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Topical Oxygen Therapy Addition to the Oxygen and Oxygen Equipment LCD Contractor Advisory Committee (CAC) Meeting for all DME MAC Jurisdictions - October 29, 2019

Initial minutes of the October 29, 2019 Topical Oxygen Healing Wound Treatment CAC meeting in the San Francisco Union Square Hilton Yosemite A Ballroom were not captured in the audio file for this event. In that brief few minutes, Noridian's Wilfred Mamuya MD, PhD opened the meeting, introduced himself as the host/moderator, and asked the in-person CAC members participating in this event to introduce themselves. The in-person CAC members introducing themselves were Jay Mandrekar, PhD, Carla Perissinotto, MD, Rita A. Popat, PhD, MS, MSPT, Marissa J Carter, PhD, MA, MAPWCA, Rita F. Redberg, MD, MSc, FACC, Sunniva Zaratkiewicz, PhD, RN, CWCN and David M. Young, MD. All CAC members noted they did not have any conflicts of interest. From that point forward, the audio file was functional, and the transcript of the proceedings follows:

Wilfred Mamuya MD, PhD: . . .who are not with us today but are calling in, and they will be able to hear and also partake in the discussion. Um David and Roee, anybody want to go first?

Roee Gutman, PhD: Sure, I'm Roee Guttman. I'm Associate Professor of Biostatistics at Brown University.

Wilfred Mamuya MD, PhD: Any conflicts Roee?

Roee Gutman, PhD: No.

Wilfred Mamuya MD, PhD: Great. And David, are you on?

David W. Niebuhr, MD, MPH, MSc: Yes I am. Hello, this is David Niebuhr. I'm a physician at the Agency for Healthcare Research and Quality in Rockville, MD and I have no conflicts.

Wilfred Mamuya MD, PhD: Thank you both. And Rita?

Rita F. Redberg, MD, MSc, FACC: Good, thanks so much. So okay.

Okay, so what I thought we would do but certainly can be be flexible was just spend a few minutes because we've all gotten the literature reviews and I will assume that everyone has already read them. But I could just spend five minutes and honestly all I would do is sort of summarize the top line from what we were sent because I thought they were very good, and mostly because at the national meetings, as Carla knows, generally we start with an evidence review from an outside expert or the person, or the group in this case, who has done the evidence review. But we did get two pretty comprehensive evidence reviews, one that was included in the CMS Decision Memo and the other ones were from the ECRI which did two health technology assessments. So I'm not going to go through all of these details because everyone did get them at the time, but they are - they separated there, they being ECRI, their two evidence assessments into topical oxygen therapy for venous leg ulcers in the lower leg and they concluded that the evidence bar evidence is inconclusive because of too few data. And they separately did the topical oxygen therapy for pressure ulcers and again concluded that the evidence bar was inconclusive. And the CMS Evidence or Coverage Memo goes through

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in really a lot of detail and is very consistent with the ECRI conclusions basically that really that there is just not a lot of good data on this topic.

And I'll just say to summarize and this is reading from now page 19 of it that they found a total of six research studies, four randomized trials, two observational studies. All reported positive findings; however, significant issues were present in each study which reduced the overall quality and strength of evidence. A number of researchers have reported the challenges that are involved in the conduct of wound care research and the methodologic difficulties that lessen the strength of conclusions and they cite them. And they did cite all of those articles. And I'll just for example they said the studies have flaws, and of course I do spend a lot of time reading studies in my job as Journal Editor, and I have to agree with their assessment that these were very, had significant flaws that really limit interpretation or confidence in the findings in my opinion: lack of randomization for at least one category of topical oxygen; lack of effective blinding of patients, practitioners and assessors suggesting the potential for differential treatment of the intervention group versus the control group; dependence on use of incomplete wound healing as the only outcome measure because we try to have clinically significant outcome measures in trials; limited evidence or durability of wound healing. Obviously another concern is that you want something that lasts and that doesn't have just a short term effect; uncertainty about the standard of care being used in the reviewed studies. Any time you have a control, you have to know what it's being compared to and be sure it is standard of care. Lack of a defined run-in period to help eliminate fast healing wounds, so if something is going to get better on its own you don't want to attribute it to the therapy; small sample sizes and inappropriate statistical analyses. The Decision Memo is much longer than that and does go through each trial. And as I said, I did read it and felt that they - I would have come to the same conclusions. And then they just go through and give more details on the problems with the outcome measures, the problems with the study designs, allocation concealments, failure to blind, incomplete follow-up and small sample size, generalizability, not using or not describing what the standard of care was, not having run-in periods, etc. So did anyone have any other questions or comments on any of the materials or anything else? Because if not we can, I think, just start with the voting questions, except

(not understandable)

Marissa J. Carter, PhD, MA, MAPWCA: I found the Frykberg trial which is a very late addition to the literature we wanted to look at starting to shift the level of evidence in some key areas.

Rita F. Redberg, MD, MSc, FACC: And did you want to make any more comments on what you thought?

Marissa J. Carter, PhD, MA, MAPWCA: One of the interesting things about these particular studies is if you divide them by type of study in terms of continuous oxygen flow directly into the wound via a cannula as opposed to some device that's actually pressurized the oxygen a little bit over the wound you find that the effect size if you compute it is a little bit different. In other words, the devices and trials that were used slightly pressurized oxygen have probably a 50-60% effect size level over the ones that used just continuous oxygen level. And that suggests to me that one, devices that use a slightly pressurized oxygen level whether it's cyclical in nature or not may have an advantage. I think we need to do a lot more trials in that regard. But looking at the Frykberg trial data definitely seems to me that that latter where you use pressurized oxygen may give us a little bit of an advantage, may shift the evidence a little bit more to coverage.

Rita F. Redberg, MD, MSc, FACC: Okay, any other comments? Dr. Young?

David M. Young, MD: Just a quick procedural question. So it looked like two of the diabetic foot studies were the continuous oxygenation and then the third one, the Frykberg or Frykbeck was the pressurized. So in our - in this analysis are we comparing apples and apples or is it that - are all of these considered to be topical oxygen and therefore we have to lump them all together? Or do we have to look at them separately? Because to me they are two separate types of treatment.

Wilfred Mamuya MD, PhD: I'll be happy to respond to that. I think for the exercise today we are looking at all topical oxygen modalities as a group. I think when we think about coverage, we usually think about coverage of a particular modality and we don't so much delve into the subtle or sometimes major differences. Uh, an example is for example bypass surgery. You can use veins, you can use arteries from the chest wall, you can use radial arteries, you can use

anything. We just say bypass surgery is covered, and whatever is used at that point is, is a clinical decision. So I think I would look at it as a global topic.

Rita A. Popat, PhD, MS, MSPT: Okay. May I just add a quick comment? So thank you for asking that question because I think I had posed that question before and I think that's what also makes it a little bit complicated because it feels like the way the, the therapy is being delivered does vary depending on whether it's continuous or a topical pressurized thing. But I just wanted to point out that the recent paper that we, we were asked to review, the Frykberg paper, is very similar to the other paper that I thought was pretty good quality, which was the Niederauer paper. And I'm just going by their ITT analysis where it was very similar patient population, similar criteria was set to you know make sure that wounds that were going to heal were not included; they had the run-in period and so on. Um what was interesting is that both found effects. The reason you know I'm a little tempered in my enthusiasm or for the evidence is that it only addresses one of the outcomes, and that's a wound healing at you know twelve weeks, and it's a little less certain because some of the other metrics were not observed. But I do agree that these two studies ad hoc were a little better done with all the good features that you would expect to see in a randomized study.

Wilfred Mamuya MD, PhD: Great. Thank you, I was just reminded for everybody speaking please introduce yourself first because we have people on the phone who can't see who you are, and so they don't know who is talking.

Rita A. Popat, PhD, MS, MSPT: Go back in time three minutes, Rita Popat.

Wilfred Mamuya MD, PhD: Thank you, Rita.

Rita F. Redberg, MD, MSc, FACC: Okay, well thanks for those comments and certainly I do think at least that Niederauer study was included in the summary in the Decision Memo. And we'll leave it at that.

So I think I can read the first question, the voting question and discuss it.

Wilfred Mamuya MD, PhD: Use the clicker with the projector.

Rita F. Redberg, MD, MSc, FACC: Oh yes, that's a better one. And what we thought we would do is discuss all of the voting questions but then, and there are 7 of them, wait until the - after we've discussed all of them and then vote as a block.

Wilfred Mamuya MD, PhD: The green button not working?

Rita F. Redberg, MD, MSc, FACC: Well it's not working for me. Okay, why don't you do it? That works better.

Carola Perissinotto, MD:

Do you know if there is a Wi-Fi code?

(not transcribable)

Wilfred Mamuya MD, PhD: Yes. (not transcribable)

Rita F. Redberg, MD, MSc, FACC: Oh, now you got it to advance? Now it's working.

Wilfred Mamuya MD, PhD: One more, Rita, and you'll get to the first question.

Rita F. Redberg, MD, MSc, FACC: Oh yes, this was clarifying I think the question that was asked. All questions do refer to the use of topical oxygen therapy. So the Key Question 1 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 wounds compared to standard of care? And anyone? You know and I think actually Dr. Perissinotto, can you start this discussion and I'm just going to call on you randomly to start discussions and try to vary it.

Carola Perissinotto, MD: Yeah, so I'm actually I'm interested in this question just having read all the literature and the men in my care for older adults at home and in hospital settings. What's interesting to me is this idea of standard of care because in many of the articles the standard of care was variable. Um and in the sense that some of the, some of the articles compared the oxygen therapy to compression, standard compression dressings versus others had a placebo,

which I believe was just the placebo did nothing. That's a little bit surprising to me in my practice, I don't know if any if any of my patients with a wound in which I would do nothing. And so that made me question a little bit about the evidence. So the other thing I would say is again in my work as a geriatrician and palliative medicine physician the, the world of wound care is so challenging because I think we have challenges with diagnosis and identification of the correct ulcers and if they are the right type. I thought some of the studies actually did a good job of actually diagnosing and explaining that there are venous ulcers without an arterial component, which frankly, in many older adults, is a rare find since many have multiple issues. Um and the other part is that even in again standard of care who is providing that standard of care is variable and we see different outcomes. And I'll look forward to hear from my, from my nursing colleagues in the wound care world also because when you work for example with home care agencies and you ask for a wound care nurse that is interpreted quite variably. And it may be that the wound care nurse goes out for the initial assessment, and then it is an LVN that does that follow-up care that doesn't actually have specific training. That is also true of physicians that are signing the orders for wound care that don't know what they are doing. That's it. So I think that there is a lot of nuances here which make, I think, the research that we are reading very challenging and I applaud the authors for attempting to do this research, but it leaves me with a lot of questions.

Sunniva Zaratkiewicz, PhD, RN, CWCN: To the nursing, sure I'll just follow that. Thank you for that nice lead in. This is Sunniva, and one of the things that I found challenging in reading the literature was the clinical end points are varying, and that makes it challenging to compare apples to apples. The other, and this is partly tied into the endpoints is the follow-up care. I mean many of the wounds that you are treating are wounds that can be recurrent. And so I don't know from any of these studies whether we had anything long term, how did these patients do over time, which would be very interesting. And thank you for the plug for appropriate education and national certification in wound care. I don't think you meant it that way, but you are right. Uh the care that is being provided by nurses who are usually the individuals who are providing topical care can vary greatly depending upon their experience and their education. And so that is a factor that I did not see addressed in any of the studies as well.

Rita F. Redberg, MD, MSc, FACC: I will just add my anecdotal experience because my mother had chronic nonhealing leg ulcers for several years before she died recently and it was very different. Depending, you know she had home care and various doctors at various - she was cared for in New York City, but the care was very different and very I wouldn't say consistent and - yes, I think I saw another. Yes, yes? Dr, Cater.

Marissa J. Carter, PhD, MA, MAPWCA: It's instructive to sometimes look at the FDA perspective for clinical trial endpoints. Um I sit on one of the subcommittees that's been at it for about four or five years now. The FDA, going back to the 2007 Guidance document that they put out there, really got hung up on complete wound healing. And that's both a blessing and a curse. Yes, it's important to heal wounds but a lot of the things that we use in wound care treatments today are designed to kick-start the wound into healing to promote collagen synthesis to deal with the bio-burden and a lot of other issues. So complete wound healing isn't necessarily a good endpoint to choose for some of these trials. On the other hand, it is an ultimate goal of most patients, except perhaps even those in palliative care that we need to heal the wound. That said, what is the definition of complete wound healing? And if you look at the FDA it is I close the wound, it needs to be fully epithelialized without drainage, and I need to repeat that process two weeks later to see if that's still true. And most of these trials did not do that. Does it mean to say that that means it's a failure? No, it means they weren't paying attention for what the FDA said largely because most of these devices and the trials associated with them were passed on 510(k). In other words they had precedence, they didn't necessarily have to spend time with the FDA on their trial designs, hour dating them and maybe doing them a little bit differently. And duration is simply one of those things that the FDA believes in strongly, does what I do when I heal the wound actually last? And that in itself is a very complex question. If you actually follow patients for about a year you will find many of these patients, up to about 50%, actually have more than one wound. Sometimes these wounds overlap old wounds. So it's almost as though you need a GPS for wound healing on feet and legs to say is this the same wound? Is this a recurrent wound? But trying to merely answer the question what's durability like, what is the recurrence rate like is fraught with problems.

Rita F. Redberg, MD, MSc, FACC: Thanks, that certainly introduced a few other topics. I mean I will say I try to look at it from the patient perspective and I think from a patient's perspective complete wound healing certainly is what's important because that's what allows you to resume you know more activities of, of daily life. I mean the 510(k) process as you know is fraught with

problems; because of it can get things passed that didn't have evidence of benefit in the first place. And then you are like something else that didn't really have evidence of benefit, but the FDA does use different criteria than CMS does, which is reasonable and necessary for us in particular for Medicare beneficiaries healthcare. Sorry, Dr. Young?

David M. Young, MD: David Young. So it seems like the three best studies in this group are, are the randomized control trials and they are all three on diabetic foot ulcers. So I'd say the evidence is stronger there than the other two, but the question is chronic wounds. So given that you know in the wound clinic we see a third diabetic foot ulcers, a third venostasis ulcers and a third pressure ulcers, the evidence would be that two-thirds of the patients that we see in a wound care clinic don't fall under any of the studies here. But that doesn't detract from the fact that for that third of the diabetic foot ulcers that there seems to be fairly strong evidence here of some benefit. Um and those trials do show I think early closure as well as durability. I don't know, some of them do and not all of them, but so I guess a procedural question is are we answering this based upon all chronic wounds or are we answering this based upon just the diabetic foot ulcers?

Wilfred Mamuya MD, PhD: I think later on there is a question that allows you to kind of get to that by asking are there any special subpopulations you can identify? I think you'll get to that question later, David.

Carola Perissinotto, MD: Carla Perissinotto, I wanted to know if I could ask another procedural question. Having served on MEDCAC I am, I'd like to know if you can share when MEDCAC decides to push the decision onto the local jurisdictions rather than keep it at the national? Is that a common thing or variable?

Wilfred Mamuya MD, PhD: Uh it's variable but I would say most of the time it is um, it is rare. Of - in my time in Medicare this is the first time it's been pushed down to my level.

Rita A. Popat, PhD, MS, MSPT: I just wanted to add, you know I actually second what - so this is Rita Popat. I think in the two better done trials I agree that there is some support.

Rita F. Redberg, MD, MSc, FACC: Can you be, I'm sorry, specific on which trials you are talking about?

Rita A. Popat, PhD, MS, MSPT: So it's the Frykberg and the Niederauer study that was intention to treat. So I'm not going by that protocol and now this is on the interim ones which I think were the ones included in the original memo. But if you actually look at their um, the ITT results, it's very similar to the Frykberg study; and if it was just about, you know, wound healing at the twelve weeks, they both seem to have a similar sort of outcome. Um but I think the point that was raised was with venous ulcers or like pressure ulcers. I think now you are looking at an inpatient setting versus an outpatient, which also makes it a little bit hard to know. But maybe we'll get to that question when we discuss other, the specific populations where you think that this therapy might work, which is coming down the pike I guess.

Sunniva Zaratkiewicz, PhD, RN, CWCN: And then, this is Sunniva, I'm just going to add to that because we are on this topic and I think you, you can't separate arterial disease from diabetic ulcers, right? Because we know that over 50% of diabetic foot ulcers have an arterial component. So then we are also looking at what does that play into the healing success or not.

Rita F. Redberg, MD, MSc, FACC: Any other comments on this one? Okay, well why don't we go on. Okay, so Key Question 2 is How confident are you there is sufficient evidence to determine that adjunctive Total Oxygen Therapy shortens the time to complete wound closure of chronic nonhealing wounds compared to standard of care? Um let's see, Dr. Mandrekar, would you like to start that discussion?

Jay Mandrekar, PhD: My concern here with most of the studies is you know I could not see the comparison between any other studies. So each study had some unique problem that I started noticing. Some had some things done as inpatient but the control happens outpatient. Some of the sample sizes are small. So the first thing when I got the materials I thought you know why not just look at as aggregate and (not understandable). But not the same outcomes are measured in the same fashion, each study had something. So that's my whole problem with the entire evaluation process you know.

Rita F. Redberg, MD, MSc, FACC: Right, and I think that was also noted in the CMS Decision Memo, it was very difficult to compare as you said and even -

Jay Mandrekar, PhD: Even the time like you know is not -

Rita F. Redberg, MD, MSc, FACC: The time wasn't stated.

Jay Mandrekar, PhD: A recommendation that you know what is the definition of a complete wound healing, and of course I didn't know but if that is not done (not understandable).

Rita F. Redberg, MD, MSc, FACC: Right, and so the endpoints were different, the duration was different.

Jay Mandrekar, PhD: Patient sample is so inpatient, outpatient, that particular thing matters too within the study as well.

Rita F. Redberg, MD, MSc, FACC: Right, and then the control group, if there was one, was different because we didn't - the standard of care differed for each. So all of that, I think, limits the ability to make a good conclusion.

Rita A. Popat, PhD, MS, MSPT:

Yeah, yeah just to add concrete evidence. So again, if I just focus on the ones that I think are methodologically stronger, there was only one study, the Niederauer, that actually reported difference in the median time. It was 28 days in the CDO group, the Continuous Diffusion versus 40 days. But the recent Frykberg study, actually there wasn't even any median time reported; because if you look at the Kaplan-Meier curves you know they were much lower than the median. Like no one had even approached the median time. So there was no median time to report for healing in comparison for the two groups.

Rita F. Redberg, MD, MSc, FACC: Yes, Dr. Carter?

Marissa J. Carter, PhD, MA, MAPWCA: Um actually, I do want to point out that if you go look at the paper, there is actually a Cox Regression which is an adjusted time to heal. Um it's a little bit different in the sense of we are adjusting to baseline variables, but it is the same kind of thing. They just took it one step further than doing say a simple time to survival, which is a Kaplan-Meier analysis. And so I'm sorry to rain on your parade a little bit.

Rita A. Popat, PhD, MS, MSPT:

Actually I, I have no problem with the adjusted analysis and actually it's interesting, because it was a randomized study and uh, of course, it's not very large. So what ends up happening is that some baseline characteristics don't get balanced out appropriately between the two groups. And it turned out if you look at Table 1 of the characteristics in the Frykberg study there were, especially the severity of wound, the levels of severity were higher actually in the treatment arm compared to the sham arm which also had standard of care. So what would this do to the outcomes? Well it would make, it would make it harder to see a signal. So I think that was the impetus for doing the adjusted analysis, which is not a problem for me. Um so that wasn't the issue, it was just if you look to, to estimate the median time you need to hit the 50% mark and you don't see that in the curve so.

Marissa J. Carter, PhD, MA, MAPWCA: One other point that I should make is generally speaking if you do well on complete wound healing you will nearly always do as well on time to heal. That said, it depends also on your sweet spot. If you actually study trajectory analysis, and we've done this in so many wounds that we haven't published all the data, but particularly for wounds that are very hard to heal and there is some evidence in some of these particular studies that's true. If you look for example at some Bonita House study you know they did extensive percentage area reduction exclusion criteria in the two week run-in some would say in - instructively very harsh. In other words they really were vigilant in taking out easy to heal wounds. If you look at the wounds that actually did heal over twelve weeks, it's actually very small and it's, if you look at the vast wound care literature, it doesn't really matter what kind of wound you want to pick, those are absurdly low rates. Which would mean one of two things: either they really went to task too harshly, or the standard of care that was used for the various science wasn't very good. Um so generally time to heal will mirror. If it doesn't, it's because something very weird is usually going on in those trials. And this is Marissa, I'm sorry.

Rita F. Redberg, MD, MSc, FACC: And it's Rita Redberg. I did have some concerns about the Niederauer randomized study, because that was the one where the interim studies found no significant and beneficial - beneficial treatment effect in the active arm. And then they went on to do a series of post hoc analyses and stated that the subjects who failed the criteria were

removed from the study. And so that 146 subjects then were referred to either active or sham, but then 46 were dropped from the final analysis, the majority due to adverse events.
So the loss of almost a third of the study subjects in that where you were referring that you were saying you thought was the good quality study really lost my confidence in the quality of that study. You know, I do think you know there were unfortunately significant methodologic issues with every study that I read. Like and I see some nodding . Dr. Mandrekar, did you want to make any other comment? And then I hear someone on the phone, just one moment. Yes, please join us?

Roee Gutman, PhD: This is Roee. I saw the - I actually read the neuro (not understandable) actually three papers which are the same, the same one. The mid-point study did not show significance because of small sample size, not because they had any issues. They probably expected something, a larger difference but there was such a small sample size, so the differences then, it was pretty much consistent afterwards. So that I don't find that as a problem. Um the last study, yes, there were people that were dropped due to adverse events, but if you look at that, they are pretty much similar on both sides, both arms. And I couldn't see any reason for the differences to be because of the treatment, so that's not - again I don't think that that's like a problem. Um and I do see that there is - there obviously the study did find significant effect in the end. Um that's just like - I don't think that those are like things to like put down those, that specific study.

Rita F. Redberg, MD, MSc, FACC: Maybe one of the statisticians would comment because in my experience I do find small sample size to be a concern, and I find you know losing one third of the study subjects, the strength and quality. So Dr. Mandrekar, would
you comment?

Jay Mandrekar, PhD: Which are we talking about? The one where the 46 patients were dropped out?

Rita F. Redberg, MD, MSc, FACC: The Niederauer studies, yeah. I'm just pulling up the study results.

Rita A. Popat, PhD, MS, MSPT:

If I may, just add, sorry, one thing while you are pulling up the study result. You know I think what's interesting is the Niederauer paper there are three of them, so we have to be a little bit careful. The first one was the interim, analysis which was preplanned because they wanted to see when 50% or whatever, some percent of the recruitment is done which is often done in clinical trials. You, you know, may do interim looks and if you see a sign for efficacy you may say wow, you know it's unethical to hold back treatment. So that was a smaller but you know I almost ignored the interim analysis, and actually I don't care to see the first protocol either, because the, the fact that you want to make use of the randomization to control for confounding. So I pretty much focused on their 2018 paper by that group, and you know it had 146 patients. Now I could be wrong but I thought this was the ITT um, and again the only, you know the only reason I'm bringing it up is that the end point at twelve weeks is very similar to the Frykberg. So that's - you know there is nothing else that was compelling about this study because they didn't study any of the other outcomes that would make a case for does this actually work. But if you just look at the twelve week point the wound healing was 32% in the CDO group versus 17% in the sham.

Rita F. Redberg, MD, MSc, FACC: And did you want to comment on the time? Because actually the question that we are discussing is does it shorten time to complete wound closure?

Rita A. Popat, PhD, MS, MSPT:

Right, so there it was here, let's just see, I think they did compare it. So they have the median days to 75% closure is what they reported was 28 days in the CDO arm versus 40 days in the sham arm. And then only a very small number was followed up at 24 weeks and no difference was seen between the two groups in terms of recurrence of you know the, the wounds, the ulcers that had healed. There was, there was, you know, no difference between the two groups but I don't know exactly how many recurred, I didn't make a note of that. I think it was a very small number. So yeah, so in that you know they report the median days as 75% closure of 28 versus 40.

Rita F. Redberg, MD, MSc, FACC: I think that could lead us into the next question because it is related, which is how confident are you that there is sufficient evidence to determine that Total

Oxygen Therapy improves the durability of chronic nonhealing wound closure? That's not what I said, oh yes I said that. Thank you, thank you. Dr. Zaratkiewicz, would you like to start this, would you like to start this discussion?

Sunniva Zaratkiewicz, PhD, RN, CWCN: This is Sunniva, I was asked if I wanted to start the discussion. I feel like we've sort of been answering this same question since we sat down.

Rita F. Redberg, MD, MSc, FACC: Might as well get to it officially.

Sunniva Zaratkiewicz, PhD, RN, CWCN: And you know I don't feel that we necessarily have enough literature that suggests that that is rigorous, that is methodologically sound. Um but that would strictly be talking about the literature. And I think that there is more of course to any decision about healthcare than literature alone. I think I'll start it by leaving there.

Rita F. Redberg, MD, MSc, FACC: Well all right well that can stray off. Do you want to comment because of your experience on what you consider standard of care? Because of course, whenever you are right, whenever we consider something, we consider what are the - what are the alternatives, are there alternatives and you know?

Sunniva Zaratkiewicz, PhD, RN, CWCN: Yeah, sure. So what's interesting to me to read these, one of them is one thing I didn't mention when I introduced myself is that I practiced as a wound care nurse for some years and then went on to manage our wound ostomy limb preservation and amputation service at my facility for many years thereafter, and my clinical research and the work that I do on a national level is all around wound healing. So when I saw some of - well much of the literature doesn't talk about what standard of care is but some of the standard of care mentioned in some of the literature is not what would be standard of care if you looked at guidelines. Um there is one study, and I'm sorry I don't even remember the author of that study, where they talked about leaving a group of wounds open to air after the topical oxygen therapy was applied. And not only for an ulcer that is draining is that far beyond standard of care, it also poses some questions about overall care of that patient. Um if you are leaving a wound open to air when we know that that is very rarely a wise thing to do. Maybe in some circumstances where you have considerable arterial disease, that is appropriate, but when you are talking about you know in other words if there was a dry gangrene present that might be appropriate, but in most wounds and certainly sounded like the wounds they were addressing in that study that would not be appropriate. Uh so there certainly was wide variation when I read this, when I read these studies of standard of care in general, and then some studies that really don't mention at all what that is. So it just is incredibly challenging to make any kind of clear assessment of the evidence when we don't even really know what you are talking about in each study.

Rita F. Redberg, MD, MSc, FACC: Dr. Young?

David M. Young, MD: Yes. So, like I'm just, you know, picking through these articles are we are discussing these? Um the Frykberg does look at durability of healing. Um I think it's the strongest study of the three that we are talking about. Um and it does show that the wounds, more of the wounds in the active arm actually stay healed than in the sham treatment arm. So the answer is based upon one study at least that there is evidence of that.

Rita F. Redberg, MD, MSc, FACC: Dr. Niebuhr, we haven't heard from you, did you want to make a comment on this or any of the previous two questions? We appreciate you calling in.

David W. Niebuhr, MD, MPH, MSc: Hi, this is David Niebuhr.

Rita F. Redberg, MD, MSc, FACC: Oh great, thanks.

David W. Niebuhr, MD, MPH, MSc: You can hear me I assume.

Rita F. Redberg, MD, MSc, FACC: We can hear you now.

David W. Niebuhr, MD, MPH, MSc: Okay, sorry. Yeah, no, I was going to point to that same finding in Table 3 of the Frykberg. So we have a relatively good quality study that talks about durability. I'm sure that we don't want to discuss it at length but there was a non-controlled randomized comparison study that also showed durability, the Blackman study, really fraught with a lot of serious flaws in the study including the fact that patients selected their treatment. Um but just from the point of view of this Key Question and the durability issue, the follow-up period was 24 months for that study. Um so I think we have some suggestion that there was more than one study that shows durability as a TOT. Thank you.

Rita F. Redberg, MD, MSc, FACC: Thank you. Anyone? Dr. Popat?

Rita A. Popat, PhD, MS, MSPT: Hi, this is Rita Popat, sorry. I will speak less. But anyway I would agree with what Dr. Young just said that it's basically - I forget the name of the other Commissioner who just chimed in - but yeah basically the Frykberg study, the most well done study, showed some benefit - but there is only that one paper that actually assessed durability, and this was a twelve month, so at one year. But yeah the um, the problem with the observational study is that it's unblinded and so, you know, I'm not convinced whether that would necessarily add much to the case to be made for durability necessarily.

Rita F. Redberg, MD, MSc, FACC: Clearly that would be a limitation, and I believe there were not assessments of blinding even in the blind, there was one study that was blinded. I'm trying to think.

Rita A. Popat, PhD, MS, MSPT: I think the two better clinical trials were blinded, yeah.

David M. Young, MD: So I have a question, this is David Young, a question to the statisticians. Um so in reading the Frykberg study, the people who were assessing the wounds were blinded to the treatment but the patients actually weren't blinded to the treatment. So does that introduce a lot of doubt into the quality of the research? So they are supposed to be blinded, but if you read the technique, so I think they put their foot into a chamber and the chamber is pressurized and you have oxygen delivered in a pressurized setting. That's what I imagined reading the the study itself. But in the sham device they get a reading on the device showing the pressure but it's not pressurized, it's actually air, non-pressurized air. So I can imagine as a patient I would know whether or not I was receiving pressurized treatment or not. So even though it is technically blinded, meaning the patient doesn't know whether or not they are being treated with oxygen, but they can clearly feel the difference between the pressurized and the non-pressurized treatment. Um and I sort of read this paragraph over and over again and I can't sort of get around that.

Jay Mandrekar, PhD: I personally don't think the patient will get that. I worked on a completely different study, menopause and acupressure, you know using a toothpick and actually the people who were pricked at the wrong place improved. So there is a lot of placebo effect too.

Rita F. Redberg, MD, MSc, FACC: That's a different question than whether they knew what their treatment was. I mean the blinding was different.

Jay Mandrekar, PhD: Just by - just it's hard for a patient. I mean if you are, if you are creating a setup that looks like something is being done to them, it's hard for them to guess that, because I would not know what the pressure it feels like. So once you put my foot in there and it's zero and starts going to say 30 or whatever, they think you must be doing it.

Rita F. Redberg, MD, MSc, FACC: Well my experience in drug studies you know when the placebo doesn't have the same tingling or whatever patients know which, which they got randomized to. I mean they seem pretty on top of it to me.

Marissa J. Carter, PhD, MA, MAPWCA: Um this is Marissa Carter.

Rita F. Redberg, MD, MSc, FACC: But anyway I mean you can do an assessment of blinding, sorry I am interrupting you . And I don't believe that was done in that study or in any of the studies. And that is always the most reassuring to me is if they actually do the assessment of blinding like was done in ORBIT, one of my favorite studies. Dr. Carter?

Marissa J. Carter, PhD, MA, MAPWCA: Um so a good analogy would be hyperbaric oxygen where we spent a lot of time trying to figure out in sham therapies in pressurized different atmospheres and so on do patients really notice different ways of doing things? Most certainly they do. However, the issue here is the difference between slight pressurization like 1.06 bars versus 1 bar can patients tell the difference between that? I doubt it.

Rita A. Popat, PhD, MS, MSPT: I had a quick comment here. Uh going back to the actual methodological question right, let's say even if the patient were to guess that I'm on placebo, I think the most important question to ask is well how does this influence the results, right, the lack of blinding? And here so what would help us understand is what is the outcome we are measuring, right? Or will the patient behavior change if they know they are on placebo? So if we believe that yes, the patient is unblinded, they can, they know, if you just look at the outcome being measured it's unlikely to be influenced by them just knowing that they are on placebo right? So unless you think that it's going to change the behavior and they are going to start

taking better care of their wound because they know they are on placebo? So if it's the latter where they actually believe I'm on placebo, I better take good care of my wound, I'm going to be non-weight bearing and so on, and take all of these precautions, what would that do? Well that would make the closure rates look better and come closer to the treatment arm. So the fact that we still see a signal would suggest that even if the lack of blinding improved the outcomes in the control arm, it remains that we do see a difference. So we still picked up a signal. Does that help address? Like this is how I tease apart the influence of lack of blinding on what is the outcome and how would this change patient behavior, and what impact would it have on the difference in the metrics that I'm observing between the two arms?

Rita F. Redberg, MD, MSc, FACC: Then of course we should distinguish patient blinding from operator blinding, from measurement blinding, and how the outcomes were determined because those are all important and separate issues.

Carola Perissinotto, MD: And then there is the -

David M. Young, MD: No, no, thank you for that clarification.

Carola Perissinotto, MD: Carla Perissinotto. And then there is the anecdotal even with placebos the amount or random things that patients do to their wounds when you are not looking. It's true. I mean honestly it's very interesting in terms of additional topical things, but that's something that you would assume would just be random but maybe in groups that may be perceived to not have any treatment.

Rita F. Redberg, MD, MSc, FACC: Did you want to make any further comments on what patients might do to their wounds?

Carola Perissinotto, MD: Uh no, just it's just very interesting because I think that you know bringing it back to the patient, wounds are incredibly distressing both to patients and family members. Um and I think that if there is a perceived lack of progression and improvement, I think people take it upon themselves to do different things whether it's getting, using different cream from other things, using antibiotic treatments, putting them out to air is a huge thing. I think there is a lot of concern that I've had, again anecdotally in my practice, but from quite a few patients with wounds, that the idea of something compressed and on the wound just does not seem natural to many people, and so there is this desire to want to expose it to get air for healing. So you know how this impacts specific studies I think there are unknowns, so maybe more relevance in groups more than others in standard care.

Rita F. Redberg, MD, MSc, FACC: Any other? Dr. Mandrekar, did you have any other comments? I think everyone (not understandable). Any comments from either of you on the phone? I guess Dr. Niebuhr we heard from you. Dr. Gutman did you want to make a comment?

Roee Gutman, PhD: No, I think, I think all that was said is correct. Uh the only thing I had is that I think that in that specific case there is only one study which is relatively small for the durability part. It seems significant, but it's certainly not its strongest status. Uh, it's not repeated at least.

Rita F. Redberg, MD, MSc, FACC: Okay, thank you. All right. Well I would say that we've gotten through or we've discussed the first three questions, and we could take a 15 minute break. I think the bathrooms are out, right out there, and then we'll reconvene at 3:15, so a twelve minute break that would be. Uh 3:15 or I guess 6:15 for those of you on the phone and we'll be able to finish discussing the next four questions and do our scoring. Thank you.

(break)

Rita F. Redberg, MD, MSc, FACC: All right. Um thanks. We'll welcome everyone back in the room, and hopefully Dr. Niebuhr and Dr. Gutman are back on the phone with us. And I think we'll resume sort of our discussion. Of course there is some overlap but we'll try to address specifically each question because at the end of this discussion we will vote separately on each question. So the next question is Key Question 4, which is How confident are you that the available evidence for Topical Oxygen Therapy in chronic, nonhealing wounds allows identification of a discrete population of Medicare-eligible beneficiaries who would benefit from Topical Oxygen Therapy? And, of course, then generally we are talking about people over 65 years old, and so the question would be how many of the studies addressed specifically people that are over 65 years old in their analyses? And Dr. Carter would you like to lead off?

Marissa J. Carter, PhD, MA, MAPWCA: Um to provide a little bit of an introduction into this um, when we look at randomized control trials everybody always says, well that's such a

narrowly defined population, you know what is the generalizability of outcomes from an RCT to real world? And we did some landmark studies a long time ago, and one of the shocking things is that only about 90% of wound care trials, the randomized control trials, are actually generalizable at all. And so one of the things I think of interest here is even though some of these randomized control trials that use TOT look very promising, are they actually manageable in terms of generalizability to the Medicare population? And the answer is not really. And I think, I forget who pointed out the fact that when we look at chronic wounds, diabetic foot ulcers, venous leg ulcers and pressure ulcers only constitute about half those kind of wounds. It's almost like we have a whole bunch of wounds that are wound with no name, we don't even talk about them, and very rarely in this country do we ever actually use any interventions of any kind to heal those wounds. And we can blame the FDA for that, because the FDA was the one that decided all wounds are not equal. They have very different mechanisms, and you guys get to do different trials in different types of wounds. If we had taken the European approach perhaps we would have done a little better. So to finish up on this incredibly complex topic, I think not that many Medicare patients will be eligible even if we assume these kinds of really trials work.

Rita F. Redberg, MD, MSc, FACC: Right, and thank you. And certainly the FDA definitions are one issue, and then, certainly for Medicare, our question is how many people were over 65 and how does their results look in those trials? Um the challenge is always, I think, in the Medicare population, and I think one of my studies like 20 years ago or maybe a little less than that but with a UCSF medical student, you know, on our faculty, Sanket Dhruva , but the question we looked at then was how closely do clinical trials reflect the Medicare population? And we specifically looked at the clinical trials that are used for national coverage decisions. So we pulled out all of the national coverage decisions and then pulled out the trials and, unfortunately, but not probably surprisingly for those of you who have looked at the field the trials, were very different than the Medicare population. They tended to be much younger, much whiter, much more male. You remember Medicare is a mostly female population, about 53% Medicare beneficiaries, 4% are women. And had many less comorbidities than, you know often they were excluded if they had renal disease or other kind of impairments that we don't exclude in our clinical practice. And so our conclusion in that study, and it was a while ago, but having followed the literature, despite a lot of efforts you know, from a lot of people, I think unfortunately we still don't see clinical trial populations that really reflect the diversity in race, ethnicity and gender of the Medicare population, certainly not the age because of upper age limits or because of the exclusions for comorbidities in the population. And I would, you know, say that this literature suffered from those same limitations as not offering a lot of information on specifically over 65. Um did you want to make a comment? Sure.

Sunniva Zaratkiewicz, PhD, RN, CWCN: Only that I would agree with what you just said. This is Sunniva. Uh and I think that's true in all of the literature, really, around wound healing is when we were, actually Marissa and I were just talking about this at the break, that the fact, the way that we waive variables and the exclusion criteria often means we create these sort of special demographics, these special groups of patients that are not generalizable.

David M. Young, MD: Um the - oh I'm sorry David Young. The only, again going back to the three papers that are dealing with the diabetic foot ulcers in a randomized clinical trial, the one paper that actually did not show a beneficial effect of decayed oxygen was the Driver, the Driver Reyzelman. However they did do a subanalysis of greater than 65 years of age, that patient population. It's the only study I think that actually breaks out the data that way. And there appears to be - and it's a small number of, it's is a small subset obviously of the larger group um, but it does appear that there was a slight beneficial effect to the oxygen treatment. So the one study that actually shows no effect as a whole study shows some moderate effects with the aged population. In the other two studies you can't make any generalizations, because they don't break out any subgroups.

Rita F. Redberg, MD, MSc, FACC: Dr. Perissinotto?

Carola Perissinotto, MD: Yeah, this is Carla Perissinotto. So a couple of questions came up to me, for me about this. One was in some of the exclusion criteria. There was one study, it was one of the smaller ones, and I'm trying to remember which one it was where they specifically excluded homebound or bedbound patients, and I thought that was an interesting exclusion criteria. I happen to be sensitive to it since that's a good portion of who I take care of, so I thought that was interesting, again, thinking about generalizability and what population we are targeting. The other thing that I was thinking about, and again getting back to this idea that in much of our research we exclude older adults or also don't account for multi-morbidity,

polypharmacy, life expectancy and goals. And so things that came out for me, and maybe this also some more questions for my colleagues with better expertise in wound care than I have is, without really understanding drug regimens, like do we know how many people were on antiplatelet agents or other anticoagulants which may have an effect or may not have an effect on people that have coexisting arterial disease? And did that, does that introduce any bias or differences in wound healing? Um so yeah, so I think still a lot more questions than I have answers.

Rita F. Redberg, MD, MSc, FACC: Does anyone specifically want to answer that question?

Sunniva Zaratkiewicz, PhD, RN, CWCN: I would just - well two things. One is I also think Driver is the individual who is the primary or at least one of the authors on the FDA Clinical End Points Trial for Wound Healing, so the same author as the study you are referring to. And this is Sunniva. But thank you for bringing up goals, because oftentimes when we look at wound healing, those of us who are on the clinician end are thinking about wound closure, and we forget that patients may not be looking for wound closure. And if we don't have that conversation and we don't get on the same page, we may not be doing our patients a benefit. Many times a patient who is living with a chronic wound may be simply looking to do something that allows them to interact with their grandkids, makes the smell go away, brings the drainage down; but they may not want to have a compression dressing on. It may decrease their quality of life such that they are not interested in that care. And so, unless we are on the same page with goals, we are doing our patients a significant disservice no matter what our clinical endpoints are.

Rita F. Redberg, MD, MSc, FACC: And the Driver study had 17 patients and you are saying that they - you thought the subgroup that was, oh and it was ages 18 to 90.

David M. Young, MD: I was reading

Rita F. Redberg, MD, MSc, FACC: So I'm not seeing that that could be a very big,

David M. Young, MD: No, it's tiny

Rita F. Redberg, MD, MSc, FACC: I mean 17 patients is already on the smaller side.

Rita A. Popat, PhD, MS, MSPT: The larger study had more patients. So the study -

Rita F. Redberg, MD, MSc, FACC: This was the Driver study.

Rita A. Popat, PhD, MS, MSPT: The 2017 had 65 in the sham - in the treatment, and 63 in the sham. So there are two papers by Driver, the 2013 is the smaller one, but then the larger one is

David M. Young, MD: 2017

Rita A. Popat, PhD, MS, MSPT: yeah, I think that's the one that you, Dr. Young is referring to.

David M. Young, MD: Yeah, so it's randomized blinded (not understandable ..continuous oxygen. Driver (not understandable). The one that we just got just recently in the emails.

Rita A. Popat, PhD, MS, MSPT: That was the Frykberg. But if I may just add - this is Rita Popat. So you know, if we ask ourselves how will we ever be able to evaluate whether it's the right, you know, does this therapy work in 65 and greater right, the Medicare population? There are two ways of looking at it. One is to look at okay, well this is patient population captured in these two, at least, well-done trials, and if you look at the age and standard deviation, you would say yeah, I mean this population is covered. But that's not really answering the question of is the efficacy, you know, good, is it just as good in this population? So how would we actually answer that question? Well for that we would have to do a subgroup analysis. And in order to be able to conclusively say that it works in this group, we would need to - these studies would have to stratify the randomization by age. None of these studies did that. It's - I think it's difficult to have them do that, given the size of these studies. Once you start stratifying, you lose your sample size and your power. Um so I don't think any of these studies conclusively tell us that whether the efficacy of these interventions of topical oxygen does you know vary in this population, all we can say is that they are included as part. And I think the Driver study, although the subgroup showed some beneficial effect, it's probably confounded because they didn't stratify the randomization.

Rita F. Redberg, MD, MSc, FACC: And I would say in terms of the generalizability, because now I did find the 2017 study they comment, this was a Phase II study, and because of that, their inclusion and exclusion criteria were designed to exclude any patients with comorbidities, which this criteria made recruitment difficult um, and it was difficult to find patients over 65 years old without kidney or vascular issues. So it really does, I think, in my opinion, that would limit the generalizability. So in our Medicare population where we don't, you know, restrict comorbidities, we treat all of our beneficiaries of course um, and most of them do have comorbidities particularly when they have wound, yeah wounds.

Marissa J. Carter, PhD, MA, MAPWCA: Um this is Marissa Carter. Actually the 2017 Driver trial was randomized, stratified by wound date and patient age.

Rita A. Popat, PhD, MS, MSPT: Oh it was stratified?

Marissa J. Carter, PhD, MA, MAPWCA: Yeah, no, the issue, really, there, is when you do subgroup analysis, your subgroup must be powered adequately, statistically speaking, and it's always going to be a smaller power than your main power for your primary endpoint. And so, any time you start fishing with I haven't done my prespecified endpoints in my statistical analysis plan, that's a post hoc thing, and you should take that with a little bit of grain of salt. Um one of the things we have not talked about is adjustment for multiplicity of statistical testing, and the best example I can give you is, if I look at trial and I really just don't know a lot about it, I start testing everything in sight, sooner or later I'm going to hit the jackpot. And the reason being is, the more you test for something, the more you are likely to find it. Um if you go down that road, what you actually do is inflating what we call a type I statistical error, and there are at least three; but the two, the really important ones are finding something that really isn't there, that's a type I, and failing to find something that is there, which is a type II. Type I to statisticians, and perhaps some of my colleagues can confirm this, is an egregious error. So one of the things we need to do in trial design is spend a lot of time trying to figure out, is how do we figure out when we are testing groups of different types of endpoints or different things that we are interested in to adjust to this testing. And in subgroup analysis in most of the trials that we are talking about here, nobody did that. Um even if you look at the Niederauer or the Frykberg trial where they did an awful lot of different testing, we need to probably adjust for a lot of those P values and some of those have become nonsignificant. You know I am generally from the school that P values are not the be all and end all of things just because it crosses some magic line to .049 doesn't mean to say suddenly you are into a brilliant magical land where everything is beautiful. You know solid work means that you need to convince me that you have some extraordinary big differences where you are talking perhaps statistical power of at least 90%, 92, 95%, and then you get those very, very small P values. So just because you get a little statistical doesn't mean to say it's anything by itself. Certainly promising, certainly in the right direction but that's it. It's not the end.

Rita F. Redberg, MD, MSc, FACC: Um thank you. To clarify, and I appreciate the points on subgroups and that there certainly are a lot of limitations to subgroup analysis, the point I was making was on generalizability which we were trying to assess, and what I was saying is that it's not just that there were a very small number of people over, well the trial was small itself, it was only 65 people but the number over 65 were small. And those that were in that were over 65 were chosen because they did not have any comorbidities; so in my reading, that is not generalizable to a Medicare population. And I don't really think we can, you know use that trial to make any kind of conclusion on how this would work in our Medicare beneficiaries, because we don't exclude people with comorbidities and most of the population with wound ulcers, and they say that in the trial they had a very hard time finding people over 65 with that inclusion criteria. So to me that would not help me in answering this question, is there sufficient evidence in the Medicare beneficiary population, because the Medicare beneficiary population has comorbidities and this trial had a very small number of people over 65 who did not have comorbidities, and none that did because that was an exclusion criteria. Did anyone have - oh Dr. Niebuhr, did you want to make any comment?

Roee Gutman, PhD: No, this is Dr. Gutman. Um so the only question if you think that, again I'm not a physician, but if you think that those comorbid - that the oxygen will work differently because some people have comorbidities then this is a question. Again I'm not a medical doctor so I don't know how those things work, but many times, right, like these drugs, or drugs are given because we know that their chemical mechanism is going to work no matter what, and we don't worry so much about the actual (not understandable). I don't know how much (not understandable) states this oxygen is, so it really, really depends on how much on a practical medical knowledge.

Rita F. Redberg, MD, MSc, FACC: Right. Well certainly the presence of comorbidities is going to slow wound healing so it would certainly affect the process unfortunately. Dr. Mandrekar, did you want to make any comments on this question? Dr. Niebuhr, did you want to make any comments? I don't want you to feel not in the discussion because we can't see you both.

David W. Niebuhr, MD, MPH, MSc: Yeah, this is David Niebuhr. Can you hear me?

Rita F. Redberg, MD, MSc, FACC: Yes, we hear you.

David W. Niebuhr, MD, MPH, MSc: Yeah, I guess I maybe read this question differently than everyone else, but when I read it as a discreet population of Medicare eligible beneficiaries I wasn't thinking of the entire population of Medicare eligible beneficiaries, but like I thought the question was asking is there a subpopulation of Medicare eligible beneficiaries. And so my thought was well, there is a sense of signal for effectiveness for the diabetic foot ulcer Medicare eligible beneficiaries. But this is my first CAC so maybe I'm interpreting the question incorrectly. I'm interested in what you think of that.

Rita F. Redberg, MD, MSc, FACC: And what were you basing that feeling on?

David W. Niebuhr, MD, MPH, MSc: Well it says discreet population of Medicare eligible beneficiaries and I guess you know I probably read it as a discreet sample or a subpopulation of Medicare eligible beneficiaries. And maybe, you know, obviously we're talking about Medicare eligible beneficiaries with chronic wounds but the discreet subpopulation that it might be effective for and we have evidence for, at least at this point, are the diabetic foot ulcer patients. So that's how I - but I'm new to this game, and so if I'm missing, if I'm approaching the question incorrectly I'd appreciate someone let me know.

Rita F. Redberg, MD, MSc, FACC: I guess I interpreted discreet population to mean the population with wound ulcers, but - yes?

Rita A. Popat, PhD, MS, MSPT: Yeah. This is Rita Popat. I actually agree, and I had also interpreted like I could have gone either way. So I was aware that Medicare population is above 65 so that was a key consideration. But in terms of identifying a subgroup specifically that would benefit from the topical oxygen if you again look at the two or three well done trials they all had very similar criteria. They were diabetics, they had to have, you know, a chronic wound present greater than four weeks but less than one year. They all had to measure size 1.5 to about less than 10 cm squared. So in terms of that subgroup I'm wondering whether that was the comment that was just made. There is a subgroup that appears in sort of two or three of these trials, but I agree that now that we've had the discussion, that maybe what we are going after is the age, and you know those types of things.

Sunniva Zaratkiewicz, PhD, RN, CWCN: This is Sunniva. I just saw the discreet subgroup as the descriptors above, the nonhealing wounds, so that population with chronic nonhealing wounds. And I think we just see more literature in the FU patients, but that's how I read that.

Marissa J. Carter, PhD, MA, MAPWCA: Um a quick comment on that diabetic foot ulcers. So if you go look at the inclusion and exclusion criteria you can actually work through some calculations here. If I had 100 patients walk into my clinic tomorrow, I would say about 30 of those will have a Wagner 1 you know, and you all know that's just a superficial thickness ulcer. Then another 30% or 35% will have Wagner 2s; you know, those are much deeper going to bone and the rest of them will have degrees of infection. And Wagner is not a particularly good classification, it's just one of those things that we have to use. So when we go back and look at the studies that we've been asked to look at, you could probably say only 25% of those patients are going to be eligible for this kind of intervention because their wounds mostly are just too severe. That's one way of looking at them. And yet I totally agree with Dr. Redberg, is when you start discounting all of those nasty comorbidities, because we really don't know how those are affected by an intervention, you narrate it down even more. We did some calculations to show that in these kinds of trials maybe 5% of all Medicare beneficiaries would benefit. So it's one of those things, it is mathematically computable but the results mostly for most of these trials would be a little bit sad.

Rita F. Redberg, MD, MSc, FACC: Yes, I think, thank you for that point Dr. Carter. It really gets to the bigger issue of why we have so many inclusion and exclusion criteria for trials, you know, and sometimes it's done to make them faster and cheaper, which, you know, because you don't - but it makes, I think, it makes the results a lot harder to generalize to our population where we don't have those inclusions and exclusions. And, you know, then to assume that, and I'm

talking now in general and not just for topical oxygen therapy, that the treatment would perform the same in this very carefully selected population, as you noted maybe 5% or less of Medicare beneficiaries in this case. It's not really reasonable because the population doesn't reflect it, and in particular you know we tend to see younger, healthier more men and a more white population in clinical trials than we do in our offices and in the Medicare beneficiary population. And, you know, I think that's a separate issue, but I do think and I know there are groups, and I've talked with the FDA about having more requirements in drug and device trials. So that's a population study that would actually reflect the population that's intentioned, that the treatment was intended for because otherwise you get into all kinds of problems and we twist ourselves in ways that I think we pay for it later by not knowing what things really will work and help our patients the most, which brings us to the next question.

So Question number 5 is How confident are you that there are no significant gaps in evidence that may impact positive health outcomes in the Medicare eligible population? Dr. Young, would you like to start off this discussion?

David M. Young, MD: You are putting me on the spot here, but I'll take the challenge.

Rita F. Redberg, MD, MSc, FACC: I knew you were up to it.

David M. Young, MD: Yeah, I think we are just sort of grinding through. I mean all of the not - so there really are just the three trials that um, that are I think everyone is discussing over and over again. The rest of the evidence is very, very weak. So just to recapitu - review them, there are the two, and all three are about diabetic foot ulcers, and two show a positive result and one shows a negative result. Um and these are very specific criteria burden trials, and we don't even know whether or not they actually are in the age 65 and older, and how much applicability there is to that. And put on top of that that when you have this label, I think what the the person over the phone was talking about, when you put in the label that these are chronic wounds, and the studies for pressure ulcers and venous leg ulcers which are the other two common chronic wounds don't have positive clinical trial data for this therapy, then I'd say that the vast majority of the evidence is very sketchy in terms of if you have the full label of chronic wounds, that we don't have good data that this treatment is good for chronic wounds, because again, a large number of the chronic wounds that we deal with aren't even studied in this. Well they are studied, but they will have positive clinical trial data. So I'll leave it at that.

Rita F. Redberg, MD, MSc, FACC: Thank you. Well that was very helpful and illuminating and I'll go down the line with you. Thank you.

Sunniva Zaratkiewicz, PhD, RN, CWCN: Well I unfortunately think there are rather massive significant gaps in the literature. Um and not only the things that David just pointed out but I would also say, even in the endpoints, it would be very helpful to look at quality of life from the patient's perspective when we are looking at wound closure. You know, we are really missing an incredibly important, maybe the most important element which is the patient's quality of life.

Rita F. Redberg, MD, MSc, FACC: Actually thank you, that's a really important point. And you know, we do talk a little bit more, I think, these days than we used to about patient reported outcomes, but you know, to me, that is certainly the most important in our Medicare beneficiary population. I mean, very occasionally, we'll talk about things that save lives, but those are very occasionally. But more often, and if we are not, I think that we need to really be, talking about things that improve the quality of life. And for wound healing, that seems like a quite applicable and relevant endpoint. I didn't see it in these trials because that's the whole thing about wound healing, is its negative impact on your quality of life about wound ulcers. Its negative impact on your quality of life, and so anything that had a benefit on wound healing should also have a benefit on quality of life, but I think that is the, that's what matters to patients. And that is what we should be asking about, but in my recollection, I didn't see any quality of life data in any of those studies that we reviewed. And joining in, so Dr. Carter?

Marissa J. Carter, PhD, MA, MAPWCA: So the only wound quality of life here is the Q-TWIST which was done in one of these cohort trials, and unfortunately, that's one of the trials that has massive bias problems. The other real issue is why don't we do, in these kinds of trials, more quality of life things, and that's really back to the FDA. Um one of the things that the FDA is going to do in the next few months based on our recommendations is to include a lot more endpoints in clinical trials, and quality of life is going to be one of them. The other big problem is we've put in quality of life in a lot of wound care trials in the last ten years but quite often it doesn't work. And everybody asks why not? And the problem is exactly what Dr. Redberg has been talking about, and that is these are sick patients; they have lots of very serious

comorbidities. Okay, so I healed one of your wounds today, do you think that's really going to change your quality of life that much? You know, and quality of life is analogous to utility where you look at a scale from 0, death, to 1, in perfect health. So nudged you from .55 to .54, that's not going to make enough of a difference, sadly.

Rita F. Redberg, MD, MSc, FACC: Sadly, yes. And I think, and as someone said before, not even if you didn't even have comorbidities, just because people often have multiple wound ulcers or one heals and another one starts, because the underlying processes are still going on.

Sunniva Zaratkiewicz, PhD, RN, CWCN: While I do agree with and appreciate what you just shared, Marissa, I think there is an element there that can be captured and certainly anecdotally as someone who has worked with patients for a number of years with chronic wounds, you can have very salient measures around the amount of drainage someone has, the amount of pain someone has, odor associated with that that can considerably change their ability to interact with their family and friends, to go out into public, to engage in things that are meaningful to them. So while it might not change certain things like maybe it won't change a pain level, maybe it won't change the amount of time that they are going to their physician and all of the struggle it takes to get there, it may make some meaningful changes. And men, of course you are looking at a lot of qualitative research, which is much harder, much longer to achieve, but I think we - it could give us information that we will never receive when we are looking simply at measurements of a wound.

Rita F. Redberg, MD, MSc, FACC: So I hear that as an argument for quality of life measures as endpoints in trials.

Sunniva Zaratkiewicz, PhD, RN, CWCN: Absolutely.

Rita F. Redberg, MD, MSc, FACC: And yeah, I agree because I think we have to do what's important to patients. And I mean otherwise we are just not really treating ourselves, but not the patients if we are getting measures that we can measure, but they are not clinically meaningful or important. Dr. Popat?

Rita A. Popat, PhD, MS, MSPT: Yeah, I just - yeah, this is Rita. So I just wanted to add, just for sake of completion here, that the Frykberg paper is the only one that actually does report quality of life. And they noticed I don't know whether they were just cherry picking, because you know these are sort of validated quality of life instruments that people use in studies. And they report an improvement on wellbeing component where they looked at the change from baseline to twelve weeks in the treatment and the the sham arm. And there was a 9.1 difference in you know improvement in one arm compared to 20.1 or something. So that was the only paper that actually addressed any of the quality of life. But I'm optimistic that as even moving forward it appears that researchers are taking that into account, and maybe more studies will come out that will incorporate this.

Rita F. Redberg, MD, MSc, FACC: And certainly if the FDA signals it, that would be a criteria for, you know, getting on the market. It would change things.

Jay Mandrekar, PhD: I just had a question, like, you know, Marissa mentioned, like, the improving slightly. So should the quality of life question be phrased regarding the wound specific to the question?

Marissa J. Carter, PhD, MA, MAPWCA: So there are a number of quality of life instruments that have been developed specific for the wound, you know. And I think back many years ago there were a lot of studies that said which one is best, and, you know (not understandable), which is the one actually that's in the Frykberg, a (not understandable) wound instrument scale, you know, that's the one that was used. Now the wound quality of life which is based on Dr. Mathias' work in Germany is eclipsing, that you know, and it's got some better statistics. But the real problem is do you use a wound related quality of life or do you use something like the EQ-5D which is more of a global health instrument? And that's a dilemma I don't think we have solved. You can do both; you know what you typically find, and I hope we would find is if you use something like (not understandable) or W-QoL, you would see a meaningful shift, and we quite often do. Which means that yes, it goes back to exactly what's been said very recently. But as far as global health is concerned it doesn't shift anything at all.

Carola Perissinotto, MD: Dr. Carter, just a follow-up question, this is Carla Perissinotto. Do you know in the quality of life is there anything around burden of treatment? There is some that's written about just in geriatric literature in terms of how much are we expecting patients and

families to do, because in some ways if you have, if you have some comparative treatments, I mean I frankly rather would do something that's put oxygen on my leg than have a compression device, but that's my personal preference. I'm wondering just because of the setup and the device if there is anything that's really better?

Marissa J. Carter, PhD, MA, MAPWCA: I think there is one or two questions in QOLs about the two we just mentioned, this is Marissa Carter again. It has something to do with the burden of my wound, you know, and it's described in different ways. It's not standardized accordingly, but it's another way of saying I just spend so much time taking care of my wound doing this and that that it's a pain to me, you know, a different kind of pain than just plain pain.

Rita F. Redberg, MD, MSc, FACC: Right. Thank you actually for raising that, Dr. Perissinotto, because that is an important point. And we are talking often about people with - who have very limited mobility and as you said just getting to the doctor or getting to the healthcare provider's office is going to take the whole day or most of the day, and is just something to factor in. So the convenience of the treatment and what are we trading off for the treatment you know, particularly as I said in people with limited years left, you want to sort of balance that burden of improvement in the time you have and how much time you spend having to go to doctors to achieve the improvement or go wherever, clinics or other offices. And did you want to make any other comments since we are going down the line? So we are to Dr. Mandrekar on this?

Jay Mandrekar, PhD: So how would you, how would you, let's say if you wanted to add the quality of life how would you, the CWI is the question I think you mentioned?

Rita F. Redberg, MD, MSc, FACC: Right, and I think that is an interesting point so around the wound specific quality of life versus, you know, a quality of life because it is certainly harder to make impact on overall quality of life, particularly in someone with comorbidities, but then you know how much - you know, I always try to think what would you want? You know how? Do you want your wounds to be better, do you want to overall feel, you know, better, and being able to get out and I don't know. I have to say when I was - not when I was Chair but back like fifteen years ago actually, when I was at a MEDCAC meeting on the drop from age related macular degeneration, and the only thing they were looking at were lines on a Snellen Chart, you know, for vision? And yet watching everyone who was coming to speak, everyone, every person, because the public come to the MEDCAC meetings and can speak, had to be helped to the, up to the podium, because they had such limited vision. And when I asked did they have questions, like, well, can you, were you able to go do your grocery shopping or read the newspaper or drive? And there were no answers for any of those and I felt like those were a lot more meaningful to patients than lines on a Snellen Chart. And it just somehow that reminded me, but it's important for us to try to relate I think the wound healing measures to the at least wound related quality of life, and then overall quality of life. Which brings us to Question 6, which is How confident are you that Topical Oxygen Therapy is generally accepted by the medical community for the treatment of chronic nonhealing wounds? And now I am going to pick on you again, Dr. Young, because you are the plastic surgeon in here, and I think maybe you are in the best position to.

David M. Young, MD: Yeah, so, just this is totally from my own perspective in practicing medicine. Um certainly we know that the hyperbaric oxygen treatment, the chamber based treatment, has wide acceptance including multiple stationary clinics throughout the country. You know every major metropolitan area has one; but I personally do not know anyone who is actually using topical oxygen treatment myself. Um that's not to say that if, if the data were good and there was good marketing and good financial risks, I mean on the part of the patients and the clinics to do so, that it wouldn't have traction. But so far I've not heard of it.

Rita F. Redberg, MD, MSc, FACC: Thank you, that's very helpful. Dr. Zaratkiewicz?

Sunniva Zaratkiewicz, PhD, RN, CWCN: Thank you for saying my name, unusual and I appreciate it. Um so similarly, I mean, I teach in the Wound Management Education Program at the University of Washington, and of course, these are things we cover. We talk about it, that it's part of clinical practice, but I also know no one clinically in my region, or maybe it just hasn't come up enough, but or in the national work that I do with wound and ostomy incontinence nurses that provides topical oxygen therapy on any type of regular basis.

Rita F. Redberg, MD, MSc, FACC: Okay, so far not hearing a lot of familiarity. Um I will add to that, I, in my informal polling, I don't think there is currently general acceptance at least in my anecdotal experience. Um I'll keep going down. Anyone on this side want to comment? Dr. Perissinotto?

Carola Perissinotto, MD: Yeah, just I'm Carla Perissinotto, just that I'm not sure that this is currently accepted as a standard of treatment.

Rita F. Redberg, MD, MSc, FACC: Thank you.

Jay Mandrekar, PhD: I'm just looking at six or four, or six such studies which can say that it's not that popular, right. Nobody is trying to make a career of it.

Rita F. Redberg, MD, MSc, FACC: Yes. Okay, and did anyone on the phone want to make a comment? Okay. So we are going to come to Key Question 7 and final question and then we will be voting. How confident are you that the evidence supports that the use of Topical Oxygen Therapy results in clinically meaningful outcomes such as complete wound closure and/or quality of life improvement in Medicare beneficiaries? Um Dr. Popat, would you like to start this discussion? Thank you.

Rita A. Popat, PhD, MS, MSPT: Sure. I think we've already discussed this question from our Questions 1 through 6, so from I think the better done studies, especially the two that showed a signal, I think if we answer the first part, if we look at complete wound closure which was the main primary outcome measured at twelve weeks, if I'm interpreting this correctly. Um then there is evidence, at least based on the signal that, you know, I too don't care too much about P values, but if you look, whether the effect is clinically meaningful, it was interesting that in both studies, actually, they had expected a much higher proportion of closure rate than was actually observed, which is interesting. I can't explain that. It's like half of what they had expected, but nonetheless, they see a signal between the two groups. The point I want to make, and I don't know how relevant this is, is that based on the definition it appears that you have to confirm the wound closure two weeks after. And only one study did that, the Frykberg study. So the other paper, Niederauer's paper, found a signal but they didn't reevaluate it at two weeks so it's a little bit limited. Um I think that helps us kind of put the landscape on wound closure. In terms of quality of life again, we only got that one paper, albeit limited, that tried to attempt quality of life, but we don't really have any other evidence to support at least based on what's been published.

Rita F. Redberg, MD, MSc, FACC: Right, yes, I agree what ECRI agree, concluded, inconclusive. Um Dr. Perissinotto? I love the way you say her name much better. I can't do it though.

Carola Perissinotto, MD: Perissinotto, this is right. Um I'm not sure that I have additional things to add. I think it's been said. Thanks.

Rita F. Redberg, MD, MSc, FACC: Thanks. Dr. Mandrekar, did you want to? And again for this last question, Dr. Niebuhr or Dr. Gutman, did you want to make any comments?

David W. Niebuhr, MD, MPH, MSc: Nope, I think that's yeah (not understandable).

Rita F. Redberg, MD, MSc, FACC: Okay, so if we can address any other issues or questions if there are any, and if not we can go on to take the vote on the seven questions that we've just been discussing. And I want to thank everyone for myself and on behalf of Noridian and CMS because really, clearly, everyone thought about the issues and prepared and read, and I really appreciate the discussion we've had. Um so everyone has a link, including people on the phone, so all voting members, and you know who you are, please go to the link I'm going to open up now on Survey Monkey. Okay.

David W. Niebuhr, MD, MPH, MSc: I just had a question, it's 1 that consists of failure to do it or which direction do we go?

Rita F. Redberg, MD, MSc, FACC: So are you asking about the question? So how confident are you? So if you are very confident that there is sufficient evidence then you would go towards the right, high confidence. If you don't - are not confident, all the way on the left. And then you have the three in between.

Rita A. Popat, PhD, MS, MSPT: I'm so sorry, I don't know where to find the link. Is this in -

Rita F. Redberg, MD, MSc, FACC: So it was in an email from Kate about a week or so ago.

Rita A. Popat, PhD, MS, MSPT: Thank you, from Kate.

David W. Niebuhr, MD, MPH, MSc: This is David Niebuhr, can I ask a question? I just want to note that there is no no confidence right? The two extremes are low or high, there is no no confidence?

Rita F. Redberg, MD, MSc, FACC: No, low is - no, it's a 1 to 5 scale and 1 would be low, so no confidence you would have to vote low, that's correct.

David W. Niebuhr, MD, MPH, MSc: Okay, thanks. That kind of affects my score, so thanks a lot.

Wilfred Mamuya MD, PhD: I think Kate will need to resend the link to a few members I think actually.

Rita F. Redberg, MD, MSc, FACC: Okay, should we wait?

Rita A. Popat, PhD, MS, MSPT: Got it. I just got it.

Rita F. Redberg, MD, MSc, FACC: Okay, can we start voting?

Jay Mandrekar, PhD: Yep.

Kate Score: Yep, you will log in as host. Something will happen here, and you will vote and it will keep the tally there but it will be anonymous.

Wilfred Mamuya MD, PhD: Why don't you resend it to everyone just in case?

Rita F. Redberg, MD, MSc, FACC: And we should vote. Resend this to everyone? Okay. David M. Young, MD and Rita A. Popat, PhD, MS, MSPT Do we vote on all questions?

Rita F. Redberg, MD, MSc, FACC: Yes, we will vote on all questions and it will be tallied. So we will get a signal when the everyone has voted. And then we can review the votes.

Wilfred Mamuya MD, PhD: So for the ones who have the link already please go ahead and you can start voting. And for the ones who don't - who hasn't, doesn't have the link? David Young, okay.

Jay Mandrekar, PhD: I'm just logging into my email.

(not understandable)

Wilfred Mamuya MD, PhD: He's a surgeon, we will forgive him.

Carola Perissinotto, MD: No judgment.

David M. Young, MD: I've been without power for four days.

(not understandable)

Wilfred Mamuya MD, PhD: Oh dear, sorry about that.

Rita A. Popat, PhD, MS, MSPT: In general like Question 7 (not understandable), like do you vote on wound closure and/or? Okay.

Rita F. Redberg, MD, MSc, FACC: And this because number 5 kind of has a double negative, how confident are you that there are no significant gaps? So if you think there are significant gaps then you would say low confidence right?

Wilfred Mamuya MD, PhD: Correct.

(not understandable)

Wilfred Mamuya MD, PhD: Okay, so that's everybody, yes. There are 8 scoring members.

Rita F. Redberg, MD, MSc, FACC: Anyone that needs more time to vote? Okay.

Wilfred Mamuya MD, PhD: David, Roee, are you done?

Rita F. Redberg, MD, MSc, FACC: Okay. Great, then I think we are done.

David W. Niebuhr, MD, MPH, MSc: Yes, I have voted.

Rita F. Redberg, MD, MSc, FACC: Do you need more time, Dr. Gutman?

Roee Gutman, PhD: No, no, I have voted.

Rita F. Redberg, MD, MSc, FACC: Oh he voted, okay, great. Okay, then I think we can close the voting. And I can read the results. Okay, so for the first Question which was more or less how confident are you that there is sufficient evidence that TOT leads to a greater incidence of complete wound closure? The vote was 2.6, which is sort of between low to intermediate, an intermediate confidence. Similarly, for the second Question on how confident are you that there is sufficient evidence that TOT shortens time to complete wound closure? Um it was 2.5. Um for the Question 3, how confident are you that there is sufficient evidence to determine that TOT improves durability? The vote was 1.5, so that's low, between low and low to intermediate confidence. Uh how confident for Question 4 are you that the available evidence for TOT allows identification of a discreet population of beneficiaries? The vote was 1.5, again low to, low to intermediate. For the fifth Question, we are dropping, how confident are you that there are no significant gaps in evidence, that may impact positive health outcomes? There clearly is a message for the need for more evidence and I think that came through clearly in our review of the literature and our discussion, the vote was 1.1. That would be low confidence. Uh next, how confident are you that TOT is generally accepted by the medical community? Um and that again was very low confidence, 1.1. And how confident are you that the use of TOT results in clinically meaningful outcomes? That was 2.1, which would be low to intermediate confidence.

So I want to thank everyone again for participation. I really feel that we had a very rich discussion and hopefully that this has been helpful for Noridian. So I'll hand it back to you Dr. Mamuya.

Jay Mandrekar, PhD: I just had a question, but it's my first time, so in this voting grade what makes it go forward? Is it like a positive finding? Like is it a score of 3 or higher or 4 or higher? Or something indifferent of this.

Wilfred Mamuya MD, PhD: No, it's completely independent, so this exercise is helpful but by itself doesn't really drive us one way or the other. So -

Jay Mandrekar, PhD: The study section decision was disappointing.

Wilfred Mamuya MD, PhD: Yeah, so you could have a -

Rita F. Redberg, MD, MSc, FACC: We are advisory only. And we vote on the quality of the evidence. I think there are many things that contribute to the final decision.

Wilfred Mamuya MD, PhD: Yeah. Well I want to thank the CAC members, you really took time out of your lives, unpaid, to wade into this discussion and for that we thank you from the bottom of our hearts. Um a week or so from now I will send an email to everyone asking for your candid opinions about how the process went and where we can do better, because we always try to improve. And I want to thank everybody else in the audience and David and Roee for -

Robert D. Hoover, Jr., MD, MPH, FACP: Fred? Yeah, this is Dr. Bob Hoover. My apologies for not being there today. There was an issue in Denver with my connecting flight and lots of snow. I was able to join about 30 minutes into the call, um, and I wanted to echo Fred's comments. We certainly appreciate the attendance at our CAC meeting on behalf of Noridian and CGS and the richness of the conversation and and the time that you've taken to thoughtfully consider this topic. Thank you.

Wilfred Mamuya MD, PhD: And again I wanted to reiterate something that Rita said, which is really not just the time but it's clear that all of you really read the literature and really thought about it. And we really appreciate that. Thank you.

Rita A. Popat, PhD, MS, MSPT: Thank you to the Chair and everyone here.