data was for surgical wounds.
- Shana Johnson: Nonhealing surgical wounds, yes.
- Gregory Brown: And so, that's, to me, different than chronic diabetic ulcers or wounds, which is where most of the evidence that you're talking about is from. Is that correct?
- Shana Johnson: Well, I guess, you mean the, the key articles?
- Gregory Brown: Well, again if, if the, if it's nonhealing surgical wounds, are we talking about nonhealing surgical wounds from a toe amputation in a diabetic, or are we talking about open wound in an open fracture?
- Shana Johnson: So, is your question, is our data more specific for the type of nonhealing wound, or is your question what are the specific studies on the specific nonhealing surgical wounds?
- Gregory Brown: It's two parts. My first one is, when you say the highest volume is a nonhealing surgical wound...
- Shana Johnson: Mm-hmm.
- Gregory Brown: ...what are the surgeries that are having these nonhealing wounds? Do we have that data?
- Shana Johnson: So, I'm seeing a no.
- Gregory Brown: OK.
- Shana Johnson: It was, it was difficult pulling the diagnoses, and that's part of the reason I referenced that a lot of the coding was very nonspecific, because I didn't want you to read too deeply into the data, because a lot of times it was just coded as ulcer or it was an extremely nonspecific code where I honestly couldn't guess the etiology of the wound, whether it was surgery or diabetic. So, it's the kind of data, I think, to take with a grain of salt, personally, because the coding is not specific.
- Gregory Brown: And the second question probably better for Dr. Quigley, because I don't think there's going to be evidence is just the sense of the diabetic wound heals, what's the probability they're going to develop another one in six months or a year or time point, or proceed to amputation. Is there a general?
- Terence Quigley: This actually... so it depends on how you define that. If you talk about another wound in the same patient, it's extremely high. If you talk about another wound at the same location, it's actually lower, because we're now focusing in on the

location. So, it kind of depends on how you define that, and I don't have the data off the top of my head, but a substantial amount of these wounds will recur and go on to amputation, because it's the old Einstein thing. If you do the same thing over and over again expecting a different result, you know, you're an idiot or so to speak. So, if a wound recurs...

Gregory Brown: I think it was the definition of insanity.

Terence Quigley: ...whatever. So, if you have a recurrent wound at the same location, we will not expend resources again, we will much more likely go straight to amputation, because it's already demonstrated it will heal, but then it will fail.

Gregory Brown: I agree with you. I would caution you, unfortunately, although that's your practice, it may not be the practice in the rest of the state.

Terence Quigley: It may not be, but...

Gregory Brown: Yeah.

Terence Quigley: ...I was asked to give you my opinion.

Gregory Brown: Yep. I appreciate that.

Shana Johnson: And I think it's of note that when we were just talking about the data and reviewing it, it was very rare or I shouldn't say it was very rare, it was very common to see multiple repeat offenders and multiple episodes of care for the same client, but I didn't put those notes up.

Joann Elmore: Mostly comments. The first two are for Dr. Johnson, and the third is for the vendor. Usually, the state report provides information on why this was chosen as a topic for us to review and information on utilization and cost and then what your recommendations are, and this is before we have the evidence review. So, I, in an era in which words matter, I was just a little caught by your second slide that seemed to be perhaps before we reviewed the evidence, you said that this promotes healing by promoting ideal wound healing environment. It seems to me that's the hypothesis.

Shana Johnson: Correct.

Joann Elmore: Not a statement. And so I just wanted to point out how we need to be careful with...

Shana Johnson: Yes.

Joann Elmore: ...words before...

Shana Johnson: And...

- Joann Elmore: ...we review the evidence.
- Shana Johnson: ...and it's interesting that you say that, and that I did that, because when yes, I said the same thing to the evidence vendor when they gave the report. Then I went and did it myself.
- Joann Elmore: So, I would just point out that this is the hypothesis...
- Shana Johnson: Correct.
- Joann Elmore: ...that we now will get to review the evidence. The second is more of a comment in which when we get these recommendations from the state, you all provide your suggestions and thoughts, which we sometimes follow, we sometimes don't, in regards to what you would recommend for cover and what kind of conditions, and I don't know that I've ever seen one go onto three pages. So, that kind of caught me a bit off guard. So, with that statement, we oftentimes realize the complexities, and we sometimes will come back to you later on in the morning, after we've gone over the evidence and have come up with our own suggestions, but sometimes we, as a committee of clinicians decide there are certain points where we just need to let the clinicians in clinical practice just assume that they will follow standards of care and FDA recommendations. So, I'll be interested to sort of listen to the evidence vendor. So, those are my two comments for you, Dr. Johnson. Then, for the vendor, I have a request. As you are going over the evidence, it will be important to me that I understand conflict of interest of these publications. It is very easy when one is assessing the size of a lesion, etc., especially if it's not placebo controlled, there is subjectivity to it, and the primary article cited by the state is one published in 2008 by Blume et.al, and there is a statement at the bottom of that that says, the cost of publication of this article were defrayed in part by the payment of paid charges. This article must, therefore, be hereby marked advertisement. So, as I looked through all of these different publications, indeed I have... agree with the vendor that the sizes are small. There is potential for biased, but I want to make certain that I also get your helping us review potential conflicts of interest in these. Thank you.
- Kevin Walsh: Joann, I think that was in the report.
- Joann Elmore: It was, but I want to...
- Kevin Walsh: I mean, there was a conflict of...
- Joann Elmore: ...make...
- Kevin Walsh: ...interest...
- Joann Elmore: ...yes.
- Kevin Walsh: ...in every single study that's been presented.

- Joann Elmore: Which was very helpful, and I want to make certain that they go over it verbally.
- Chris Standaert: Yeah. That is part of their structure anytime concerning bias and components of bias. That's part of their whole process. Other questions for Dr. Johnson? No? OK. We will move on. We will go to public comment. We are a bit early, but I assume... so, at 8:45 or 8:50 I will ask for people on the phone who might want to comment publicly, so we make sure we give that window. So, Josh, who do we have? We have... we will safely make that. We have seven people who signed up to make a public comment, one of which is Dr. Quigley. I don't know that you need to, do you have a separate public comment?
- Terence Quigley: I don't.
- Chris Standaert: OK.
- Terence Quigley: I was just trying to follow the rules.
- Chris Standaert: Then we have six people who have signed up, and we'll just go in the order in which they signed up.
- Josh Morse: We do have some [background noise] that may be [background noise].
- Chris Standaert: Do we go in the order they signed in or this order?
- Josh Morse: Let's go in this order here and then circle back.
- Chris Standaert: So, we have, well they're not all the, are they all the same? They're all, huh, Carmen Hudson. OK. So, four of you had pre-signed up. So, we'll go in the order in which you signed up, and then we'll go, go through the other two individuals. So, please, when you come up, you have three minutes to address the committee. Please introduce yourself. Tell us your relevant connection to this technology, conflicts of interest, if you were paid to appear here, you were paid to travel here, somebody else funded all that component of your comments, then that's helpful for us to understand, and it's essential that you do, that you let us know. So, our first speaker, William Struyk.
- William Struyk: I would ask that the physician go ahead and go first out of respect for her schedule.
- Chris Standaert: OK. That's fine.
- Carmen Hudson: Good morning. Thank you for letting me address you. I am Carmen Hudson. I am a physician. I'm a surgeon by training. The last four years I have solely done advanced wound care. I have the privilege of taking care of people in two settings. Number one is I go around to skilled facilities, so I have a unique experience of hands on wound care in a very vulnerable population. My second role is at the Cherry Hill Wound Clinic at Swedish, which is purely outpatient

wound care. I find it very interesting listening to the data, because this is a very difficult subject to do...

Chris Standaert: Just state any conflicts of interest, please, and your connection to...

Carmen Hudson: I have no conflicts of interest other than taking excellent care of people. Nobody has paid me to be here. I was asked... we work with KCI, and they just said are you interested in making a statement. So, I drove myself down here, and I have not received any compensation. So, addressing the evidence base, this is one area that you're going to try and look at the evidence, and this is going to be nearly impossible. You can see by the presentation by Dr. Johnson that the wounds are incredibly varied. The people who have those wounds are incredibly varied. Our best data, the Dr. Armstrong paper, he pretty much takes care of people. He's a podiatrist, takes care of people with diabetic foot wounds, their amputations. He's brilliant, and his good results are due to a multidisciplinary clinic. So, it's not even limited to negative pressure wound therapy, but that is a key to his care. So, the evidence that you're going to have is not going to be very good. For me, on the frontlines, I see this every day, making it possible for people to go to work. So, not only do you have the cost of the therapy, you're saving, in most cases, you're saving the length of time that you're treating a wound. You're also allowing a certain subpopulation of people to go back and be productive. I'm getting the one minute... a productive working environment, and we have two people right now that I can think of in our clinic that would not be working without a wound vac. So, there are multiple impacts on costs of... total cost of care for the wound, plus patient satisfaction and patient being able to be productive. The other thing that I would like the statement of... sorry, the signs are distracting me. So, what...

Randall Carson: [inaudible] ...and I'd like to give up my time to the doctor.

Chris Standaert: We've done that before.

Carmen Hudson: OK. I can keep talking, because I'm very passionate about this subject because we see people, as we get out from the radiation for breast cancer, radiation for all of this, we are seeing many more chronic wounds that cannot be... nothing else works besides negative pressure wound therapy. This is my daily experience. You're not going to find it in any papers yet. It's going to be very hard to study, because nobody wants to walk around with a draining wound for the control group. So, in considering evidence base and how this is going to be funded, I think it's important to talk to clinicians and maybe talking to clinicians who work in wound center, because I think you're going to get a sense of how important this therapy is. It was very interesting to me to see the five-year wound vac, because that would never happen in our clinic. If a wound is not healing, then it gets switched out for another therapy. So, the ability of people who do this every day, to use this therapy, I think, is very important, and if we're looking to cut costs by the five-year wound vac, maybe having some way to review those outliers rather than eliminating it for the bulk of people who use it and who benefit from it. Then just to address a couple of them, some of these things that we look at in our...

and we have to fill out about three pages of paperwork to even get negative pressure wound therapy now. So, I think that demonstrates for wound clinics that a nurse has to take an hour of time from patient care. That is how much we believe in it. It's not a whim. It works for us. It works for our patient, and I send out a plea, also, to review the necessity, the levels of paperwork, because we have a small clinic with no administrative support, and making it available for those clinics that know what they're doing and employ it in an educated fashion, is very important also to me to see happen. Then, lastly, the addressing the contraindications and when we don't use it and when it's not going to work, also very important. Because I work in skilled facilities, sometimes these are... we do use wound vacs on necrotic osteomyelitis to manage the last few days of a hospice patient to eliminate required nursing care that is disruptive. So, there are some instances that a clinician should be able to use against the contraindications based on the clinical intervention and the patient and what it is going to be used for. So, though we have nice evidence base, but it's not really good evidence, saying that maybe this isn't the best thing, I think you still have to rely particularly on... with the varied treatment possibilities, relying on trained clinicians that see this every day. It's going to be anecdotal, but I think it's very important, and I don't think that just because it's anecdotal makes it any less important. Thank you for your time.

Chris Standaert: Thank you. I just want to point out one thing about the comment there. There is no part or role or intention of our committee to cut costs. That is not a primary incentive. That has nothing to do with why we are here in that term. So, we are here to consider efficacy, safety, and costs and to ensure that treatments received by citizens of Washington are effective, safe, and cost-effectiveness in terms of other options for care. That's our job. So, the cost-cutting is not our role. It's not our job. It's not part of what we consider, just so you understand. I just want to be clear on that, just so it's not out there. Mr. Struyk, do you want to speak?

Bill Struyk: I would, please.

Chris Standaert: OK.

Bill Struyk: Hi. Good morning. For the record, my name is Bill Struyk. I'm here on behalf of AdvaMed. I'm a paid consultant for AdvaMed. On behalf of our member companies, we would draw your attention to what we perceive to be the program's need to consider coverage policies of health plans in reviewing technologies and for vendors to be more careful in reporting health plan coverage policies. The Health Technology Assessment program relies on a hierarchy of evidence valuing random control trials as the most valued evidence; however, many FDA approved devices, or pardon me, many FDA devices are approved without RCTs. So, the evidence that you most value isn't available. Health plans do not cover technologies that don't provide value. I think everyone's aware that it's... health plans will not pay for something that does not work. It's a pretty simple process. First, per the Hayes group report, the Healthcare Authority selected only certain plans to have their coverage policies on outpatient negative

pressure wound therapy to be reviewed. Two independent organizations, the Washington Osteopathic Medical Association and the Washington Federation of State Employees commented, commented that the Hayes group was not accurate on several of its reported findings, in its draft report, that is, leaving the impression that outpatient negative pressure wound therapy was not covered. This was true both for the Oregon Health Evidence Review Commission and Regence. There, if you would switch, and I am sorry, I'm not adept at... the screen isn't illuminated... to the third overhead, one back please. I found this in some of the literature that was published by the health technology program. This comes from Blue Cross/Blue Shield technology evaluation center, and it reported the following, and I will call attention to the highlighted or bold section. The evidence is sufficient to determine qualitatively that the technology, negative pressure wound therapy, that is, results in a meaningful improvement in the health net outcome and that emphasis is added. As you may know, and I think you all are aware, that your decisions do not apply equally to all of state purchased healthcare. For PEBB, public employee benefit members who receive their... and retirees who receive their care... I've got to yield, a get out of jail card that is. The fee for service... your decisions apply to fee for service but do not apply to those PEBB members and retirees that receive their care through managed care, primarily Group Health. For this technology, Group Health closely follows the Noridian local coverage decision. There may be times that your decisions may not agree with the coverage policies of health plans and I would encourage you to extend the treatment required by Revised Code of Washington 182-55-035.3, which you all have memorized, but it says...

Chris Standaert: OK, can you, you need to, are you concluding or?

Bill Struyk: I'm getting dang close.

Chris Standaert: OK, please.

Bill Struyk: Well, I got a yield.

Chris Standaert: Oh, OK. I'm sorry. I didn't know what that meant. I apologize.

Bill Struyk: No.

Chris Standaert: It was a reset.

Bill Struyk: It was obscure.

Chris Standaert: OK.

Bill Struyk: That requires the program to stay... the committee to cite the evidence that you rely upon in reaching a coverage decision that's different from physician specialty and patient advocacy organizations. And I think that same requirement would likely be extended to health plan coverage decisions where you're in conflict with that. I will read, finally, and mercifully for you folks, a paragraph from the

Washington Federation of State Employees letter on this issue. They, the Washington State Federation of State Employees, also take this opportunity to respectfully raise concerns about the level of due diligence in the reporting coverage policies of the selected health plans, limiting research to a mere website review. The impression that we were left was that negative pressure wound therapy was not covered by plans, when in fact, it appears it is a standard of care for certain patients with wounds that are not healing and needs no further evidence to merit coverage. Reliance on the Health Technology Assessment program evidence hierarchy could likely result in coverage policies that would negatively impact patient outcomes. That concludes my remarks. If there are any questions, I'd be happy to answer them. I've got 30 seconds remaining. I will yield my time.

Chris Standaert: Thank you. Is that Wei Lin who yield, is... did... I'm not sure what your name is. OK. OK. Then Randall Carson would be next.

Randall Carson: I yielded my time.

Chris Standaert: Oh, you yielded your time.

Randall Carson: But can I make one comment. [Not at microphone, unable to hear.]

Chris Standaert: We are not device specific. We follow the technology that is given to us by our evidence vendor and as directed by our state agencies is what we do, and if there's a... we're not debating this, but if there's some issue that you have a technology that doesn't fall under this, you bring that up with the state not with us. We talk about our evidence.

Randall Carson: [inaudible]

Chris Standaert: We talk about the evidence we have. That's what we do. Again, if there are discrepancies with what falls under that definition in terms of device, that's for the state to determine, not us. So, we'll talk about the evidence we have, but thank you.

Gregory Brown: Can I ask a clarifying question?

Chris Standaert: Yes.

Gregory Brown: Is that the P-code?

Randall Carson: That's correct. Thank you.

Chris Standaert: Next would be Misty Wood.

Misty Wood: [inaudible]

Chris Standaert: Oh, you don't have a comment. OK. Alia Griffing, am I missing the last, is there another consonant at the end? Griffing? OK.

Alia Griffing: Thank you. My name is Alia Griffing. I am on staff with the Washington Federation of State Employees. So, I am here in that official capacity. I traveled up. I will be reimbursed for my travel today. So, I wanted to not repeat the comments you heard from Bill Struyk, as he was describing the letter that we submitted. Hopefully, you've seen a copy of that, but what I do want to talk about is, our fear is that there could be a scenario where PEBB subscribers have no coverage for a technology that is... or a device that is commonly covered. So, I think that's specific to negative pressure wound therapy but also, I think, in the work that you do here in general. So, I am reminded of bariatric surgery where we had a scenario where Group Health Cooperative subscribers were covered in ways that were consistent with NIH criteria and national standards whereas UMP members were not. That has since been fixed, but those are the scenarios we're trying to avoid here. So, I was happy to see the information that was in the Health Care Authority slide this morning detailing marketplace practices and wish... I was a little disappointed with the Hayes report. I haven't, I admit I have not looked at the final report. I did look at the draft, but there are two areas where it was commenting on website review and no further detail. So, I just urge you to dig a little deeper than that and appreciate your time.

Chris Standaert: Thank you. Alright, 8:50 and we are within our public comment. Is there anybody else in the room who wants to address the committee? No? Can we open up the phone and see if there's someone on the phone listening who might want to address the committee, as well? So, if somebody is listening on the phone, this is the meeting of the Washington State Health Technology Clinical Committee. We are in the timeframe for public comments to the committee on negative pressure wound therapy. If there's someone on the phone who would like to address the committee, please speak up and introduce yourself. Hearing none, I assume we don't have anybody there. OK. So, we will move on. Done with this, yes. So, next is our evidence vendor to help us.

Candi Wines: Good morning. This presentation accompanies the Health Technology Assessment negative pressure wound therapy home use, as you have all heard in previous discussions this morning.

This second slide in the deck is a list of shorthand and abbreviations used throughout the presentation. It's for your reference.

The presentation is divided into five sections, the background; the scope, methods, and search results; the findings; and then a section on practice guidelines and payer policies; and conclude with an overall summary and discussion.

As presented to you earlier, negative pressure wound therapy involves the application of subatmospheric pressure or suction to the surface of a wound. It's

intended to provide a moist, warm wound bed and remove wound fluid. Devices may promote several actions associated with wound healing.

This figure shows a generalized negative pressure wound therapy application with a foam dressing, adhesive film, and tubing that connects to a pump. Continuous or intermittent controlled negative pressure is applied across the wound and wound effluent is collected in a canister.

Numerous devices are commercially available, and they vary in many aspects, such as size, portability, disposable or reusable parts, and also source of power. Dressing changes are typically performed every 48 to 72 hours, and usually no less than three times per week. Some models are designed to stay in place for several days.

The potential or purported benefits of negative pressure wound therapy include symptom management, reduced frequency of dressing changes, and potentially cost-effectiveness compared with alternative therapies, because of faster healing times that may lead to lower overall treatment costs. There are also potential harms. These include pain, retention of foreign bodies from the dressing, bleeding, infection, death from infection or bleeding, and complications stemming from loss of electricity for powered devices.

Safety concerns, particularly those related to home use prompted the Food and Drug Administration to issue a preliminary notification in November of 2009. The alert stated that complications are rare, but they can occur in any setting where negative pressure wound therapy systems are used. Most of the six reported deaths and 77 serious injuries reported to the FDA in a two-year period between 2007 and 2009 occurred at home or in a long-term care setting. The FDA issued a follow-up, or an updated safety communication in 2011 that included an additional six deaths and 97 injuries, since the previous alert. These FDA notices are labeled as archives on the FDA website and no more recent notifications were identified.

The FDA alerts included education for providers that listed the contraindications shown here. These contraindications appear on most device package labeling and some device labels also include untreated malnutrition, as a contraindication.

The provider education also included patient risk factors to be considered before negative pressure wound therapy use, and these are shown here on slide 11.

The wound types of interest for this Health Technology Assessment were chronic wounds. These are defined by type or etiology and not by duration. Chronic wounds may be caused by pressure or shear, or be related to an underlying condition, such as diabetes or vascular disease. They included venous leg ulcers, diabetic foot ulcers, pressure ulcers, and mixed etiology chronic wounds. Patients with chronic wounds may experience a range of severity, including substantial limitations in mobility and poor health-related quality of life. Also of interest were surgical wounds. Surgical wounds typically heal by either primary intention

or secondary intention. Primary intention is when the wound is closed by sutures or other means, and secondary intention is when a wound is left open for the healing process. So, excluded from this review were studies of wounds associated with burns, trauma, fractures, or skin grafts or flaps.

The policy context slide is a reminder of the policy context for this topic. The agency was interested in the home use of negative pressure wound therapy in terms of safety, efficacy, cost-effectiveness for chronic and nonhealing wounds.

Studies of patients with chronic or surgical wounds comparing negative pressure wound therapy with other wound care methods or comparing different negative pressure wound therapy devices and reporting at least one of the clinical patient safety or cost outcomes of interest and were conducted in the home setting were sought for this Health Technology Assessment.

Setting was a key characteristic for determining eligibility. Studies were included if they were described as home or outpatient setting, and studies with mixed inpatient and outpatient populations were included if they provided information on the proportion of patients or the proportion of therapy days, in the inpatient versus outpatient or home setting.

The key questions focused on clinical effectiveness, harms, and varying effectiveness for safety and subgroups, as well as cost implications.

The search for evidence began with identifying systematic reviews with a focus on similar wound types and home setting. Update literature searches were conducted to identify additional eligible primary studies.

This figure shows the flow of literature through the search and selection process. Three systematic reviews you can see in the upper right hand corner here. Three systematic reviews considered to be of good quality were identified. One of the systematic reviews was published by the agency for healthcare research and quality in 2014. They focused on chronic wounds in the home setting. The other two systematic reviews focused on surgical wounds and were produced for the Cochran collaboration. The authors of these reviews screened a large volume of literature and ultimately found few eligible publications for their reviews. For example, the literature search for the ARQH systematic review yielded 5912 unique citations and the final number included studies with seven. The two Cochran reviews screened almost 800 citations and one of them included two studies, and the other included nine studies.

So, after we selected these three systematic reviews, we conducted update literature searches to capture new literature, since their publication, and we screened 1441 citations from PubMed, Embase, and manual searches of key references, and ultimately included 24 articles representing 17 studies. This included 11 primary studies that came from the original systematic reviews. 12 of the studies were populations on chronic wounds and five studies with populations in surgical wounds. I'll just take a sidebar here to say of those 17

studies, 14 of them did report funding or professional relationships with device manufacturers. Three of them did not report funding sources or a conflict of interest.

Although a review of review methodologies was employed to identify some of the included primary studies, standard practices were used in all other phases of the review process, which means all individual primary studies, whether they came from the systematic reviews or from the update literature searches, were assessed for eligibility, abstracted, and quality rated. Each individual study was given a rating of very poor, poor, fair, or good. Bodies of evidence were graded as very low, low, moderate, or high.

Moving on to the findings: For key question 1A regarding all chronic wound types together, the overall quality of the body of evidence from six studies, which included two randomized controlled trials and four observational studies. So, it's considered to be low.

The next two slides provide a high-level description of the studies of chronic wound types and the results are shown later. For the effectiveness of home use of negative pressure wound therapy to treat chronic wounds, studies were organized based on the type of wound investigated. The evidence for specific outcomes for each wound type varied in volume and quality. The chronic wound category with the most studies for this key question was diabetic foot ulcers represented in four studies. Results for two clinical outcomes of interest and one patient centered outcome of interest were available from these studies. Two other studies focused on patients with pressure ulcers and one clinical outcome was available from these studies. Evidence for the home use of negative pressure wound therapy for treating arterial or venous ulcers consisted of one study that reported one clinical outcome. Evidence of two clinical outcomes was available from two studies evaluating mixed etiology wounds.

Slide 25 shows the results for complete wound healing from three studies of patients with diabetic foot ulcers. The direction of effect in each study favors negative pressure wound therapy. The results shown from the Blume study is the proportion of patients who achieved complete ulcer closure within the 112 day active treatment phase. Lavery reported a proportion of patients achieving a successful treatment endpoint at 12 and 20 weeks, and the Yao study reported the hazard ratio for negative pressure wound therapy patients compared with matched controls.

Results from diabetic foot ulcer studies are continued here on the next slide, and only the Blume study reported time to complete wound healing. A median time to complete ulcer closure was statistically significant in favor of negative pressure wound therapy. One study, the Fife study from 2008, used a surrogate measure to assess pain and found no difference between groups.

Slide 27 shows the results for complete wound healing for arterial or venous ulcer patients from the Yao study. Those who received negative pressure wound

therapy had a higher incidence of healing than those in the non-negative pressure wound therapy group.

Two studies reported on complete wound healing for patients with pressure ulcers. Neither result was statistically significant, and the direction of effect was different in each study. The Ford study, 22 patients with 35 ulcers completed the trial, and results were analyzed per ulcer rather than per patient. The authors of the ARC systematic review calculated the risk difference and the confidence interval, which shows the difference is not significant.

Different wound types were analyzed together in two studies. Lerman and colleagues studied the Snap device compared with the variety of other wound care methods. Statistical significance of complete wound healing was not reported. The difference in mean time to wound healing was statistically significantly different. The Yao study reported a statistically significant difference in complete wound healing when all wound types were combined.

Switching now to key question 1B and surgical wounds. Four randomized control trials reported clinical or patient centered outcomes. The reasons for surgery were different across the studies, as were the comparison treatments. Three assessed the use of negative pressure wound therapy in patients with surgical wounds, healing by secondary intention, and one reported on the use of negative pressure wound therapy for surgical wounds healing by primary intention. The aim of this study was to assess the routine use of negative pressure wound therapy after uncomplicated knee arthroplasty. In this study, negative pressure wound therapy was used for eight days with the average length of hospital stay being four days, so part of the care was received outside of the hospital. With respect to surgical wound healing by secondary intention, the overall quality of the body of evidence is considered to be low. For surgical wounds healing by primary intention, the evidence is insufficient based on one small randomized control trial with limited results for eligible outcomes.

One study reported results for complete wound healing. That study reported that among patients with diabetic foot when related to amputations, a higher proportion of wounds were healed in the negative pressure wound therapy group than in the standard moist wound therapy group. Three studies reported time to complete wound healing. One found no difference between negative pressure wound therapy and silicone dressing for patients being treated for pilonidal sinus, and one study found the median number of days to complete wound healing most statistically significantly shorter in the negative pressure wound therapy group compared with a group receiving alginate dressing for deep vascular wound infections. In the third study, patients with diabetic foot related amputations receiving negative pressure wound therapy healed faster than the standard moist wound therapy group.

Results from two of the studies of wound healing by secondary intentions suggests no difference between groups for patient-centered outcomes of pain, quality of life, and return to prior level of activity. A small randomized control

trial in which patients who received bilateral knee arthroplasty served as their own controls, reported better scores for dressing leakage, and wound protection for the negative pressure wound therapy knees than the conventional dry dressing knees, but no other quality of life factors were statistically significantly different. Risk factors included odor, itch, movement, body image, self-esteem, personal hygiene, sleep, and pain.

Moving to key question two and safety. Six studies, two randomized control trials and four observational studies reported on adverse events in patients with chronic wounds, and five randomized control trials reported adverse events in patients with surgical wounds. The overall body of evidence for harms associated with the home use of negative pressure wound therapy for chronic or surgical wounds is considered to be low.

Few studies reported adverse events. Among those that did, reported rates of adverse events were lower in the negative pressure wound therapy or there was no statistically significant difference between groups. This slide shows the results for amputation, infection, bleeding, and edema from three studies of patients with diabetic foot ulcers.

The results summarized on the next slide are from three studies that included patients with pressure ulcers or mixed etiology ulcers. Only one of these provided a comparison and conducted statistical tests for significance. This study found that home care patients with pressure ulcers who are being treated with negative pressure wound therapy, this was a group of 60 patients, were less likely to experience emergent care or hospitalization for wound problems than those not receiving negative pressure wound therapy and this was a group of 2288 patients.

One of these studies reported various complications that required withdrawal from the study in the negative pressure wound therapy group but did not report adverse events for the comparison group. These events included allergic skin reaction to the dressing, bleeding post-debridement, worsening of lower extremity edema, and maceration to the periwound skin.

With regard to harms reported in the studies of surgical wounds, infection rates were reported in four out of five studies. In one of these, the rate of infection was higher in the negative pressure wound therapy group than the standard treatment group but statistical sign was not reported. In one study of patients undergoing knee or hip arthroplasty reported a four-fold reduction in post-surgical wound complications for the negative pressure wound therapy group compared to the control group, but the results did not reach statistical significance.

Other adverse events reported in these studies included readmission, mortality, and blisters. In most cases, the significance was not reported or there was no statistically significant difference.

Key question three pertains to the varying clinical effectiveness or safety. Overall evidence for this key question is considered to be very low. Among the chronic wound studies, two compared different negative pressure wound therapy devices and two provide information about the role of wound size and chronicity. No studies looked at comparative effectiveness in relation to clinical history, duration of treatment, or patient characteristics. One randomized control trial of patients with surgical wounds assessed the role of wound chronicity and healing among patients with diabetes who had partial foot amputations. The next few slides provide details of the findings from these studies.

One randomized control trial comparing the SNaP device with the V.A.C. device found no difference in the proportion of wounds healed over time, but among 105 patients who completed an exit survey, 79% of the SNaP device treated patients compared with 58% of the V.A.C. treated patients indicated that they agree or strongly agree they were able to perform normal daily activities. Similarly, more SNaP patients reported that their activity level either increased or stayed the same. Pain and rates of adverse events were similar between the groups.

One retrospective national claims database analysis compared the KCI V.A.C. with non KCI models. At three months and six months. Wound related readmission rates were statistically significantly lower for the KCI V.A.C. group compared with the non-KCI device group across all wound types.

One study among patients with diabetic foot ulcers examined healing in relation to ulcer size and wound duration at 12 and 20 weeks. The authors concluded the negative pressure wound therapy treated patients reached a successful wound treatment endpoint more rapidly and the benefit was apparent in all wound sizes.

One study among patients with mixed etiology wounds evaluated whether the timing of negative pressure wound therapy application had an effect on healing. The ulcers in the early treatment group had a higher incidence in wound closure compared with those in which negative pressure wound therapy was initiated later.

And finally, a secondary analysis from a randomized control trial assessed the role of wound chronicity and wound healing after partial foot amputation in patients with diabetes. Results indicate no statistically significant difference between the groups for the proportion of either acute or chronic wounds achieving complete wound closure; however, time to complete closure was significantly different, in favor of negative pressure wound therapy for both acute and chronic wounds.

For key question four, we identified six economic studies. All studies found that the primary negative pressure wound therapy device of interest in that study, which was either the SNaP device or the V.A.C. device, resulted in cost savings over usual care or alternative negative pressure wound therapy devices. These analysis are limited by the quality and applicability of the evidence used, and all of the studies were funded by device manufacturers.

The following three slides briefly summarize the methods and purpose of each study. Hutton and Sheehan used decision analytic modeling to compare the cost of the SNaP device with standard care and electrically powered negative pressure wound therapy devices over a 16-week therapy period. Costs were based on literature, comparing negative pressure wound therapy with modern dressings and Medicare reimbursement rates. Costs of treatment included direct costs and other healthcare costs for diabetic lower extremity wounds. Driver and Blume conducted a post-hoc analysis of a randomized control trial of patients with diabetic foot ulcers receiving V.A.C. and those receiving advanced moist wound therapy. Costs were calculated from patient's healthcare utilization.

The Lavery study aimed to assess the differential cost of care in the outpatient setting between negative pressure wound therapy and wet to moist therapy to treat diabetic foot ulcers. The 20-week expected cost of care was calculated using weekly costs of nursing visits, supplies, and physician costs. Apelqvist conducted an economic analysis based on data from patients who completed at least eight weeks of treatment in an RCT of diabetic patients with post-amputation wounds. Investigators aim to evaluate resource utilization and direct economic cost of care for patients treated with the KCI V.A.C. device compared with those who received moist wound therapy. Direct costs were calculated retrospectively using data on resource use for each patient.

A Markov model analysis was conducted by Flack and colleagues to estimate the cost for amputation avoided and the cost per quality adjusted life year. For the KCI V.A.C. device therapy compared with traditional and advanced wound care dressings, data from published sources were used to define progression and selected clinical trials provided information about the effectiveness of treatment with respect to healing rates. Costs for traditional advanced and V.A.C. dressings were obtained from reimbursement data and expert opinion. Costs for antibiotics and utility weights per quality adjusted life years came from published literature. Law and colleagues conducted a retrospective claims database analysis of all patients who had submitted a claim to major insurance company for negative pressure wound therapy in an outpatient setting in the United States at 3-month and 12-month treatment periods. Chronic wounds comprised 81% of the wounds. Acute wounds were also assessed. Negative pressure wound therapy with KCI V.A.C. device compared with non-KCI model devices in this study.

This portion of the presentation is an overview of payer policies and practice guidelines. Details and links to policy documents are provided in the full report. Many of these were discussed previously, so this will be a brief review of the information you heard earlier. At the direction of the Washington State Health Care Authority published coverage policies for the following organizations were sought. Centers for Medicare/Medicaid services, AETNA, Group Health, Regence, Blue Cross/Blue Shield, and the Oregon Health Evidence Review Commission. Of note, the lack of a published coverage policy does not necessarily indicate that a

payer does not provide coverage. It just means it's not a written policy necessarily.

For the Centers for Medicare and Medicaid Services, there is a local coverage determination that states the negative pressure wound therapy pumps and supplies are covered when ulcers and wounds are encountered in an inpatient setting, or in the home setting when the criteria are met. Some of these were described, too, earlier. Similarly, AETNA covers negative pressure wound therapy pumps, as medically necessary for ulcers and wounds encountered in inpatient or home setting. Group Health Cooperative covers negative pressure wound therapy pumps and supplies for wound edema, exudate management, and stimulation of granulation for an initial 14-day course when the criteria are met for ulcers and wounds in an inpatient setting or in the home setting, and there is a goal of therapy clearly stated, and there are no contraindications for use, as identified in the policy. No published coverage policy was identified for the Regence Group. With respect to the Oregon Health Evidence Review Commission, no published coverage policy was identified; however, the prioritized list of health services references a guideline note regarding negative pressure wound therapy that applies to several lines within this list. This guideline note is quoted on this slide, and in addition, the Oregon Medical Fee and Payment Rules provide a maximum limit for monthly device rentals under code E2402.

The next two slides summarize five practice guidelines pertaining to negative pressure wound therapy and different wound types. Generally, the guidelines do not mention setting of care. Four of the five guidelines support the use of negative pressure wound therapy in some circumstances, and one guideline states that the group could not make the recommendation on the use of negative pressure wound therapy and nonsurgical diabetic foot wounds because of the lack of available evidence.

Another guideline does not support the routine, primary use of negative pressure wound therapy for venous leg ulcers.

So, to begin the overall summary and discussion, this slide is a reminder of the definition of the quality of evidence grades for the body of evidence. Most of the evidence presented was assessed as low or very low, as summarized in the next slides.

Results for key question 1A included studies that generally were consistent for the few outcomes that were reported in more than one study, suggesting negative pressure wound therapy improves wound healing and time to wound healing compared with other wound treatments, particularly in relation to diabetic foot ulcers; however, the quality of evidence was considered to be low. For key question 1B, overall, the results favor negative pressure wound therapy for the clinical outcomes reported, complete wound healing in one study, and time to complete wound healing in two of three studies; however, the overall quality of the body of evidence was considered to be low.

With respect to safety, the quality of the overall body of evidence for harms associated with the home use of negative pressure wound therapy for chronic wounds and surgical wounds is considered to be low. Contributing to this body of evidence were six studies of patients with three different types of chronic wounds and five studies among patients with surgical wounds.

For key question three, evidence from five studies was considered to be of very low quality, and as they are such, we cannot make a statement on the findings.

The economic analyses included for key question four provided information about the cost of negative pressure wound therapy compared with usual care or other devices. All studies found that the primary device of interest resulted in cost savings over usual care or alternative negative pressure wound therapy devices.

So, in conclusion, there are many gaps in the evidence regarding the home use of negative pressure wound therapy. Future work needs to include larger, more rigorous prospective studies and consistent definitions and measurements for direct outcomes across studies would also be helpful. Publications with better reporting of study protocols, including settings and details about who changes the dressing and comparators and other treatments are needed. Clear descriptions of inpatient and outpatient care would help identify studies applicable to the question relevant to home use. This is key for performing future comparative assessments, as wound care is highly dependent on factors, such as who performs the care, the complex nature of wound care, the wide variety of products, and differing backgrounds of providers make it very difficult to replicate across healthcare settings. Lastly, there is a need for more studies examining the response to treatment according to patient characteristics, such as comorbidities, smoking status, and age. Thank you.

Chris Standaert: Thank you. So, now is the chance for the committee to ask questions to you directly based on your presentation. You obviously can't go anywhere until we're all done, whether you want to or not. You can't flee yet. So, for the committee, this is a good time to ask questions, and then as we go through our discussion, the evidence vendor will be available to keep asking questions, as they come up. I just want to clarify one thing about the scope of our topic and our decision. This is outpatient in-home use and that was in the PICO tables. It was in the key questions, and it looks like you excluded 35 studies due to setting. So, if there is data, good, bad, or indifferent, on, I assume, skilled nursing facility or inpatient use of these devices, we don't have it.

Candi Wines: Right.

Chris Standaert: And therefore, our decision has nothing to do with those applications. I have no idea why the state drew that line, but my assumption, then, is we're talking about home and outpatient use only, and again, our... the agencies will have to figure

out what they do with inpatient or skilled nursing facility use, because we won't be addressing that, correct?

Candi Wines: 90% of the care was in the home or outpatient setting, that is why...

Chris Standaert: That's why you...

Candi Wines: ...the topics was...

Chris Standaert: ...picked it that way.

Candi Wines: ...scoped to that, yeah.

Chris Standaert: OK.

Gregory Brown: So, for definition purposes, inpatient care, does that include skilled nursing facilities?

Candi Wines: So, inpatient care was inclusive of acute facilities, such as hospitals and long-term care skilled nursing facilities.

Gregory Brown: So, home health, excuse me, adult family homes are not considered to be there. That would be considered home care?

Candi Wines: No. I don't, we didn't come across that as a description in any of the studies, but I don't think it would have...

Chris Standaert: I think from our standpoint, though, so from a committee's standpoint, we're talk... we're saying home or outpatient. We're not looking at inpatient use. We're not looking at skilled nursing facilities. We don't have that data. Where the State draws that line and defines something as skilled nursing care on a continual basis. That is really going to be up to them, ultimately, not us how they define that and how they... that's billed and paid for, but they draw that line.

Dan Lessler: Adult family home would not be considered skilled nursing. So, it would be outpatient for that specific question.

Seth Schwartz: I think this is challenging, because along those lines, what I'm concerned about is, when we're looking at efficacy data for the technology, I think it would be valuable to know, 'cuz if this is... if we look at the inpatient data and find that this is a highly successful treatment, I might have a different perspective on how I look at this relatively low-quality outpatient data, because... and so I think that... I guess, I'm going to ask Hayes if those papers were just simply thrown out or if there was any... if they can make any comment about the use of this technology in the inpatient setting, whether there are higher quality randomized trials or other studies that would indicate whether this is efficacious or not.

Candi Wines: So, we did not evaluate the studies described as in those settings.

- Chris Standaert: And I think part of the dilemma there is the continuation. You start somebody on treatment inpatient and then you send them home. All we know is the home. I mean, and somewhat these are... you could make the argument there are distinctly different ulcers that are treated inpatient or outpatient, just strictly different patient groups. People who are sicker and more dependent are more likely to be inpatient, I would assume, but like they said, most of it is outpatient. Again, that limits our... so, you in your head as a committee, so I think that [inaudible]... we're limited to that.
- Gregory Brown: I think the issue is a more practical one from a DRG perspective. Anything that's done in the inpatient setting isn't broken out as a separate payment. So, I mean, if I use it in an open fracture in the hospital, it's included under the DRG for the fracture care. So, the state can't change that DRG nor does it have any interest, I'm sure, and so anything inpatient would be covered under those payments. I understand what you're saying.
- Seth Schwartz: I mean, this is a totally different point, which is, I'm just trying to understand the technology and I'm looking at the feasibility of these studies. It's challenging to do a study in an outpatient population. It's much easier to do when you have these patients you can see them every single day and you can do probably better assessment of whether the wound is healing or not. So, that... I was just more curious along those lines, but I completely understand your point.
- Gregory Brown: I guess the way I rationalized it is, really what we're looking at is, is this an effective technology for treating chronic wounds, whatever the source, venous, arterial, diabetic, mixed, surgical, postsurgical, in an outpatient setting.
- Chris Standaert: Essentially, yes.
- Gregory Brown: And so, anyway.
- Chris Standaert: Is everyone clear... I just want to make sure we're on the same page there. So, I understand. So, questions from the committee on data on the report on...
- Gregory Brown: I have a question. So, when you talked about the outcomes that you reviewed, or that the studies reported, it was an earlier question to Dr. Quigley. I didn't see anything about recurrence rates or need for amputation, further amputation. Is that a correct statement?
- Candi Wines: Amputation rates were covered under harms. I'll try to find that study, as I'm talking.
- Gregory Brown: OK.
- Candi Wines: We did not look at information on recurrence. Some studies noted that patients may have had multiple wounds, but the study focused only on the wound receiving the negative pressure wound therapy care other than the one study I

mentioned where the analysis was done per wound. So, 20, I think it was 22 patients with 35 wounds. So, no information was gathered for this report on the recurrence after the healing was documented or not.

Chris Standaert: What was the longest duration of follow-up for a wound after wound closure was identified on these studies? How long did they follow people to make sure the wound stayed closed?

Candi Wines: That's a good question.

Chris Standaert: I had trouble wrapping my head around that as I heard that. So, I didn't see that these were durable. The durability of this I didn't see.

Candi Wines: Right. Many of those studies didn't provide great detail about follow-up after treatment. They described follow-up periods, such as the Yao study, which was a retrospective study, looked at a cohort over a period of eight years, 2002 to 2010. There is a table in that paper that shows person years of follow-up for each wound type. So, there is some variation there, and one of the studies applied treatment for six weeks, so 42 days. One study reported duration of treatments a mean of, I think, somewhere around 56 days for one group and 70 something days for the control group, but follow-up after that was poorly described mostly, yeah.

Gregory Brown: So, that's what I'm trying to understand is, the way I see it being reported is that they measured time to healing, and if they said it healed at three and a half weeks, but it recurred at five weeks, they didn't report that. Is that a correct statement?

Candi Wines: Well, we didn't record that outcome, and I can't recall if some of the studies reported it or not.

Gregory Brown: OK.

Candi Wines: We didn't record that.

Chris Standaert: Other questions for the vendor? Carson?

Carson Odegard: I have a question about the Yao study. This is just a methodology question, but when you see such significant or hazard ratio.

Chris Standaert: You're talking about the Yao study. Stay close to the mic there.

Carson Odegard: Oh, sorry. Sorry. Talking about the Yao study, because I... when you see such significant hazard ratios and then you look at the bulk of the patients are mixed ulcers. So, when, like on slide 27 arterial ulcers are about half the study population. So, do they pull those patients out to get those hazard ratios, or that was taken in the mixed?

- Candi Wines: No. They did analyses based on wound type. So, they had analyzed all wound types together in the mixed etiology wounds, and then they did analyses based on wound type. Some patients may have had more than one wound type, so they might have been in more than one group.
- Carson Odegard: Right, but so they took the 173 out of 342...
- Candi Wines: Yes.
- Carson Odegard: And studied that group.
- Candi Wines: Yes.
- Carson Odegard: OK.
- John Bramhall: Do you come across any subjective data when you look through your information, subjective in the sense of what the patients themselves appreciated about the different ways that their wounds could be dressed? You know, I'm thinking that someone's got a bulky, wet gauze on their leg versus a little cling film. Did you come across any comments on that in the literature?
- Candi Wines: So, we did look for, like a patient-centered outcomes. Typically, we were looking at quality of life surveys or assessments. A couple of studies reported on quality of life outcomes. One I mentioned was the study that conducted the exit survey that compared two different devices with each other, and the other study was the study on the bilateral knee arthroplasty where they asked about care on two different knees in the same patient. So, those were surveys given to the patients in the study, and they gave feedback in that form, but generally information about patient experience was lacking.
- Chris Hearne: Did you get a sense of how far along these wounds were when people were enrolled into the studies. So, how long had this chronic wound been present before they got started on the therapy?
- Candi Wines: Mm-hmm. There, again, a couple of studies I reviewed talked about application of negative pressure wound therapy at different stages of chronicity, and they were defined, I think, similarly in the studies that looked at it, acute or chronic based on months of duration and in the patient characteristics part of the evidence table, there is more information about duration, average duration I think, on wounds for the patient populations when it was reported.
- Chris Standaert: So, no questions. I'd be curious about your comment on what Dr. Elmore brought up before, that one of our prime RCTs was funded by the manufacturer, statistics were performed by the manufacturer, and apparently, it looks like its publication was paid for by the manufacturer, and the publisher classifies it as an advertisement. Your comments on the inclusion of that as high level evidence in an evidence-based study, an evidence-based report, it struck me as curious. I'm

not used to seeing medical research classified as advertisements by the publisher. Nor am I used to seeing that considered as high level evidence.

Candi Wines: Right. So, we did... we rated this as a fair quality randomized control trial. There was some discussion about including it or not. It is a study that looks at both inpatient and outpatient population. So, it's a mixed population. So, the applicability to this question was uncertain, although the majority of care was reported as being an outpatient basis. So, we thought that it did provide some information of relevance to the question of home use and yes, there were some methodological flaws, but we didn't identify anything that would be egregious or downgrade it to a poor quality. So, we rated it as fair.

Chris Standaert: There was a relatively critical commentary on this paper. This is the paper by Blume we're talking about that really blistered it a bit, including issues of discontinuation, which was 50 people in one group, 43 including self-withdrawal, withdrawal by investigator, ineffective therapy. They just pulled people out of the study for very unclear reasons, and the commenters found that bothersome and the commenters couldn't recreate their statistical results from the statistics they published. There's a whole question of it being an advertisement, a peer review and all these other issues sort of come to mind. So, you know.

Kevin Walsh: I would follow up and ask, what basis did you rate this...

Chris Standaert: On what basis did you rate it fair, yeah?

Kevin Walsh: ...I, I don't, yeah. I mean, they can exclude whatever data they want to portray whatever they want, and then that's called high quality work?

Candi Wines: Did you want me to? OK. I, I don't have my rubric in front of me right now, but we did put it through our checklist for our grading individual study quality, and based on randomized control trial design and other criteria, it was downgraded. It started as a good. That's how we usually start with randomized control trials. We downgraded it to fair. I can look at my notes during the break and give you more details if you need it.

Karen Crotty: Can I make a, sorry. This is Karen Crotty. I'm with the vendor.

Chris Standaert: Yeah.

Karen Crotty: Just on the issue of conflict of interest and looking at risk of bias, it's difficult to do. A manufacturer funded study does not obviously in itself mean that something is going to be of poor quality. What we try to look for is, if there's a protocol, for example. Was there a deviation from protocol? Were the statistics changed from the protocol? From what, as Candi pointed out, methodologically, what we are tasked to do is look at the risk of bias for things like were the groups comparable in the beginning and were they comparable at the end. What are the things that happened throughout that might make us question that. Attrition is one of the biggest things in a randomized control trial that would cause us to

downgrade something. If there was not only overall large attritions, but if the differential attrition between the groups was significant, that's a big red flag for us. So, there... as Candi said, there were some red flags here.

Chris Standaert: But the, I guess part of... the fact that the publisher considers it an advertisement. That's what the paper says.

Karen Crotty: Yeah.

Chris Standaert: Right. So, you're calling it a randomized control trial. The publisher calls it an advertisement.

Karen Crotty: The publisher also called it a randomized control trial. It, I'm... I'm with you.

Chris Standaert: So, you know?

Karen Crotty: I just...

Chris Standaert: It's just troublesome, that's all.

Karen Crotty: ...sure.

Chris Standaert: Personally, but I'm just curious on your thoughts of it. Other questions?

John Bramhall: Is there pro forma. I've seen that before though, and I'm ignorant, actually, about the meaning of it, but the implication is that if [inaudible] charges [inaudible] for an article that it has to be listed as an advertisement. Is that pro forma or?

Chris Standaert: It looks like they're following...

John Bramhall: I've seen it before.

Chris Standaert: ...a regulation, yeah. It looks like they're following a...

John Bramhall: I've seen it with [inaudible].

Chris Standaert: ...a regulation.

John Bramhall: [inaudible]

Chris Standaert: It says...

John Bramhall: So, it might not be the big red flag that it looks like on the face of it, but I'm ignorant about how [crosstalk].

Chris Standaert: ...it says they followed a... where is it. It says they followed a per yeah. Accordance with 18USC Section 1734.

John Bramhall: Oh, right.

Chris Standaert: Are you familiar with that one?

John Bramhall: Yeah. Yeah.

Chris Standaert: Yeah. Solely to indicate this fact. So, they had to do it based on whatever funding or financing they had to do. So, there are other structural concerns I have with that paper, but other questions or comments? OK. So, we can take a break for a few minutes, and then we will come back and have our discussion. That's our schedule, right? Take a break, clear your heads. We'll come back and we'll talk about this. Thank you.

Alright. So, this is the portion of our meeting where we, as a committee, can discuss the evidence and our perspectives and how we view this. After we discuss, we will, at some point, move to our decision tool and run through our perspective on the evidence and come to a vote. So, anybody want to start with some perspective on where they think they are? This is always helpful to know what people think. There are things you think you know or things you see, if there are concerns you have, things you don't see that you want some input from other people on the committee, that helps. Some varying perspectives make us all smarter.

Gregory Brown: So, if I could make a disclosure first. Over five years, I received some institutional support from Smith and Nephew on a hip fracture study and prior to that I did some lecturing at a resident fellows course for surgical approaches in anatomy that they sponsored. I received some speaking fees for that. I was never a consultant, but since one of the people in the room brought up Smith and Nephew as the manufacturer of these devices, I wanted to disclose that. If there's any concern on the committee, I'm happy to excuse myself. If not, I just want to make sure, so, before I participate that that's known.

Chris Standaert: Do you have an ongoing relationship or relationship in...

Gregory Brown: I do not.

Chris Standaert: ...the last couple of years?

Gregory Brown: No.

Chris Standaert: I think our disclosure form has a time limit, yes? The last two years?

Josh Morse: Yes. In the RCW, if you are employed or contracted with a health technology manufacturer, the period was 18 months prior to or during your time on the committee.

Chris Standaert: So, it preceded 18 months before the committee? So does anyone have... anyone want to throw a shot across the bow to start here? Go ahead, Tony?

Tony Yen: It seems, overall, the literature is quite poor, just generally speaking, but with what we can see with the available data, my tendency is that this actually works in a very specific population. It seems like we're kind of going over across ground of other recommendations via other societies or other guidelines that are currently in place. My tendency is to think that this is actually a technology that is viable and that's safe to some extent in selective populations.

John Bramhall: I'm quite... a bit conflicted, as this is the first time that I've sat through one of these formally. I come across the use of this technology on a daily basis in an inpatient setting and so, in that setting, which is know is not the setting we're discussing, in that setting, the technology is used at the discretion of an expert, a wound care expert or a vascular surgeon, or a burn surgeon in my setting. It's clear that the technology is very effective in those settings when it's prescribed by somebody for the appropriate period of time for the appropriate time of wound. Here, we are discussing something where the evidence is very flimsy. The studies are not being done. That doesn't mean that the studies, if they were done, would come to a different conclusion, but it was sort of very loose ground to tread on. So, I have a problem in the sense that I know that the technique works in a certain setting. I believe it to be effective because of the trust that I place on colleagues who also think it's effective, and probably in a home setting the results that you get with any technology are very much predicated on the judgment of the person prescribing it. So, basically what I'm saying is that wound care is a very complex and very subjective area of work in my opinion, and what we're tending to do here is maybe say thumbs up or thumbs down to a technology that, if it's applied in the right context by the right person on the right patient, is very effective. The concern is that if you give a thumbs up to a technology, it becomes more broadly applied in areas where perhaps it hasn't been demonstrated to be effective, and that's where I'm a little conflicted. If we approve it at the state level, then its use becomes validated and maybe it's then used by practitioners in a setting where it's inappropriate, and we just don't have the data that'll help us think that through, I don't think, but my prejudice, just to start it off, is the technology in the right setting is clearly effective, and my basis for saying that is, it appears whose opinion I judge to be effective working in an inpatient setting, but I don't have a lot of experience with the outpatient population.

Chris Standaert: One, if you aren't conflicted, our days would go a lot faster when we're here. So, that is... for the most part, if there is clear evidence, I mean, it does or it doesn't work, we don't see it, right? If it's totally obvious that it does or doesn't work, they don't need us. Our charge is to use the evidence, and I... I'm not trying to be argumentative, but as a counter, the idea that we do what we think works in our patients as a clinician. I agree, and everything I do I don't have evidence for, but there is no shortage of procedures in medicine that are soon to be standard of care and effective that are proven not to be with the correct study. That's a fairly routine thing in medicine. So, I think we ought to be a bit cautious about, "I know it works. I see it works. It works when I use it when my person uses it." This sort of... the risk of confirmation bias, right, becomes tricky. Again, we're not

taking inpatient medicine. Maybe it is different. Maybe they're different wounds. Maybe, again, those are different populations than what we're talking about here. Maybe there is something different, but we wouldn't know, because we don't have the data, but we have to be careful about the... we're supposed to, you know, this job is a mix, this committee is a mix... we're supposed to use the evidence, but again, we're clinicians. So, some clinical understanding of context matters, and we'll talk about that as we get into sort of our tool of discussion about importance of outcomes and efficacy and all that.

Seth Schwartz: So, I have a few comments.

Chris Standaert: Yeah.

Seth Schwartz: I mean, first of all, I'm still trying to understand why we're reviewing this topic, and I'm looking at what we were shown. I think the biggest concern I can see is this sort of outlier group of patients who are... this thing is slapped on them for a year or five years or whatever, and clearly we haven't seen any evidence for its effectiveness in that situation. The reason I ask the question about what was happening in an inpatient basis and whether we have any data about that is because I think if we have proof that a technology is effective for treating something that is maybe not exactly what we're looking at but close, my sort of pretest probability of whether or not this is going to be an effective treatment changes and went from a hypothesis for the research that they're doing here changes. So, I'm not just randomly throwing this at somebody, but I have valid reasons to think it's going to be effective in treating wounds, and then I see even low quality evidence that that's true, I'm more likely to believe it. So, that's kind of how I'm approaching this in my mind. So, I don't struggle so much with thinking that this might be effective for some of these wounds that are in the early phases of chronicity rather than a five-year wound type of thing. The other thing I think about is...

Chris Standaert: But the evidence could be the other way around, too.

Seth Schwartz: It could absolutely be the other way around, and that's...

Chris Standaert: Yeah.

Seth Schwartz: ...and I totally acknowledge that I think this is fairly low quality data, but if I go into it with the understanding of this technology being effective in an acute setting, I'm more likely to believe it, and I don't think we have the data to prove that. I think there's some perception around the room that it's probably effective in the acute setting, but we don't know that for sure, and we weren't given that data. I think the second point I would make is about the... this question of effectiveness versus efficacy. So, the question may be, so you're taking a technology that may be very easy to use. You slap this thing on somebody and for three days you don't have to touch it again, and they're getting adequate wound care during that timeframe versus a situation where you need to do three times a day dressing changes and how they are actually... are they actually doing

that in a home care setting. So, it may not be that this is a better technology. It simply may be a better way of delivering wound care in an outpatient setting. So, I don't know, and I don't think the studies tease that out at all, but it still may be valid if we have an... if we have something that works simply because it's an easier way to do wound care. So, I think that's another thing that's rolling around in my head when I think of this, and when we're making a decision about whether this is a good technology to apply in that setting, I have to think about, well that's a very valid point if it doesn't cost any more, and I have no understanding from any of this data about whether it's more costly, less costly, equally costly. I don't know that. So, I'm finding I'm having a hard time getting context around that question, too.

Chris Standaert: Maybe Dr. Quigley can help us, because my understanding is there are numerous ways of treating a wound and a lot of is local expert opinion is sort of what people do, and some products require three times a day wet to dry dressing changes and some require... some have coverings that go on for days at a time and aren't. The wound isn't manipulated three times a day. So, the perspective of this in context of other things that are being done.

Terence Quigley: So, in preparation for this, I looked up some of the statistics at the Northwest Hospital Wound Care and Hyperbaric Center. So, we treat, at any one time, between 130 and 150 patients. That's how many patients are being actively treated in our wound care center by six or seven providers five days a week. Of those, approximately 10 to 15 are on negative pressure wound therapy. So, we're talking 10%. I was actually surprised. I thought it was going to be higher than that, but that is exactly what we're doing, and this is an average over the past three, three and a half years, well actually three years, 11 months, whatever.

Chris Standaert: Do you think there's some rational differentiation between people who get it or don't?

Terence Quigley: Oh, there definitely is and...

Chris Standaert: There definitely is.

Terence Quigley: ...we have criteria, many of which were nicely reviewed here. We have criteria on who gets negative pressure wound therapy and who doesn't. For example, one example is, as a vascular surgeon, I think there's very little efficacy for negative pressure wound therapy in venostasis ulcers. We don't use it. Now, there are others that do, and it's approved by CMS for that reason, but we don't use it because, for instance, the Society of Vascular Surgery, to which I am a subscribing member does not recommend it for that, and there is really very little data to show that's it more effective than the current methodology. So, that's an example. We don't ever use it in pressure ulcers that are necrotic. I will apologize for my CME. I'm not looking for a job, so I'm lazy in updating it, but over the past four years, I have given a dozen talks on wound care, and there are three great advances to wound care in the past 40 years. One is negative pressure wound therapy. That's number two actually, advanced wound therapies, and wound

care centers. That's one of the great advantages. All these patients were treated in individual offices. They were good doctors. They tried hard, but it's very high maintenance to treat wounds. Wound care centers provide a focused expertise on wounds and part of our focus is negative pressure wound therapy. It's been a tremendous advantage. That's got to be appropriately applied, as everybody at this table recognizes.

Gregory Brown: What was three?

Terence Quigley: Advanced therapies, like skin substitutes and such.

Gregory Brown: I didn't hear hyperbaric oxygen.

Terence Quigley: Well, hyperbaric therapy has been around, since 1650. Hyperbaric oxygen was discovered, obviously it was there in the 1700s, I believe, and then hyperbaric oxygen therapy didn't come about until the 1800s. So, it's been around for a long... so when I said last 30 to 40 years, I can't include that. It's been a long time.

Gregory Brown: So, I, if I may address, Seth's question. As someone that treats inpatients with this technology, I think it is a completely different patient group. So, I do not think there's any applicability of how a patient with an open fracture is treated with a negative pressure wound therapy compared to someone with a chronic diabetic foot ulcer. So, I think that looking for that information doesn't help us answer this question. The thing that I did treat, not as much in this practice, but my previous practice, was I did a number of amputations and my concern, and I think this is where the state is coming from is putting this on for up to five years, it's just an effective treatment and things like doing a toe amputation instead of a definitive treatment of possibly a below-knee amputation, because it's a dysvascular foot. You happen to have an ulcer on one toe, but the rest of the foot is just vascular. You're just waiting for a different ulcer. So, the hyperbaric oxygen, the negative pressure wound therapy on some of these things, if there's a vascular problem you can fix with vascular surgery or revascularization, great. If there's not, I'm not sure that all the money being spent on diabetic wound care really changes the ultimate outcome, and that's why I was asking about new ulcers or reopening of an ulcer or ultimately leading to an amputation. So, I'm also concerned with things like osteomyelitis as a contraindication, now we need to get MRIs on every one of these ulcers to make sure there's no osteo underneath it before we can use it. So, suddenly, we're ordering all these additional studies that don't change that.

Terence Quigley: I'm going to correct that a little.

Gregory Brown: OK.

Terence Quigley: It's untreated osteomyelitis.

Gregory Brown: OK.

Terence Quigley: So, osteomyelitis is being treated actively with intravenous antibiotics, negative pressure wound therapy is not contraindicated. It's untreated osteomyelitis. I think if you ask the Hayes group, they will tell you that that's what the data says.

Chris Standaert: Carson?

Carson Odegard: Well, Greg and Seth kind of answered one of the questions, but the question I have is, there was a concern about... was it Joann said about agency recommendations being so long. I'm just wondering in looking at that and listening to this discussion whether we need to direct the conversation towards limitations and recommendations than individual wounds, because it seems that the data shows a lot of the mixed popu-, you know, mixed wound population as being [crosstalk].

Chris Standaert: If you go to the... so, you can look at the... I looked at the agency [inaudible], too. We have to use the data to get there, right, and I personally have a bit of a leap from what I read to what is there and how I would draw the circle so well, and we can think about this a couple ways. You could view this in totality and say for all sort of nonhealing wounds, or you could break it up and you could talk about a diabetic foot ulcer. You could talk about a pressure ulcer. You could talk about an open surgical wound. You could pick out the individual wounds. We do seem to have varying degrees of data on those. When I looked at it, I have trouble with the Blume study, obviously, although that was diabetic foot ulcers, so, plantar dorsal ulcers. The one from Armstrong really was... that was for people who had... diabetics who had an amputation transmetatarsal or distal that didn't heal after the amputation, which brings us to the question of dysvascular. Maybe some of those people, frankly, should have had a different amputation, but that was a very focused study on that population. It's a very distinct population. That's not an ulcer in the heel. That's not an ulcer elsewhere in the leg, and the Yao study was a retrospective cohort and you look at the groups they had, they weren't very equivalent, in terms of disease prevalence or location of wound, and they just weren't... it was a [inaudible]. So, how... we have to start... we have to start drawing lines if we get into that section, and I think we have to consider, do we have data to help us draw lines about distinct wound types, or do we have particular clinical concerns that would make us lean more one way, more the other, or can we approach them as a whole, depending on what we see? What do you think, Joann?

Joann Elmore: Well, a few comments. First, I've heard, and I think appropriately so, is some committee members asking did we miss evidence from the inpatient side that would be clinically relevant to our discussion in the outpatient potentially, and I quickly looked at the Cochran reviews and their search strategy, and they did not seem to specify or eliminate inpatient versus outpatient. I know that our evidence vendor based their search and their articles on Cochran. So, hopefully, we did not miss any, but when we ultimately come up with our decision, we have an open time period in which the vendor and the public can educate us before we do the final vote if there is anything that we missed. So, my suspicion is that

we didn't, but I wanted to say that we will have time to see if there is anything we missed that can be brought to our attention.

Chris Standaert: Well, I mean, the public has had access to the document for quite some time to bring evidence to our attention if it's not there.

Joann Elmore: Right. I don't think we missed anything. I don't think...

Chris Standaert: So, uh...

Joann Elmore: ...we did.

Chris Standaert: ...you know, us making a decision saying, well, and we'll see if somebody else has something else for us is not the way to do this. We need to...

Joann Elmore: Well, no. I'm just saying that there will be that opportunity...

Chris Standaert: There, there...

Joann Elmore: ...yeah.

Chris Standaert: ...always is.

Joann Elmore: Yeah, OK.

Chris Standaert: There always is and again, so our key question and our PICO, we're limited to outpatient therapy. So, the distinctions of outpatient therapy would be, you probably had a different wound. You're probably a different population, and you have an entirely different delivery mechanism, right? This isn't done by a wound nurse who's rounding in the hospital every day looking at the wound. It's done by somebody at home.

Joann Elmore: Right.

Chris Standaert: It's entirely different. So, I would argue they're probably very...

Joann Elmore: OK. Well, I was just...

Chris Standaert: ...different patient populations.

Joann Elmore: ...basically I was trying to say that I don't think we've missed anything. That was kind of...

Chris Standaert: Right.

Joann Elmore: ...the way I was going. So...

- Chris Standaert: I do agree with Seth's concern that there may be data in there that would tell us the fundamental viability of the biological process occurring here that we just don't have, again, good, bad, or indifferent, and we can't bring them in anecdotally, because that just...
- Joann Elmore: ...OK. Alright. Let's go on. So, my second point is to state the obvious, as a clinician, I'm an internist. I take care of these patients. These are challenging to treat. My heart goes out to the patients and their families. So, I do wish that we had appropriate treatment for them that was evidence based. It is helpful to me, I do appreciate the anecdotes, but we're supposed to be evidence based. So, therefore, with my second hat as an epidemiologist, I have to step back and say why couldn't they do a randomized placebo controlled trial or at least blinded assessment of the wound closure and time to wound closure? Why not? To me, that would have been a much higher quality of evidence. With that in mind to summarize kind of what I have heard of the evidence, there does seem to be some supportive evidence among diabetics. It is low quality. It has potential for bias, but that to me seemed the strongest of the existing data, which are low quality. It seemed that for the many other potential clinical scenarios, I didn't see a lot of positive strong evidence. For our other outcomes, I was disappointed that we didn't have outcomes such as the patient's perception of this, because that's important, and the family. When I discharge patients, sometimes it is easier to know that something is going to stay on for two to three days, and there are certain patients that that's beneficial. We did have some studies on pain, quality of life, return to work, no significant difference. For the other key questions, so for key question one, maybe something on diabetes, I was disappointed. I didn't see anything on the other specific clinical diseases, and so I would... I'm asking the group to help me if you think that there is adequate evidence in the other disease entities. For key question two on safety, I was disappointed and feel that we don't know enough about safety. For key question three, it's inadequate, we don't know about specific patient characteristics, and key question four on costs, that is reliant upon an adequate evidence base, which I didn't see. So, I think that is, as usual, sort of the uncertain. So, I guess I would hope that the group would tell me your thoughts on specifically in the diabetic patient, whether you think it fits the bar, and then all the other diseases that we tried to review.
- Seth Schwartz: Can I just make a quick comment about safety? I was struck by how little safety data there was, which, and it's always difficult to say that evidence of absence or absence of evidence, you know? Is it because it's not happening? So, I've not been impressed with their being a significant risk to this technology. I didn't see that. That's actually, Dr. Quigley, I would ask your opinion, if you have any sense of what the real risk is of using this technology.
- Terence Quigley: I think the real risk is very low. I mean, one of the contraindications is, you don't put this device, or use negative pressure wound therapy in patients who have exposed blood vessels. So, one of the risks is bleeding. You don't do that, and if you do that, it's not the therapy that's failing, it's the medical judgment that's failing, and you have to separate that. My experience with bleeding in patients who are on Coumadin or Plavix or other antiplatelet, anticoagulants, is that the

bleeding that occurs clogs up the device and it just doesn't work. So, we don't use it in patients who have a risk of bleeding, because it doesn't work. You're sucking on a big blood clot in a foam. So, again, it's the people who are using it that drive this more than the therapy itself, and if you have people who are familiar with the therapy and are using it appropriately, paying attention to the contraindications, which are well known and well described, the therapy is very effective and extremely safe, extremely safe.

Chris Standaert: Well, I mean, the FDA report from 2011 says since 2007 they have a report of 12 deaths and 174 injuries from 2007 to 2011.

Terence Quigley: What did those people...

Chris Standaert: So...

Terence Quigley: ...die, I don't know. The injuries, we see injury from this all the time, and the injury is kind of maceration of tissue in the immediate periwound area, and that is usually due to the fact that the wounds are very, very wet. We're trying to fix that, and negative pressure wound therapy is a great way to fix a wet wound. Are you going to get some collateral damage, i.e. a little maceration of the tissue right around it? Yes, you are. Is that technically an injury? Yes, it is. From a risk-benefit ratio, I would continue the negative pressure wound therapy in the face of that 'injury.'

Chris Standaert: ...[inaudible] seems to be the, it says bleeding is the cause of most serious adverse events.

Terence Quigley: And if you put this thing on a blood vessel that opens up, that patient will get all of their blood sucked into a canister. That is a contraindication to the use of the therapy.

Chris Standaert: What do you think? I want to hear from all corners?

Chris Hearne: I tend to agree with you that the evidence seems strongest for, at least for key question number one, seems strongest for diabetic foot ulcers, but just looking at the key articles, in my mind, I sort of, I'm glad we had that discussion about the Blume article, because I didn't quite realize that, that they had called it an advertisement. In my mind, this is... if I'm looking at this correctly, that's the main randomized control trial for diabetic foot ulcers, and we only have one other one that's very small and nonsignificant. So, without this sort of bolstering that evidence, it's really hard to... initially, my thought had been yes, that it seems like there is some evidence for diabetic foot ulcers, but then if you take away, sort of set that Blume article aside, it's very hard to say that.

Chris Standaert: What do you think, Laurie?

Laurie Mischley: I agree with the limitations in the published data that we're looking at. I think everything that has been said, I'm on board with. I tend to weight the clinicians

anecdotal responses a little more heavily, just in terms of hearing that there isn't a huge risk to the intervention and I think, as a clinical trialist knowing how difficult it is to get funding from non-invested parties, you know? It is the paucity of data is not necessarily an absence of good data. I mean, it's just really hard to get studies done, to get studies funded, and the limit... the absence of data shouldn't necessarily count against the intervention. So, our charge is evidence-based medicine, and while I appreciate the hierarchy of evidence-based therapies, I do tend to hear the clinicians who use the therapies saying that they're advocating for it, and I'm thinking, really in terms of putting the patient first, making... I can't come up with really good reasons to not make the option available if the experienced clinician deems it's a good option. I see it... I'm trying to flip it the other direction and I'm asking... there's not a safety concern that I find that makes me want to... that gets my alarm bells up. So, I think I'm weighting the clinician's anecdotal experiences as evidence more than I hear around the room.

Chris Standaert: There is a, you know, you have to think through yourself. Is the onus on the technology to prove that it works before it's applied without the assumption that it is... if you assume it's helpful before you assess it, you don't really get anywhere. So, does the evidence prove... does the technology prove itself or does it not prove itself, or does it... which goes first, you know? Or do you have to prove that it does not work or do you have to prove that it does work, you know, and how you weigh that and what your other options may be for treatment and what happens in the continuum of care without it in various settings, but all the things we've seen work are not necessarily good for people, right? So, it's not that more is always better. That's the tension in doing this.

Gregory Brown: So, my question is, does this change the natural history of a diabetic foot ulcer, and my other question from what Dr. Quigley brought up is, is the bigger issue here where it's used. So, use of a negative pressure wound dressing in a wound clinic sounds like it may have a very different outcome than by a physician in their own office, you know, doing that. So, and the fact that in their clinic they use it only on 10% of the patients. So, it's got to go into nutrition. It's got to go into their glycemic control. It's got to go into their, if it's dysvascular, can it be revascularized? I mean, there's so many other issues to say that this technology is what's healing the wound, to me, is not looking at the whole picture.

Chris Standaert: Lack of long-term data I find problematic, right? So, just seeing a wound closed, you know? Wounds can epithelialize over, but that doesn't mean the wound is actually healed, right, or it's resolved? Is it going to stay that way? Is it going to recur, and the glaring absence of what happens a year later? What happened to these wounds? What happened to these patients? What happened to these limbs? Did they get... what happened? I would love to know, because I don't... that's the whole... the whole intention of healing a wound is it's a long-term deal. This is a long... this is a four-quarter game, right? This is long-term. You want the wound to close, but it has to stay that way and stay healthy, and the osteo has to go... has to not be there, and you need vascularity to keep the limb viable. Otherwise, you're sort of spinning your wheels a bit. I don't see that anywhere.

I don't see it one way or the other. I don't see that it does or doesn't. I just don't... they're not... the one patient, the Blume study said we'll follow them for three to nine months, but they didn't report it. Yeah, Carson?

Carson Odegard: You know, we didn't see that in the state data either, and, you know, that was my question. When we look at, you know, the individual... look at the 10% that was stated of inpatient care, I'd like to see from the State what percent the State pays for these things in the greater scheme of wound care, and if it's 10%...

Chris Standaert: Do you guys have any idea what percentage of patients with a chronic wound being treated through home care or treated with negative pressure wound therapy? Do you have any idea? That's a great question.

Male: Good question. We don't know.

Joann Elmore: I'd like to ask the vendor a question. Sometimes, we add qualifiers to our recommendations, and I've heard repeatedly the importance of experienced wound care centers, experienced clinicians, but yet do we have evidence to guide that. It makes a lot of sense practically, clinically, and I was trying to look through Blume article, etc., to see, you know, were these clinics in which the patients who were enrolled in these low-quality studies, were at least the clinics experience wound care clinics, and I couldn't really find that to guide me.

Candi Wines: With respect to the Blume study specifically, it was a multicenter study, 37 diabetic and wound care clinics. So, presumably those are specialized clinics. Some of the other studies also mentioned outpatient care in specialized clinics that came to outpatient clinics for their wound care. Does that answer your question?

Chris Standaert: This gets tricky for us. So, the setting issue on... so equal access to all people in the state is really tricky, right? I'm not sure you can get to the same quality of wound care clinic from the middle of the state. They may, or may not. Maybe they do.

Kevin Walsh: Let me answer that for you.

Chris Standaert: That's why we have cross-state representation.

Kevin Walsh: Yakima had a wound care center.

Chris Standaert: That's past tense.

Kevin Walsh: It's closed. So, I'm in Ellensburg.

Chris Standaert: Mm-hmm.

Kevin Walsh: So, I'm... the question I'm asking myself is, so my patients are not going to have access to a wound care center. So...

Chris Standaert: Right.

Kevin Walsh: ...I'm going to generalize myself to be, you know, the dweeb primary care doctor in East sagebrush, Washington. So, you're... we're making a decision... everybody's talking about wound care centers and about inpatient therapy. So, let's erase all that from the equation, because that's not what we're talking about. There's basically no evidence here that I see presented that's applicable to the question I'm trying to answer for myself, which is, when you turn this loose, because we're going to approve it... so, when you turn this loose and I can use it, and I'm seeing a patient with an ulcer that's not improving, and I have the possibility of using this technology, guess what? I'm going to use the technology, because maybe it will help, and I don't know... I don't have access to other modalities or specialists to help me with that care. So, I'm assuming that we're going to approve this with conditions. So, I'm looking through here trying to understand the conditions that the State has recommended make common sense to me, but I don't see them based on any evidence. So, I'm not sure how we're going to generate, from the literature that we have, I don't see how we're going to generate conditions that are going to help me out there understand when to use this, when not to use it, and what... when it's not working anymore, and when to continue on with it. So, it's... I'm very perplexed, because I don't see, at the end of this, much help.

Chris Standaert: I just want to finish my statement on the setting issue, because it comes up a lot, and we have newer people here. So, one, we can't control setting. There isn't equal access to settings around the State. If there is some governing body that certifies and identifies and deems certain settings as a specialty or areas of expertise or whatever, which there are in some that are nationally and internationally recognized. We've used that before as a criteria. That usually pops up in our studies that they've used those studies. They use those centers with that governing or certifying body to define it. Then, we have some ground to do that. If we don't have that, we have no... we have no way to do this. We can't insure access, and even if the article says they are wound care centers, what does that mean, right? So, how... is there a definition for that? Is there a certifying body? Is there some national standard or international standard being used so we know that one center is another center isn't just I don't know what that means. So, in those... in that setting for us to then address setting in our terms is really sort of a very slippery slope into nowhere, because if we can't go there we shouldn't go there, I think, and issues of research and things being done under research protocol, under a study protocol are implicit in anything we say is not covered. The State can always choose to cover something under research protocol. So, we never have to specify that. That is always an option for them, even if we say no to everything, that is always an option. So, they can they approach them and say I want to study it, can I use it, and they can decide whether it's good enough to use it or not. So, you can take that off your head a little bit.

- Terence Quigley: I can answer the one question about certifying wound care centers. The answer is no. If you wanted to go out next week and open the standard wound care center, you could do so without any objection from anybody. You're labeling your practice and how you label your practice, facial plastic surgery, wound care center, vascular surgery, that's your business. Nobody can tell you you can't do that.
- Seth Schwartz: So, I think there's two ways we've gone about this. One is to use this concept of certification, you know? Is it something that demonstrates the quality of the place. The second way to look at this is, what are the key elements of what a wound center does and call those out as far as conditions. I'm kind of on board with Carson. While I'm frustrated with the low level of evidence, I think I'm having a hard time thinking we're not going to approve this at all, because I think there's some evidence to suggest it's effective in at least some circumstances. I think it's clearly not effective for these really prolonged wounds. So, one of my... I would have the question for the evidence vendor in a second, which is, what's the generalized duration if that's in any of the data, of the maximum length over which this was thought to be effective. Like, in other words, are the end points of some of these studies two months or three months or one month or whatever that is, because I think that's important, because that may be one of the criteria we think about. I think also, as far as categorizing what we're trying to see is, we want to know if it's effective in an individualized patient. So, I think we would want to limit the use of this technology for patients in whom it's effective. In other words, if they do a month and it needs to be reassessed and if it's not having any effect, then it shouldn't be prolonged. So, I think there are some criteria that are common sense, but we may be able to link at least loosely to the existing research to come up with those criteria. So, again, I would turn that over to the evidence vendor. As far as... we've talked about the follow-up issue, but I mean, more in terms of what the... how the assessments were done and at what time points, and was there some endpoint at which they were either kicked out of the study or it was deemed ineffective or anything like that.
- Candi Wines: Well, the Blume study keeps coming up. So, they defined a period of active treatment phase as 112 days, but one thing they report in the paper that the duration of therapy for negative pressure wound therapy was 63.6 +/- 36.57 days compared to 78.1 +/- 3.29 days for the comparison group. So, they had an active treatment phase defined for the purposes of the protocol and then.
- Chris Standaert: Again, they discontinued 43 patients from that arm, 8 self, 11 withdrawal, 5 ineffective treatment, and a number of adverse events. So, yes, that's the numbers they gave, but this is the whole problem with the study, right, and to base things on this is really tricky, because that might be the average length, but what happened to these people who were taken out by the investigator, because they weren't healing, and they would have been taking two years to heal, and that would have skewed their numbers? I don't know.
- Kevin Walsh: They weren't taken out because the results were favorable.

Chris Standaert: They weren't taken out because they healed, no. That would be a safe assumption, I would think, but we don't know.

Terence Quigley: Actually, that's not true. We have people who are healing rapidly with a wound vac, and we discontinue the vac, because it's clear they're healing. We've accomplished what we wanted to accomplish, and now we revert back to standard, damp wound care for the completion of epithelization. You know, all wounds are going to get a certain size where the wound vac you can't make it work, 'cuz it won't fit. So, all our patients are discontinued before the wound heals. All of them.

Chris Standaert: No. He wasn't saying that they don't discontinue the device once it heals. He's saying, if the patient healed, they probably wouldn't be in the numbers who were discontinued by... they probably would be in the final results.

Kevin Walsh: They would be calling that a win.

Chris Standaert: A treatment success, yes, but we don't know.

Male: A question for you, Dr. Quigley. In your experience, if somebody does not see benefit within the first month of negative pressure wound therapy, are they likely to go onto see benefit in month two or three, or can you say after one month of no benefit, you know, this is not going to work?

Terence Quigley: That's a very good question. At our wound care center, every single patient in active therapy is reviewed every four weeks, so, at 4, 8, 12, and 16. If at four weeks, there is no benefit, hyperbaric oxygen therapy is stopped. Wound care... negative pressure wound therapy is stopped. Whatever we're doing is stopped, and we have to say, as I pointed out earlier, not using insanity but idiocy, if what we're doing is not working, we have to change what we're doing. We use four weeks. Four weeks is what we use, and we do it... and then after the next four weeks, at 8 weeks, we're looking at it again saying, is it working? Is it not working, and we may change again. So, four weeks is what we use. I don't know if there's any... there's certainly no literature data to hammer that home, but that's what we use.

Chris Standaert: This goes back to Kevin's question. If you're in practice, and you have a diabetic, and they live 100 miles from your office in the middle of farm country, and they have a wound, and you give them a treatment of some sort, you bring them... you have to bring them... you obviously have to bring them back, but this idea of how long you go. Let's hope you don't wind up with this for five years. They're clearly not healing if they have it for five years, right? So, nobody's assessing that they're getting better, and how you define better and, you know? That becomes a tricky question for that practitioner, and then if... so one approach that you're familiar with doesn't work and you have to switch, I suspect most people when they see something isn't working eventually will switch it, but they have to have other choices to switch to that they think might work then, or they wind up sending them, saying, you need to go to the wound center at wherever this is, assuming

there's tertiary expertise there, which, as you pointed out, may or may not be the case actually.

John Bramhall: You're using the term work. It seems to me you're applying success in wound healing. I'm not particularly too loose about it. If someone's got this thing on for four years, maybe it's working in the sense that it's controlling their symptoms, their weeping wound, and that's a hard thing to get at in the evidence here, but you know what I'm saying? If it's... if someone's leaving it on for four or five years, it's there for some reason, and the reason clearly isn't that the wound is healing. The reason is perhaps that it's a convenient thing to have in your pocket, something that's sucking away at the juices that otherwise smell, drip, you know what I mean? So, success isn't necessarily wound healing in some settings. You could postulate success is control of unpleasant signs and symptoms.

Chris Standaert: That goes back to your original question about patient reported outcomes, right?

John Bramhall: Yeah. Yeah.

Chris Standaert: So, is there an impact on quality of life from the...

John Bramhall: I mean, when you see these things, these things... they're neat. They're tidy. You know, I'm not advocating for it, but I'm just saying, they're neat and tidy. They're on... it's a little aquarium pump in your pocket, perhaps, and it's the equivalent of an indwelling catheter for pain with a delivery of agent over time that's convenient and saves you going back to the clinic, you know? There's a whole list of subjective things that could be good about this technique...

Chris Standaert: Mm-hmm.

John Bramhall: ...that just aren't captured and you'd have to, like I'm doing, I'm speculating.

Chris Standaert: Somebody would have to actually study it.

John Bramhall:: Yeah. Yeah.

Chris Standaert: That's our... but that's our charge, right? Somebody would actually have to go get the evidence to say this is a reasonable thing to do.

Terence Quigley: That's absolutely correct. I will tell you anecdotally the majority of patients, so I'm going to say more than 50%, do not like negative pressure wound therapy. They do not like it, and they're very happy the day we suggest it's no longer necessary, which is one of the reasons we discontinue it. It is... it's not a little canister in your pocket. It's a heavy thing. The [inaudible] devices are separate, but the devices that we use are heavy canisters. They're noisy at night. They have to be changed. You have to make sure the batteries don't wear out. They have to be plugged in. So, you have to be near a plug-in. It's annoying. I would say quality of life is much better with a non-wound vac device wound dressing.

- Chris Standaert: We're talking about ambulatory outpatients is who we're talking about, outpatient, not necessarily ambulatory, but outpatient, in-home setting.
- Terence Quigley: Now, there are ambulatory...
- Chris Standaert: Yeah.
- Terence Quigley: ...there are smaller devices you can put over your shoulder like a purse and carry it, but it's still annoying.
- Chris Standaert: Maybe we should move on to our tool and start helping ourselves put some boundaries around here and see if we can see some clarity in the mist here, or clear the mist and see whatever's left. So, if you go to page five of your document. So, we're going to run through this. We have modified this some for people who have been here before. We have modified this a little bit. We are going to try and use this slightly differently, and for those of you who are new here and listening, we do several things. We have safety, efficacy, and costs, and we're going to talk about all three of them. Then, we'll have a vote on sort of how we view the evidence on those three topics, safety, efficacy, and cost. Those are all nonbinding votes. Those are sort of the general gist of the committee on how they view the data here. Then, we move towards, eventually, a binding vote on coverage, coverage with conditions, or no coverage, and what I hope to get out of our first round here is just an idea of where are we going? It may become clear we go to no coverage. It may become clear the majority of the people want coverage without conditions. It may become clear that people want to talk about can we find circles to draw. That's where we're going to get to, ultimately.
- So, go to page five. We're going to talk about safety first. It's on top here. So, we have a number of outcomes here, and I want to talk about the ones, if we have... some of these... with this issue of sort of, is the outcome particularly important, and then do we have data on that, right, are two separate questions. Do you think there are outcomes on which we actually have decent data for safety? Or are there high level safety issues for which we have at least limited data that makes us concerned, and this has been prepopulated. We're certainly open to other safety outcomes one might put in here.
- Gregory Brown: I think we have data both from the FDA warning and from Dr. Quigley saying that bleeding and mortality are an issue if it's used over a blood vessel, and so...
- Chris Standaert: Mm-hmm.
- Gregory Brown: ...it's a contraindication for use. So, I don't know how that, again, any device if it's used improperly can have safety issues. So, I mean...
- Chris Standaert: Those are high level... those are high level safety concerns.
- Gregory Brown: ...yeah.

- Chris Standaert: Right? This is not an annoyance. This is, like...
- Gregory Brown: Well...
- Chris Standaert: ...bleeding and death, right? So, a high level of concern, but what we don't... I don't see them documented well on our studies, but I see the FDA report, which is a non... a different mechanism for identifying them. Do people see other safety areas of particular concern that they saw evidence either says this is relatively safe? This is a big concern, but I don't see it? Or that I'm pretty comfortable that this is helpful in this regard.
- Tony Yen: I think we have weak evidence that shows that it's relatively safe, but the evidence is just very weak in terms of infection, bleeding, mortality, and amputation.
- Chris Standaert: Relatively safe, but on a weak, low-level evidence basis from which to say that with some preexisting high level concerns from the FDA that are also hard for us to quantify necessarily.
- Tony Yen: Yeah, and the FDA, what the 2011 report, the concerns about bleeding, amputation, mortality, infection, etc., I'm not too sure, you know, as Dr. Quigley has also stated, I'm not too sure why these people had the adverse outcomes. Was it because of the device or because of their underlying condition? It's really hard for me to say that.
- Chris Standaert: You don't know.
- Tony Yen: You don't know.
- Chris Standaert: But are we... we don't... we're probably not confident on data, even regarding amputation or skin reaction or Emergency Room visits [crosstalk].
- Kevin Walsh: Well, as Greg pointed out, the studies don't extend long enough for you to even have any information.
- Chris Standaert: We do have important safety concerns that just are not addressed by the literature is what we have, right? So, Emergency Room visits and hospitalizations are important outcomes, but we don't have data on them confidently to take us one way or the other.
- Gregory Brown: I would have a hard time attributing any Emergency Room visit or hospitalization to the device or the technology. I mean, these are people with diabetes and significant comorbidities. So, I don't think it's the technology that's precipitating any of that.
- Chris Standaert: In the Emergency Room?

- Gregory Brown: And that's what I say. So, I guess my gut feeling is that, if used properly, it is very safe. Again, the exception is, as Dr. Quigley pointed out, if you put one of these over a blood vessel and it ruptures, that's a serious adverse event.
- Chris Standaert: OK. So, we'll move to efficacy, and ultimately, you know, the idea here is, does this really help patients, right? If it clearly hurts them, that's one thing. If it really helps them, if it clearly helps them, that's another thing. That's what we're trying to figure out. So, efficacy, effectiveness, so this is prepopulated for us. We can pick other ones. So, it's prepopulated with wound healing, time to wound healing, pain, wound closure, which is probably slightly different than wound healing, activity levels, quality of life, and those sorts of things. So, of these, people feel these are all important outcomes or are some of these of lesser importance to us? They're different. They're... we have measures of wound healing. We have measures of patient reported outcomes. I see patient quality of life sort of factors.
- Gregory Brown: Of the study that I focused on was, there was no difference in healing rates, but if it did heal, it healed more quickly. So, I see a subgroup in there that if you try it and it's working, it's helping. If you try it and it's not working, then it's not going to change the healing ultimately. So, to me, there is at least a glimmer of...
- Kevin Walsh: What study, Greg?
- Joann Elmore: What study are you talking about?
- Gregory Brown: I can't remember which one you listed. There was no difference in ultimate healing rates, but there was a faster time to healing in the ones that healed. Do you remember which study that was?
- Carson Odegard: It wasn't Armstrong, was it?
- Seth Schwartz: Wait, can I ask a quick question. Thinking about this question about complete wound closure and patient perspective, and I'm thinking, you know, I've been thinking about this all along. I've been thinking, well, we want to get this wound closed all the way, and obviously that's the ideal outcome, but in your experience, is there a significant benefit to the patients if you have a five-inch wound that you convert to a two-inch wound or a three-inch wound, you can convert to a one-inch wound, those patients would be considered a failure based on complete wound healing outcome, but from a patient perspective, is that still considered, I mean, would patients view that as valuable.
- Terence Quigley: A patient who goes from a five-inch wound to a two-inch wound is not going to fail. They are going to heal. They've demonstrated that.
- Seth Schwartz: OK.

- Terence Quigley: By the fact they've gone from five to two. Now, we may discontinue wound therapy at two inches because it's healing and we can use something else. Patients will be much more... much happier not having to mess with it.
- Seth Schwartz: So, if they're on the trajectory to wound... to shrinking, you are confident that is going to go the rest of the way.
- Terence Quigley: Yes.
- Seth Schwartz: OK. Thank you.
- Kevin Walsh: Kevin, and to answer your question, it's slide 45. It's on the partial foot amputation patients. It said no statistically significant difference in proportion of acute and chronic wounds achieving complete closure, but time to complete closure was significantly different in favor of negative pressure wound therapy.
- Joann Elmore: The question is, statistical significance versus number of actual days if the vendor could look that up for us. In fact, while the vendor is looking that up, a lot of the discussion is about diabetic foot ulcers. Are there any other clinical scenarios in which people feel...
- Chris Standaert: So again...
- Joann Elmore: ...the data supports...
- Chris Standaert: ...and because this study is not diabetic foot ulcers. This study is post-amputation healing. This is not diabetic foot ulcers.
- Kevin Walsh: Is this Armstrong?
- Joann Elmore: Well, that's true. It's partial...
- Chris Standaert: Yeah.
- Joann Elmore: ...foot amputation of the foot.
- Kevin Walsh: Which Armstrong are you talking about, Armstrong 2012?
- Joann Elmore: 205, 207.
- Gregory Brown: It has them both in there.
- Chris Standaert: And what, I think with that one, that's key question three. That's not a differentiator. Can...
- Joann Elmore: [crosstalk]
- Chris Standaert: ...a subcategory, right?

- Joann Elmore: Right. I know.
- Chris Standaert: So, is there a difference in acute or chronic? What they found was no difference in acute or chronic wounds, but that time to wound closure was in favor of negative pressure wound therapy regardless of whether it was acute or chronic is what they're saying.
- Joann Elmore: That's a good point, and it's in a diabetic after an amputation.
- Chris Standaert: Diabetic after amputation.
- Carson Odegard: Your original question was wound healing, wasn't it, or was it closure, because the Lehrmann study is the one that was on the... primarily the time of wound healing. So, I was wondering what your original question was? Was it the time of wound healing?
- Gregory Brown: It was in this idea, is there a subgroup that's benefiting.
- Carson Odegard: Oh, yeah.
- Gregory Brown: And, I was saying this suggested that there is a subgroup.
- Kevin Walsh: Am I wrong? I thought all of Armstrong studies were comparing two different technologies. They weren't com-... the comparator wasn't routine wound care.
- Joann Elmore: [inaudible] therapy was the comparator in at least one of them that I know of.
- Gregory Brown: It says here, standard treatment.
- Candi Wines: So, the Armstrong 2005, 2007 publications were negative pressure wound therapy and standard treatment. The 2011 and 2012 were comparing two different devices.
- Chris Standaert: So, if we look at our outcomes, right, so complete wound healing and time to complete wound healing. They are relatively important outcomes, because that's what we're trying to do, and our data is... does somebody see data that says that this works in a given population or that it doesn't work in a given population, or they just don't see enough data to help them be clear either way? Not much data. We talked about our patient reported outcomes, so quality of life, pain, return to prior activity, I would think we'd all agree are important to our patients compared to morbidity or limb loss maybe, but they're important and they're all reflective of all those other factors, but we don't have any data on any of them that was convincing one way or the other, I didn't think. No?
- Laurie Mischley: What we did have was nonsignificant.

- Chris Standaert: It was not... so there was data, but it was not... low-level data that was not significant, right? So, that's an important outcome. OK. We'll move on. Cost-effectiveness. Joann, you had a comment on cost that was fairly to the point.
- Joann Elmore: Analysis based on low and inadequate data provide no information. I don't think we have any information.
- Chris Standaert: Comments on cost? I don't doubt cost is important. I think cost is important, and I think that some of the other, I mean, my understanding of other treatments is they're expensive, too. Some of these things are quite costly. I just wish I knew the difference.
- Seth Schwartz: I think I'm struggling with that one, as well. I think it's very standard that we do not have good cost-effectiveness data. So, I'm not bothered by that. What I'm bothered by is I feel I have no concept of what the... just the cost of the actual course of treatment is with this. So, and possibly our medical directors can help us with this. So, in other words, I mean, if this costs \$10, I'm much less concerned than if it costs \$1000, and if the alternative is... and what the range of treatment is. Part of the reason I'm struggling with this is, because while this is a technology, I'm almost seeing it as kind of a one tool in the management of things. I kind of almost equate this to when we looked at robotic surgery. We came to the realization that the robot doesn't necessarily effect safety in every situation, but it's just a different tool that should be at the discretion of the surgeons to use, and I'm kind of having a hard time not thinking about this in a similar way. So, I would love to know a ballpark, what does it cost for someone to use this technology for, you know, a month of care or something like that. Do our medical directors have any of that... any data along those lines?
- Male: Actually, that's Kris. I know that we've got... I mean, we don't have it at the...
- Carson Odegard: It's in the report.
- Chris Standaert: In the slide. It was roughly, what 90 to 100 dollars a day the last couple years in the uniform group and in the Medicare it was, like, 50 or 60 bucks a day?
- Shana Johnson: I'll bring up my [crosstalk].
- Chris Standaert: [crosstalk] roughly? And then how long? At five years, that's a lot of money. In a month, that's not a lot.
- Shana Johnson: So, I've got my cost lights up. It says average paid per day in 2015 for PEBB was \$97 and PEBB, as you know, 50% healed within one month. For Medicaid managed care, average... well that's average days of therapy.
- Joann Elmore: So, around \$3000 a month.
- Shana Johnson: Well I guess I'm seeing \$1300 a month or \$1300. It doesn't say there a month though. I'm guessing it's month.

Chris Standaert: 50% healed a month. Is that meaning 50% of people are no longer using it within a month, in a month? You don't know if they're healed. You just know that it's done. So, either it's working and they're healed or they're... it's not working and somebody pulls the plug on it so to speak. So, relative to other things in medicine, that \$100 a day. Kris is in the room.

Kris Urv-Wong: On the days, too, one of the things that happened was, there was a switch from payment going per day to per month. So, a lot of individuals actually finished in less than a month, but when you're doing sort of the conversion over, trying to do apples to apples, you lose that fineness that you get there. So, in actuality, there are people who are using it for less than a month and already ending it off. Does that make sense?

Chris Standaert: Either that, or they just don't like it.

Kris Urv-Wong: I just wanted to add that.

Chris Standaert: But we don't know that. OK. So, our issues of direct, cost-effectiveness is probably our most issue here... or cost-effectiveness compared to other things would be what I'd really want to know, because all this stuff costs, right? There's no cost-free mechanism. These are expensive... you know, bad things to have, right, and they can be very expensive, and the surgical solutions can be very expensive. So, I would love to know cost relative to other things knowing that everything in this sphere is real money, but I just don't know that. That would be what I would want to know. OK.

And our last category is special populations. And, this was broken down to chronicity, size, and device type. I think we would also, I don't know. Is there we... wound category or patient category might well fall here, but we talk about them some [inaudible], but there is a venostasis wound the same as a dysvascular post-amputee diabetic wound as a dysvascular non-amputee diabetic wound, as a pressure ulcer, as a surgical wound, right?

Kevin Walsh: We don't have to parse it out that way. I think the best we can parse out is post-surgical and not.

Chris Standaert: You think there's differential evidence on postsurgical and not, to some degree.

Kevin Walsh: I'm saying that you can look at postsurgical results...

Chris Standaert: Right.

Kevin Walsh: ...and you can look at chronic wounds or acute wounds that are not the result of surgery. That's about as granular as you can distinguish this, I think.

Chris Standaert: So, we're going to move onto our non-binding vote. This is our pale yellow cards in front of you. We're going to start with safety, and we have a new choice. We

have unproven, less safe, and I would say if you think there are significant safety concerns where it is less safe than other alternatives you vote less, because safety is a high import-, especially of high importance. If the evidence shows it's equivalently safe to the comparators looked at in the studies that we actually got to see in our data, if you think it's more effective in some circum... more safe in some circumstances than the other options, that's fair to say also. The more or all is qualitative. That really applies only to the indications we're considering, right? So, again, we're outpatient home use. So, that doesn't account... that's not every single patient everywhere, but it's the preponderance of what we saw.

So, safety. Is there sufficient evidence this technology is safe for indications considered? Unproven, less, equivalent, more, and some more and all. Is it safe?

Josh Morse: Please hold up your cards, because we've added a category, so it's going to take a little longer. Five equivalent, and one less, and four unproven, and that adds up to ten votes.

Chris Standaert: And that's what we have.

Josh Morse: Yes. Thank you.

Chris Standaert: Alrighty. Our math worked. So, efficacy, and this question, we changed it a bit, because we had some confusion for a while on our efficacy question, being more or less. The point of this question is, is there sufficient evidence this technology has a meaningful impact on patients and patient care? So, if there are patients for whom you think this is a meaningful, clinical impact on their lives, on their health, on their clinical care, it's important to identify that, right? That's what we're looking... that's the importance. That's the prime driver of your response here, and if you think the reverse is true, that it actually is a drag on those sorts of things or has a detriment, then that's when you go less. Alright. These are all nonbinding. So, efficacy, effectiveness. So, is there sufficient evidence that this technology has a meaningful impact on patients and patient care?

Josh Morse: OK. Four unproven, six some.

Chris Standaert: Were there six? I saw two here and all four there. OK. Cost-effectiveness. I'd love to see how the statistics on cost-effectiveness votes. Cost-effectiveness. So, is there sufficient evidence the technology is cost-effective for the indications considered?

Josh Morse: So, nine unproven and one [inaudible].

Chris Standaert: Alright. So, if you use this to inform our discussion, we have a bit of a split, but we have a preponderance of people who think there are areas where this is effective, and we have one vote that is less safe in circumstances and a preponderance that we don't know anything about cost-effectiveness. So, for those who think it is more effective in some circumstances, helping us all understand that to make sure that you all are thinking the same things and talking

the same things and what the base of that is would be useful. So, somebody who voted more or even if they don't want to say they voted that way, if they think that way, that would help the group, I think.

Gregory Brown: I voted unproven, but I think there are patients that it does help based on Dr. Quigley's experience in that sense. So, I don't think there's enough... I don't think the evidence is strong enough to say... to remove it from coverage completely. So, I don't think it's proven effectiveness, but I think there is a subgroup that it probably helps, and so I...

Chris Standaert: Let's pull up our screen for a second, because we need words of intellect.

Seth Schwartz: I would make a comment about that. I think Kevin made a good point that the level of evidence that we have does not afford us the granularity, I think, to very definitively say yes, we'd cover for diabetic ulcers, no we wouldn't cover for arterial ulcers. I struggle with that. So, I kind of would flip it and say, because I think that there is some suggestion that it can be effective in certain patients, but would be say to put the onus on assessment and demonstration of effect for continued use. So, in other words, that you would have to... the criteria could be something along the lines of with proven benefit at assessment at two weeks or one month or whatever it happens to be and treat it in that fashion.

Male: I absolutely agree with that. I think that heads off that problem of getting to the territory of we're going on for months and months and months without any benefit and also allows people who are making these decisions to kind of find the answer.

Chris Standaert: So, we're going to try and write... the way this works is, we have to have... we have to say something, right? There ultimately has to be a statement that we vote for or against, and we get this issue of, we have cover or no cover or cover with conditions. So, the only way to get to cover with conditions is come up with language that it seems people, at least some people on the committee, would like to see voted upon, and then the vote would go... you could expand it and say cover everywhere. You could deny it and say don't cover at all. You could agree with those terms and say cover with those conditions. That's usually how we do this. I usually don't want a binding vote until I know what they're voting for. So, let's talk about this some. So, if you're saying one condition you would propose...

Seth Schwartz: For the outpatient treatment of chronic nonhealing or of nonhealing wounds, it would be covered under the condition of reassessment of effectiveness at one month of therapy, something like that, and then, I would also point out that I think we should be very clear about the contraindications, that this only can be used in patients without contraindications. Obviously, that's what happens in clinical practice, but if we're worried about the expansion of this treatment, I think that should be called out very clearly.

Chris Standaert: ...[inaudible]. For the outpatient treatment of nonhealing wounds, help them out?

- Seth Schwartz: The absence of com-, of... in the absence of contraindications with reassessment of effectiveness after one month of therapy.
- Chris Standaert: One month or each month?
- Gregory Brown: I was going to say... I would suggest with a minimum of monthly reassessments for up to four months based on the Health Care Authority recommendations... or the directors' recommendation. I mean, we can change that, but I'm just saying, that's where we start, in a 12-month period. So, I don't want to... using it for four months, [inaudible] healed, you know...
- Chris Standaert: [crosstalk]
- Gregory Brown: ...four weeks... four months and one week, oh, it's open again, we're going to put it back on for four months. So, that's it not just this, you know?
- Chris Standaert: So, [inaudible] proposes four, a maximum of four months in a 12-month period?
- Carson Odegard: Well, that was the discontinuation criteria, wasn't it?
- Seth Schwartz: The one thing I would point out, too, is for the same wound.
- Chris Standaert: I suppose there is [crosstalk]...
- Seth Schwartz: So, in other words, if you, you know, if you have one on the opposite foot.
- Gregory Brown: I actually don't think it should be for the same wound, because if, you know, if it's on the second toe and that heals, and then it's on the third toe.
- Seth Schwartz: But what if you have it, what if you have it and you have effective treatment for a month and a wound closes on your left foot and then one opens on your right foot? Do we not offer it in that circumstance?
- Gregory Brown: If it closed in a month, they still have three months left in their one-year period. No, I'm serious. Again, to me, the issue, and I brought it up, is what's the natural history? If they have open ulcer after open ulcer after open ulcer, then treating them four months with a negative pressure wound therapy for each individual ulcer makes no sense to me.
- Seth Schwartz: I think that's a reasonable point if it's on the same foot, but what if it's on the other foot, or what if it's on an upper limb or something. I guess, I mean, I think that you're right that if you want... if you're worried about the abuse or misuse of it and that we're in [inaudible] by limiting to four months, you effectively end that problem, but I think that you also exclude some potential circumstances where it might be beneficial for those patients.

- Chris Standaert: You could also argue there, a very large wound, a big pressure ulcer on a hip, a spinal cord injury patient that goes bad, or a large surgical abdominal wound that dehisces might not heal in four months, but that's the tricky part.
- Kevin Walsh: That's the agencies' recommendation. The wording is that you basically... beyond four months, medical necessity would be given individual consideration.
- Chris Standaert: Add that sentence. You could add that sentence. So, add another sentence, Kris. Are you typing? Who's typing? Beyond four months, what was your sentence Kevin?
- Joann Elmore: Medical necessity will be given individual consideration.
- Kevin Walsh: Medical necessity beyond four months will be given individual consideration. The medical necessity beyond four months will be given individual consideration.
- Josh Morse: This is Josh. I just have a comment on that. I think another way to say that that might be necessary to replace medical necessity with agency discretion.
- Chris Standaert: Again, medical necessity beyond four months, continuous treatment will be dependent upon agency discretion. Continuation of treatment. It takes out the medical necessity word.
- Laurie Mischley: Why would we want to take out the medical necessity word?
- Josh Morse: That's how the agency can make a discretionary decision. You'll be employing your ability to make medical necessity decisions. I don't think this committee has the authority to give you that authority, basically, to say you'll use medical necessity to make that decision.
- Laurie Mischley: OK, but that is how we make all our decisions.
- Josh Morse: I understand.
- Laurie Mischley: OK.
- Chris Standaert: But we don't have to say it then.
- Seth Schwartz: I would just... I think we've lost... I think the reassessment in one month is critical, but also demonstration of effectiveness. In other words, I don't care, yes. I see you every month but nothing's working is not really limiting the way we want it to limit, so, I would add demonstrating improvement or, yeah, I don't know exactly how we classify improvement, but, improvement.
- Kevin Walsh: The agencies' wording is wound healing is defined as improvement occurring in either surface area or depth of the wound. That seems reasonable. Does that seem reasonable to you, Dr. Quigley?

- Terence Quigley: Yes. That's exactly what we use in our wound care center. We measure every wound and take a picture of it every [inaudible].
- Seth Schwartz: So, then maybe you should say, continuation beyond one month requires evidence of improvement. As defined by whatever the terms you just used, depth and size of the wound, and you might also say not just beyond one month but at each month interval, I think, is a good point.
- Kevin Walsh: We could just start with their wording and parse that, as opposed to reinventing it, since we're pretty much developing consistent language.
- Chris Standaert: At some level, people voted for some circumstances it's more effective. So, I struggle with data to support anything that's up there. I don't see any data to support that, personally. I don't know it's unreasonable, but the data doesn't really help me get there very easily. So, people voted there were circumstances they thought it was more effective, and does that mean all chronic nonhealing wounds? Do people, do we need to be talking about diabetic wounds, postsurgical wounds? What... what do we talk about? Are we sort of just leaving this open to the discretion of the treating population regardless of the absence of data, you know? That's the tricky part here.
- Seth Schwartz: The data is challenging. I mean, I think there was probably some of the best evidence for surgical wounds. I think there was... because that's the situation where you've had an amputation with healing after amputation. So, it's kind of mixing the diabetic foot ulcer and the surgical population.
- Joann Elmore: Are you talking about the Armstrong papers?
- Seth Schwartz: Yeah. Yeah.
- Joann Elmore: So, those were diabetics who have had an amputation who had some sort of acute or chronic wound. So, it was basically a diabetic with acute or chronic wound, similar to the...
- Seth Schwartz: It was postsurgical.
- Joann Elmore: ...yeah. It was postsurgical, but it could have been a 'chronic wound.' So, how long postsurgical was it.
- Seth Schwartz: Well, that I don't know. How do you define that? I mean, how do you define that? I mean, what's, I mean...
- Chris Standaert: And that's [crosstalk].
- Seth Schwartz: ...[crosstalk] wound healing should not be very long for a postsurgical wound. So, if it's not healing in a matter of days, it's probably going on.
- Chris Standaert: I mean, a nonhealing...

- Seth Schwartz: [crosstalk] how to define that.
- Chris Standaert: ...amputation, the end of an amputation in a diabetic nonhealing does not necessarily heal quickly, because the problem is, they may never heal versus a large incision for an abscess in somebody's paraspinals that got opened up and is going to heal by secondary intention that is eight inches long because they had, again, an abscess in their paraspinal. That's a whole different ballgame. Those people are not dysvascular and probably will actually heal relatively well, but they're different populations, and then, unfortunately, the agency has postsurgical as one of our categories, and we don't really know what it is. We don't know if these are diabetics with amputations or if these are dehiscence, or if these are infections, or if these are... we have no idea what they are.
- Kevin Walsh: We don't... we can't parse that out, Chris. We don't have any evidence that...
- Chris Standaert: No.
- Kevin Walsh: ...helps us.
- Chris Standaert: That's what I'm... I understand, but that's my...
- Kevin Walsh: We can parse out postsurgical and other. That's as far as we can parse it.
- Chris Standaert: We can, and, but you know, this issue of nonhealing you can parse, I guess.
- Kevin Walsh: Nonhealing is a category of... I'm talking about if we're coming up with criteria, the only separation you can make is between postsurgical wounds and other, isn't it?
- Chris Standaert: Well, no. That's the question I'm posing, again. Again, there's the issue of it's effective somewhere.
- Male: At the four-week level, I mean, in your setting, you were postulating, at the end of four weeks, you're not going to do nothing. So, the question really is, is there an alternative therapy that we're not discussing here that is better for some patients than the vacuum dressing that was put on for four weeks. Again, we don't have that information, but, I mean, we're not going... you're not going to stop therapy at four weeks and do nothing. You're going to revert to something else, and maybe Dr. Quigley, so 10% of the Northwest patients in the wound center are getting vac dressings placed, and... so, for those people that don't succeed with the vac dressing, of the 10%, what happens then? What do they, do they go to an alternative therapy?
- Terence Quigley: Well, we have to assess why they're not succeeding. Are they malnourished? Are they just 95 years old and age clearly plays a role in this. Or is there chronic infection that we're not recognizing. There's all sorts of reasons a wound stalls.

- Male: Opens up the field again. I understand.
- Terence Quigley: Right. So, we just have to reassess, and we have an algorithm to reassess a wound. You know, one of the things we use negative pressure wound therapy for is just a couple of weeks, make it look good, and then put a skin graft on it, which closes a wound much, much quicker than any conventional dressing, and that really, really helps the patients, and it's very cost-effective, because you're not spending all that time and energy. So, there's all sorts of scenarios with the use of these negative pressure wound devices. Most of them are temporary. I mean, we rarely use as an end in and of itself through the whole process. At some point, we have to stop it, just because the wound gets too small, but most of the time, we're stopping it well before that and using some alternative therapy.
- Male: I think in the setting of chronic wounds, one of the questions is, you know, do we need to see that a different therapy has been tried and given a fair shake before you can move on to negative pressure wound therapy and if so, how should that language be incorporated in this?
- Male: Go back to the agencies. Oh, I see, yeah.
- Kevin Walsh: So, they're proposing that traditional therapy be tried first before you go to... this is for chronic, nonsurgical wounds before you go to negative pressure wound therapy.
- Laurie Mischley: Dr. Quigley, can you weigh in on whether or not that's appro..., I mean, do you...
- Terence Quigley: Well, I can tell you that from my experience, I don't think I have ever seen a patient with a chronic wound who comes in for evaluation and treatment that we slap a wound vac on. I don't think that's ever happened, because we have to assess the wound. Most of them need debridement. It is a contraindication to put a wound vac on an un-debrided wound, for example. So, sometimes those patients can be debrided in the wound care center and then they're bleeding like crap. So, we can't put the stuff on then, because it'll just clog up the foam. So, sometimes they have to go to the operating room and be debrided. Occasionally, I will place the wound vac just right after the debridement, but most of the time, we'll assess the wound for a couple of days just to make sure that the infection is clear, because you don't want to put an occlusive device on an infected wound. That just doesn't make sense. Well, it's just not good medicine. So, there's... I can't remember. In fact, I don't think I've ever treated a patient where I've just slapped the wound vac on the first time I've seen them. It doesn't happen. We have to assess, and while we're assessing, we are using other modalities. It may be very quickly, within a week, that we decide that the wound vac may be the best method going forward with our experience, but we're usually trying other things first, but most patients would prefer that we do try other things first. The wound vac is cumbersome. It's... unless you're in a nursing home where it doesn't matter, because they're going from wheelchair to bed or nonambulatory patients, but for ambulatory outpatients, it's cumbersome.

- Gregory Brown: I might remind the group that that's your practice.
- Terence Quigley: That's correct.
- Gregory Brown: So, what I'm hearing is...
- Terence Quigley: That's absolutely correct.
- Gregory Brown: ...it is certainly reasonable to suggest or require that you try something else first before you go first to that, because that may not be how other providers do it.
- Seth Schwartz: The challenge though is if you try and limit, say for what period of time or anything like that. I mean, to say you have to try something else first is almost not really... it doesn't really limit things unless we put some duration on it, because... so what, you put the... slap the wet to dry on for a day before you do it. Does that... is that a meaningful limitation of use, but we don't have really any data to suggest what that timeframe should be for trialing another methodology, and we didn't really even see data that it's necessary to do that. I mean, clearly, from a practical standpoint it is, as a wound assessment tool, but as far as if you see a wound, wound vac might be more effective than something else, we don't have data to say that that's true or that's not true.
- Chris Standaert: So, did you see data suggesting you're actually depriving a patient of appropriate care if you don't put this on them immediately?
- Seth Schwartz: No.
- Chris Standaert: I didn't.
- Seth Schwartz: And I'm not saying that we should. I'm just saying I think it's hard to...
- Chris Standaert: So...
- Seth Schwartz: ...limit... it's hard for me to conceive what the limitation is.
- Chris Standaert: ...you know, again, I'll argue, you don't really have data for this. I understand it. I understand the rationale and the clinical rationale. We're in level five data, unfortunately, and if you thought there were, you know, a problem, like if you didn't get this... like, with other things we've had no data, but, like, if we didn't do it, somebody might die, right? That's a different situation. That goes to our outcomes. We have critical outcomes that if we don't attend to them immediately, then that may actually change our thinking. So, in this one, the idea that you actually define some other measure being taken before or some other assessment of the wound or some other thing hardly seems unreasonable to me, because I don't know that there's a deprivation factor here.

- Seth Schwartz: I think that's reasonable, but I also don't agree with saying we have level five evidence. I mean, if you look at this just for diabetic foot ulcers, we have a Lavery study, which is grand and retrospective, but it's a cohort study of over 2000...
- Chris Standaert: OK. Not quite level...
- Seth Schwartz: ...patients that...
- Chris Standaert: ...five, sorry.
- Seth Schwartz: ...shows that at 12 weeks twice as many people have a healed wound versus the other. I think that's pretty significantly compelling to say that we may be dragging on therapies unnecessarily if we don't offer this to patients early, or at least make it available if that's the appropriate thing for that individual patient. Now, again, I hear what you're saying. I'm not saying that we need to... it's life... a matter of life or death that we offer this on day one, but I think there is evidence to suggest that it's going to shorten the course of treatment for certain patients and I'm not sure why we need to limit use to say they have to try something else that may be less effective, if we can't define what those boundaries are. So, again, I'm not saying we shouldn't do it, I'm just saying, I'm struggling with how to do it.
- Tony Yen: I support Kevin in terms of, like, adopting much of the agency language. Probably the only thing I would change a little bit or tweak a little bit are the contraindications and having the FDA 2011 contraindications in there. That's about it. I think it really does... I think the agency recommendations really kind of encapsulate at least much of what I'm thinking internally.
- Joann Elmore: I believe those are listed on slide ten of the vendor. I was going to suggest that, as well. I'm seeing a discussion around three bullet conditions from the group. One has to do with some sort of definition of failure of conventional therapy. I see the irony in us attempting to draft something in the absence of evidence but yet I also see the irony of us potentially voting to approve something with inadequate evidence. So, I think we're balancing equipoise on both sides here. So, for the three bullets, it seems number one is some sort of failure of conventional therapy. Number two is contraindications, and I agree. I would just say FDA contraindications and risk factors being considered. Then, number three, the time limitations and that you want to see improvement month to month and after four months agency discretion, but then the only question I keep asking is, do we... is this just at the discretion of any kind of wound? Is it only diabetics? Is it only... I'm trying to hear from the group, are we just going to leave that open? In other words, I should ask our clinician here, our expert, of the patients you use this on, are almost all of them diabetics or?
- Terence Quigley: You know, I don't have that data, but I would say 50%.
- Gregory Brown: I think what I heard in the initial presentation was that the coding is so poor that we have no idea what they're being used for. So, I don't think there's any way, based on coding, to ask, you know, to restrict or...

Terence Quigley: I would disagree with that a little bit, because as we code for our billing, and we have to obviously code everything. Anybody who is a diabetic, it's coded as a diabetic, and anybody who is a diabetic who has a wound below the ankle has a diabetic foot wound. It's not a diabetic wound. It's a wound in a diabetic patient, and there's a difference. So, we classify all those patients as diabetic foot wounds. All they have to do is have diabetes.

Chris Standaert: But we're, we're going and getting into some difficulty here in that, again, the statement that everybody does what you do is not true. Right? And whether people think you are reasonable or unreasonable, whatever you do is not what everybody else does. I guarantee you that, because reading the literature, there is so much variability in what people say, and you read the AHRQ report. So, there's basically not enough evidence to say anything about outpatient wound care with these devices, right? Wound options are all over the map and I've known a number of wound nurses, and they all have their own things they like, right? This is good in my hands. I know what to do with this. I don't know what to do with that product. So, it's all over the map. So, as we get into that kind of granularity, that's really difficult when you go there, and coding is really tricky, because the state tries to pull out what's there, but I guarantee you there are people who just say, this is an ulcer. They don't know what ulcer. ICD-9 is like [inaudible] and they're... they just click what they got to click to get out of the chart, right? So, using that as, like, we're going to draw meniscal indications based on what people put into their chart to bill is, like, we shouldn't be doing that is my own thing. That's not where we go for the data. These clinical judgments are way better than that. So, we'll go there. So, anyway, so we'll keep going. Carson.

Carson Odegard: So, the agencies tried to parse this out, and my concern is the... we don't have any evidence to support these recommendations. So, the... I don't know how we can... I don't know how we can go about that doing that according to the individual ulcers or the surgical wounds. I mean, we...

Chris Standaert: It's not that it doesn't make sense to say you need good nutrition and diabetic control. Again, we don't have... there's... I mean, we could say all sorts of things that sound like they make good sense, but in some way we have to decide how far can we go, right? And if we're getting totally out of anything we even looked at, we probably shouldn't be commenting. We should leave it more open. Either you say or you leave it more open. Those are your choices. Creating things out of pure thin air gets a little tricky.

Male: Noridian has statements about comprehensive wound care being tried first, the comprehensive wound care, which I assume includes vascular distribution, albumin, the comprehensive, what he said. So, that seemed to be reasonable language as the precursor. You try something, which is comprehensive wound care, and if that's failing, we would not want to take this away as an option. Is that a true-ish statement? We don't have any data. We really don't have a lot of information, but would we want to take it off the table? Probably not. So,

therefore, it's approved with some hedging around, right, but the precursor has to be a comprehensive wound care that's been attempted. That seems reasonable.

Chris Standaert: You're doing lots of cutting and pasting over there, and I'm trying to follow what you're doing.

Kris Urv-Wong: I just took the conditions.

Chris Standaert: Starting with that thing that says general wound care measures is where you're starting with what the agency had?

Kris Urv-Wong: Yes.

Chris Standaert: Can you make that a little bigger for those of us over 45? Thank you. I'll make do. That's fine. Do we say that, or do we say comprehensive wound care.

Joann Elmore: Yes, comprehensive wound care for one month with failure, as defined the same way we're going to define it later on. I almost feel as if we're prescribing too much. I mean, clinicians know adequate nutritional care. In the past, we have wanted to not prescribe things that most clinicians will follow. I realize we have no evidence, but I feel like we have no evidence on some of the later stuff. I almost feel like just one month careful follow-up and failure to improve if we prescribe it, the definition of [crosstalk].

Seth Schwartz: I would agree with that. I think when we've tried to really parse these and be very specific, it's when we've had good data to suggest it is or is not effective in certain circumstances, and we don't. We've typically wanted to leave that to the discretion of the clinicians, and I think that's appropriate here as well.

Chris Standaert: So, we are, on our decision, supposed to consider the evidence and start with the highest level of evidence and if... we didn't talk about this. This didn't even come up. These conditions didn't even come up at all. It makes sense to me, the adequate nutrition to help somebody heal, but we didn't look at it. So, to say that, we're really step out of...

Kevin Walsh: I'd be comfortable if we cut everything except the wound is improving.

Chris Standaert: ...except the wound what?

Kevin Walsh: Is improving. I mean, the condition is the wound... at a monthly evaluation, you have to be able to demonstrate improvement in size or depth, but all the other things about nutrition and no.

Seth Schwartz: I mean, the only way we've gone about this is, we've looked at sometimes the entry criteria into the randomized trials. So, if they'd specified those things, we sometimes pull those sorts of things out that can be useful. I think we haven't seen any of that in the studies we've seen other than that patients were in some

sort of program, either a wound care center or a diabetic center. So, if they specific what that entails, great, we can use it and we can... but I don't think we have that. All we can do is make assumptions about what that means. So, we should leave it as vague as that.

Chris Standaert: We probably could use the phrase of, you know, following a comprehensive wound care evaluation or something akin to what you were saying that Noridian has. So, you get some idea that somebody's looked at this and thought about other things, for a nonhealing wound, if you want to get there. Again, I think that stuff we're treading into ground that we don't, we aren't justified treading into. So, that paragraph needs to go away or be replaced with other language that people are comfortable with.

Joann Elmore: So, are people comfortable with one of the conditions, the first condition, failure to improve after say one month under comprehensive wound care, as defined by either surface area or depth of the wound? It's not evidence based, but remember some of our later conditions are also not going to be evidence based, and I think you were articulate in saying that it's not... we have seen no evidence that this will harm the patient, and that's the most important. I don't want to harm patients.

Male: What I don't understand is, what is comprehensive wound care? Like, that is, like, exceedingly vague to me, and, you know, I'm really frankly concerned about access issues for people who are out there in more of our rural sort of areas and, like, there's no wound care center. We're just going to say...

Joann Elmore: I didn't say a wound care center. I just said, you know...

Male: But what does that mean?

Joann Elmore: ...comprehensive wound care. In other words, they've been treated by a clinician for a month and however the clinician wants to treat it, hopefully high quality care, and it's not getting better.

Male: I do feel strongly that what the agency has put down, that is actually what we're trying to come to a conclusion about and instead of eliminating that language, I think that is actually what, perhaps, you're... I apologize if I'm misspeaking, but to me, that is actually what I feel is more comprehensive wound care. For me, that encapsulates what we should be doing before we proceed to negative pressure wound therapy.

Chris Standaert: I would argue that if you don't say something like that, then somebody in the... when you're in a medically isolated region just sort of a wound comes in and they slap this on it. The data that that's a good thing to do is not there. The argument that you shouldn't take it out of the hands of people caring for wounds that really aren't healing because there's a whole collection of evidence free treatments that they have to pick from anyway, and they're all probably relatively expensive makes sense to me, but the idea that you say something that makes... otherwise,

somebody in an outlying area just walks in with a wound and they put this on there. Is that we think should be happening with this? Or do we think there should be something happening before that and therefore some comprehensive evaluation.

Kevin Walsh: What is the Noridian language? I'm having trouble finding it.

Male: One of the early slides, the very first. Yeah, page 15 on Johnson's presentation.

Joann Elmore: Wound therapy program must have been tried or considered prior to.

Chris Standaert: In some ways, what you are doing by putting that clause in there is saying that people really have to think through the care of these wounds before they put this on there. So, you're going to be... yes, the words are vague, but they do... they mean something, and it's... sometimes you put that... the bar that you have to think about... you have to have said at least you've tried other things. It has to be documented. You've thought through the wound before you do this. Just by saying that, you will change care. You will make people then pursue other avenues of... just by saying that and making people put that in their notes and document that, you will change care.

Joann Elmore: So, should we put back in the agency recommendations, which are just real good clinical care.

Seth Schwartz: Slide 20.

Chris Standaert: No, but we can...

Joann Elmore: No, the agency recommendations, slide 19, of general wound care, in other words...

Chris Standaert: ...we just took that out.

Joann Elmore: ...yeah, we took it out...

Chris Standaert: [crosstalk]

Joann Elmore: ...yeah, we took it out, but the question is, I'm hearing you guys come around to sort of wanting to just make certain that basic appropriate wound care has been evaluated and applied to the patient.

Chris Standaert: We don't know what that is. So, you could leave it to the providers to determine what they think is basic general wound care. We have no way of sorting out wet to dry, what's an appropriate... so what albumin level? Do you want to go there? I mean...

Joann Elmore: No.

Chris Standaert: ...no. So, we...

Joann Elmore: OK.

Chris Standaert: ...get a...

Kevin Walsh: So, we have to... isn't the charge if we're going to write a recommendation that's different than the standards that we come up, with evidence to support that difference?

Chris Standaert: Our real charge is that if we really differ from Medicare NCD that we have to define why. We do have to state that we looked at other clinical guidelines, which are highly varied, in terms of what they say. We have to say we looked at appropriate clinical guidelines. We looked at appropriate payer policies, and then if we are grossly in discord with them say why.

Kevin Walsh: So, I...

Chris Standaert: But it doesn't, but the default is not that we follow what a professional society said or what one payer said.

Kevin Walsh: ...that's not what I said. That's not what I said.

Chris Standaert: I know.

Kevin Walsh: You're agreeing with what I said.

Chris Standaert: Yeah.

Kevin Walsh: So, I...

Josh Morse: I'd like to pause. I want to interrupt and just, let's make sure that we agree on what the requirement is, because it's the same for national coverage determinations, as it is for medical society guidelines. So, we give the same consideration to an NCD as a professional guideline.

Chris Standaert: OK.

Josh Morse: And that's typically how you've worked when you justify if there's a difference in the end. And we can review the statute if you'd like to clarify.

Kevin Walsh: I'm trying to... so, that was the... that was the introduction to what I was going to say. So, if that's true... I'm trying to go back to why are we... why are we including language about comprehensive wound therapy at all, because there's no evidence, right, that we require that before we go to negative pressure wound therapy. So, what I'm saying is if you go back and you look at the Medicaid policy, look at Noridian, look at AETNA, they're all saying try traditional wound care first.

- Joann Elmore: And that's what we want to add. Don't just jump to this.
- Kevin Walsh: Well, that's... well what I'm saying is, there is a... we're being consistent if we say this. Even though there's no evidence, we're being consistent with what the standards are.
- Chris Standaert: If you took the Noridian statement on page 15 of Dr. Johnson's report, and you took out the exact ulcers, because we decided we don't have great reason to differentiate by ulcer type, you would have a statement saying a complete wound therapy program must have been tried or considered prior to negative pressure wound therapy, and then either continue... they have discontinuation of coverage. Any measurable degree of wound healing has failed to occur over the prior month, wound healing is defined as improvement occurring either in the surface area, length times width, or depth of the wound, four months, including the time it was applied in an inpatient setting prior to discharge home have elapsed using [inaudible] in the treatment of the most recent wound. That's what they say. That's pretty close to what you guys are saying.
- Seth Schwartz: I think that's...
- Chris Standaert: It's a fairly succinct version of this language and obviously then we are in agreement with a major governing body of some sort.
- Male: I'm comfortable with that language.
- Chris Standaert: So, you could go to page 15 to Noridian in Dr. Johnson's report and copy that and take out the four lines below a complete wound therapy program. Obviously, there are contraindications to the device with the device, and the FDA has defined contraindications. We could define them or we could let the medical world stay within their medical contraindications. So, those four lines, chronic stage three or four pressure ulcer down. Stop. Yeah, get rid of those four. Get rid of those, because we're not parsing by ulcer is what people are saying. It is vague, but there are some boundaries that are being placed here, and you are encouraging people to consider appropriate wound care and routine follow-up. What do people think?
- Joann Elmore: Do we need to discuss how to word the third bullet about contraindications and risk factors and somehow just refer to the FDA, sort of attention to the FDA contraindications, risk factors.
- Male: We should either include it or refer to it.
- Joann Elmore: Mm-hmm.
- Carson Odegard: Right. I think we should.
- Laurie Mischley: Maybe just be a little more explicit in the discontinuation of coverage that a monthly evaluation is required. I don't... it says in the prior month.

- Joann Elmore: It says the prior month. It's kind of nicely covered.
- Chris Standaert: Yeah. It says over the prior month.
- Laurie Mischley: OK. That sort of states that you would see that... you have to see them every month or else you can't state that. So, Joann would like a third bullet point.
- Joann Elmore: I don't know what the first word should be, attention to FDA contraindications and risk factors. I don't like the word attention.
- Chris Standaert: I don't like the word attention.
- Joann Elmore: But in other words, they have to whatever FDA contraindications are in existence we agree with.
- Seth Schwartz: You could almost put that as an exclusion criteria or something like that. You say, this treatment is not to be offered in patients with FDA contraindications.
- Joann Elmore: What about the risk factors? Probably just the contraindications by the FDA?
- Chris Standaert: What risk factors?
- Laurie Mischley: At least mention people on anticoagulants and things like that just to [crosstalk].
- Chris Standaert: Yeah, those are the contraindications. So, treatment should not be applied to patients with contraindications, as defined by... well and then you have to put the label of that FDA paper. It has a number and a label and has a defining...
- Joann Elmore: Website 2011.
- Chris Standaert: ...but it has a defining code for that paper published by the FDA and people can always find that document if we find that code.
- Male: It's fairly complete language in this guideline. The pressure ulcer advisory panel. I don't know who they are, but it's 2014, that was in the guidelines component page 10. I don't know if you want to quote it, but it's recommended in adequately debrided necrotic or malignant wounds and it goes on with a number of other comments that all seem very pertinent, but it's just a professional guideline.
- Chris Standaert: So, you could say... I have the exact wording of the title of the document that will have all this stuff in it. You can use that or you can cut and paste everything out of it. Yeah. It's the FDA update on serious complications associated with negative pressure wound therapy systems. How about just the FDA safety communication on negative pressure wound therapy from February 24, 2011. FDA safety communication from February 24, 2011, and safety is also capitalized.

- Joann Elmore: And instead of this being a third bullet, it should be a main bolded. So, this is the third main bolded condition. So, we have three conditions. I don't like that wording, no.
- Chris Standaert: Treatment should not be used in patients with?
- Joann Elmore: Patients with contraindications, that's better.
- Chris Standaert: Treatment should not be used in patients with. So, we'll get rid of not applied to. [inaudible] after treatment, the, yeah, should not be used in. Get rid of not applied to. How are we doing, people? Do we like this?
- Josh Morse: I think... a little advice on that. I think treatment not covered for patients with.
- Chris Standaert: Oh, not covered for. I'd almost like it to be stronger. This is not just not covered, but, like, you shouldn't put it on people who have, you know, like an exposed vessel. Where are you going? Can you go back to the conditions for us? Treatment not covered in patients with. What do we want? Do we want not covered or should not be used? Who are covered, so. Yeah. I guess we don't have jurisdiction over this. Not covered. Treatment is not covered in patients with... is not covered in... and get rid of should not be used. Yeah, there you go. Right. That's a good clarification.
- Carson Odegard: Being the devil's advocate here that if it's not covered for those indications, a clinical decision could be made without coverage, and it would go against FDA recommendations.
- Chris Standaert: So, for clinicians in various environment [inaudible] work, does this work with you? Yeah? OK. So, unless anybody has any amendments to this or changes in the language or doesn't like a word, if there are... when we come back to vote on this again to finalize our vote, fundamentally changing the whole thing is difficult. That poses challenges for us. If there is a grammatical error or something like that, they will pick that up, or we will pick that up if there's some subtle word that changes meaning, we can pick that up. So, little things like that we can get at in a few months if we had to. We'd like this to be as clean as possible. The agency will look at it and determine whether they think they can really follow our language or not and they have language corrections for us sometimes that we are OK with and sometimes we are not OK with, because it changes our intention.
- Alright. So, we're going to vote. So, your choices are cover, which means regardless, we're going to cover it where anybody wants to use it, all conditions. For, these are for outpatient and somewhere that's clear on this, right, that this is for outpatient or in-home use, right?
- Joann Elmore: The stem of this before the [crosstalk].
- Chris Standaert: The stem of this is that this is for outpatient or in-home use, because that's our... right. You can say not cover, which means these are not... you don't think we

should be covering it, which is fine, or you can say cover. If you vote cover with conditions, these are the conditions. OK? Alright. So, let's go to my tool for a second, because I have to ask you the question in the correct way. So, based on the evidence vote, committee, we already took our vote. So, based on the evidence about the technology safety, efficacy, and cost-effectiveness, negative pressure wound therapy in the outpatient or in-home setting is either... now you vote, not covered, covered unconditionally, or covered with conditions meaning these.

Josh Morse: Ten cover with conditions.

Chris Standaert: Next, we make sure this meets with our... do we have good reason to be discrepant from other things? I think we might have had good reason should we have chosen to. I'm not sure everybody had good reason for the [inaudible], but we are relatively... I think we are relatively in line with our mandate of guidelines and other policies. Yeah? So, we're done, yeah?

Joann Elmore: Well, I want to make one comment. We're in mandate with the other guidelines, but our group was convened to evaluate evidence and then vote based upon evidence, and this has given me indigestion, because most of us voted that it is unproven efficacy, unproven safety, and yet we just voted to cover with conditions. So, I hope that more research will be done. I hope it will be higher quality. Some of the studies we didn't even dig into. They were really, really low quality, and we didn't get into some of the details of them. So, I was kind of disappointed at that.

Chris Standaert: Well, briefly, the majority did vote that there was efficacy or effectiveness in some.

Joann Elmore: Some? Oh, OK.

Chris Standaert: Yes. The majority did vote that way.

Joann Elmore; Oh, OK.

Chris Standaert: So, and largely we then voted unproven and equivalent or unproven for safety. So, are we good?

Josh Morse: Yes, and there was no national coverage determination to consider in this case.

Chris Standaert: Right.

Josh Morse: Thank you.

Chris Standaert: For people in the room and people on the phone, this is the meeting of the Washington Health Technology Clinical Committee from Friday, November 18th, 2016. This is our afternoon session. Our topic this afternoon is fecal microbiotic transplantation. I'm not sure if that's better before or after lunch, and that's our

topic today. We are going to follow our schedule and agenda, which goes Washington State Agency Utilization and Outcomes. Dr. Lessler will present first. He's stressing and warming up over there. Then, we will have a period for open and public comment, and there was a sign-in sheet where people could sign in if they want to speak. Anybody in the room during that section who says they want to speak, please just raise your hand and let us know, and you can speak to the committee, and we will open up the phone lines to see if anybody on the phone wants to make a public comment to the committee. Following that, we will have our evidence report by Spectrum Research and the committee will discuss that. So, that being said.

So, everybody knows. There are new people here today. The meetings are recorded, and they are transcribed. So, everything you say is recorded and transcribed, and the person who is transcribing may know some of our voices, because we've been here awhile, but those of you who have not been here, he or she will have no idea who you are. So, we're going to go around the room and introduce yourself so that they pick up who your voice is, and it might be helpful, especially if people haven't been here that long to say their... just to help the transcriptionist so we get all this accurate. So, again, I'm Chris Standaert. I'm the Chair.

Josh Morse: Josh Morse.

Christina Surawicz: Chris Surawicz.

Seth Schwartz: Seth Schwartz.

Chris Hearne: Chris Hearne.

Carson Odegard: Carson Odegard.

Kevin Walsh: Kevin Walsh.

Tony Yen: Tony Yen.

Laurie Mischley: Laurie Mischley.

John Bramhall: John Bramhall.

Gregory Brown: Greg Brown.

Joann Elmore: Joann Elmore.

Chris Standaert: And that's all of us. OK. Take it away.

Daniel Lessler: Great. Thanks, and I'm Daniel Lessler from the Health Care Authority. I am going to present on the topic of fecal microbiotic transplantation. So we can jump right in here. So, by way of background, actually we're going to be talking about this

technology in two contexts. One is for the treatment of clostridium difficile and the other is for the treatment of inflammatory bowel disease. Now, it's going to be... just with a brief background on clostridium difficile, also known as C. difficile. So, this is a gram positive spore-forming anaerobe that produces toxins. These toxins, A and B, are capable of producing quite severe diarrhea in patients who are infected with the bacterium and that are producing the toxin. Just to give you some sense epidemiologically of the importance of this, first I would mention that usually infection with C. difficile is associated with antibiotic use, and in 2011, I believe this is a study by CDC, there were 453,000 cases of C. difficile infection and 29,000 associated deaths. So, can obviously be quite a severe infection with bad outcomes. Approximately 25% of the infections were estimated to be community acquired, as opposed to hospital acquired.

I found this an interesting slide from New England Journal, and this just demonstrates the increasing incidence of C. difficile over the last 15 years or so, or 10 years I should say in terms of what's on the slide, and as you can see, the incidence is going up pretty much in all age groups, but especially in elderly and middle-aged people. So, it's an increasingly common disorder.

The diagnosis is either by enzyme immunoassay or DNA based tests for toxic genes. Up to the present, the treatment has typically been for the index case, or the first course of treatment being with antibiotics and vancomycin or metronidazole are most commonly used, and then there's fidaxomicin, which is effective but quite a bit more expensive, and typically for those people who recur after a first course of treatment, a second course of antibiotics has been indicated and used, but in people who recur beyond that, this has been, I think, and Dr. Surawicz can speak more to this, historically a difficult disease to treat, and that's really where fecal microbiotic transplantation has come to play. This, essentially, is exactly as described in some sense, a transplant of stool. So, a stool is obtained from a healthy donor and is instilled into the GI tract of the patient, the thought being that the microbiota provide resistance against bacterial pathogens and that by restoring the microbial diversity in the gut, it's possible to then alleviate infection. So, that's the basis for fecal microbiotic transplantation.

Fecal microbiotic transplantation has also been evaluated, to some extent, and I would assume there are ongoing studies in inflammatory bowel disease. So, inflammatory bowel disease, most commonly we're talking about ulcerative colitis or Crohn's disease, ulcerative colitis being a chronic inflammatory disease that involves the mucosa of the rectum and proximal extension into the colon toward the cecum, whereas Crohn's disease is a patch, nontransmural inflammation that can affect any part of the GI tract. Symptoms include blood in the stool, abdominal pain, fatigue, bloating, and weight loss. There is some thought that aberrancies in the host microbiota might play a role in the pathogenesis of inflammatory bowel disease and hence the interest of fecal microbiotic transplantation in that context.

So, the interest here... this really came up probably in discussion amongst the agency medical directors a few years ago, two years ago by the time it gets to this

group. I would say at that time, the concerns that we had were mostly concerning efficacy and the safety. The concern for cost was somewhat less prominent.

Current state agency policy is here for PEBB or Uniform Medical Plan. Fecal microbiotic transplantation is covered treatment for patients with recurrent second or subsequent episodes of *C. difficile* infection. It requires, in Medicaid, fee for service and managed care, it requires a prior authorization, currently not covered for Labor and Industries and requires prior authorization with the Department of Corrections.

As I mentioned, fecal microbiotic transplantation really, from our standpoint... from the standpoint we were considering bringing this forth to this committee, was really viewed as an emerging technology and the overall utilization, as you'll see with agency data... well, actually, we've aggregated it across Medicaid and Uniform Medical Plan, because it's quite low at this point. The average age of patients is 49. Here, just to give you some numbers, this... you can see there has been an increasing number of people being treated, and this is Medicaid and Uniform Medical data, and here is the cost, although you know I'd actually... Kris, I'd have to ask you. Is this just, Kris, on the cost data, is this just UMP or is this aggregate? That is aggregated? OK. So, pretty low cost up to this point.

So, the key questions for this evaluation have to do with the evidence of efficacy and effectiveness of fecal microbiotic transplantation, this is both now for treatment of *C. difficile* and for inflammatory bowel disease. So, evidence of efficacy and effectiveness, number one. Number two is whether or not the route of administration matters whether by NG or by colon. Evidence around the safety of fecal microbiotic transplantation and whether or not there is differential efficacy or safety in subpopulations and finally, looking at evidence of cost-effectiveness.

So, I'm going to cut to the chase here just in terms of our interpretation. Obviously here, the Spectrum presentation will be more detail in terms of our take on the evidence, as presented by Spectrum. So, first for the treatment of *clostridium difficile*, available evidence supports the effectiveness of fecal microbiotic transplantation in the treatment of recurrent *C. difficile* and the role of fecal microbiotic transplantation in the treatment of primary or initial *C. difficile* infections is not clear. Then, at this point, there is insufficient evidence to determine the effectiveness of fecal microbiotic transplantation and the treatment of inflammatory bowel disease. With respect to safety, typically what's available suggests that the procedure is relatively safe and typically there are some minor associated side effects and more serious adverse events, such as bacteremia, sepsis, and death appear to be rare. I would mention that there is very limited data on long-term safety of fecal microbiotic transplantation.

With respect to administration, there is low-quality evidence that there's no difference between frozen versus fresh feces in fecal microbiotic transplantation and insufficient evidence regarding the route and timing of administration, so

whether that be via the colon or NG, and available evidence suggests that fecal microbiotic transplantation is cost-effective relative to antibiotics.

There is no CMS national coverage determination on fecal microbiotic transplantation, as was noted in the report from Spectrum. Many plans cover fecal microbiotic transplantation for *C. difficile*, typically for recurrent infections that have either failed vancomycin treatment. The exact criteria varies somewhat from plan to plan.

With respect to clinical guidelines, the American College of Gastroenterology has a guideline from 2013, and the bottom line of that is that fecal microbiotic transplantation should be considered in patients where a third recurrence of *C. difficile* after a trial of post-vancomycin regimen and the European Society of Clinical Microbiology and Infectious Disease has a somewhat similar recommendation that fecal microbiotic transplantation in combination with oral antibiotic treatment is strongly recommended for multiple recurrence of *C. difficile* infections unresponsive to antibiotic treatment.

So, the agency recommendation is that fecal microbiotic transplantation be covered with conditions. So, fecal microbiotic transplantation fresh or frozen feces administered either by NG or via the colon is covered for a third recurrence of *C. difficile* infection after a post-vancomycin regimen, and fecal microbiotic transplantation is not covered for treatment of inflammatory bowel disease. So, with that, I'll stop and see if there are any questions.

Chris Standaert: Questions for Dr. Lessler?

Christina Surawicz: Chris Surawicz. That was a great presentation. The one piece that's missing is what about the patient with not recurrent but refractory [inaudible], the really sick patient, because there's no randomized control trial of fecal microbiotic transplantation trial for that, but there are small series suggesting that it has been effective and maybe could be considered on a case by case basis.

Daniel Lessler: Sure. Chris, so maybe, you know what?

Christina Surawicz: It's emerging.

Daniel Lessler: Right. The... I guess how do you define refractory in that, I guess that was, because I thought of refractory as being recurrent or not having a response to antibiotics as refractory.

Christina Surawicz: Yeah. The terminology has been confusing, but recurrent is when you get better and then you get another episode. So, that's recurrent. Some of the literature calls that refractory, as well, but refractory really are the people who are so sick, they're in the ICU. They're heading for a colectomy. So, it's a separate group. Sometimes, it's called fulminant.

Daniel Lessler: So, would these people...

- Christina Surawicz: So, these would be, it could be their first episode, but they're really, really sick, and they aren't getting better with maximal medical therapy. So, sometimes, the patients are so sick, they're in the ICU. They're just not getting better. So, then, the options are do you take out their colon or do you consider fecal microbiotic transplantation. So, there's no randomized control trials of that, but there are some series of using stool transplant in those patients where they get better and don't end up going to the OR with a colectomy or worse, don't end up dying. So, it's a separate small category and maybe you don't want to discuss it today, but I think it's important, because it's I think something that should be considered on a case by case basis. I can't recommend that everyone in that situation have it. It really has to be a case by case individual decision.
- Chris Standaert: So, you're... just to clear up a few things, you're getting a little ahead of us here, right? So, our committee, Dr. Lessler gives us what he just gave us, their perspective on sort of what they have and their interpretation of the data. Then, we are really obligated to make determinations on the data we get. We, as a committee, don't go get the data. That's sort of gotten for us, right? And like any systematic review type format arises from the key questions that are derived from the departments, the industry, and the public who have time to offer suggestions and questions, and that's where we go.
- Christina Surawicz: OK.
- Chris Standaert: So, I, yes, I was watching the presentation and wondered about nonresponsive *C. difficile*, right? So, some people start out with a version that is already not going to respond to standard antibiotic therapy, is that recurrent or is that... what is that, but we'll have to parse that through, as we go through our data, and that's what we do.
- Christina Surawicz: Thank you.
- Chris Standaert: Other questions for Dr. Lessler? No skipping quite so fast. Question or no? So, it's not used very much. It was, like, what 28 patients or something? Is that what I saw?
- Daniel Lessler: Yeah. I mean, but I think and Dr. [inaudible] might be able to comment on the extent to which it's being used more commonly now, as *C. difficile* becomes more common.
- Chris Standaert: Right.
- Seth Schwartz: I would just have one quick question. Just in terms of why we're addressing this, when I think there's... we saw the data on increasing the risk of... or the prevalence of *C. difficile* or at least it has been increasing, but it seems like that inflammatory bowel disease is a concern. Can you just comment about what the... where the real driver was for us reviewing this topic?

Daniel Lessler: To, well...

Seth Schwartz: In other words, what... in effect, if it's an inexpensive therapy that's not being frequently used for a condition that doesn't come up that often, we don't usually ask to look at those types of things. So, is the concern that there is going to be an explosion of use of this technology in inflammatory bowel disease? Is that the concern, or is it not?

Daniel Lessler: I think we were looking at it as an emerging technology. I mean, really, it was the C. difficile that brought the topic forth, but then in considering that we were going to be doing an evidence-based review, looking at it as an emerging technology, it made sense, I think, to look at it in other context in which it was possibly going to be possibly utilized.

Chris Standaert: But, you know, we don't choose our topics. We get them, but we definitely have been asked in the past about things that are on the horizon and coming out. I think, in part, to get ahead of the curve. You don't really want to be in a position of having to either ensconce or reverse what has become a standard of care that could have been looked at more critically previously, I suppose, and if it's getting fairly high in the population in the hospital in people who are ill, it might get used a lot more, and they're just looking for what evidence is there to tell them what to do, I assume, is why they're doing it, because it probably... maybe it's underutilized already. Maybe it's over-utilized. I assume that's why they did it. Other questions? OK.

So, we are in our window for public comment. Nobody signed up for public comment. Is there anybody in the room, there are three of you, anybody want to talk to us? Nah? OK. Can we go to the phones? Let's check and see if there's somebody on the phone. So, for those of you who may be on the phone, this is the meeting of the Washington State Health Technology Clinical committee from Friday, November 18th, and we are discussing fecal microbiotic transplantation. This is the time of the meeting in which the committee can hear comments from the public. So, if there is someone on the phone who would like to address the committee, please let us know so that we can hear your input. Alright. I take it we have no one on the phone. Alright. We're going to move on. Alright. So, next is the presentation from Spectrum, our evidence vendor. Ms. Brodt, you're going to present? Is that what? OK. So, Erika Brodt is going to present the data from Spectrum.

Erika Brodt: Alright. Well, good afternoon. My name is Erika Brodt, and I'll be presenting the evidence for fecal microbiotic transplantation on behalf of Spectrum Research. I'd like to take a minute to acknowledge my co-investigators, Robin Hashimoto, who was the lead investigator on this report, and Andrea Skelly, who is here with us today.

So, Dr. Lessler did a really nice job giving some background, so I'm going to try go a little quicker through this, but briefly, as stated already, fecal microbiotic transplantation is a procedure by which a stool from a healthy donor is introduced into the recipients bowel in order to restore the normal balance of bacteria in the gut. It's considered after antibiotic treatment has failed, and it's now pretty well established that a healthy gut flora is largely responsible for the overall health of the host, and the gut has trillions of bacterial cells, and when there is a disruption in this bacterial homeostasis, that is, in the healthy levels of microbiota diversity, that is thought to be a factor in the pathogenesis of some gastrointestinal conditions, such as clostridium difficile infection. One of the indication for fecal microbiotic transplantation considered in this report, which I will discuss next.

So, recurrent or relapsing C. difficile infection, or CDI, is currently the only FDA approved indication for fecal microbiotic transplantation. As already said, the bacterium produces toxins, which cause diarrhea and gastrointestinal inflammation and can lead to dehydration, kidney failure, and even death if it's not adequately treated. After conventional treatment with antibiotics, approximately 20 to 60% of patients experience a recurrence, and multiple recurrences are associated with increased resistance to antibiotic treatment. It can also develop into chronic CDI.

Fecal microbiotic transplantation has also been used off-label for the treatment of inflammatory bowel disease, which has already been said is an umbrella term that describes several conditions related to chronic inflammation of the digestive tract. The most common forms are ulcerative colitis and Crohn's disease, which can be differentiated by the location of the inflammation. As you can see from the symptoms listed, inflammatory bowel disease can be debilitating and sometimes leads to life-threatening conditions. It's characterized by gradual onset with periods of active disease and disease remission, and there is currently no cure for inflammatory bowel disease. So, treatment focuses on managing inflammation and gastrointestinal symptoms.

Before discussing the fecal microbiotic transplantation procedure itself, I'd like to touch briefly on the process for donor selection and screening, which focuses on risk reduction. So, in a clinical setting, the feces used for fecal microbiotic transplantation is derived from donors who can be relatives or close friends, or universal donors, volunteers, whose blood and stool have been screened for pathogens and transmissible disease, and I've listed just a few of the major things that the blood and the stool are screened for there. This is an FDA requirement, and it must be done using FDA approved methods. Additionally, each donor completes a screening questionnaire that includes questions regarding factors

known to increase the use of transmissible diseases, and that is similar to the current protocol for screening blood donors.

So, regarding the fecal microbiotic transplantation procedure, itself, the methods for preparing stool and administering fecal microbiotic transplantation are not standardized, and we found various ways of doing it in the literature. Fecal microbiotic transplantation can be prepared from fresh or previously frozen stool. When it's fresh, it's advisable to use the sample within 24 hours, although within six hours is preferable, and actually in the RCTs included in our reports, all but one did use fresh feces implanted within six hours. Fecal microbiotic transplantation is then usually delivered in liquid form mixed with water, saline, or 4% milk by means of a naso-duodenal or nasogastric tube for implementation into the upper GI tract or retention and/or colonoscopy if it's to be delivered into the lower GI tract. In our report, all of these modes of delivery were represented with colonoscopy used the most frequently in the included trials.

So, briefly, these are our key questions, and they're pretty standard looking at the efficacy and effectiveness of fecal microbiotic transplantation, the safety, differential efficacy or safety, and cost-effectiveness. Question two is a little bit different and asks whether fecal microbiotic transplantation varies by any of three factors related to the procedure, specifically the route of administration, the timing of administration, and the type of preparation. Of note, the conditions, *C. difficile* and inflammatory bowel disease, will be presented separately in this report, since they are such different disease entities.

Briefly, our population, again, we're interested in the treatment of recurrent CDI or inflammatory bowel disease, and the intervention, as I said, is fecal microbiotic transplantation and in the included trials, this could be done with or without bowel lavage. Comparators included alternative treatments, such as antibiotics and placebo, which could also be done with or without bowel lavage in the included trials. As we talked about for key question two, we also compared different types of fecal preparation, routes of administration and timing.

The primary outcomes of interest were cure for CDI and disease remission or symptoms improvement for inflammatory bowel disease, as well as mortality, either disease related or all cause, the need for repeat or additional fecal microbiotic transplantation procedures and adverse events. Secondary outcomes of interest are also listed here. In general, these were not well reported in the literature, and all outcomes were primarily reported over the short term, as Dr. Lessler said. We have very little evidence over the longer term for a lot of these outcomes.

Regarding study design, the focus was placed on studies with the least potential for bias. For key questions one through four, the focus was placed on RCTs when that data was available, and only formal economic analyses were considered for the evaluation of cost-effectiveness, key question five.

Regarding the literature search, the period ran through the beginning of September and did not place a limit on the start date, and I apologize. There's an error on this slide I did not catch, but we only included a total of 30 studies, 7 RCTs and 3 nonrandomized comparative studies instead of the five shown there, as well as five formal economic evaluations, and additionally 15 case series were summarized.

So, I'm going to present the results in terms of the overall quality of evidence, which is based on HRQ's recommendations and our application of grade, which I think you all are fairly familiar with. We grade the overall strength of evidence separately for each primary outcome using the domains shown here, and each primary outcome measure will then get a final strength of evidence rating, and this represents how confident we are that the evidence reflects the true effect. That is, is our confidence high, moderate, low, or do we have insufficient or very little confidence. For this report, we most commonly downgrade the quality of evidence due to risk of bias resulting from methodological flaws in the studies and for risk of precision that results from small sample size.

OK. So, turning now to the results for key question one, efficacy and effectiveness. As I stated previously, each indication was evaluated separately beginning with recurrent *C. difficile* infection or CDI. This slide gives the brief overview of the entire evidence base that we found and was included in this report. In the slides that follow, the focus of our discussion will be on the RCTs. As you can see, there were a total of 3 RCTs for this condition, 2 small RCTs at moderately low risk of bias that compared fecal microbiotic transplantation versus antibiotics, specifically vancomycin, and additional small RCT that compared fecal microbiotic transplantation to placebo infusion, in this case autologous feces, so the patient's own feces, and that study was low risk of bias.

Now, I apologize. These slides look a little busier than I had hoped, but I'll try to direct your attention to where I'd like you to look. So, beginning with the comparison of fecal microbiotic transplantation versus vancomycin for the treatment of recurrent CDI, in both trials, cure was the primary outcome and was defined as the absence of recurrent CDI, that is CDI related bacteria plus two or three negative stool tests for the *C. difficile* toxin after a single treatment. As you can see by the pooled effect estimate down here, if I can point, that a single treatment with fecal microbiotic transplantation resulted in significantly more patients achieving cure over two and a half months compared with the standard vancomycin treatment. The risk difference was 45% and actually, both trials were terminated early following an interim analysis that demonstrated considerably higher cure rates with fecal microbiotic transplantation.

The next slide discusses the outcome of the need for additional fecal microbiotic transplantation procedures, and this was given due to CDI recurrence during the time period, and one RCT reported that compared with vancomycin, significantly fewer patients in the fecal microbiotic transplantation group, as you can see from the pooled estimate, required an additional fecal microbiotic transplantation procedure due to CDI recurrence, and subsequently cure without relapse was

achieved in three of the four fecal microbiotic transplantation patients and 15 of the 18 vancomycin patients who underwent additional fecal microbiotic transplantation procedures.

Moving on to mortality, I have pooled results across two small RCTs suggest no difference in mortality attributed to CDI within two and a half months of treatment. As you can see in the conclusion column here, two deaths occurred in both groups in one trial, and in the other trial, no CDI reported deaths were reported.

Similarly, regarding the risk of all-cause mortality, as you can see from the forest plot below here, the pooled effect estimate suggests no difference between the fecal microbiotic transplantation and vancomycin groups, again, through two and a half months follow-up, and looking now at the first row of the table above, which corresponds to that forest plot, you can see that two deaths occurred in each group in one trial, all of which were attributed to CDI, and one death occurred in the vancomycin group in the other trial. The second row of the table contains data from one of the RCTs, which additionally tracked all-cause mortality through eight months post-discharge, and while fewer patients in the fecal microbiotic transplantation group died through this time period, the risk difference was 23%. The difference did not reach statistical significance. There were a total of 3 versus 6 deaths respectively.

So, I'm now moving onto the comparison of fecal microbiotic transplantation versus placebo, but we're still talking about recurrent *C. difficile* infection. One RCT considered to be at low risk of bias provided the sole evidence for this comparison. Placebo consisted of infusion with autologous feces, as I mentioned prior, as opposed to donor feces in the intervention group. Again, cure was the primary outcome in this trial and was defined as the resolution of diarrhea, that is less than three unformed stools per day, in the absence of antibiotic treatment with no recurrence, no stool testing was performed in this study, and after a single treatment, you can see that significantly more fecal microbiotic transplantation patients, 91% versus 63% in the placebo group, achieved cure.

Regarding the outcome of need for additional fecal microbiotic transplantation procedures, repeat fecal microbiotic transplantation using donor feces was offered to all patients who had a CDI recurrence during the two-month follow-up. Compared with the placebo group, significantly fewer patients in the fecal microbiotic transplantation group underwent a second fecal microbiotic transplantation procedure. Subsequent cure was achieved in all patients who underwent an additional procedure.

Regarding mortality, for those patients with complete follow-up in the trial, no deaths, either CDI related or all-cause, were reported to occur in either group, the donor or autologous feces group through six months; however, the sample size is small.

In summary, for the treatment of recurrent CDI, fecal microbiotic transplantation shows significantly greater efficacy than both vancomycin and placebo regarding the primary outcome of cure and resulted in less need for additional fecal microbiotic transplantation procedures. Mortality, both CDI related and all-cause, were similar between the groups, but again, sample sizes were small.

So, still talking about key question one, but moving onto the evidence for our second indication, inflammatory bowel disease, as stated previously, the most common forms of inflammatory bowel disease are ulcerative colitis and Crohn's disease. The only comparative data identified came from two small RCTs, both of which included patients with mild to moderately active ulcerative colitis. Therefore, from this point forward, I'll be referring to this indication specifically as ulcerative colitis. These two RCTs compared fecal microbiotic transplantation versus placebo. One used water via a retention enema and the other autologous feces delivered via a naso-duodenal route. One trial was very high quality meeting all the criteria for a methodologically sound RCT, while the second was poorly conducted by RCT standard, considered moderately high risk of bias.

Like for the previous indication, the following results will focus on data from the randomized control trials only, and due to variation in the definitions of primary outcomes, results were not pooled across the trials.

So, the primary outcome in both trials was a composite of clinical remission plus an endoscopic response; however, this was defined differently by the trials, as you can see in the left hand column over here. While slightly more fecal microbiotic transplantation than placebo patients achieved this outcome in both trials up to three months follow-up, both trials ended early after interim analyses found and observed treatment effect of much less than expected, per protocol. The trials refer to this as futility. Specifically, one study expected a remission rate of 50% in the fecal microbiotic transplantation arm. That's the study in the top row. As you can see, only half, about half of that achieved remission. In the second study, a 70% remission rate was expected, and as you can see, only 30 patients in the fecal microbiotic transplantation arm in that second row achieved remission.

One trial also reported clinical remission alone, which is a component of the composite outcome reported previously and found no difference between groups at three months of follow-up.

For the outcome of clinical response, again defined differently by the trials, both RCTs reported no difference between the fecal microbiotic transplantation and placebo group over two to three months of follow-up.

Regarding the need for additional procedures, specified here as rescue therapy for ongoing disease flare, there was no statistical difference between the fecal microbiotic transplantation and placebo groups through three months.

Regarding other outcomes for this comparison, we had insufficient evidence for the primary outcome of clinical remission plus endoscopic response over the longer term in one RCT, and we had no evidence for mortality. Also, one RCT reported on symptom improvement and quality of life, secondary outcomes for this report, and found no difference between groups at two months.

So, in summary, in patients with ulcerative colitis, the data is unclear regarding the primary outcome of clinical remission plus endoscopic response; however, fecal microbiotic transplantation may provide a benefit over placebo in the short-term, and all other outcomes reported were similar between groups, and no trial reported on mortality.

So, moving onto key question two, regarding whether fecal microbiotic transplantation efficacy varies by route, timing, or preparation. The only evidence we identified came from studies evaluating the use of fecal microbiotic transplantation for recurrent *C. difficile* infection. No data was found in the inflammatory bowel disease population. For the comparisons of the route of delivery of fecal microbiotic transplantation, colonoscopic versus nasogastric and timing of fecal microbiotic transplantation, timely versus delayed, the top two rows. All outcomes for which data was provided occurred with similar frequency between the two groups; however, the strength of evidence was insufficient for all outcomes. Therefore, the following slides will focus on the comparison, for which we do have some confidence in the evidence, and that's the type of fecal microbiotic transplantation sample used, fresh versus frozen feces. One larger RCT and one small retrospective cohort were identified for this comparison, and consistent with key question one, the results presented in the slides that follow will focus on data from the randomized control trial.

So, cure, defined as the resolution of diarrhea in the absence of antibiotic treatment with no recurrence through 3.25 months occurred with similar frequency between the frozen and fresh feces group after a single fecal microbiotic transplantation procedure.

Also, a similar incidence is CDI related mortality, about 2% was reported in both the fresh and the frozen feces group in the same RCT. There were two deaths in both groups through about three months' follow-up.

Similarly, there was no significant difference between groups for the outcome of death from any cause, although the incidence was slightly lower in the frozen feces group, and I don't have a separate slide for the summary, but in general, there is no evidence that frozen and fresh feces for fecal microbiotic transplantation differ in efficacy when considering cure rate and the incidence of mortality, both CDI related and all cause.

So, for key question three, safety, all included studies were evaluated for harms and complications. For the indication of recurrent CDI, evidence on safety was insufficient for the comparisons of colonoscopic versus nasogastric fecal microbiotic transplantation and timely versus delayed fecal microbiotic

transplantation. We did have some safety evidence for fecal microbiotic transplantation versus vancomycin and versus placebo, or autologous feces, and fresh versus frozen feces. For inflammatory bowel disease, all noncomparative data on safety was rated as insufficient; however, we do have some data for fecal microbiotic transplantation versus placebo regarding safety.

So, in each of these slides that will follow for safety, the top row will list serious adverse events and the bottom nonserious, and these are classified the way that the studies classified them. So, starting with the treatment of recurrent *C. difficile* infection or CDI for the comparison of fecal microbiotic transplantation versus vancomycin, no serious adverse events, including procedure-related death, occurred in either treatment group across two trials through two and a half months of follow-up, and in the bottom row here for nonserious adverse events, one trial reported that infection, constipation, GI complaints, indigestion, nausea, belching, vomiting, abdominal cramps, and diarrhea all occurred with similar frequency between the two groups.

Similarly, for the comparison of fecal microbiotic transplantation versus placebo or autologous feces for recurrent *C. difficile* infection, no serious adverse events were attributed to the procedures in either group through six months, as reported by one small RCT, and in the same trial in the bottom row, you'll see a number of nonserious procedure-related adverse events occurred through six months' follow-up. In fact, all occurred within one week of the procedure, and they are listed, as I said... they are all listed there in the slide. Other than chills, which occurred in slightly fewer donor feces than autologous feces patients, the authors reported no difference between groups in the frequency of these nonserious adverse events.

Moving on to the comparison of fresh versus frozen feces for fecal microbiotic transplantation in patients with recurrent CDI, again, no serious adverse events were attributed to fecal microbiotic transplantation in one RCT with 3.25 months follow-up and one retrospective cohort study with two months follow-up. And in the bottom row, for nonserious adverse events, in the first 24 hours following fecal microbiotic transplantation, mild to moderate symptoms related to the procedure, were reported to occur with similar frequency across both groups; however, data were not stratified by group and patient numbers were not reported. The most common complication was transient diarrhea.

Now, a number of studies evaluating patients with recurrent CDI reported adverse events in the fecal microbiotic transplantation group only and did not compare it to the placebo or vancomycin group. Numerous nonserious adverse events were reported to occur, as measured up to 48 hours after the procedure in 3 RCTs, 1 cohort study, and 2 case series, the most common of which were diarrhea, abdominal cramps, and abdominal discomfort or pain. All other noncomparative data for safety, such as serious adverse events and nonserious adverse events at other time points were graded insufficient strength of evidence.

Turning now to safety results for the ulcerative colitis population. Overall, there were no differences between the fecal microbiotic transplantation group, donor feces, and the placebo group, autologous feces in the occurrence of any serious adverse events in either of the two trials over two to three months of follow-up. The rates were 8 and 6% including the things I have listed here, such as worsening colitis, new diagnosis of Crohn's disease, C. difficile infection, severe illness from CMV infection, and severe small bowel Crohn's disease, late abdominal pain, and operation for cervical carcinoma, and those latter three were not stratified by treatment group in the trial.

Regarding nonserious adverse events, a number of mild procedure related adverse events were reported by one trial. When considering all outcomes, overall, no significant difference was noted between the fecal microbiotic transplantation group, donor feces, and the placebo group, fecal microbiotic transplantation using autologous feces. Most events were transient and disappeared spontaneously within two days. However, when considering each event individually, there were two events that occurred differentially between the groups, and these are listed on the slide here. Increased stool frequency, or diarrhea, was more common with fecal microbiotic transplantation, whereas abdominal cramps were less common with fecal microbiotic transplantation. Again, all other periprocedural events occurred with similar frequency.

So, in summary for the treatment of both recurrent CDI and ulcerative colitis, there is no evidence that fecal microbiotic transplantation differs with regard to the frequency of serious and nonserious adverse events when compared with standard vancomycin treatment and placebo infusion, and between different types of fecal preparation.

So, for key question four, differential efficacy was evaluated by 1 RCT that compared frozen and fresh feces in patients with recurrent or refractory C. difficile infection. The subgroup specified a priority were age, less than 65 versus greater than or equal to 65 years, hospitalization status at the time of the procedure, whether they were an inpatient or an outpatient, the type of C. difficile strain, and baseline C. difficile severity, mild, moderate, or severe. None of the subgroups analyzed appeared to modify cure rates, and the strength of evidence was insufficient for this conclusion. All other comparisons for CDI, we had no evidence, and similarly, there was no evidence of differential efficacy and safety in the inflammatory bowel disease population.

Five formal economic analyses were identified, all cost utility studies, that evaluated the cost-effectiveness of fecal microbiotic transplantation versus antibiotics, all for the treatment of C. difficile infection. So, we're talking about key question five now. Overall, they were relatively well conducted and used adult hypothetical populations. One study assumed patients were treated for a first recurrence of CDI while the other four assumed patients had recurrent CDI. The studies were conducted in the United States, Canada, and Australia and were performed primarily from a payer perspective. Costs came from various sources, including CMS, and as you can see, the time horizons for these studies varied fairly

widely from three months to one year. Some of the costs included in these models were treatment, typically to include the donor testing for fecal microbiotic transplantation, which sometimes can be expensive, hospitalization for recurrent CDI, adverse events, and outpatient visits. The clinical effectiveness outcome was reported in terms of quality adjusted life years, the values for which were derived from the published literature and included cure, recurrence following initial cure, mortality, adverse events, colectomy, fulminant colitis, hospitalization, and ileostomy.

So, the conclusion reached by all studies in general was that fecal microbiotic transplantation was more cost-effective than antibiotic treatment for first or recurrent CDI, and specifically in the base case analysis, fecal microbiotic transplantation via colonoscopy was found to be dominant or more cost-effective compared to vancomycin in all five studies, and conclusions were similar when comparing fecal microbiotic transplantation to metronidazole or fidaxomicin, other antibiotics, in patients with recurrent CDI in two studies. Some sensitivity analyses were performed and, in general, supported the conclusion that fecal microbiotic transplantation was the more cost-effective treatment. The studies did have several limitations, however, as you can see on the slide. There was lack of long-term follow-up. The longest follow-up we had was up to one year, use of hypothetical populations, use of nonrandomized studies for assumptions regarding clinical outcomes, assumed high cure rates, and in the economic studies, I would like to point out the cure rates were 81% to 95% versus 52 to 80% cure rates, which we found in the RCTs in our study. They also included relatively low recurrence rates following fecal microbiotic transplantation and did not analyze complicated or severe CDI. As I said, there was no evidence in inflammatory bowel disease population. Are there any questions?

Chris Standaert: Questions from the committee? This issue of sort of recurrent, recalcitrant whatever. I was trying to read through three of the RCTs to figure out what they were treating, and they all sort of said they had a course of antibiotics. I wasn't clear that worked. How do you define... I would have defined recurrent as in it got better and came back, but they may be describing recalcitrant. I'm not totally sure about what I'm reading, and one of your economic studies used this as a firstline treatment, which I didn't see any studies on, and I thought that you said in your search for your PICO's, you were looking at recurrent, and you mentioned a number of case series. I'm just wondering if you restricted your search to what people would call recurrent or if you actually went looking for this as a primary treatment in some circumstances, how that... the distinction of those words came up in your search.

Erika Brodt: That's a good question. To be honest, I'm not sure if we limited our search to recurrent. I know that for the most part, fecal microbiotic transplantation is not used unless patients have had multiple recurrences of CDI and have tried antibiotics and failed. So, that's how we defined recurrent or refractory here, is just CDI that was not responding to antibiotic treatment. In the appendix tables we can determine, if you'd like, how many courses of antibiotics patients had prior to be enrolling or how many recurrences they had.

- Chris Standaert: It says also, it just said... they tried one... they tried a course of antibiotics. So, that would be... so, it took ten days of [crosstalk].
- Erika Brodt: Yeah. I believe one of the RCTs, the inclusion criteria was one or more courses of antibiotics, as an inclusion criteria, but I believe that the median number of recurrences in patients when they... after they were actually enrolled was three.
- Chris Standaert: Right.
- Erika Brodt: So, some of the trials didn't necessarily limit it to recurrent, but I don't know if the patients just aren't coming in until...
- Chris Standaert: So, if you'd look at it. I'd just be curious what you... whether you guys search... put recurrent into your search terms.
- Erika Brodt: Sure. Andrea?
- Chris Standaert: Or whether you... how the studies defined that.
- Erika Brodt: Sure.
- Andrea Skelly: Is this on? There we go. OK. In the appendices, you can find the search strategy, and the search was very broad. It did not limit by first or recurrent. It was intentionally kept very broad, and in terms of the number of recurrences, there are... let's see, on page 74, patient characteristics are listed for the C. difficile comparison, and in the appendices also, there are details of the number of recurrences. I don't know if Cassie, you have some additional information on that.
- Cassie: For two of the RCTs, it was greater than 1 recurrence, and for the third, Kelly 2016, it was greater than 3 with a means for almost universally were around 3 recurrences for the patient populations.
- Chris Standaert: Questions?
- John Bramhall: I had a question, page, so page 12 you've got some data from the ulcerative colitis trial, and it's just... it's just a curious question. The trials were ended due to futility.
- Erika Brodt: Mm-hmm.
- John Bramhall: And I wasn't quite sure, did you have any information about what that meant in the context of a trial?
- Erika Brodt: Yes, and you're talking about the slides, correct?
- John Bramhall: Yeah. Slide, so slide 24, sorry, slide 24.

- Erika Brodt: Thank you.
- John Bramhall: It's on our page 12.
- Chris Standaert: They were so far below their expected response rates is what she said.
- Erika Brodt: Correct. Yeah. So, both trials did interim analyses and in their protocols they had determined them... to be honest, I don't know how they determined these expected rates of remission, but they did determine a priority of 50%, the trial on the top.
- John Bramhall: Alright. OK.
- Erika Brodt: Moayyedi expected a 50% remission rate and only 24% had achieved it.
- John Bramhall: So, it just, it fell below the...
- Erika Brodt: Exactly...
- John Bramhall: ...what they're trying to.
- Erika Brodt: ...even though, as you can see, it does look like fecal microbiotic transplantation did a little bit better, it still wasn't doing as well as they had hoped.
- Christina Surawicz: What happened in that trial was that they stopped the trial, they continued to follow the patients, and then a few patients actually responded. So, then they felt that it was a positive study. Interestingly, the patients that responded all had the same donor. So, it raises the question of whether some donors are better than others.
- Erika Brodt: Mm-hmm. Thank you.
- Chris Standaert: Do we have other questions? So, we can ask her questions once we get going in our discussion, but hearing no more questions, you're all good.
- Erika Brodt: Great thank you.
- Chris Standaert: No, thank you. We are ahead of schedule and could just keep going. We could take ten minutes. We just started an hour ago. People want ten minutes? No? Keep going. Alright.
- So, let's move on. So, now we talk about our own interpretation of all this and what we think. We actually have some data. I do think it's worth noting that the studies that I saw at least were funded by public sources. So, you can actually do RCTs with noncommercial money on important topics. I know it's hard to believe, but contrary to what some may say elsewhere, it is possible. That seems to be what happened here.

- Christina Surawicz: The other studies are coming.
- Chris Standaert: The commercial studies?
- Christina Surawicz: Yeah, they're coming, of the commercial products. Those are coming.
- Chris Standaert: Oh, there are commercial products for this?
- Christina Surawicz: Yeah. There's a whole lot of commercial products in development.
- Chris Standaert: Right. Somebody saw money somewhere and decided to.
- Seth Schwartz: Of course they can't allow us to just give our stool away.
- Chris Standaert: Yeah, apparently not.
- Laurie Mischley: I just have a question about in clinic, you know, I'm seeing 50% after a single treatment. What happens to the other 50%? How many transplants are done on a per... came someone go in for repeat transplants? Do you go to a different donor?
- Christina Surawicz: I can just tell you what our practice has been.
- Laurie Mischley: Yeah.
- Christina Surawicz: That's that about 90% efficacy, and I have to tell you, the first time I did a stool transplant, the results, which was 2004, the results were so dramatic. I wouldn't have continued doing it if it wasn't so dramatic, because it's pretty gross. It's a gross procedure to do, but the results are so dramatic. So, in general, my experience and that of many of the people that are on a listserv where we share experiences, about 90% effective. When it doesn't work, then you put the person back on the vancomycin. So, everybody's on vancomycin or something to suppress the C. difficile. You stop it a day or two, then you do the stool transplant. In the 10% or so who recur, we put them back on vancomycin, and then generally repeat the fecal microbiotic transplantation but using a different donor.
- Chris Hearne: Are you typically doing fecal microbiotic transplantation on folks who have a single recurrence or multiple recurrences, or where do you?
- Christina Surawicz: So, it's multiple recurrences, yeah.
- Chris Hearne: Yeah. So, your chance of that first recurrence is only about 10 or 20%. So, you can treat them again with an antibiotic, but once they have that first recurrence, then their chance of further recurrences just goes up dramatically more to 46%, but you don't want to jump into this right away. If you did it for the first episode, you'd be treating a lot of people unnecessarily. If you even did it for the first recurrence, you would be doing it unnecessarily for a lot. So, you really... it's a

small group of people but for whom there really aren't any other treatment options.

Chris Standaert: What do people think of our data? Let's start there. Do we have data? Yeah? These aren't huge studies. They're not 200 people. We have two separate topics. We have C. difficile and we have inflammatory bowel disease that seem different. Somebody help me out, C. difficile. What do we know?

Tony Yen: I'll bite. So, I think we have good data for C. difficile and very poor data for inflammatory bowel disease. My interpretation of the data is that I think the data supports fecal microbiotic transplantation for C. difficile certainly. I don't think that the data supports treatment for inflammatory bowel disease is the bottom line. In terms of forms or fresh versus frozen, route of administration, I think that's all up in the air.

Seth Schwartz: Can I ask this question? I'm trying to understand, for C. difficile the reasoning for doing this makes tremendous sense to me. For inflammatory bowel disease, it doesn't so much. So, I'm curious... for inflammatory bowel disease but for Crohn's and for ulcerative colitis particularly, what is the logic behind using this in that situation?

Christina Surawicz: Well, I think there's the whole area of the microbiome and the research in it and the public interest has just exploded in the last five or ten years, and because the treatments for severe inflammatory bowel disease are immunosuppressive drugs with a lot of side effects and some risks associate with that, I think those patients are really grasping for something else. Since there is data that changes in the microbiome may contribute to inflammatory bowel disease, but again, cause or effect or related to medications? Who really knows? People want to use stool transplantation for irritable bowel syndrome, which doesn't even have any mortality associated with it. They want to use it for autism. There's just a tremendous interest in the public. So, it's being driven a little bit by public interest, but also just by recognition about how important the microbiome is. So, that's looking at it... a lot of that early work was done in Australia. The first stool transplantation was by a guy who had ulcerative colitis, a physician who had ulcerative colitis, and he gave himself enemas and he got better. So, he published it. I mean, that's one way to get your stuff in the literature. That was quite a while ago, but that was a dramatic case, but there are a lot of little individual cases where people got better. So, that led, then, to the RCTs, which I consider pretty interesting and not terribly strong, but there's a lot of interest in that.

Chris Hearne: The thing that struck me about the ulcerative colitis studies is that the comparator arm is a placebo and not the standard of care for ulcerative colitis. I'm just wondering if you think that's appropriate, or?

Christina Surawicz: Well, they were... they continued on their regular medications.

Chris Hearne: OK.

Christina Surawicz: So, it wasn't exactly... it was fecal microbiotic transplantation... their standard therapy and then fecal microbiotic transplantation versus placebo.

Chris Standaert: So, we have issues of efficacy, cost, and safety. We need to talk about all of them. So, do people feel the RCTs, I assume, on *C. difficile*... it sounds like people feel they are relatively compelling for recurrent *C. difficile*. It seems to do something. Yeah? Any problems? A lot of problems with it? It seems like bloating and diarrhea are *C. difficile* problems, but colonoscopy problems or procedurally related things, but not a lot of major safety events in there anywhere. Yeah, Carson?

Carson Odegard: I've got a safety question. You know, I don't know how serious or... including the deaths in all-cause mortality and mortality, statistics were in the efficacy slides, apparently just one death per group. How much emphasis would you put... I mean, how are these deaths evaluated?

Christina Surawicz: So, the... in the Cammarota study, that was an Italian study where they did colonoscopy fecal microbiotic transplantation versus vancomycin, I think. At the colonoscopy, they saw pseudomembranes, and the first two people... they just did a single fecal microbiotic transplantation and those two patients died, probably because their colitis was so severe. They changed their protocol then and started doing repeat fecal microbiotic transplantations in those patients, and then they got better. So, it kind of brings up what I brought up earlier. Yes, they had recurrences, but they also... if you've got pseudomembranes, then you've got pretty severe disease. So, I think that was really, I think, an important study, because it really raises the point of, maybe we should be considering this in those really sick patients. Then, Monica Fisher at the University of Indiana did a whole series of a large number of patients of those really sick, what we call severe and complicated, not getting better people and had really pretty good results with long-term survival. So, I don't think we'll see an RCT, but it raises that separate group of what I call refractory fulminant.

Chris Standaert: I would ask the committee that when you have questions on data and studies, the evidence vendor is how we're supposed to do this. So, if we get into data that we don't have presented to us and then trying to decide on an individual's, however much I respect you, the individual interpretation and presentation of that gets a lot trickier, right? It hasn't been publically vetted. It hasn't done any of this. So, as you all think, you know, when you have questions on data and literature, the starting point is our evidence people. So, for clinical perspective on that, certainly, that's a valuable role of the clinical expert. So, just so you're aware if we start building off of things that are not what fall into the scope of what was obtained through our evidence report and given to us embedded and publically commented, available for everybody in the whole world to see and comment on, and then we pull in different things, that gets tricky for us, right? We're not following our process, and for our... for what this is worth, you know, our process has to be valid. If we don't follow the process laid out in our statute and follow our processes defined in our legislature and timeframes for public

comment and what we look at, following those is what validates our decisions. So, we just have to be mindful of that. Other questions, comments, input?

Joann Elmore: I had a question for the evidence vendor. Let's see, slide eight in the evidence vendor, you talked about population inclusion criteria, and you had a parentheses there that said conditions for which fecal microbiotic transplantation use is investigational, such as obesity, metabolic syndrome, slowed transit constipation were excluded. So, this is slide eight, and my question is, where does this parenthetical bullet come from? When I read the four C. difficile articles, and their inclusion criteria were things like patients who were immunocompromised, they are excluded. Patients in the ICU, they were excluded. So, can you explain that about obesity, I mean, because if we can't use this in obese patients, that's a third of our U.S. population.

Erika Brodt: Well, I think in that instance, it's meant to treat obesity, not in obese patients who have C. difficile. It's if this could somehow help them lose weight or control their, yeah, [inaudible] their weight.

Joann Elmore: OK.

Chris Standaert: I don't know. We could probably move on to our coverage tool, I would think. I'm not seeing lots of other ground to explore before that. If we look at page five of the second half of our book. So, again, our charge is to look at evidence, and we have to consider all three of these components. So, we have to make sure we discuss them and documented our impression of them and our discussion therein. So, safety, they were divided into serious adverse and nonserious adverse events by our evidence vendor and largely by the investigators. So, serious adverse events would be things like death and colectomy and that sort of thing, I would assume, yeah? And do people see evidence that that is an issue? We have some trouble, but we don't have lots... these aren't huge numbers.

Joann Elmore: Yeah. I found the safety data in adequate. The numbers were 40 patients. That doesn't tell me enough about safety. So, I think we need to then just think of what are the safety issues with placing an NG tube, performing colonoscopy, and infer.

Chris Standaert: But then you have to go... there are issues of death. There are issues of transmission of an infectious illness. I mean, all these things are sort of there and may be in 40, 50, 80, 200 people you don't see it. You know, a lot of our safety data comes from much larger longitudinal studies, and I don't see any... there's nobody looking at 2000 people who had this to say, what happens here? What happens with, I mean, you know? If there are other unpredicted outcomes, alterations in immune system, alterations in other sorts of things, then we don't know.

Christina Surawicz: A registry is being established.

Chris Standaert: But we don't know. I understand.

- Christina Surawicz: I'm just saying, no. No. I'm just saying that...
- Chris Standaert: I gotcha. Right, but we, we don't know.
- Christina Surawicz: For the future.
- Chris Standaert: Right.
- Christina Surawicz: The registry was finally funded.
- Joann Elmore: And we can't use it unless it's published.
- Christina Surawicz: No. No. No. I'm just saying, it's... it'll be nice to have... we've all wanted this information, and so there is a registry that's being established, so.
- Chris Standaert: Right. It will be nice to have.
- Christina Surawicz: For the future. Yeah.
- Chris Standaert: Right. So I...
- Christina Surawicz: Ten years.
- Chris Standaert: ...all sorts of things in ten years, which is lovely, but it, from our standpoint of considering safety, we have to consider the fact that there may be unforeseen consequences here that we don't anticipate, and because our populations sample actually is quite small, is really small. This isn't 2000 people even. This is... we're in the couple hundred maybe with all this stuff they've pulled. So, we're in very small numbers and there may be unforeseen circumstances that we are not anticipating. So, that should fall into people's consideration in some way. On serious adverse events? Some, but not terribly concerning to anybody? Yeah. OK. Effectiveness and efficacy. So, with this one, well it's prepopulated for us, and we have two issues, right? We have the, this says both C. difficile and ulcerative colitis on it. C. difficile they have, there is treatment of the illness, of the disease itself, and then there's the effect on mortality as the other outcome in here. There probably are other outcomes, and there probably are patient centered outcomes that aren't recorded here. I assume with treatment of disease, they'd likely be more favorable, but they weren't recorded that I saw. So, these are... cure here is the intent right? So, it's an important outcome for us? Yeah? I'm just getting head nods. And somebody help me here. So, this is better? This is helpful? We're getting good outcomes. We're getting higher cure rates? We're getting lower rates of additional treatment because we're getting better, yeah? I'm getting more head nods. OK. We have to put all this in here somewhere. We did not have evidence of mortality associated with it, increased mortality associated with the treatment, though again, small numbers. Ulcerative colitis, what do people think? So, we have separate scores for ulcerative colitis. Inflammatory bowel disease in general?

- Seth Schwartz: There isn't any compelling evidence for that.
- Chris Standaert: No compelling evidence, alright.
- John Bramhall: Well, we got improvement.
- Chris Standaert: Improvements in rates of remission, improvements in?
- John Bramhall: As I cited before, it was 24% improvement, right? It was considered to be a high-strength study by the vendors. So, I'm not promoting it, but it's just there was an improvement over placebo, 24 to 9%.
- Chris Standaert: But that would be, was...
- John Bramhall: But it wasn't considered valuable, because it didn't reach the threshold.
- Chris Standaert: Right. So, if that...
- John Bramhall: ...[crosstalk].
- Chris Standaert: ...in the second study, that number wasn't significant. I didn't see the statistics for...
- John Bramhall: Correct.
- Chris Standaert: ...that first number, but that was not significant. That would be high level evidence of ineffectiveness. So, high level of study is not necessarily, that means the quality of the study, not the positivity or negativity of the results. That means you have a very good study, it shows something doesn't work. Yeah, go ahead.
- Erika Brodt: To clarify in that first study, the high quality study, it was significant statistically, just barely. The confidence interval was 3% to 34%, but it was statistically significant. In the poor RCT honestly by how we like to rate things, they did not find a statistical significance, but the difference was 10% between groups. Again, I don't know what's clinically relevant.
- Chris Standaert: And neither study really could keep going because their response rates were too poor to justify further...
- Erika Brodt: Correct.
- Chris Standaert: ...monitoring and treatment and enrollment.
- Seth Schwartz: Well, that's just an endoscopic score, right? That was symptom relief? It was all of it? OK.
- Erika Brodt: Yes. It was a composite of clinical remission plus an endoscopic response.

- Chris Standaert: Whatever outcome, we probably have insufficient data, though, to really say with great enthusiasm one way or the other. Cost? We do have cost studies. Sorting out the state cost was a little tricky for me. They don't have that many patients, and I'm not sure, I'm not sure what they're counting in cost from the state level, whether it's actually preparation of the material, whether it's screening of the donor. Whether it's...
- Kevin Walsh: I don't think it matters, because...
- Chris Standaert: ...all that stuff.
- Kevin Walsh: ...the rates that they're quoting are hypothetical and they're vastly different than the reported rates. I don't think...
- Chris Standaert: Well, I guess from a state level I had a question. So, if you're treating a patient for this and the treatment is to go to a family member or someone else who wants to donate who then has to have their blood drawn and all that, whose insurance does that fall under? Do they bill the donor or do they bill the?
- Christina Surawicz: The donor.
- Chris Standaert: Dan, do you know? Do you know who gets billed... so, if there's a donor who has to donate and has to get their blood drawn, that charge goes to the donor or it goes back to the?
- Daniel Lessler: I mean, I don't know for sure, but I would assume that we end up covering the cost of whatever, you know, getting the donor material? We don't? Because...
- Christina Surawicz: Vague, you know, it's been a question that's been discussed a lot because of the ethics of it, and the development of stool banks has been really a step in the right direction, because then you can just buy the stool, which ends up being [inaudible], but then the cost of having the [crosstalk]...
- Chris Standaert: Screening each donor. Yeah, because you can get lots of samples out of one prescreened person.
- Daniel Lessler: [inaudible] Massachusetts for example, if you buy, right. If you, if you... so the, so the donor doesn't, but I would assume that the cost of purchasing that is going to pass through the [inaudible].
- Chris Standaert: To the treating patient, the cost of purchasing, yeah.
- Christina Surawicz: The frozen stool that we buy, that goes to the patient.
- Chris Standaert: Right.
- Christina Surawicz: But when we were using patient directed donors...

- Chris Standaert: Donors, you have to...
- Christina Surawicz: ...those people...
- Chris Standaert: ...bill them.
- Christina Surawicz: ...were getting their blood and stool tests done and billing their own insurance.
- Chris Standaert: That may skew our cost data a bit potentially in that setting, but... because we probably don't capture that. So, costs, were you all impressed by the cost savings? Is the cost [crosstalk]?
- Seth Schwartz: We never love cost-effectiveness studies here. I mean, they're better than we normally see, but I think...
- Chris Standaert: I was going to say.
- Seth Schwartz: ...Kevin brings up a valid point that if the, if the cure rates are not comparable with what we see in the effectiveness trials, it's... you have to question the data, although clinically the 80 to 90% may be more realistic with what we're hearing, but I think...
- Chris Standaert: Are you working through telepathy? Did you bring that up, the cure rate thing? They brought, yeah. OK. He's shaking his head. That's what I thought. So, the cure rates may... and our studies are modeling studies. Are they modeling studies largely?
- Erika Brodt: Correct.
- Chris Standaert: They're not direct treatment cost studies.
- Erika Brodt: Correct.
- Chris Standaert: Right. And so, then where all those modeling studies, we're at the mercy of their assumptions, and if their assumptions do not meet clinical reality, then we don't know, they're not so viable. So, if they overestimated treatment response, that would influence the validity of their numbers. So, no direct cost studies, again, all modeling studies based on various assumptions.
- Erika Brodt: That is correct. Yes. Markov and decision tree.
- Chris Standaert: OK. So, populations. Do we have enough to help us here by age, hospitalization status, severity? We have small studies. We have, we don't have massive numbers to pull this out. I saw exclusions based on medical things. I didn't see exclusions based on any type of demographic variable on people over age 18 basically, but I didn't see other restrictions.

- Christina Surawicz: The [inaudible] study excluded people over the age of 75. That was the NIH funded study.
- Chris Standaert: OK. And again, we don't seem to have enough evidence of differential effectiveness within these treated populations. You think you might want to treat the people over 75.
- Christina Surawicz: Well, they were sorry that they had that towards the end of the trial when they were enrolling their few patients. They wished that they had.
- Chris Standaert: OK. So, we're going to move forward to our nonbinding vote. So, we're going to consider all indications at once. So, this is inflammatory bowel disease, this is C. difficile, this is whatever else we saw in our evidence. Let's start with safety. Is there evidence that this technology is safe for the indications considered? Unproven, less, equivalent, or more? Safety. Compared to other treatment alternatives, the comparators in our...
- Josh Morse: OK. I think I see eight equivalent, one unproven. Are you missing one?
- Chris Standaert: So, effectiveness. So, is there sufficient evidence that the technology has a meaningful impact on patients and patient care? Again, you can vote unproven, meaningfully less improvement in some population, equivalent, more in some populations or more in all populations under consideration, all indications.
- John Bramhall: You're grouping the ulcerative colitis?
- Chris Standaert: We're counting everything. We're taking everything at once here, yes.
- Gregory Brown: Is there any indication for any component of the groups?
- Chris Standaert: No. So, is there meaningful impact in patients and patient care in... for some of the covered indications.
- Gregory Brown: Oh, OK. Alright.
- Chris Standaert: Yes, or all of the covered indications or none.
- Josh Morse: OK. That is ten some, more in some circumstances.
- Chris Standaert: Cost-effectiveness. Is there sufficient evidence the technology is cost-effective for the indications considered?
- Josh Morse: OK. Seven unproven.
- Chris Standaert: Alright. So, move to our binding vote, we have a whole bunch of somes in there. So, it is probably not everything and by discussion I wouldn't think so. I suspect we're drawing a line between C. difficile and inflammatory bowel disease is what I suspect. So, can you pull up our board for us? For the agency perspective, if we

were to use the word recurrent C. difficile, would that equally apply to failure of primary treatment?

Daniel Lessler: I've been sitting here contemplating that very question. It's an interesting question, because... so the... and I'm actually trying to think in the context of prior Health Technology Assessment decisions. So, is a recommendation with respect to the use of a particular technology in certain circumstances where you're saying, yes, no, relevant to those circumstances? To what extent does it apply in some similar yet distinct circumstances. So, here, I mean, I think... my thinking on that is that if you say specifically for recurrent, then I would say that we would have the leeway... that the coverage decision would not... may not apply to this... it's really sort of a distinct clinical entity, really, I think is what we're... in some sense is what we're saying, you know? Somebody who has been treated, resolved, and then recurred versus somebody who has an initial infection and Chris correct me if I'm wrong, who become very sick, who do not respond to antibiotics. So, never really clears the infection, so never can be... never can become recurrent. The other thing I would say in my... and again, I would appreciate, Chris, your comment here. In my reading about this, it did... you know, it seemed to indicate that there is at least up to this point, somewhat limited evidence in... you know, if you want to say recalcitrant. I can't remember the... or fulminant infection. I suspect that one of the reasons, maybe, that Spectrum... I mean, so there are no RCTs, and there probably is very limited, maybe a case series, and that's probably why it wasn't sort of pulled in by Spectrum in the context in which they were doing their work. So, I think it... you know, it poses an interesting question, these circumstances. My inclination would be to suggest... and I don't know whether you want to call this out, would be to say that this coverage decision would specifically relate to the clinical circumstances in recurrent, and it might be a good idea to actually spell out, in this case, what is meant by recurrent, just because some of the confusion we've had, sort of, with the semantics earlier on.

Seth Schwartz: I think we heard in some of these RCTs, it was not clarified which patient population we were dealing with exactly. So, I don't know that we would want to exclude these patients. We kind of have the reverse perspective, which is that we would say in recurrent or recalcitrant because we can't differentiate in the studies whether those patients were pulled out or not.

Chris Standaert: I have three in front of me. I have Kelly in front of me. I have...

Gregory Brown: What if we just said failed antibiotic treatment?

Christina Surawicz: Kelly was all recurrence.

Chris Standaert: Wait. Wait. Wait, please.

Christina Surawicz: Yeah.

- Chris Standaert: So, I have three in front of me. I have one that says at least three recurrences, which is Kelly. So, it says at least three recurrences. This says all patients had at least... all suffered from at least three recurrences. I have this one from Cammarota, which says after one or more courses of specific antibiotic therapy, at least ten days of vancomycin or at least ten days of metronidazole, were considered for inclusion. So, they had a recurrence of C. difficile after a course of antibiotic therapy, and then the other study by van Nood says, where are its patients?
- Joann Elmore: Recurrence after at least one course of adequate treatment.
- Chris Standaert: Relapse is the word they... relapse of infection after at least once course of antibiotics. So, I... relapse is different than recur, because that means it doesn't really necessarily go away. So, I think you could say, we have recurrence and relapsing. We have recalcitrant. Those are sort of our words to choose from.
- Gregory Brown: No, because two of them...
- Joann Elmore: But it's actually relapse that you want.
- Gregory Brown: ...because two of the three say failed a single course of antibiotics.
- Chris Standaert: Well, they all say failed a single course of antibiotics, at least one course of antibiotics. They all did that.
- Joann Elmore: And that's different than getting C. difficile five years later and jumping right to...
- Chris Standaert: Right.
- Joann Elmore: ...transplantation. So, I think we want to be careful.
- Chris Standaert: So, they all failed. So, these are all after failure of one course of... so, I guess we could say...
- Joann Elmore: At least one. Some of them were up to three.
- Chris Standaert: ...for...
- Gregory Brown: OK, but can't we avoid the whole issue of defining these if we just say failed the...
- Chris Standaert: Yes.
- Carson Odegard: Yeah, right.
- Gregory Brown: ...course of antibiotic.
- Chris Standaert: Yeah.

- Gregory Brown: Vancomycin or metronidazole.
- Chris Standaert: For patients who have failed the standard course of antibiotic therapy for C. difficile.
- Erika Brodt: Would it help to say what the FDA says?
- Chris Standaert: In terms of what?
- Erika Brodt: Well, what they say is for C. difficile that has not responded to standard therapy. That's what their language is.
- Gregory Brown: Is fecal microbiotic transplantation a drug or a device for the FDA?
- Erika Brodt: Right now, it says a drug, but it should be a tissue.
- Chris Standaert: It's a drug, yeah. They're going to call it a drug. Why is Synvisc a device, you know? I have no idea.
- Gregory Brown: Because they had some smart attorney that knew it was easier to get a device through than a drug.
- Chris Standaert: Yeah, than a drug, exactly. So, this is for patients with C. difficile, right? This is for Kris. So just write, yeah, C. difficile. Patients who have failed the standard course of antibiotic therapy.
- Gregory Brown: You might want to mag that about 200% for me, but I don't know about anybody else.
- Chris Standaert: This is more liberal than some of our coverage policies in here, which are multiple courses, but we're following what the data says. They say... two of these studies say one course... they failed a course of antibiotics and not all the subjects failed only one, many had failed multiple courses, but that was their inclusion criteria, which gives us something to go on.
- Gregory Brown: My guess is the patient [inaudible].
- Chris Standaert: It's a pretty miserable disease, I'm sure.
- Gregory Brown: It's a miserable disease, but an NG tube or a colonoscopy to... you want to try another course of antibiotics, or do you want to have a colonoscopy or an NG tube? I think most patients would say let me try another course of antibiotics.
- Chris Standaert: Well, patients who have failed a standard course of antibiotic therapy. So, we could get into defining it as vancomycin or Flagyl, or whatever we want to, or we can give the clinicians leeway for what's appropriate.
- Joann Elmore: I think appropriate course of antibiotic therapy for C. difficile.

- Chris Standaert: We're trying to leave it to some local control, I would think...
- Joann Elmore: Yeah. I don't want to...
- Chris Standaert: ...in terms of what they...
- Joann Elmore: ...specify...
- Chris Standaert: ...treat in their population.
- Joann Elmore: ...like the agency recommendations had specifically said post-vancomycin, but I want to just say appropriate treatment for C. difficile.
- Chris Standaert: It would be covered in those people, right?
- Joann Elmore: Mm-hmm.
- Chris Standaert: And frankly, if we just make a statement saying patients who have C. difficile who have failed an appropriate course of antibiotic therapy, that would... we'd be done.
- Joann Elmore: Yes, and I would like to go that way, as opposed to what the agency recommendation, because they had said by NG or colon and what happens if it comes with a pill. So, I would rather leave it simple.
- Chris Standaert: It seems like the whole thing's evolving, and delivery methods are evolving, and we may be a bit ahead of the curve, and it's hard to define how they deliver it. It would seem irrational, because we had no evidence to say otherwise.
- Joann Elmore: And we're never irrational.
- Chris Standaert: Well, our job is to try hard not to be irrational, right? So, we have to, yeah, but we didn't see any evidence to say that one route is more effective than another, and if that's still in play in the medical community, we should let them do that.
- Josh Morse: This is Josh. I have a question. Is there any... does the FDA apply any relevant standard to this, or would this be... I went... my question is about where this would be applied. I mean, this is probably currently in very specialized locations, but the way this is written, you're not limiting it to any facility, provider type, FDA standard.
- Chris Standaert: Well, you get into... there are FDA indications for it, yeah? So, you guys had FDA indications for the... what... where is that?
- Erika Brodt: It's considered investigational by the FDA.
- Chris Standaert: What did you guys give us?

- Erika Brodt: Well, but the FDA, yes. It's investigational, but the FDA does regulate it as a drug or... so they require certain things, like donor screening [crosstalk].
- Chris Standaert: You had a slide on that though, didn't you?
- Erika Brodt: Mm-hmm.
- Chris Standaert: So, what slide is that?
- Erika Brodt: The, uh, donor screening...
- Chris Standaert: No, the FDA slide.
- Christina Surawicz: They haven't given guidance on specific screening tests. They've been very, very vague on specifics. They've been vague on specifics, yeah, and they say that it's investigational but can be done for C. difficile that's not responded to standard treatment. For any other indication, the provider would have to have an IND.
- Erika Brodt: Right.
- Christina Surawicz: So, there's a lot of variability in how it's done. We would like to see more regulation and lately, they've been saying that the donor should be known to the patient or the provider, which is putting the whole question of stool banks into question, and they've taken public comments on that months and months ago, but we haven't heard them make a decision on that either.
- Chris Standaert: Our studies don't talk much about the donors, who they are or where they came from, and they refer to using different donors if not effective the first time.
- Laurie Mischley: This is Laurie.
- Chris Standaert: Volunteers in another study.
- Laurie Mischley: Well, I can just speak to... I was invited to participate in a collaboration with somebody in Portland that was doing this out of an old converted house, and it made me very nervous, so...
- Chris Standaert: In a house.
- Laurie Mischley: ...it was a very non-clinical environment that I had some concerns about the way the whole operation was happening. So, I do think that we are... this is... in the absence of regulations, there is potential for...
- Gregory Brown: But I mean, the bottom line is, in order to bill the State, they have to [inaudible]. You're going to have to do the procedure in some sort of licensed facility. I mean, maybe for sample collection. Well, I mean, so can you provide medical care and bill the state outside of [crosstalk]?

- Chris Standaert: Could you? Well, I guess you could treat this as an outpatient, right? You have somebody, an outpatient, who takes antibiotics at home and gets C. difficile and you give them vancomycin and they don't get better, and then you somehow, you know, I saw a study on frozen capsules. Right, so they're...
- Gregory Brown: That I understand, but just the description I'm hearing is that that's not, you know, you can... the patient can do it in their home if you give them a prescription or a medication or drug or whatever. That's not going to somebody's house like you're describing.
- Laurie Mischley: My point... I mean, this was a legitimate clinic. It was just not what I would feel comfortable saying met muster by way of standards that I consider safe and appropriate.
- Joann Elmore: Appropriately screening...
- Laurie Mischley: Exactly.
- Joann Elmore: ...before things are stuck back into a patient.
- Laurie Mischley: Exactly.
- Joann Elmore: And so by our saying that we approve financial coverage and we have the condition that they have to have failed one appropriate treatment with antibiotics, we are not adding in here anything about the quality of what is then transfused back into the patient, and I don't know if... I don't think that that's our role, but...
- Gregory Brown: I was going to say, that's not our burden for the...
- Joann Elmore: Yeah.
- Gregory Brown: ...for the State to determine. For the State to determine who is an appropriate provider and what's an appropriate setting, I mean, we... we aren't trying to mandate that.
- Chris Standaert: I guess the definition, what is the scope of the procedure, right? So, if the procedure involves all of this, that's all the scope of the procedure, it's like a different thing. So, it's... technically, it's a drug, but it's not FDA approved as a... that's interesting. So, we don't do... we don't address drugs. So, there's a whole separate committee that does that in this State. Our committee is not... drugs are not under our purview. Is this a drug? I'm serious. Drugs are not under our purview?
- Josh Morse: This is very much like spinal injections.

Chris Standaert: So, the procedure... the procedure of doing it. So, I guess the drug committee would then address the concept of the actual drug, Dan? I mean...

Daniel Lessler: Yeah, the...

Chris Standaert: How do you guys pay for this?

Daniel Lessler: ...huh?

Chris Standaert: Do you guys pay for this as a... somebody bills it... do they bill a colonoscopy? Is that what you're actually... or they bill drop of an NG tube? Or what do they... what do they actually bill when they bill you? Gastric lavage?

Daniel Lessler: I, you know, I would assume that the bill includes the cost of the procedure, professional fee, and then some cost for the stool, you know?

Christina Surawicz: Well, it's pretty variable. There is a billing code that was developed a couple years ago for fecal microbiotic transplantation for, like, putting the stool in there that I think the infectious disease people use, because they would use it by enemas. I think that...

Chris Standaert: That's a CPT code. There's actually a...

Christina Surawicz: Yeah, a CPT...

Chris Standaert: ...procedure...

Christina Surawicz: ...code.

Chris Standaert: ...procedural code, but that has a very...

Christina Surawicz: Right.

Chris Standaert: ...distinct description of the clinical work involved with that code, then.

Christina Surawicz: Right. And it's pretty minimal. I mean, it's not a lot there.

Chris Standaert: Right.

Christina Surawicz: It's pretty small. I would...

Chris Standaert: But that's a procedure. It's...

Christina Surawicz: ...I would just say that these are complicated patients, and we've had a very... I actually had an I&D for a while until the FDA said we didn't need one anymore. You need to have proper evaluation of the patient to make sure that they really do have recurrent C. difficile and the patients in my clinic, about a quarter of them actually have irritable bowel syndrome. They might have had C. difficile, but they

end up actually coming with what turns out to be IBS and not C. difficile. So, you want to make sure it's the appropriate patient. Then, you want to have an appropriate donor or frozen stool. Then, you want to have what you think is the best delivery method for the patient, which could be NG or enemas or colonoscopy. Appropriate material, and then appropriate follow-up. So, we have a protocol where we did a 24-hour phone call, a two-week phone call, and a three-week follow-up, a three-month follow-up. So, I think to have anybody feel like they can do this, I think, would not be a good service. Now, this may not be relevant to your discussion. It's just... I'm just saying from our practice, and I think I know the group you're talking about, because I've heard about that.

Chris Standaert: It makes it tricky for us, though, because we don't... we say you can use it for a diagnosis. We don't ensure that physicians are diagnosing correctly, right? That's a whole different thing, right? That's not our purview at all. This is all assuming somebody's doing the right thing for somebody, which is our default assumption of our clinicians in the State that they actually make the diagnosis correctly. We don't define that. In this case, I don't think we would define that, because they would have to have the definition of the illness in the first place. Again, we had this discussion in the morning. If we don't have things that are recognized in some way a center of something that is authorized to do this, how do we then say, you have to do X Y and... we can't be that body. So, are we comfortable just saying this is... in these patients with recurrent C. difficile who have failed a course of standard antibiotic therapy, this is approved and leave it to the practitioners to then be responsible for making sure they're appropriately applied, delivering the medication such as this is, and leave it there. So, that goes back to our one sentence condition.

Daniel Lessler: Chris, if I might add. I think also in this instance, likely prior authorization criteria would apply. So, there's the opportunity, at that point, to say... to assess, has the patient been appropriately diagnosed with C. difficile.

Chris Standaert: So, we're going to prove it, and then you're going to prior-authorize it?

Daniel Lessler: And then and so forth.

Chris Standaert: It doesn't work that way, though, does it? If we approve it, do you...

Daniel Lessler: Oh, sure.

Chris Standaert: ...still need prior authorization for it even though we've... I guess injections you do, don't you?

Daniel Lessler: Excuse me?

Chris Standaert: Yeah. I guess for the epidural injections that we [crosstalk].

- Daniel Lessler: Yeah. No. I mean, we... to assure appropriateness, we do that all the time. We do it consistent, I mean, if you have a coverage decision, we do a consistent [crosstalk].
- Chris Standaert: You want to make sure people are meeting the conditions of the decision.
- Daniel Lessler: Right.
- Chris Standaert: OK. Yeah. That makes, OK. So, this is for patients with C. difficile infections who have failed an appropriate course of antibiotic therapy. Then, you all would then vet people for the appropriateness of whether clinicians are doing what they're supposed to do here, right? Yeah.
- Joann Elmore: And then who is going to vet that the... what's being transfused is appropriately screened and adequate quality? I guess we're leaving that... it's not on our purview.
- Chris Standaert: The physician is clearly on the hook if they give somebody something. I mean, heaven forbid somebody gives somebody a sample with hepatitis C in it, but if they fail to screen that, then I... everything I just read, I suppose you would be failing the standard of care for that procedure. That seems to be the de facto standard of care at the moment. I would think, yeah? So, take out the comma there. So, this would just say, this is covered... a covered procedure for this. Questions? Edits? What do you think, Josh?
- Josh Morse: Well, that would be covered with conditions, right? This would be the conditions?
- Chris Standaert: This is the conditions.
- Joann Elmore: Mm-hmm.
- Chris Standaert: Yes. This is our condition.
- Josh Morse: So, it seems like this is in conflict with some of the guidelines, which may or may not be a bad thing, but on slide 15, that's where the American College of Gastroenterology says consider this in a third recurrence. Then European Society of Clinical Microbiology consider this for multiple recurrent C. difficile infections. It says multiple recurrence. That means two or more. [inaudible]
- Chris Standaert: Largely, because that's what our studies say. The two... these RCTs, that's what they did. After one or more courses of antibiotic therapy.
- Joann Elmore: But then again, those were the first two very small studies that were open label by Cammarota and van Nood. After that, the studies... I mean, those were each of, like, 20 patients, and Cammarota 16 patients that were transfused and van Nood. After that, the larger, subsequent studies by Lagier and Kelly, those are the ones that would only transfuse after it was the third failure relapse with

appropriate attempts at treatment with antibiotics. So, it's true, we are sort of moving the sort of potential ability to be transfused earlier.

John Bramhall: [inaudible] recommendation is the same, right, recurrent infections? They don't state a number. So, at a national level they're agreeing with what they're saying.

Chris Standaert: Do we have an LCD? No? So, no Medicare or anything? No NCD? No LCD? No nothing? It's covered under Medicare? There's a CPT code, so, assuming that has a RVU attached to it, it warrants a tracking code, it would be paid for, but I don't know what that... I don't know that part. Is the CPT code paid for, or is that a tracking code? It's paid?

Josh Morse: I found two codes. One's a G-code.

Chris Standaert: Yeah, that's a full-on code. It's not a T-code. So, are people comfortable with one, or do people want three?

Gregory Brown: Two out of the three studies said one.

Male: [inaudible]

Chris Standaert: Kelly was different. Kelly... I don't know if it was in the inclusion criteria, but they said they all had suffered from at least three. So, it's different than the other two, which said at least one. Yeah, one to five, one to four. Yeah. Some of them had one, but it doesn't tell us how many had one.

Joann Elmore: I guess I could go either way in that I'm still worried about what exactly protocol are they following. I think we have a lot more to learn. It's not... the screening sort of isn't standardized. So, if people want to move it back to three, that means that it would be a little more cautiously applied.

Seth Schwartz: I'm a little bit less concerned about overuse in the C. difficile situation than in the inflammatory bowel disease situation, and I think one of the advantages of leaving it as one is that it captures what we were talking about earlier, which is these patients that are essentially recalcitrant, as opposed to having to call those out separately. So, I think that's probably the advantage of leaving it as is.

Chris Standaert: Yeah. I think in our last... now, our last topic, the issue of so what if you didn't have that? Did you know things would go badly if you didn't have that? I think in this case, C. difficile is a really miserable illness. People are miserable. They're frequently hospitalized. It's intense care when you're in the hospital. They can get very, very ill. They can die. So, if you're in a circumstance where somebody is quite ill and they failed an appropriate therapy and you're in a space where you could do this and you thought it was the right thing to do, should we say no? Should we say that's not what we should do and have that as a [inaudible].

Kevin Walsh: Two of the studies had entry exclusion of more than one... one failure. I'm comfortable with that.

- Joann Elmore: I will move that we add in exclusion for any use within inflammatory bowel disease and we move to vote.
- Christina Surawicz: Could I make a comment about the inflammatory bowel disease first?
- Chris Standaert: You can make a comment, sure.
- Christina Surawicz: OK, because some of the inflammatory bowel disease patients actually have C. difficile and so we've been using fecal microbiotic transplantation to get rid of the C. difficile in the inflammatory bowel disease patients, but not to treat the inflammatory bowel disease.
- Chris Standaert: Well, we don't have to, so you are correct. So, if we just leave this as C. difficile, you can treat C. difficile in anybody who has it. So, if you don't mention inflammatory bowel disease, it's not a covered condition. This is our covered condition. You don't have to say it is an excluded condition. You just say it's not covered. That way, you avoid the confusion you were running into that you have somebody with it who has this and then you get hung up in the... all that nonsense. So, it's actually easier if we just leave it at this.
- Joann Elmore: Perfect.
- Josh Morse: Well, I'm going to present an opposing view and say that if you don't have... the fact of the matter is that you reviewed this for basically two conditions.
- Chris Standaert: Mm-hmm.
- Josh Morse: If you don't put the other condition that you considered in there, then it does create challenges for those who then try and interpret it, because you have to go back and look at, well, what was included? What wasn't included?
- Seth Schwartz: Josh, I think we've pulled out... I think we're saying for the indication of C. difficile here is our statement. We will have a second one that's for the indication of inflammatory bowel disease it is not covered, but that would be for the treatment of inflammatory bowel disease, not for the treatment of C. difficile and inflammatory bowel disease [crosstalk].
- Chris Standaert: OK. Then we're voting twice.
- Seth Schwartz: Yeah.
- Chris Standaert: So, but we...
- Gregory Brown: But it was presented as two things.
- Chris Standaert: ...except we've been discussing this all as one thing, so far. So, we said, this is for all... this is our indication of our indications. It was presented as several different

- indications. So, if our key question says, for indications of C. difficile and inflammatory bowel disease, this is our covered condition. Doesn't that say that? Or do you want us to vote twice?
- Josh Morse: I think what Dr. Schwartz is saying is, if you add a bullet that just said the other condition that it's not covered for...
- Joann Elmore: For treatment.
- Josh Morse: ...for treatment of inflammatory bowel disease, then that would be a whole complete package of what is covered with conditions as an indicator on there. That would be very...
- Chris Standaert: OK.
- Josh Morse: ...[crosstalk].
- Seth Schwartz: I think you could do it as one vote if you wanted to.
- Chris Standaert: You would say fecal microbiotic transplantation is not covered...
- Joann Elmore: For treatment of.
- Chris Standaert: ...for treatment of inflammatory bowel disease.
- Kevin Walsh: You say it's only covered for patients with C. difficile infection who have failed an appropriate course of antibiotics.
- Chris Standaert: We get caught up on semantics a little bit, because when we went with these conditions that we went through in our voting, we voted on safety, and it counts all as the same thing, all as one treatment modality for all indications that were presented to us. So, therefore, of those, we just have to pick it out. I don't think it's a big deal to say it, but I'm not sure we have to myself, because [inaudible]. So, as long as we keep it all there as one thing, we make one vote, then we don't have to backtrack.
- Josh Morse: OK.
- Chris Standaert: OK?
- Daniel Lessler: Chris, can I just say, I think from the standpoint of the agency medical directors to the point that was made, and it sounds like this is the way you're going, but specifically saying that fecal microbiotic transplantation is not covered for inflammatory bowel disease would just have the clarity that sometimes helps.
- Chris Standaert: Are we good with this?
- Joann Elmore: Mm-hmm.

Chris Standaert: Alright. Any comments or are we going to move to our vote? So, this is our binding vote. Based on the evidence about the technology safety, efficacy, and cost-effectiveness, it is now either not covered at all, covered unconditionally, which means this all goes away and it's just covered, or covered under certain conditions, which would be this.

Josh Morse: Ten covered with conditions.

Chris Standaert: And then we have no Medicare coverage determinations. We have a smattering of... we talked about it already, a smattering of other various guidelines and other things we're broadly in line with, and I think what we stated is clearly defined by the literature we have. So, if we differ in any way, it's because the literature we looked at told us to go this way.

Josh Morse: Great. Thank you.

Chris Standaert: We're done.

Josh Morse: So, we do have just some quick updates before we adjourn. In the back of your binder, there are some slides that go over what's to come, as far as topics down the road. One other update is, there is currently an open recruitment for one committee member. As you may or may not know, Dr. McCulloch has indicated that he will be leaving the committee in the future, once we find a replacement. So, we are working with stakeholders and we've released an announcement seeking applicants. Because of the legislative change that occurred last session, we are seeking nominees from the Washington State Osteopathic Medical Association and the Washington State Medical Association. So, we're coordinating with them, hoping to have anybody who applies work with them for a group of nominees from those groups to choose from. So, that's ongoing. The next meeting, as you know, is January, and the topics for that meeting are the pharmacogenomic testing and artificial disk replacement, which is a rereview. In March, we have one topic, the extracorporeal shockwave therapy. In May, varicose vein treatment, and treatments for migraines and other chronic headaches. I don't have any other updates for you at this point. Does anybody have any questions about what we're doing right now? OK. Thank you, very much.

Chris Standaert: We have no key questions in process. We have no other thing for which we should be providing input at this point.

Josh Morse: Well, there are, yeah. So, I didn't want to...

Chris Standaert: Are we in the open comment period for these?

Josh Morse: There is an open comment period right now for the pharmacogenomic report that lasts a couple of more days, only until Monday for the report.

Chris Standaert: OK.

Josh Morse: For the draft report, right? For the artificial disk replacement, it's the same situation. The draft report should be out for comment right now for a few more days. For the topics that I mentioned this morning that will be happening in the fall, we have not developed or released draft scope or key questions. So, those will likely sync with your next meeting.

Chris Standaert: OK.

Josh Morse: Yeah.

Chris Standaert: We are adjourned.