Topical Oxygen Therapy

Meeting Date & Time: December 11, 2024, 12:00 p.m. CT
Location: Virtual Meeting
Note: During the meeting, one voting CAC panel member's vote was noted to have been registered twice due to a technical issue. The DME MACs have removed the duplicate vote from the final scoring, which can be found in the posted key questions.

DR. SMITHA BALLYAMANDA: Just as a quick housekeeping reminder, if you are not speaking, please put your phones or computers on mute just so we don't have any feedback, background noise. Also, it would be helpful if you could just say your name just before you start talking. But I think everybody's showing up under their own name, so we should be good to go and be able to identify who's speaking. So here we go.

Good afternoon, everybody. I am Dr. Smitha Ballyamanda from Noridian, the JA Medical Director. Dr. Angela Jenny is also with Noridian. She's the JD Medical Director. With me today, I also have Dr. Sunil Lalla and Dr. Robert Hoover from CGS. They are representing Jurisdictions B and C respectively.

We welcome you today for our CAC meeting. This CAC panel meeting is focused on an important topic, evaluating the quality and certainty of evidence supporting topical oxygen therapy's use for diabetic foot ulcers.

Next slide, please.

We'll go, let's quickly walk through the agenda for today's meeting. So, we've already kicked things off with our welcome and introductions of the medical director. We will also introduce the CAC panel, and then we'll provide an overview of the CAC process so that everyone is clear on how today's meeting will unfold. And then we'll go into the main meeting event. We'll dive into the discussion and scoring of the 16 key questions. So as a reminder, although there are 16 key questions, it's the same question, but for topical oxygen, and then again, the same question for intermittent topical oxygen therapy. I'm sorry, continuous and intermittent topical oxygen therapy. So that's why they're 16, because although there are eight same question stem, we're asking those questions as if they were applicable to both continuous and intermittent topical oxygen. This is this discussion of the key questions; this is really the bulk of our conversation will happen and where the CAC panels expertise will really shine. Then finally, we'll wrap things up and review the next steps and make sure everyone knows what's next. Sounds good? I'll make that a rhetorical question. We'll keep going here.

So, let's go on to the next slide.

So, I want to take a moment to introduce the CAC chair, the esteemed Dr. Rita Redberg, who is a cardiologist practicing general and preventative cardiology at the University of California in San Francisco. She was also the editor-in-chief of JAMA Internal Medicine from 2009 to 2023. Dr. Redberg was also the CAC chair during the CAC panel discussion of topical oxygen therapy in 2019 and she was kind enough to come back and help us out again for this CAC panel.

I'll now call on each CAC panel member to allow them the opportunity to introduce themselves. Please state your name, your affiliation, your area of expertise, and any conflicts of interest. So, we will start with Dr. Anahita Dua.

DR. ANAHITA DUA: No problem. My name is Anahita Dua. I'm a vascular surgeon at the Mass General Hospital and associate professor of surgery at Harvard Medical School. And I am associate director of our wound care center here, clinical director of research and director of our limb salvage program, and I'm thrilled to be here. Thank you for having me. Maybe you're on mute. I don't hear anything else.

DR. SUNIL LALLA: If you're speaking again, you may be on mute.

DR. SMITHA BALLYAMANDA: I'm sorry. I am. I was definitely on mute. The next person was Dr. John Lantis. However, I still don't see that he has joined. So, the next person is Dr. Jay Mandrekar.

DR. JAY MANDREKAR: Hi, my name is Jay Mandrekar. I work at Mayo Clinic. I'm a biostatistician. My academic rank is professor of biostatistics, and I have a joint appointment in neurology department here. So, I have a professor of neurology rank as well. I do not work in this specific area, but I had served as a member back in 2019 for the similar set of questions.

DR. SMITHA BALLYAMANDA: Okay. Thank you so much. Next, Dr. David Niebuhr.

DR. DAVID NIEBUHR: Hello, everyone. My name is David Niebuhr. I'm with the Agency for Healthcare Research and Quality, (cough) excuse me, in the Evidence-Based Practice Center group. I'm training in family medicine, public health, preventive medicine. I don't have any firsthand expertise in chronic wound care or diabetic foot ulcers, but I have led two evidence reviews related to chronic wound healing. And I was on the prior CAC in 2019. I have no conflicts of interest. Thank you.

DR. SMITHA BALLYAMANDA: Thank you so much. Next, we have Dr. Regulski, who will be our industry representative and is part of the CAC panel today, but he is a non-voting CAC panel member as the industry representative. Dr. Regulski, if you wouldn't mind introducing yourself.

DR. MATTHEW REGULSKI: Sure, hello everyone, my name is Dr. Matthew Regulski. I'm the director of the Wound Institute of Ocean County here in New Jersey, part of Robert Wood Johnson's system. I've been in practice for 21 years. I'm treating thousands and thousands of chronic wound patients every year. I kind of specialize in wound healing, diabetic limb salvage, and reconstructive surgery. I have multiple peer-reviewed articles and multiple RCTs in wound healing. So, I have no conflicts. Thank you very much for allowing me to be here.

DR. SMITHA BALLYAMANDA: Thank you so much. And then we have Dr. Naz Wahab.

DR. NAZ WAHAB: Hello. My name is Naz Wahab. I am a practicing wound care physician in Las Vegas, Nevada. I've been practicing for over 21 years for wound care as a whole. I am an associate professor at Roseman University College of Medicine, and I'm medical director of three local hospitals here for wound care as well. And I'm very pleased and happy to be here. Thank you.

DR. SMITHA BALLYAMANDA: Thank you, Dr. Wahab. And finally, Dr. Alan Wyatt.

DR. ALAN WYATT: Hi, I'm Alan Wyatt. I'm an internist and undersea and hyperbaric medicine specialist. I'm clinical faculty at the Louisiana State University Health Science Center in New Orleans, where I'm also the medical director for the Hyperbaric Medicine Unit at University Medical Center. No conflicts of interest.

DR. SMITHA BALLYAMANDA: Thank you, Dr. Wyatt. All right, so since we're running a little behind, I want to go through the next part a little quickly. So next slide. It's an overview of the CAC process and key questions. Next slide. There we go.

The DME MACs have assembled a panel of these highly qualified specialists. This panel includes a national group of clinical researchers, professors of medicine and physicians, as you've heard, who bring a wealth of knowledge and experience to the table. And today's meeting, we'll be discussing the 16 key questions that are crucial to understanding the evidence behind topical oxygen therapy for diabetic foot ulcers. It's important to note that only the DME MAC medical directors, the meeting facilitators, the CAC chair, and the CAC panel members will speak during this meeting. We want to focus specifically on the insights of the CAC panel. We won't be monitoring the questions feature on the webinar platform. So, if we can keep the flow focused on the actual discussion, that would be very helpful. Again, we appreciate everyone's cooperation in ensuring that this meeting stays on track and is productive. So, it's all about getting your expert input. So, you know, let's make the most of it. So, at this point, I'm going to hand over the mic to our esteemed CAC panel chair, Dr. Rita Redberg, who will provide a brief overview of the evidence and begin the CAC panel discussion of each CAC panel key questions related to topical oxygen therapy for diabetic foot ulcers.

Dr. Redberg, Dr. Redberg, is your computer on mute? We can't hear you if you're speaking. Dr. Redberg? Okay, I'm not sure what's happening. Dr. Redberg, are you able to unmute yourself? Okay, I also, while we're waiting for Dr. Redberg, I did receive information that Dr. John Lantis is having a difficult time connecting and is being provided a link, so he will be joining us.

DR. SUNIL LALLA: Smitha, I sent a chat to Dr. Redberg asking her to log off and log back in. Maybe that will help.

DR. SMITHA BALLYAMANDA: Yes, that would be great. I also sent her a message just in case

she's unable to hear us. Let me send an email just.

DR. RITA REDBERG: Hi there.

DR. SMITHA BALLYAMANDA: Hi, there we go. I just sent you an email. OK, no problem.

DR. RITA REDBERG: No, as I had too many tabs open on my browser and couldn't find this tab to go back to, sorry. OK, so I will, I'll start the meeting. I did hear everything. I just couldn't unmute. So again, I think you already introduced me. So, I'm glad to be back again with Noridian to talk about total oxygen therapy. And because we do have a lot of voting questions, as everyone knows, we discussed this five years ago. We have a number of trials, some randomized, some observational. And what I'd like to generally look at the question of how do total oxygen therapy or intermittent oxygen therapy, improve the wound healing process and contribute to the care of Medicare beneficiaries, in particular in terms of quality of life. There were a lot of, although most of the studies find some benefit in their defined outcomes, there were a number of methodologic issues, which I'm just going to remind the committee of, because this is really why we're back here, is looking at whether the quality of the evidence in what we have reviewed allows us to make any conclusions of whether there is benefit for Medicare beneficiaries.

So the major categories of flaws with the current literature are lack of randomization for at least one category of the topical oxygen, concerns about the effectiveness of blinding so that at least one of the categories of the patients, the practitioners, or the assessors knew which intervention, whether they got the intervention or the control particularly important in the assessment so that there were even in the randomized studies, lack of discussion, whether there was allocation concealment, meaning that the subjects, it wasn't clear how the randomization occurred and whether the whole integrity of the randomization progress is that it's random. And if there is no discussion in the papers, as there was not of the allocation concealment process, which would allow all subjects to have an equal chance of receiving the different treatments, one can't assess the integrity of the randomization scheme. So, the allocation concealment was poorly if it all reported. Also, in randomized trials there has to be use of the intention to treat principles so that everyone who was intended to get the treatment is included in the analysis and that was also not adhered to. Medicare considers that incomplete wound healing, I'm sorry, incomplete wound healing is not an adequate measure of quality of life and benefits of patients and incomplete wound healing was sometimes the measure used. There was, there were also studies that did use complete wound healing, although in those studies there were questions about the durability of the wound closure and the recurrence. And there was also a lack of independent verification of whether the wounds were healed or unhealed after treatment. And independent verification would certainly increase the validity of the outcomes.

Other issues with the study were lack of evidence for improvement in function in the patients who had chronic wounds, limited evidence for durability of the wound healing, and uncertainty about the standard of care that was used in the study. We're always looking at a control of total oxygen therapy plus standard care versus standard care alone. So, it's very important to understand standard care was up to current standards.

There were very commonly small sample sizes included in the studies, sometimes commonly less than a hundred patients. There was a lot of loss to follow up by the end of the study, commonly 20% of the population was lost to follow-up and thus not included, which would change the results if they had been, and there were issues with inappropriate statistical analyses.

So those are the methodologic concerns that we're here to talk about today, and we can have further discussion and then start the scoring questions.

DR. SMITHA BALLYAMANDA: Yes, that sounds like a plan.

DR. RITA REDBERG: Ok

DR. SMITHA BALLYAMANDA: We'll likely have to reduce the number of time we have per question as depending on how long we have the preliminary discussion, but we can open it up to CAC panel members to address some of the concerns. Rita, is there anything in particular you want to kick off or would you like to go right into the key questions?

DR. RITA REDBERG: Um only if CAC members have any comments otherwise, I think we can which we're certainly open to if anyone wants to add anything otherwise, we can go into the key questions and I think we had I can start with the first key question but then we can and rotate among the panelists to lead each key question. I think that is what we had planned on.

DR. SMITHA BALLYAMANDA: Yep, yes, that would be perfect. Thank you.

DR. RITA REDBERG: So, do any panelists have comments currently?

DR. MATTHEW REGULSKI: This is Dr. Rogalski, I was reading every single one of these papers and the studies and making typewritten notes for all those as being your industry representative, but I do have a few, a couple of things just to say. Is that okay, Dr. Redberg?

DR. RITA REDBERG: Yes.

DR. MATTHEW REGULSKI: Okay. CMS in the 2017 decision memorandum clearly delineated that there are two distinct topical oxygen approaches, continuous and intermittent, with separate reimbursement codes. Since then, the overall evidence direction for topical oxygen has been consistently positive, showing faster and more complete healing efficacy at 12 weeks, which is the time period wound care therapeutics have historically been measured against by CMS and others.

So, the 2022 systematic review of meta-analysis by Carter that solely looked at topical oxygen RCTs with at least 12-week complete healing outcomes showed an average risk ratio of 1.59 or 59% more likely to heal at 12 weeks compared to standard care alone and assigned a B level grade overall. She gave an A grading for intermittent and the C for continuous, though it was a B grade overall. So irrespective to which of the two approaches used overall, it's indisputable. The topical oxygen helps diabetic foot ulcers heal at a higher efficacy at 12 weeks.

Now, focus really should be on the newer, higher quality evidence published since the DME MACs less considered coverage of topical oxygen back in 2019 and it's been supplied to the committee members here. Note that the topical oxygen, there are different approaches to then full body HBO. And even though many of the wound healing specific mechanisms are related, they should not be conflated. Something that CMS highlights in its 2017 decision memorandum when topical oxygen was separated from HBO national coverage determination.

So, I just wanted to point that out. Thank you, Dr. Redberg, for the opportunity.

DR. RITA REDBERG: Thanks so much. I will note that we do have that 2022 meta-analysis, but a meta-analysis of studies that have flaws doesn't overcome the flaws in the studies.

DR. MATTHEW REGULSKI: Sure. And I understand what you're saying, but I, from Carter's analysis from that and from the new, especially on the Frykberg RCT, I think has some really incredible methodology that I will like to point out when it comes time. Indisputable, good stuff, so thank you.

DR. RITA REDBERG: I think I would refrain from words like indisputable, because that is your opinion.

DR. MATTHEW REGULSKI: Okay. I'm sorry. Yeah, that's my, I apologize.

DR. RITA REDBERG: Thank you.

Okay, we can start with the first key question, and remember, we are voting on the confidence in the evidence, and all of the questions will have the same format, so hopefully that will allow us to go through them fairly efficiently, because we have an hour and 10 minutes at this time.

All questions refer to the use of topical oxygen therapy in the Medicare eligible population only. So, again, this is another issue with some of the studies is that the patients were not Medicare population age. They were a younger population. Medicare population is generally an average age of 73, mostly women, and has multiple comorbidities. But this is all questions refer to the use of polling.

And so, the first one is, how confident are you that there is sufficient evidence to determine that adjunctive total oxygen therapy leads to a greater incidence of complete wound closure of chronic non-healing diabetic foot ulcers compared to standard of care alone. So, we have a few minutes, we'll say four minutes for discussion and voting.

DR. MATTHEW REGULSKI: This is Dr. Regulski, may I answer or throw out some discussion?

DR. SMITHA BALLYAMANDA: I believe we have a pers(on), we're supposed to go through the list,

DR. RITA REDEBERG: Yes

DR. SMITHA BALLYAMANDA: One of each key question, so everybody gets a turn to talk.

DR. RITA REDBERG: Right.

DR. SMITHA BALLYAMANDA: Rita, do you have a list, or do you want me to?

DR. RITA REDBERG: I have a list in front of me, so I can start with Dr. Mandrekar.

DR. SMITHA BALLYAMANDA: OK, thank you.

DR. RITA REDBERG: And I have one, two, three, four, five, six, seven people on the list, including Dr. Regulski. I'm going to go in this order.

DR. JAY MANDREKAR: Yeah, so can I go ahead?

DR. SMITHA BALLYAMANDA: Yes, please do.

DR. RITA REDBERG: Yes.

DR. JAY MANDREKAR: So I'm going to be talking in general in terms of intermittent and continuous combined. My concern with this one is there are some studies that I looked at it that had a positive outcome, but most of the evidence that I see specifically for complete wound closure for chronic is much limited because sample sizes have been much smaller, which limits the power. Also, the issue that I noticed is patients were not like controlled at the time of randomization as you mentioned that there are so many other confounders need to be taken into account such as patient's comorbidities, wound characteristics, or presence of infection. So those things were not controlled in many of the studies.

So, my general impression about this particular question is low to moderate, there is insufficient evidence, in my opinion, to conclude definitely whether the adjunctive continuous oxygen therapy leads to greater incidence of complete and chronic diabetic foot ulcers.

So, large well, most of the publications that I have read here suggest that you need to have a large well-controlled studies to better understand and accounting for subgroup analysis targeted specifically for chronic, non-healing, diabetic foot ulcers if somebody wants to make a definitive conclusion.

DR. RITA REDBERG: Thank you. Dr. Niebuhr, Dr. Niebuhr, did you want to comment? I think you might be on mute while you're talking.

DR. DAVID NIEBUHR: Sorry.

DR. RITA REDBERG: Sorry and I'm just going to suggest, if people want to address total oxygen intermittent and continuous at the same time, it might help us on timing, because we are so tight on time.

DR. DAVID NIEBUHR: Yeah, sorry.

DR. SMITHA BALLYAMANDA: Yes, that was this is Dr. Ballyamanda, that would be my suggestion is if we could just address both intermittent and continuous, it would give us about eight minutes to discuss the question for both intermittent and continuous in the interest of time. Thank you.

DR. RITA REDBERG: Which is still just a minute per person. So just keep that in mind when you're talking.

DR. SMITHA BALLYAMANDA: Yes. Yep. Approximately a minute per person. Thank you.

DR. DAVID NIEBUHR: OK, I thought for intermittent oxygen, and the best study that I read was on the Frykberg 2019 study. I was impressed that, (cough) excuse me, they used a sham placebo standard care plus the sham. I thought that strengthened the study design. The sample size was 220 diabetic foot ulcers, which I would concede is perhaps not as large as it could be, but this is a relatively rare condition, and they had to use a multinational multi-center to get that sample size. I thought the design was really good. They, in addition to being double-blinded, they had random permeated block design, they had sample size calculation, they had two-week run-in, they intention analysis, they did multivariable logistic regression, Cox proportion hazard model, they did weekly digital wound images, they had a single-blinded central assessor with an automated wound measurement software, all that I thought strengthened it. They found a significant hazard ratio of 4.66, which I think is pretty strong in this business or really in any trial business. And so, I gave it a low intermediate.

For continuous, I thought that there was two relatively good quality studies, the Niederauer study, and sorry, and the Lavery study. I don't think the designs are as strong as the Frykberg, but they both had over 120 sample size 12-week follow-up. They did not have a sham placebo and I didn't see sample size calculation. So, some of the methodology was a little bit weaker, but it was, you know, reproduced by two different samples, two different investigators, both with statistically significant results, and I think clinically significant odds ratio about one point, or both odds ratio about 2.0. So, I thought the evidence was a little bit stronger for continuous versus intermittent. I'll stop there. Thank you.

DR. RITA REDBERG: Thank you. Next, Dr. Lantis.

DR. SMITHA BALLYAMANDA: Dr. Lantis, I believe he was able to join. Would you like to jump

right in?

DR. JOHN LANTIS: Yup. Can you hear me? Yes? No?

DR. RITA REDBERG: Yes.

DR. SMITHA BALLYAMANDA: Yes. Yes.

DR. JOHN LANTIS: Great. Love Google. It's a great app. Anyway, that being said, I actually completely mime what was just said before. I mean, Frykberg's study had the sham. It's not going to be huge. They're just not going to; you're not going those studies. I mean, that's a fallacy if that's ever going to exist. But that study did take into consideration as much as you could basically answer. But on the other hand, per your question, none of these studies across the board, you know, really are going to look at a mean population age of 73 years of age. So, if that's the one criteria we have to think about, that's not going to be answered. The other thing I just want to very quickly say is, quite frankly, intermittent oxygen and continuous oxygen being delivered somewhat differently in different mechanisms are actually used for different disease processes. So that's just a period end.

DR. RITA REDBERG: Thank you, Dr. Lantis. Dr. Wahab?

DR. NAZ WAHAB: So a couple of things, one is that the technologies are different and so I think looking at them obviously differently, but also those patient populations that will have to utilize these are different. For example, if you have more than one wound on a foot or a limb, you might need to use device that would encompass the whole limb versus if you have one treating, the continuous versus intermittent. I think there's a lot of nuances that will have to actually go with the patient population and the patient type and how you would choose the technology based on that. So, I thought that it was, one, it was actually very helpful to have the meta-analyses because in general, when you're looking at chronic wound healing, it's quite complex. And to have both evaluated, regardless of the fact that, yes, there are study design issues in both, I think Thanigaimani, who mentioned in his meta-analysis that I think it was an of about 49 people in each group across the board of the randomized control studies, which, again, I think is a limiting factor. But having said that, every single one of the, at least the meta-analyses, tried to kind of deal with the bias, deal with the lower numbers, deal with the issues of non-compliance and standard of care also. And when you look at that side by side, you know, the Carter, Sun, Connaghan, Thanigaimani, all of them actually recommended that oxygen, topical oxygen therapy could improve wound healing. And some were more definitive than others, but I think overall when you're looking at this type of plethora of information, it's good to see this. And I think for me, the likelihood of this helping patients, and by the way, I have used topical oxygen myself, it is a modality that does work. And so I think for patients who have completed their standard of care, have not healed, this is just like any other technology that we would like to utilize. And I think that the meta-analyses do show that there would be an improvement in wound healing and a trajectory, particularly if the endpoints are 12 weeks.

DR. RITA REDBERG: Thank you, Dr. Wahab. Dr. Wyatt?

DR. ALAN WYATT: Yes, I'd like to echo for, in the case of intermittent anyway, I'd like to echo the comments that have previously been made. I think the Frykberg study is a pretty good study, and it shows that there is a benefit. However, there's just so few studies looking at the intermittent that, yeah, I had to go with sort of intermediate low on that, simply because of the number of studies. With the continuous, again, echoing earlier sentiments, there were more studies. They were not quite as good, I think, but again, those studies, and as was just mentioned, you know, the meta-analyses all did agree that it does seem that there is a positive effect here, but there are a lot of the questions that we have to deal with today, especially the durability, limitation, things like that, that really haven't been addressed. So, again, I think for continuous, probably I would go with intermediate because more studies but not quite as good quality, and then intermediate low on intermittent, not because the study wasn't good because there were so few.

DR. RITA REDBERG: Thank you, Dr. Wyatt. Dr. Dua?

DR. ANAHITA DUA: Thank you very much. I actually resoundingly think that the intermittent topical oxygen has actually very strong data for a couple of reasons. For the RCTs that are performed actually, I mean, while the numbers may seem low, I think, you know, we're kind of used to seeing in like cardiac literature and like, you know, these thousands of patients to prove things, but the reason that you have thousands of patients is because the difference is so small that you need to have thousands of patients statistically to be able to show something. I think the reason that these studies, and there was power calculations done, that the reason that there are lower numbers is because they are indeed the intermittent therapies showing such a good result that indeed you don't need to have thousands of patients to demonstrate that this is happening. I

think the other big thing to focus on is the recurrence aspect of it too. I mean, one of the elements about the intermittent there's the whole idea of stabilization issue. And I think that was shown as well with recurrence rates, again, from studies.

In terms of the continuous oxygen, it's interesting like for meta-analyses, I mean, meta-analyses, they all sound good and they're a higher echelon of data. However, they are exactly that, meta-analyses. So, you're combining data from a variety of groups. And you know, again, I mentioned I'm a vascular surgeons. So taking a patient with normal flow to the foot, but a diabetic foot ulcer, and taking a patient with an ABI of 0.6, which is much lower blood flow, and also a diabetic foot ulcer, and just saying diabetic foot ulcer, and then sticking them in a study, that would be a meta-analysis that would be done correctly in terms of how you're doing the study, but the data would be garbage. And so, I land on the intermittent topical oxygen therapy. Actually, in my opinion, having very strong data, I also have a lot of anecdotal evidence, though I'll focus on here, have used it and indeed see the difference. And for the continuous, I mean, we've sort of been talking about continuous for years. We know about it, and no one has ever come down and said, yes, it's good because the data has always been weak. So that's where I land on this intermittent oxygen. I'm very confident it has sufficient data to determine that it leads to a better wound closure of chronic non-healing wounds.

DR. RITA REDBERG: Thank you, Dr. Dua. Just gonna ask people to mute when you're not speaking There's some extraneous noise here. I'm just going to comment again, and then go to Mr. Regulski. Or actually, Mr. Regulski, do you want to comment? And then I will comment, and I will say, after this, we're going to have much shorter discussions, because we're all going. This has been over a minute per person. Go ahead, Mr. Regulski.

DR. MATTHEW REGULSKI:

Yes, ma 'am, thank you. Well, I like the Frykberg study, because it was, the design was highlighted in the 2017 CMS decision memorandum as example of the level of evidence and study design that they would like to see. It has high quality and low risk of bias. It's very in the Frykberg RCT demonstrating far better healing at 12 weeks. And they did do a 12-month durability study showing that complete healing at 59% as well. And recurrence outcomes, these were on what we call University of Texas stage one and two moderate ischemic infected diabetic foot ulcers. They did measure quality of life for patients with intermittent topical and demonstrated improved outcomes across all domains of the wound care patient specific quality of life measure. They use the Cardiff Wound Quality of Life scale, which is a very validated scale to do. They had an independent assessing group. They had an independent steering group as well. And they are also being recommended with an A-level recommendation by the American Diabetes Association, the Wound Healing Society and the International Working Group on the Diabetic Foot Ulcer. So, durability is really high because they checked it out to 12 months when normal wound healing such as skin substitutes only go to two weeks. So, the durability was significant. The healing outcomes at 12 weeks were far better than any of the Medicare approved devices of skin substitutes, negative pressure, or even HBO at this point. So I think it's very robust data, the highest study designed.

DR. RITA REDBERG: Thank you.

DR. MATTHEW REGULSKI: and the outcome's up to 12 months.

DR. RITA REDBERG: Thank you, Dr. Regulski.

DR. MATTHEW REGULSKI: Yes, ma 'am, thank you.

DR. RITA REDBERG: I will comment a few things. One, I understand that everyone here or some people have anecdotal or case experience. That is not what we're considering today. So, the fact that you have done this, and you think it works, this is why we do studies because there is a lot of room for interpretation of your own experience. And we're looking at standard of evidence from high-quality randomized control studies. Again, a meta-analysis of weak, methodologically flawed studies only aggravates their flaws and their problems. It does not improve the data at all. And finally, with this Frykberg study, although they do say at the start that they had 220 patients, they only randomized 73, and this 12-month data has 27 patients in each arm. They lost, they had 37 at the 12-week point, and they got down to 27 at the 12 months, so I don't consider that a strong endpoint. It was such a tiny study. Seven percent of patients, seven, sorry, 20% of the patients, seven and six, in each group were lost to follow-up and two people died in each group and one was amputated in each group. So again, although there were certainly features of that study that were stronger, I don't think that it was large. It was limited by loss to follow-up and by the problems that we just discussed.

At this time, we're going to take votes on those two first voting questions. And Smitha, do you want to read them, or should people just vote with the link that was sent to everyone?

DR. SMITHA BALLYAMANDA: If folks want to, we're actually planning on doing the form voting at the end after we discuss

DR. RITA REDBERG: Oh OK

DR. SMITHA BALLYAMANDA: each question.

DR. RITA REDBERG: So we can keep with the discussion.

DR. SMITHA BALLYAMANDA: So, yeah, yeah, we can keep going.

DR. RITA REDBERG: Okay. That makes it a little, with encouragement

DR. SMITHA BALLYAMANDA: And we are down to one minute. I am going to have to interrupt people just to keep us going.

DR. RITA REDBERG: I think we're going to have to go even less than a minute because we are.

DR. SMITHA BALLYAMANDA: Yeah, I think so.

DR. RITA REDBERG: But we're going to take key questions three and four now, is that correct?

DR. SMITHA BALLYAMANDA: That's correct.

DR. RITA REDBERG: All right. And so, this is key question three. The three is for intermittent and four will be for continuous, but the same question. How confident are you there is sufficient evidence to determine that adjunctive total oxygen therapy shortens time to complete resolution of diabetic foot ulcers compared to standard of care alone. And again, we'll start with Dr. Jay Mandrekar and just please try to keep your remarks short. Thank you or to new points.

DR. JAY MANDREKAR: So for the question number three and four, I have similar concerns as I pointed for the other questions. Sample sizes are lower. Most of the studies, the end point was not timed to healing. So, also the variable types of patient factors that were not considered, for example, healing times might be influenced by factors such as wound size, infection, diabetes controlled or not, circulation. So, it makes it kind of hard for accounting for those things in the analysis, as pointed out by many presenters before. Most of the studies have a smaller sample size, so accounting for these things is not an easy challenge in this particular scenario. And so, my overall summary for this is, I rank it as intermediate evidence based on whatever is presented.

DR. RITA REDBERG: Thank you, Dr. Mandrekar. Dr. Niebuhr?

DR. DAVID NIEBUHR: Yeah. For intermittent oxygen, I pointe again to the Frankfurt study in which they said they reported a median time to complete healing of 56 days in the active arm and 93 days in the control, which is statistically significant. That's one study, set of limited evidence.

For continuous oxygen, the Niederauer reported time to 50%, diabetic foot ulcer closure was significantly shorter in patients with continuous diffusion oxygen, a mean of 18.4 days versus 28.9 in the control group, again, statistically significant. The Driver study, which is a lower quality, 2017, found a non-significant difference. 63 days in the transcutaneous oxygen, 77 days in the control group. Not a lot of evidence, so I fall down on about low intermediate or intermittent and maybe intermediate for continuous. Thank you.

DR. RITA REDBERG: Thank you. Dr. Wahab.

DR. NAZ WAHAB: All right, this mute keeps getting me. The Frykberg study for me was very helpful in this. I do understand the limitations that others are talking about in regards to discussion of whether the vascular status was addressed, whether the diabetes was addressed. These are things that are usually done in the inclusion criteria. So, I feel that a lot of that was taken into account. And you know, having said that, that some of the studies showed a significant difference with 56 days versus 93 days in that Frykberg, I think that that was very important and is very strong in showing that there is a decrease in time to closure.

DR. RITA REDBERG: Thanks so much. And I'm timing everyone, so I'm going to thank you and move on to Dr. Wyatt.

DR. ALAN WYATT: I don't really have anything original to add to that. I agree with the first doctor that intermittent, the studies, I think, are getting better, but they're still not there. So, if the question is sufficiency of evidence, I would come with intermediate low for the intermittent and probably intermediate for continuous, based on sufficiency of evidence.

DR. RITA REDBERG: Thank you, Dr. Wyatt. And thank you for being so succinct, too. Dr. Dua, what do you think?

DR. NAZ WAHAB: I will be very succinct as well. I think that there is high evidence for the

intermittent oxygen resolving the diabetic foot wounds. I do agree with what was said initially as the first point about it. Some of the endpoints are a little bit different, but I do think that the evidence that exists is solid, and I believe it. I would say for continuous, I'm gonna say intermediate evidence.

DR. RITA REDBERG: Thank you. Dr. Lantis.

DR. JOHN LANTIS: The intermittent therapy, I think, did change with the Frykberg study due to the quality of it. Prior to that, I was more skeptical. I think the Frykberg study is not that dissimilar from multiple other studies in this etiology, and that has to be taken into consideration, so it looks like a lot of other studies, and it did well. So, I would say intermediate for intermittent and maybe less or so for continuous.

DR. RITA REDBERG: Thank you, Dr. Lantis and Dr. Regulski. You're on mute.

DR. MATTHEW REGULSKI: I'm sorry. I agree. I'm sorry about that. I agree with Dr. Dua assessment as well as Dr. Lantis. I think it's a high quality of evidence, given its group sequential design, given its p-values that it reached 0.0022 at 97.8%. It's an analysis, again, the most stringent intent-to-treat approach and using very severe wounds with significant ischemia and significant infection as well. So, which was better. And again, the high quality and low risk of bias in the Frykberg study with 100% Cochrane score as well. So I would be, I'm very confident and the continuous is lower because there is risk of bias in those and they use more superficial wounds, not as deep wounds as in the Frykberg study.

DR. RITA REDBERG: Thank you. Okay, I'm gonna go on to questions five and six. I would suggest if you've already made the point about a study like the Frykberg study, it's not necessary to repeat it for the, so that we can keep moving through the 16 questions. Okay, question five is how, again, this is first intermittent, and then the second is for total oxygen therapy. How confident are you that there is sufficient evidence to determine that adjunctive total oxygen therapy? I'm sorry, the second is for continuous, results in durable wound healing of diabetic foot ulcers compared to standard of care alone. Again, Dr. Mandrekar.

DR. JAY MANDREKAR: So in my opinion, I rank it as an intermediate. Not many studies have focused on the long-term outcomes. So, the most trials are focusing on the wound closure rates and time to healing, which may not directly necessarily correlate with the durable long-term healing. Sample sizes, I already pointed out so issues in many of the studies. Studies are not mainly focusing on the recurrence rates or sustainable closures after the initial healing. And there are several factors that can affect those recurrences, which I'm not sure if they're controlled for or not, for example, poor circulation, ongoing pressure, neuropathy, et cetera. And so based on that, I have ranked it as an intermediate for this particular durability issue.

DR. RITA REDBERG: Thank you so much. Dr. Niebuhr.

DR. DAVID NIEBUHR: Yeah, I went with low intermediate for intermittent oxygen. The Frykberg study showed a 56% closure, compared to 27th in a sham at 12 months, and low confidence for continuously Al-Jalodi study (cough) excuse me, showed 85% closure in topical oxygen therapy patients and versus 60% in the center of care at one year mark. So, low intermediate and low confidence. Thank you.

DR. RITA REDBERG: Thank you very much. Dr. Wahab.

DR. NAZ WAHAB: Yes. I thought that it was a big feat to even try the durability studies on these. There were two particular studies, one showed at 12 months, and one was looking at 12 weeks. I thought both were about intermediate in level of evidence to show that, but having said that, many of these wounds were lower levels of wounds, lower severity of wounds, and so in general, if they were healing, I think that you were probably preventing an amputation and hopefully improving durability.

DR. RITA REDBERG: Thank you. Dr. Wyatt.

DR. ALAN WYATT: Yes, I think it's low intermediate for both, because there simply weren't many people looking at it. Again, 12 months in this 12-week study, I don't know that you'd call that sufficient evidence to really hang your hat on. Although, obviously, it looked like they were helping, and they were lasting longer, but again, not sufficient.

DR. RITA REDBERG: Thank you. Dr. Dua?

DR. SMITHA BALLYAMANDA: Just one second. I'm sorry to interrupt. I keep hearing some boinging sound. If you're not speaking, please put yourself on mute. Thank you.

DR. RITA REDBERG: OK, Dr. Dua?

DR. ANAHITA DUA: Hello? Yes, good. So, I think for the intermittent oxygen, actually, I thought that there was one of the points I mentioned earlier that I actually felt that's what the data supports the most, that there is some durability in the wound healing. I agree with what was said about preventing amputation. Ultimately, the question becomes how long you need it to be durable for. In my case, I don't want the patients to recur. The recurrence rates are decreased in the studies that are shown, so I would give this high evidence for the intermittent. For continuous, it's the same as before. I feel like it's maybe mid to slightly high, compared to standard of care, which would not be any oxygen. Thank you.

DR. RITA REDBERG: Thank you. Dr. Lantis.

DR. JOHN LANTIS: Most of the comments have been made. The paper, you know, they support maybe prolonged, this prolonged healing, but quite frankly, it doesn't make a lot of scientific sense to me. So, I'm not sure I believe it, but the papers support it low. I would say low for intermittent and lower for continuous. There's nothing for continuous.

DR. RITA REDBERG: Thank you. And Dr. Regulski.

DR. MATTHEW REGULSKI: Yes, ma 'am. So for, for the, when we look at clinical studies, most people go out for follow-ups and durability for two to four weeks. At least they attempted to go out in the intermittent to 12 months, showing a six-fold lower recurrence rate for that. Remember, a diabetic foot ulcer does have about a 40% to 50% recurrence within one year. So, to show this significant reduction in that, I'm very confident in the intermittent oxygen. But on the continuous, there is no RCT evidence for showing durability, just some low-quality case series inferred data.

DR. RITA REDBERG: Okay. Thank you. And I'm going to read the key question seven now. The first one will be for intermittent and the second is the same question for continuous. And now we're looking at amputations. So, I don't think we saw a lot of data on, but how confident are you that there is sufficient evidence to determine that adjunctive total oxygen therapy lowers the risk of amputation in adults with diabetic foot ulcers compared to standard of care alone. And I'll just note the Frykberg studies did show equal amputations in both arms at the 12-month data was two in each. Starting with Dr. Mandrekar.

DR. JAY MANDREKAR: My confidence level is low for the amputation because the studies are not targeted to measure the amputation, mainly targeted for wound closure and stuff. Not all studies are having extensive follow-up of developments or longer when potential amputation can also happen. As again, pointed out earlier, the sample sizes or randomization are the issues that I keep noticing with this one. And so based on all of these factors that I just mentioned, I have ranked it as low confidence for lowering the risk for amputation.

DR. RITA REDBERG: Thank you. Dr. Niebuhr.

DR. DAVID NIEBUHR: I totally agree. I put low confidence for both intermittent and continuous. I think this is a rare event. I think none of the studies had this as a primary outcome. I don't think they had an adequate sample size for amputation. Al-Jalodi, I believe did a post-hoc analysis following up to a year out and said there was one major amputation in the center of care group, but I think the bottom line is low confidence are both intermittent and continuous. Thank you.

DR. RITA REDBERG: Thank you, Dr. Niebuhr. Dr. Wahab.

DR. NAZ WAHAB: Yeah, I think I mentioned this in my last comments that the ability to look at this due to the lower sample size is very difficult, but I think there's probably intermittent level of evidence assuming that some of these are avoiding, that they're healing and hopefully potentially avoiding amputation as well.

DR. RITA REDBERG: Thank you. Dr. Wyatt?

DR. ALAN WYATT: Yeah, I would agree with Dr. Mandrekar. Low on both. There's just no evidence.

DR. RITA REDBERG: Short and sweet. I love it. Dr. Dua?

DR. ANAHITA DUA: I think I'm going to say, sorry, I'm going to say intermediate on both. I mean, I can make the jump that obviously if you heal the diabetic wound, you lower the risk of amputation, but the actual outcome of amputation is not in either one. So, I agree with what was just said, intermediate for both.

DR. RITA REDBERG: Okay. Dr. Lantis. You may be on mute. I don't hear you. Okay, we'll go to Dr. Regulski. Okay. Maybe there's a problem with audio. I didn't hear either of Dr. Lantis or Regulski.

DR. MATTHEW REGULSKI: Oh, I'm sorry. I'm sorry. I apologize for this button. I look at the Yellin in real world data, which was a traceable IRB study on 202 patients out of the VA in both the raw

unmatched outcomes and when you did match using statistically recommended propensity scoring, they did have an 82% reduction in hospitalization and a 73% reduction in amputation. And as a guy that treats thousands of wounds a year, if I can heal these wounds and prevent those problems, that's key for me. As far as, so on the intermittent, it's intermediate, the intermediate and high, I would say in continuous, there is really no evidence on the continuous, just in low-quality case series and from that inferred data.

DR. RITA REDBERG: Okay. Thank you. We're going to move on to key question nine, and this is also for intermittent and continuous, though it's about generally accepted by the medical community, which probably depends where your medical community is, and I didn't see so much data on. I don't know, Smitha, have you had any other comments on this question in particular? What data to use? Okay, we'll,

DR. SMITHA BALLYAMANDA: No, no.

DR. RITA REDBERG: We'll open this for discussion. How confident are you that total oxygen therapy is generally accepted by the medical community for treatment of diabetic foot ulcers? We'll start with Dr. Mandrekar.

DR. JAY MANDREKAR: Okay, so if you want that, this was done, discussed back in 2019 and we are back again discussing it. Doesn't seem to be much evidence has been added since then. And again, it goes back to saying the same thing that lacks the high-quality randomized studies with inconsistent evidences. That could be one of the reasons that is not widely accepted probably in the medical community. I will look at my medical colleagues on the call to make the comments on that. But my feel for the studies that I reviewed, nothing specifically highlighted the fact that this will be the definitive treatment that we'll be using or something to that effect. And so my enthusiasm for this one is low confidence.

DR. RITA REDBERG: Yeah, I agree, and I have the same recollection from five years ago and unfortunately, I don't think the quality of evidence has improved.

DR. JAY MANDREKAR: Exactly, the number of studies, 80 to 90% studies that we just reviewed now are the same that were reviewed before 2019.

DR. RITA REDBERG: Yes, and the continued small numbers.

DR. JAY MANDREKAR: And I mean, I just said the statistician, know, whenever the grant gets rejected, we look at the comments and we address those things. So, whoever works in this particular research area should have looked at this 16 questions or whatever and created the studies to address some of those things. That way they could have addressed all of those challenges like, you know, in larger single study.

DR. RITA REDBERG: Yes, I agree. And I would say as a medical editor, we were very cautious about meta-analyses because you have to look at the quality of the data.

DR. JAY MANDREKAR: Exactly, yes, yes.

DR. RITA REDBERG: Okay, next, Dr. Niebuhr.

DR. DAVID NIEBUHR: Yeah, I'm gonna differ, I'm sorry. I found low confidence for intermittent oxygen, but I fall down on, (cough) excuse me, intermediate confidence for continuous. I'm not a clinician in this area, but I was impressed by the fact that there was one, two, three, independent clinical practice guidelines, Chen, Yellin, and Lavery that all recommended it. Also, four systematic reviews. Now, I hear what you're saying about the quality of the evidence going into a systematic review, but I think of the four, the Carter systematic review was done to grade standards, which I think is the gold standard, and their level of evidence was moderate for effectiveness. So I think, you know, we can argue, can the evidence be improved? I don't think we can argue, but we can call for better evidence. I think at this point in the field, my thinking is that in terms of the acceptance by the medical community, it's probably moderate for continuous oxygen. Thank you.

DR. RITA REDBERG: Thank you, Dr. Niebuhr. Dr. Wahab.

DR. NAZ WAHAB: Yeah, I think, you know, for someone who's practicing in this field for the last 20 years, and I understand that that may appear to be anecdotal, but, you know, International Diabetic Foot Group recommends it. You know, we're looking at American Diabetic Association. When you're looking at these guidelines that they're putting out, there's quite a few mentions of topical oxygen utilization. And so I think that it is generally accepted. I think that there are limitations on why we're not able to do that in the United States. One is perhaps that there's no payor source for it, but others that, you know, reality, I think it's limited in access, and that's perhaps why some of you are not seeing that but for those of us that are in the diabetic world, we see it quite a bit. So, I do think that there is some general acceptance, especially since there's

quite a few guidelines with them included.

DR. RITA REDBERG: Thank you, Dr. Wahab. Dr. Wyatt.

DR. ALAN WYATT: Yeah, in general, I would agree with Dr. Wahab. I mean, it certainly appears to be getting recommended more by the ADA, and I know, although I've never used it myself, the VA pays for it, and the VA across the street, the podiatry group there has begun using it a lot more. So, I probably have to go with intermediate there because it does seem to be growing in popularity.

DR. RITA REDBERG: Thank you. Dr. Dua.

DR. ANAHITA DUA: I'm in the same world as Dr. Wahab and I completely agree with what was just said. At least in my world, it is accepted. There are multiple communications. I live in Massachusetts. MassHealth is looking at this very closely to cover. There are already multiple other states that are doing that and that's all based on data, obviously. And so it certainly in our community is accepted. The only reason it's not used widely is because of access, which is obviously what we're here for as well. Certainly not the case for continuous, which we've all had for a while. Not every patient is being pushed into that. So in my community, very high for intermittent oxygen.

DR. RITA REDBERG: Thank you, Dr. Dua. Dr. Lantis.

DR. JOHN LANTIS: I would say in the general community in New York, although it's been, it's not well available necessarily. I would actually say it's not, you know, it's not widely used or recognized, honestly.

DR. RITA REDBERG: Thank you, Dr. Lantis and Dr. Regulski.

DR. MATTHEW REGULSKI: Well, you know, in this world of when I am trained thousands of wound patients, you know, I look at these guidelines, the American Diabetes Association gives it an A rating, the Wound Healing Society gives it a level one rating, the International Working Group on the Diabetic Foot gives it positive ratings. All the meta-analyses and those things are all recommending that because oxygen affects every phase of the wound healing cycle. So it's needed and the problem is again with these societies that are recommending giving it a grade one and A, is the access problem, which I hope we can rectify, but it doesn't significantly affect all phases of wound healing.

DR. RITA REDBERG: Thank you. We move on to key questions 11 and 12. How confident are you that the available evidence for total oxygen therapy in diabetic foot ulcers allows identification of a discrete population of Medicare eligible beneficiaries who would benefit from total oxygen therapy? And again, we'll start with Dr. Mandrekar.

DR. JAY MANDREKAR: So the lower sample size now is going to become much more problematic situation in this one, because Medicare population includes individuals who are elderly with lots of comorbidities. So, the studies need to be accounting for subgroup analysis targeting for the elderly versus for different comorbidities. I don't see the studies are powered for that. Most of the studies are not designed for Medicare eligible patients. Also, within Medicare, if there are certain types of patients that might more benefit from this treatment based on some biomarkers or clinical indicators or something, that is also not possible. So, my general feeling about this particular question is I rank it as low confidence for both intermittent and continuous oxygen.

DR. RITA REDBERG: Thank you so much. Dr. Niebuhr.

DR. DAVID NIEBUHR: Yeah, I'm going to go with low intermediate for both intermittent and continuous. I think it's fair to say that none of these studies were exclusive to the Medicare eligible population. My reading, they had mean ages anywhere from 55 to 63. And I did not see a subgroup analysis restricted to the 65 and older. I'm not aware of a reason why topical oxygen therapy would be less effective in over 60 and under if it's independent of other, you know, like arterial or other factors. So, I'm going to fall down on low intermediate confidence for both. Thank you.

DR. RITA REDBERG: I didn't see those sub-analyses either, and obviously things change with aging. Next is Dr. Wahab.

DR. NAZ WAHAB: Yeah, I mean, I do think that some of the studies, like the Serena study specifically looked for at least 50% of enrollees to be 65 or older. When you looked at the average, it was about 61.9 years plus or minus 9.5. I think that might be slightly younger than the average Medicare population, but I think it would encompass that. Doing a sub-analysis, yes, would decrease the number of participants in that, and I think that would, you know, be very difficult

to assess then. But I do think that there is enough data here to show that it does help Medicare beneficiaries.

DR. RITA REDBERG: Thank you. Dr. Wyatt.

DR. ALAN WYATT: Okay, so this question gave me a little trouble because, yes, if you're looking at strictly at the question Medicare population, then yes, the ages were all wrong to really be able to draw any conclusions. If you're looking more generally at the similarities between the studies and can you actually come up with a set of criteria, I think that the ones that were presented in the Delphi consensus from the meeting a few years ago here in New Orleans that I was not a part of, I do agree with those, but again, the age and is this a Medicare population? I guess not.

DR. RITA REDBERG: Thank you. Dr. Dua.

DR. ANAHITA DUA: I agree with what's been said, especially Dr. Wahab. I think that the beneficiaries would be Medicare eligible people, primarily looking at the age. It's really 60 and over 65 and over, and those are the patients that get the longstanding diabetes, therefore get the diabetic foot ulcers, and therefore are the ones that would benefit from the oxygen therapy. So for me, high evidence here, and I'd say low intermediate for continuous for this population.

DR. RITA REDBERG: Thank you, Dr. Lantis. Dr. Lantis. You may be on mute. Okay, let's move on to Dr. Regulski.

DR. MATTHEW REGULSKI: Yes, ma'am. You know, in the intermittent for the Frykberg study, the average age was 64.6. And for us in the wound care space, we're seeing younger and younger patients with diabetic foot ulcers. I have patients in their 30s and late 20s because they're not taking care of themselves, have diabetes. And I've had to do an amputations on 30-year-old people because of gangrene and problems caused by that. So, for me, in the Frykberg studies, particularly in the intermittent study, there's high quality of evidence to show that these Medicare aged people, but again, diabetes encompasses all the scope. For the continuous part, it's still a low quality and more inferred data on those, but there's still significant people, especially in 64.6 years for me. So I say intermediate to intermediate high for the intermittent and low for the continuous.

DR. RITA REDBERG: Thank you. Okay. Moving on to key question 13, we are doing great. How confident are you that there are no significant gaps in evidence that may impact health outcomes in the Medicare eligible population? So again, for this question, think about the data you've reviewed. And are there remaining questions, particularly we're looking at health outcomes, so things that would be meaningful that Medicare beneficiaries would feel. And again, starting with Dr. Mandrekar.

DR. JAY MANDREKAR: Yeah. So, in my ranking, I'm going further the down and down and down as we progress with the questions going from 1 to 16. So, most studies do not specifically focus on medical eligible populations. Studies goal was to have wider range of population captured for generalizability purposes. And so, there was no room for them to adjust for sample size upfront or have a subgroup analysis post-op. And so, the results that are given there are not giving me any confidence in this particular thing. So, the gaps include lack of specific evidence for older adults with complex health conditions, limited data and long-term outcomes, insufficient subgroup analysis, and absence of standardized guidelines for comparative effectiveness studies. And so, I would rank this particular, these set of two questions as low confidence.

DR. RITA REDBERG: Thank you, Dr. Mandrekar. Dr. Niebuhr.

DR. DAVID NIEBUHR: Yes. Low confidence of both intermittent oxygen and continuous, specifically, there are gaps in the evidence for risk of amputation, quality of life, and people aged 65 and older. Thank you.

DR. RITA REDBERG: Thank you. Short and sweet. Dr. Wahab.

DR. NAZ WAHAB: Yes, I think that there are some gaps, you know, again, as actually Dr. Niebuhr just mentioned, but in general, I don't think that the gaps are so overwhelming that we should not look to ensure that these technologies are, and don't negate the fact that there is an improvement wound closure and decrease in size of wound and length of time to wound closure. So, I think that although there might be some gaps, as Dr. Niebuhr explained, I feel like that there's at least intermediate evidence that supports the topical oxygen.

DR. RITA REDBERG: Thank you, Dr. Wahab. Dr. Wyatt.

DR. ALAN WYATT: Again, on a strict interpretation of the question, there's not a lot of data that actually focuses on the Medicare population, that age range. But again, that's not to say I don't think this is probably going to be a good thing. I've never used it before, but I actually plan on

doing it now after having looked at these studies. I'm going to give it a try. But again, Medicare population, it really, it doesn't look like there was a lot of trial patients that were in that group.

DR. RITA REDBERG: Thank you. Dr. Dua?

DR. ANAHITA DUA: I have nothing to add to what's already been said. I would say slightly, like four for the intermittent oxygen and three for continuous.

DR. RITA REDBERG: Thank you. Dr. Lantis?

DR. JOHN LANTIS: Just echo the previous comment intermittent.

DR. RITA REDBERG: Okay. And Dr. Regulski?

DR. MATTHEW REGULSKI: Yes, ma 'am. You know, when I was reading on the Frykberg study, they did use a quality-of-life tool called the Cardiff Wound Impact Schedule, which is a well-validated wound care-focused quality of life survey, which demonstrated substantially, improved substantially quality of life for patients with those ulcers healed across all functional domains. There was 21 domains in their design, which they did meet for that. So, it's, for me, being in this space, it does give me great confidence to be able to use that device. For the continuous aspect, again, it's a lower quality of evidence seen in the Serena study and the Niederauer study, again, more superficial wounds than in the Frykberg study, which was much more severe, more neuropathic and ischemic wounds, but they did measure quality of life and had significant impact, according to the Cardiff wound impact schedule for me.

DR. RITA REDBERG: Thank you.

DR. JAY MANDREKAR: But the question was…

DR. RITA REDBERG: We'll turn to our last question now. The last key question is 15 and 16 and again I'll just remind you that we're right now evaluating the evidence and so we're not your experience and your feelings and you're about this technique. It's not what should be guiding your assessment and voting but actually the evidence that we've reviewed. This question focuses on quality of life, which is very, of course, important to us and Medicare beneficiaries. How confident are you that the evidence supports that the use of total oxygen therapy results in an improvement in quality of life in Medicare beneficiaries? Dr. Mandrekar.

DR. JAY MANDREKAR: Yeah, so based on several studies that I have looked at, I don't see the studies are targeted mainly to assess the improvement in quality of life, let alone in the Medicare beneficiaries. So wound healing may not necessarily translate to improvements in quality-of-life outcome, in my opinion. Also, the quality of studies is highly variable. Studies are not just focused on Medicare beneficiaries. And so, if somebody wants to have the quality-of-life assessment as a part of their protocol, they need to have accounted for the sample sizes for accounting for the Medicare beneficiaries and doing the subgroup analysis. Also, specific populations of Medicare beneficiaries, which is basically primary older adults, may experience different outcomes compared to younger and other populations. So, the definitions of the quality of life might be slightly different based on who you are looking at. And so based on these comments that I made, my confidence is low.

DR. RITA REDBERG: Thank you, Dr. Mandrekar. Dr. Niebuhr.

DR. DAVID NIEBUHR: I went with low-intermediate for both intermittent and continuous. I concede about the Frykberg study and the quality of life instrument. My problem is that I don't think that was a primary outcome, you know, with an A priority hypothesis and sample size calculation. I think this is an important issue as it is from a patient perspective and it deserves to be powered adequately, that kind of thing. So again, lower to immediate for both intermittent and continuous. Thank you.

DR. RITA REDBERG: Thank you, and certainly I agree, it's probably a paramount issue for patients of quality of life. Dr. Wahab.

DR. NAZ WAHAB: Yeah, I think, you know, there's been about four out of the roughly six randomized control studies that did do some sort of quality of life, but it was not all the same. I did think that all of them were positive, and I disagree with some people who were saying that if you don't heal a wound, you have an improved quality of life. I know that that might be an indirect indicator, but I do think that that is an indicator in general as well. So, I think that there is, out of four out of six did have quality of life indicators.

DR. RITA REDBERG: Thank you. Next, Dr. Wyatt.

DR. ALAN WYATT: Yeah, I basically just echo Dr. Niebuhr. I agree with everything he said.

DR. RITA REDBERG: Okay, that sounds excellent. And next is Dr. Dua.

DR. ANAHITA DUA: I echo Dr. Wahab and what she said, and so I think that there is evidence, and so high level for me for intermittent oxygen.

DR. RITA REDBERG: Thank you. Great. And Dr. Lantis?

DR. JOHN LANTIS: Yeah, I mean, the quality of life data is, I'm never very confident in it, because a lot of people don't, if you look at the starting points, their life is not as impacted as you would think be. So, I have a lot of issues with the quality like data. For the papers, the intermittent outranks standard or continuous though.

DR. RITA REDBERG: Thank you. And Dr. Regulski.

DR. SMITHA BALLYAMANDA: Looks like we've lost Dr. Rogalski. I don't see anyone.

DR. MATTHEW REGULSKI: Sorry, I apologize. It's this darn button. I echo Dr. Lantis' comments, at least in the Frykberg, we have a well-validated tool of the cardiac wound impact schedule showing substantial improvements in their lives, and when you heal wounds and get people back on their feet, when they can get back to their job and to their lives and see their family, that's a tremendous impact in their quality of life, instead of amputate them.

DR. RITA REDBERG: Okay. Thank you all for the robust discussion and comments and review of the evidence and your thoughts and comments on all the voting questions. I think we are now up to the part where you score the key questions. And I think all of the voting members have received a link. So we can take a few minutes now to vote, and then we'll score the questions. So, I think we'll probably monitor when all the votes have come in, and...

DR. SMITHA BALLYAMANDA: Yep, thank you. I believe all the CAC panel members should have received a rating form in your emails this morning. Please click on that link and complete the rating form. And we'll have our coordinator, I believe, Jody is taking, looking at them. And as soon as we have all the votes, we will go over the votes together. So, we'll just take a few minutes for that. Thank you.

Just as an update to everybody, we have four people who have, I'm sorry five people who have voted so far. So, we're just waiting on three more folks to finish their votes. Then we can go over them together. Thanks. Dr. Redberg, did you receive your link as well?

DR. RITA REDBERG: I did. Yes. Thank you.

DR. SMITHA BALLYAMANDA: Okay. Just making sure.

DR. RITA REDBERG: Ya, I voted.

DR. SMITHA BALLYAMANDA: Okay. Thank you. All right. We have six who have voted. We're just waiting for one more. Just as a reminder, once you've put in your votes, if you could remember to hit the submit button, maybe that's why we're waiting for the one more person. Not sure, but the submit button is at the very bottom, thanks.

DR. RITA REDBERG: Will people get a confirmation, so they know they've submitted and voted correctly?

DR. SMITHA BALLYAMANDA: I believe there's a page that pops up to show that it's been submitted.

DR. RITA REDBERG: Do you have everyone's?

DR. SMITHA BALLYAMANDA: Not yet. I think we're still missing one person. CAC panel members, were you all able to vote?

CAC MEMBER(S): Yes, I did. I have voted.

DR. RITA REDBERG: I didn't get a page. Should I go back and do it and submit?

DR. SMITHA BALLYAMANDA:

Yes, yes. There should be a link and then it has to be submitted, yep. Okay, looks like we have all of the votes. Okay, thank you for sharing. So, we will go through each question. And again, this is for intermittent and continuous oxygen.

So, for intermittent oxygen, how confident are you that there is sufficient evidence to determine that adjunctive TOT leads to a greater incidence of complete wound closure for chronic non-healing diabetic foot ulcers? I can't see the rest of the question here. Let me just pull up the key questions. Give me one moment. Okay. How confident are you that there is sufficient evidence to determine the adjunctive TOT leads to a greater incidence of complete wound closure of chronic non-healing diabetic foot ulcers compared to standard care alone. And for intermittent, we landed

at one, a rating of one for 25%, a rating of two for 25% and three for 12%.

Next. This is for the same question, but for continuous oxygen. And we've come in at 2.63.

Next question. How confident are you that there is sufficient evidence to determine that adjunctive TOT results in durable wound healing for diabetic foot ulcers compared to standard? Oh, I'm sorry. I skipped a question. How confident are you that there is sufficient evidence to determine that adjunctive TOT shortens the time to complete resolution of diabetic foot ulcers compared to standard care alone? And for intermittent oxygen, we're at 2.75. For continuous oxygen, we're at 2.38.

Next question. How confident are you that there is sufficient evidence to determine that adjunctive TOT results in durable wound healing of diabetic foot ulcers compared to standard of care alone? For intermittent, we're at 2.75. For continuous, we're at 2.0.

Next questions. How confident are you that there is sufficient evidence to determine that adjunctive TOT lowers the risk of amputation in adults with diabetic foot ulcers compared to standard care alone? For intermittent, we are at two. For continuous oxygen, we're at 1.75.

Next question. How confident are you that TOT is generally accepted by the medical community for the treatment of diabetic foot ulcers? For intermittent, we're at 2.75. For continuous, we are at 2.75.

Next question. How confident are you that available evidence for TOT in diabetic foot ulcers allows identification of a discrete population of Medicare-eligible beneficiaries who would benefit from TOT. For intermittent, we landed at 2.75. For continuous, we're at 2.38.

Next question, how confident are you that there is no significant gaps in evidence that may impact health outcomes in the Medicare-eligible population? For intermittent, we're at 2.38. For continuous, we're at 2.0.

And last question, how confident are you that evidence supports that the use of TOT results in an improvement in quality of life in Medicare beneficiaries? For intermittent, we've landed at 2.5. And for continuous, 2.13.

Okay. Rita, would you like to say any other comments or statements before we adjourn?

DR. RITA REDBERG: Just to thank everyone. I know we went through a lot of studies and a lot of questions and a lot of discussion and I really appreciate everyone's thoughtfulness and work in preparing for this meeting, for your care of these patients, for all coming together today to try to do what's best for Medicare beneficiaries, and bringing your expertise and knowledge to this meeting. So, thanks so much. And it's always hard to go through a lot of questions in one time, but I thought everyone did a great job, and thanks for allowing me to participate. Did anyone have other comments or?

DR. ANAHITA DUA: Just can I just ask what happens now like that what's is it going to be as it should be covered? Is there like how does it work?

DR. SUNIL LALLA: The medical directors take the evidence and the comments from today's meeting under advisement.

DR. ANAHITA DUA: Thank you.

DR. SMITHA BALLYAMANDA: Yes.

DR. ANAHITA DUA: Also, is the competence ratings, do they, is there like a good rating versus a bad rating or do we have any kind of an idea of that?

DR. SMITHA BALLYAMANDA: It's really just to show where you've landed upon looking at the evidence and then we use those ratings. It's not really good or bad. It's did you, were you able to answer the question that was asked and how confident were you to be able to answer it based on the studies that you reviewed. So, I think there is actually, did anybody vote twice? Because it looks like we had eight votes, and it really should be seven. Please give me a second while I confirm with the team. But I'm asking, did anyone vote twice?

DR. RITA REDBERG: I hit that submit, Smitha, so it's possible when I submitted, because I didn't think I hit submit twice when you said we were still short, and I shouldn't do it.

DR. SMITHA BALLYAMANDA: Okay, okay. I think I'm getting information from the team that we should be okay and we'll decide what to do once we get the actual votes and go from there.

DR. ROBER HOOVER: Yeah, this is Dr. Hoover from Jurisdiction C. I think just to answer the last question about the CAC scoring. The CAC is kind of early in the policy development process in

that the purpose of the CAC is to look at the strength and the quality of the evidence. And that was probably reflected. I think you saw that in the question on the graph. We then go back and do our own analysis of the literature and then sort of throw it all in a pot, take everything into consideration before we draft a proposed policy that goes out for 45 days of comment. You're certainly welcome to comment on that proposed LCD when it goes out. This is an early step in the process.

DR. SMITHA BALLYAMANDA: Thank you, Dr. Hoover.

DR. DAVID NIEBUHR: Thank you.

DR. SMITHA BALLYAMANDA: So just want to wrap things up. A heartfelt thank you to our revered CAC Chair, Dr. Rita Redberg, and each of our dedicated CAC panel members. I know that it took a significant amount of time to review and prepare for this discussion. So, we want to thank you for your valuable time, your expertise, and commitment to this important discussion. Your insights today will significantly contribute to making an evidence-based decision that will ultimately benefit patients and the healthcare community. And so, we're really deeply grateful for your thoughts and contributions and continued support. Your dedication to advancing evidence-based practices in healthcare is instrumental. So, we really appreciate it and wanna thank you. Oh, I see a hand up. I'm sorry, I just noticed that Dr. David Niebuhr, did you have a questions?

DR. DAVID NIEBUHR: Yeah, do I understand that Medicare has the option to make like kind of a provisional regional coverage decision, the requirements for reporting of outcomes and that kind of thing. The reason I ask is that, for example, the durability and the amputation risk are extremely rare rates, like rare occurrences. And I wonder if that would be an ideal opportunity for like real world data that might be collected through, you know, a registry of some sort.

DR. ROBERT HOOVER: Yeah, Dr. Niebuhr, this is Dr. Hoover. In the National Coverage Determination process, which is a process sort of similar to this, but done on the, by CMS and their coverage and analysis group, there is something called coverage with evidence development, and that's one of the options that CMS has when they're looking at a National Coverage Determination. They can do exactly what you're talking about is set up a system for, you know, sort of a provisional coverage determination. We do not have that option at the DME MACs. Ours is kind of an all or none. It's either reasonable and necessary or it's not reasonable and necessary. And that is not the coverage with evidence development is not an option that's been given to us by Congress, or CMS.

DR. SMITHA BALLYAMANDA: I agree with what Dr. Hoover said. And however, there is a pathway to do that through CMS, if those feel very strongly. We can, there is an option to do that, but you'd have to go through a CMS.

DR. ANAHITA DUA: And I just say, like, just as someone who does this, just to keep this in mind, you know, I mean, these questions are okay, but they're not perfect for what, I mean, it's such a, you know, is this going to be beneficial for Medicare, for beneficiaries of Medicare? It's such a kind of vague, sort of like interpretable type thing. I think at the end of the day, you know, at least here, and the reason I'm taking this opportunity is because you guys are here, that, you know, we don't have anything good in this space. Wounds are billions of dollars, as you guys know, and we need something that works, and this does work. There is RCT data on it, which is pretty rare, especially in vascular pats, which is really very rare to get. And we're seeing people that are healing, not recurring, and that's really the crux of things. I don't know if it like makes sure that they don't get divorced or whatever else is going to help them in the quality of their life, but the wounds are healing, and these guys are doing well, and we need something covered that will help us. And I know that there's a history with wound care products where a lot of stuff was passed that maybe wasn't so great, the data wasn't so great, so Medicare CMS can almost be a little gun shy, but this is really something good and so I just hope that it's not just like oh we need it to be like a thousand percent and then we'll cover it you know this is very clearly doing some big things and so I would hope that that would just be taken under consideration for the ones that do this it does work and it would be great to have it available to the patients that need it.

DR. SMITHA BALLYAMANDA: Thank You Dr. Dua. I just want to address some of those comments so when we are looking at these studies applicable to the Medicare population it means we're looking for those findings and recommendations among that particular group, because which are primarily those that are age 65 and older and a few folks that have disabilities. And so, they tend to have different healthcare needs compared to younger populations. As people age, they often experience a higher incidence of chronic conditions, functional impairments, and other health issues, and also are often taking on, are taking currently multiple medications and affected by certain disease processes such as cardiovascular disease, diabetes, arthritis. I mean, I don't need to go into it, but basically the Medicare population often has more complex medical needs than younger populations due to multiple comorbidities and higher rates of hospitalization.

And so, you know, if there was an endless—there is this opportunity to go through the clinical evidence development as well as process matures, but that's why we really focus on that Medicare population as they are a different and complex group, thanks.

DR. ANAHITA DUA: That's exactly it. Actually, that's what I'm starting to say, that if you were to cut this and say this should—like, let's say—and this is not going to happen, but let's pretend you said, you know what, this is only available to people over a certain age group. I would absolutely say that should be people 60 and over because exactly what you said. So like for these guys, you know, when you're asking about like durability and these sorts of things, you know, if I have a 85 year old guy with diabetes with a bad wound that's not healing or venous stasis ulcers that repeatedly keep coming back every, you know, six months, I'm dealing with it, somebody like that, you'd revolutionize their life if they were able to get this type of therapy, the wound heals and then the tissue over the top is more balanced so it doesn't break down as much, that's exactly the patient. So, but for me, I mean, I don't even see people really below 60 because of the job. So, that's who I'm specifically talking about. And that's the type of person I think would benefit the most. So just since you said these comments are gonna be part of the whole story, because when I look at those numbers, they're all what, three, three, three, three. I mean, I don't know how helpful that is. And I don't know if you'll ever get a group of doctors together about anything, that'll all be fives. So, I guess it's just something to point out that I think the conversation is really key.

DR. SMITHA BALLYAMANDA: That's exactly right. You're absolutely right. There is going to be different experiences and perspectives and that's why we lean on the evidence and the quality of evidence that's why that becomes so much more important, and methodology and approach becomes really the pivotal aspect of it that we can focus on and use to support where we land.

Dr. Regulski, you have your hand up.

DR. MATTHEW REGULSKI: Oh yes, I just want to say thank you very much. And I just wanted to echo what Dr. Dua said because a diabetic foot ulcer is the number one reason diabetics are admitted to the hospital. No other reason. And it's costing us $38 billion a year and 5,200 people a day are diagnosed with diabetes in this country. So, I hope we take into the whole clinical spectrum of what is going on. And the case does have RCT data to prove that it can do this recommended by all the societies, especially for us that are knee deep into this stuff, treating thousands of these wound patients here and seeing the devastating complications and the mortality risk associated with amputation. This could be a game changer for our Medicare beneficiaries and people that are suffering with, not only a few other ones, but especially the diabetic foot ulcer, since it occurs every 1.2 seconds. So, I hope we take a look at that whole gambit, the whole spectrum of the evidence and the outcomes. And thank you for the opportunity today. I appreciate it very much.

DR. SMITHA BALLYAMANDA: Yes, thank you all. So, Dr. Mandrekar, and then I'll have some final statements before we close. Go ahead, Dr. Mandrekar.

DR. JAY MANDREKAR: Yeah, I just have a quick comment that my reading, I'm not a surgeon, I'm not a clinician. So my reading is just based on what is provided to me. If I'm a surgeon operating on five patients and they all recover, I'm going to say, oh, this is working beautifully, right? But that's not what I'm seeing in the papers that are published. So ultimately, if I'm a patient, I want to make the decision to go for the treatment or not, is what is in the literature. And so that might be the reason why the reflection is threes, whereas a couple of people who saw it in their practice might have given fours and fives.

DR. SMITHA BALLYAMANDA: Thank you, Dr. Mandrekar. I appreciate those thoughts. And so it brings me back to the final conclusion, and we will adjourn the meeting at this point. But supporting medical necessity decisions with credible, high-quality clinical evidence is essential to ensure not only patient safety but optimizing resources and maintaining compliance with, you know, coverage determinations. It provides that foundation for making consistent, effective, and fair healthcare decisions. So ultimately leading to better patient outcomes and more sustainable healthcare practices. So, I appreciate everyone's experience that you've shared. However, this discussion and this meeting is specific to the evidence that was provided. And that's what we will be looking at as we move forward to making a determination. So, with that being said, I wanna thank everybody again for your time. And again, your invaluable contribution and commitment to this process. Have a wonderful day and thank you again.

CAC MEMBERS: Thank you so much.

Thank you very much.

Thank you.