NewSTEPs
A Program of the Association of Public Health Laboratories™

Critical Congenital Heart Disease Technical Assistance Webinar

May 9, 2014

Presentations:

- Research on the Masimo Equipment—Anne de-Wahl Granelli, PhD
- Covidien Equipment—Scott Kelley, MD
- FDA Approval Process for Pulse Oximetry Equipment—Neel Patel, MEng and Sandy Weininger, PhD

Moderators:

- Thalia Wood, MPH, Specialist, NewSTEPs
- Marci Sontag, PhD, Associate Director, NewSTEPs

Please direct all comments/questions pertaining to this presentation to Thalia Wood at Thalia.wood@aphl.org or 240-485-2701.

Thalia Wood: Once again, welcome everyone. This is Thalia Wood with the Association of Public Health Laboratories. We're going to go ahead and get started. I'm going to mute the lines right now. Speakers, once again, remember to do star seven to un-mute yourself before you speak. Thank you.

Automated: The conference has been muted.

Thalia Wood: Marci, you want to go ahead and start with our introductions?

Marci Sontag: Thank you, Thalia. Welcome everyone. This is Marci Sontag with NewSTEPs and the Colorado School of Public Health. We're very excited about this morning's webinar. The topic for today's call will be pulse oximetry equipment, really giving a foundation for the different types of equipment that's out there. What's to consider when looking at this different equipment, and having the two big manufacturers represented so we know what is out there. Then finishing our call with the FDA approval process for the pulse oximetry equipment, or what the FDA looks at when they're considering this type of equipment and the considerations that go into that.

With that, our first speaker is Dr. Anne Granelli. We are just very honored to have her on our call today. I'm sure many of you are familiar with her really pivotal work that was published in the British Medical Journal in 2009, the foundation for really how we're doing CCHD newborn screening across the country in which she reported screening of almost forty thousand infants in Sweden. That laid the groundwork for the algorithms that are being used today around the world.

We were initially introduced to Dr. Granelli by Annamarie Saarinen, a close friend and ally of NewSTEPs and the CCHD community here in the United States. We were honored to be introduced to her and be able to gain some of her expertise in the large settings of CCHD newborn screening. When we reached out to Masimo to have them present, they asked that Dr. Granelli present, because much of her research has been in using their device. In her research study, she has used the pulse oximetry equipment that has been manufactured by Masimo.

With that, we're very excited to introduce Dr. Anne de-Wahl Granelli. Anne, are you on and ready to ... Press star seven to un-mute.

Anne Granelli: Yes. Thank you very much. Can you all hear me?

Thalia Wood: We can. Thank you, Anne.

Anne Granelli: Thank you. First of all, I'd like to thank you at NewSTEPs, Marci, for inviting me to speak at your webinar. I'm really honored to be here. I'm going to go right into the next slide, please. I'm going to state my conflict of interest. I want to just make sure that you know that during all my research about CCHD, I had no conflict of interest at all. However, after I finished my PhD, I had been invited to present my research. I had been offered an honorarium from NewSTEPs, from the Newborn College, from Masimo, and from Covidien. Next slide, please.

While I have already been so nicely introduced by you already, I want to tell you one thing, and that is that I have been working eighteen years at Queen Silvia Children's Hospital in Sweden. That is one of only two centers in our country that perform pediatric cardiac surgery. With that, I want to go to the next slide, please, and jump right into a case study.

This is Friday night at our hospital. Our pediatric cardiologist is on call. This baby has just been diagnosed with TGA. That is Transposition of the

Great Arteries. This is, for you who doesn't know exactly the term, it's the most cyanotic lesion you can have. This is a CCHD baby. The prostaglandin infusion was started. It was monitored on our ward, as I said, and showed a post-ductal separation of eight-five percent. This baby didn't have an arterial line, so the doctor needed to decide do this baby need a pulse oximeter monitor. He decided that there were no need to. Next slide, please.

However, this baby happened to be accepted for our first study. In our first study, we compared different oximeters and we had a newborn control group and a large group of CCHD babies. When we put the Masimo SET device on the same baby that was on monitor, it displayed a separation of only sixty-five percent. That is eighteen percent difference. We didn't have an arterial line. We didn't know the true blood gas value. This was done under optimal measurement conditions. Now the doctor looked at two different monitors, difference of eighteen percent, and he actually ... Could I get the next slide, please?

He actually changed his clinical decision based on this, and performed a septostomy. We were quite shocked by that difference. We wanted to find out is this an exception or not. We did a clinical study to find this out. Next slide, please.

We wanted to find out, in optimal measuring conditions, we wanted to compare different pulse oximeters. All the oximeters we use our PICU and in our pediatric cardiac ward at the same time as the blood gas was drawn. We compared them to the Masimo SET. We had fifty-six [inaudible 00:06:02] these measurements. Please, could I have the next slide?

On the top, I [inaudible 00:06:09] because that was new generation oximeter. That's why we used the Masimo SET. There were some deviation away from the true blood gas with Masimo SET. When we looked at the lower figure, we saw a significantly larger amount deviating from the line of unity. I apologize for the bad quality of the picture, because my scanner didn't work. I had to take [inaudible 00:06:37]. I apologize for that. What was so shocking was that when we compared our own devices, and we are, as I said, one of two hospitals performing pediatric cardiac surgery, we found difference as large as twenty-nine percent. This is optimal measuring conditions. These are cyanotic babies.

This is actually happening, and we had no idea before we did this study. Next slide, please.

My [inaudible 00:07:09] disc is available online at that address if anyone would be interested. It's from Gothenburg University in Sweden. Next slide, please.

As you already mentioned [inaudible 00:07:23] that the most famous part was the multi-center study that was published in BMJ. Next slide, please.

That was the reason I was invited to the meeting in Washington, DC, in January 2011. Together with Dr. Ewer, he and me were invited as international experts and tried to share our research at that meeting. Next slide, please.

As you already know, all of you, the outcome was published and also pre-published and endorsed by [inaudible 00:07:59]. Next slide, please.

Present at that meeting was representative from FDA and different advise non-sectors as well. I truly apologize to Sandy, because you should be there and I didn't put your name. I apologize for that because Sandy should be there because he was present at the other meeting in 2012, the following stakeholders meeting. Next slide, please.

The recommendations were at that meeting to use motion tolerant oximeter for the babies screening measuring functional saturation and cleared by FDA. Also, as you all know, it should be based on the recommended algorithm and performed by qualified personnel. Next slide, please.

I'm going to move over to the following year's stakeholders meeting, the second one. At that meeting in Washington, DC, we had come to five different research priorities. The only one of these research priorities that was regarding equipment was discussed that you need to compare oximeters perfectively. We also need to validate the accuracy in those saturations. In the low saturation span that we need to find out the performance, because the low saturations are the babies with CCHD, and they are the most vulnerable babies. I have been looking out for papers addressing these in a large sample of cyanotic babies. I have not found any published prospective studies so far. I have seen, and I will come to

that in a few slides, that the large prospective studies have mostly been done with the Masimo SET. Next slide, please.

Why am I talking about the new generation oximeter? We are talking about newborn babies. The most vulnerable ones with a life-threatening congenital heart disease. In order to get these right, the oximeter needs to be able to read through motion because babies do move. It needs to be able to read through low perfusion. In our first study in Sweden, in our method evaluation study, two-thirds of the newborns had the low perfusion. They had [inaudible 00:10:42] through time. It also needs to be able to read through low saturation in cyanotic babies.

Another thing I've seen in studies [inaudible 00:10:52] conventional oximeters. That's why it was recommended or endorsed by the large heart organizations, and that we talked about that we need a new clearance for FDA. Now we're talking about screening and not monitoring. This was a new way of using this equipment. Next slide, please.

I'm going to talk a little bit about our research. I want to guide you. This was the first study we did, and we did a [inaudible 00:11:25] evaluation study. We had two hundred normal newborns. We didn't even assume that they were normal. We echoed all of them to confirm that they had normal cardiac anatomy. Those two hundred babies we compared with two different oximeters. They were obtained [inaudible 00:11:44] the results. When one oximeter attached to the right hand, the other one was reading the measurements on the foot, and then I swapped places. Next slide, please.

I'm going to show you the bottom of the picture first. With the conventional hand-held oximeter, forty percent or more of the normal newborn babies displayed a saturation less than ninety-five percent. Ninety-five percent through red dotted line. You can see a little part of that line. I'm talking about normal babies here displaying subnormal saturation in at least forty percent of the cases. Next slide, please. Sorry, one more.

Above the baseline are results from the Masimo SET technology. One to two percent of the normal newborn babies displayed a saturation of less than ninety-five percent in one to two percent of the cases. That was significant difference. Next slide, please.

Hopefully you are with me now, and you see both oximeter percent. There you see the red dotted line indicating ninety-five percent saturation. The red dotted line is the optimal cutoff when you measure and compare by curves. It is only the newborn babies that were normal. When we went further in our perspective studies, which I don't have time to talk to you about here, we couldn't even analyze the data with the conventional oximeter because the saturation spanning the normal is too wide. Next slide, please.

Now I'm going to stop talking about the studies I've been performing. I want to move on to the perspective multi-center studies that have been accomplished in recent years.

Thalia Wood: Anne, excuse me. This is Thalia. We actually have at the last two slides, and then we have the other slide set after the FDA talk. We're on the slides of the photographs now. Are you able to see the slides on your screen?

Anne Granelli: No. I don't see any screen at all. What slide are you on? Did you see the multi-center studies slides?

Thalia Wood: We did see that slide. Now we're on the final two slides of all the photographs. Slide set 3B is at the very end of the presentation today, in case we wanted to use that one.

Anne Granelli: Oh, okay. Could you please go back to the multi-center studies slide? I just want to mention the Chinese one.

Thalia Wood: Okay, this is the one with the graphs on it? Is that correct?

Anne Granelli: It's called multi-center studies. It's listed from Sweden, Norway, Germany, UK, Cologne, and China. If it's not-

Thalia Wood: [crosstalk 00:14:49]

Anne Granelli: The last contribution, which was just published a few weeks ago from China, they screened over one hundred and twenty-two thousand babies. Most of these studies were using the same technology as I did in my research. However, the German study with the question mark, they state they used pulse oximeter. They didn't state any brand. In the Cologne study, they said they used SET technology, Nellcor, and [inaudible

00:15:19], but they didn't say what device exactly or what kind of sensors. They did state that they said that the difference between oximeters could be due to the [inaudible 00:15:32] curve. Nest slide, please.

Hopefully you have a slide that says saturation versus PO2 nonlinear regression curve for [inaudible 00:15:43]. This is also [inaudible 00:15:45] from my thesis. When we did the comparison between the different oximeters we had at our unit and with SET technology and blood gas. We looked at the [inaudible 00:15:58] curve as well. We found that the Masimo also deviated. This is the [inaudible 00:16:03] slide. The lower one showed that the slow for all the other oximeters was even outside the ninety-five percent confident interval for Masimo. They deviated much further away from the true arterial blood gas. Next slide, please.

I want to just say a few words about this technology. I really needed to study that when I wrote my thesis. The reason that this technology is reading to motion. I tried to do this as simple as I can. This technology is patented. This is approved by FDA for screening for CCHD. When a baby moves, conventional oximeters average the time, because then also the venous blood is moving. Oximeters normally think that the moving blood is arterial blood. Then they get a little bit confused when they get both the venous motion and arterial motion. They tend to average.

If you remember the first comparison I did, you could clearly see that at least forty percent of the normal babies displayed lower than ninety-five percent. It was because oximeter averaged the moving baby, or because it interpreted the low perfusion as low saturation. What the Masimo technology does is that they have something called a peak speaker. It only concentrates on the peak with the highest saturation, and says this is the highest saturation. You don't need to dwell on the lower peaks, because that must be something other. Then it enhances the signal on the arterial valve. That's how they explain that to be motion tolerant. Next slide, please.

Actually, I can take this one and the next and the next, because this is solutions that you can have different kinds of monitor, but you can also have SET technology incorporated. Unless you know much about it, you need to really look at your equipment and see what has been integrated with Masimo because it could be [inaudible 00:18:22] something totally different on the monitor. Next slide, please.

Thalia Wood: Anne, this is Thalia. Once again, we are actually on the final two slides of the photographs.

Anne Granelli: Yeah. Is it the Covidien slide now?

Thalia Wood: No. We're not doing that slide set at the moment. We're doing the final two slides of the photographs with you and Dr. [Malley 00:18:45] and-

Marci Sontag: Anne, we're going to save those FDA vetted slides for the FDA talk at the end.

Anne Granelli: Okay. I can just say one thing. I was going to show some pictures from Covidien. What I'm going to say is that I have done my research in Sweden. I have never done a comparison with Nellcor because I compared with all the devices we had in our PICU, in our pediatric cardiac ward, and in our research. At that time, we didn't any Nellcor at all. I have not done any comparison with Covidien. However, I have done some research and looked at their [inaudible 00:19:21]. I can leave that to Covidien as well. Are we at the take-home message picture now?

Thalia Wood: We are at the picture, the slide that has the picture with you and Dr. Kemper and Dr. Malley.

Anne Granelli: Okay, so it's no take-home message slide either. Okay. You can show that picture with the people. I just can wait to say at the take-home message that there is a significant difference between different pulse oximeters that's been clinically validated on cyanotic babies. The message I want to give is to make sure to use the proper devices as they're cleared for CCHD screening. As far as I know, I will be happy to listen to Covidien. I actually know more than I say now. The Masimo devices are FDA cleared because of the SET technology that I've already done research about as well.

The second last picture is yes, that is just ... I just have to say that I have been amazingly blessed, because I had the opportunity to meet almost all of the authors of the multi-center studies or authors from US review studies. The last slide, please.

Not only clinicians are interested. This is of huge interest around the world from developing countries to European countries. I had the fortune to meet minsters from Viet Nam and from Sweden, and even the former President of the United States. I want to just finish up with very good

news from UK. You might already know that, but two days ago, thanks to Dr. Ewer's tremendous work there, UK now has a national recommendation to screen for CCHD.

Thank you so much for your attention.

Thalia Wood: Thank you, Anne. That's wonderful news about the UK as well.

Marci Sontag: Thank you so much, Anne. That was wonderful. Next we have a presentation by Covidien. I'm very pleased to introduce Dr. Scott Kelley. He is the Chief Medical Officer for Covidien. We also have Nicole Malcolmson on the line as well, in case there are other questions additionally for Covidien. Scott, star seven to un-mute your line.

Scott Kelley: Okay, I think I have successfully un-muted the line. Again, I would like to thank Margie and Dalia for organizing this effort at really facilitating the implementation science of delivering critical congenital heart disease screening to more and more newborn babies, not only in the United States, which I think is the majority of our participants on the call today. As we heard from Dr. Granelli, spreading this around the world, so that this very simple and easy-to-use technology can help identify these vulnerable babies and get them the type of care that they need.

For the next fifteen minutes, I'd like to focus on specifically the Nellcor technology, and it's role in congenital heart disease screening. As this slide shows, as the Chief Medical Officer for Covidien specifically in the Respiratory & Monitoring Solutions Group, I do have a conflict of interest because they are my employer. Next slide, please.

Some of the learning objectives that I hope to touch on today is a very brief overview in a graphic format of the clinical data that supports the efficacy of pulse oximetry as a screening tool to identify these vulnerable babies, a perspective from one of the authors, Dr. Kemper, regarding the technology, and a little bit finer look at the Nellcor pulse oximetry technology that is very applicable for CCHD screening. Finally, I'll close with what are the additional educational and clinical resources that our company, Covidien, provides to clinicians as they begin to implement their efforts at newborn screening. Next slide, please.

As Dr. Granelli identified, there have been a number of large studies, and more recently very large studies, looking at the sensitivity and specificity

of screening with pulse oximetry to identify babies with critical congenital heart disease. Some of the earliest studies in the early two thousands actually used Nellcor technology, but they really weren't powered appropriately to identify large scale populations incidences. More recently, we've seen very large studies including Dr. Granelli's forty, fifty, thousand patient studies, and the more recent study from China involving over one hundred thousand babies, that again continue to identify the efficacy of pulse oximetry screening to identify these babies. Next slide.

I do believe there's been a lot of debate about what is the importance, or the bare minimum requirements, for pulse oximetry technology. That's one of our focuses in today's discussion. Dr. Kemper, who wrote a consensus with the lead author on the consensus statement recommendations, offered this perspective around the time of the follow-up meeting that Dr. Granelli referred to, that any hospital-grade pulse oximeter cleared by the FDA for use in neonates is suitable for CCHD screening.

He also identified that it's important to understand how the entire system works together. There is the monitor and the sensor, as well as the algorithm that brings the data from the baby and actually calculates that pulse saturation value. The importance of that was identified by Dr. Granelli. I think Dr. Kemper had a lot of foresight in identifying that reusable pulse oximetry sensors are a viable solution, particularly as we think about the challenge, the implementation challenge, of screening every newborn baby in our hospitals. Next slide, please.

If we look at the specific recommendations put forth in the strategies paper published in Pediatrics, I would like it to be clear that the Covidien Nellcor pulse oximetry meets all of these screening technology recommendations. Our pulse oximetry technology and our current generation of oximeters are motion tolerant pulse oximetry. They report functional oxygen saturation. They've been validated in low perfusion conditions. We have clearance now from the FDA for use in newborns. With some of our sensors, we can provide an accuracy of plus or minus two percent in neonates. Next slide, please.

Again, emphasizing Dr. Kemper's perspective, it's important to consider the entire system. What you see here are a variety of stand-alone pulse oximetry devices that range from the bottom of the slide, a hand-held device, to various bedside pulse oximetry devices. At the top is a more

sophisticated respiratory patient monitoring system. We also, and as Dr. Granelli identified, Nellcor pulse oximetry technology may be embedded inside other larger multi-parameter monitors manufactured by the major companies around the world. Whether or not that would be the specific device utilized in the implementation of routine newborn screening is going to be a hospital-based decision.

Many of the monitors on this page are more portable and can actually be brought by themselves to a baby's bedside to conduct the newborn screening examination and the algorithm approach that's been identified. This current portfolio all has motion tolerance clearance. Many of these devices also provide connectivity to an electronic medical record or provide options for data download. I think, as we look at implementation science, the documentation side of what are the values of the screening so that in those babies that either in the past had an indeterminate or failed their examination, we have appropriate documentation to then proceed down the next step in the care pathway if they are actually identified as at higher risk for critical congenital heart disease. Next slide.

In addition, it's very important to realize that a pulse oximeter requires a sensor to be applied to the baby or the neonate's foot or hand, actually in screening to be applied to both of those. Covidien Nellcor manufactures a range of sensors for collecting pulse oximetry data. At the top of the slide here are single patient use sensors designed for only use on one baby at a time. We offer both adhesive and non-adhesive sensors for the newborn and premature infants.

As we go down the slide, you see a range of reusable sensors that may be appropriate in hospitals to provide screening of multiple babies by cleaning the devices or changing the adhesive strips between babies. I think these are very important considerations as hospitals look at how are they going examine and screen every single newborn that they will take care of and provide that reassurance to the parents. Next slide.

On the left-hand panel, I think this is important information, is that for any technology system for pulse oximetry it's important to know what the performance characteristics, not only of the system, but for the particular type of sensor being applied to the baby. What you see here are the published accuracy specifications for the range of Nellcor sensors that we produce. In general, it's important to note that the higher accuracy is done through single-use adhesive sensors. There may be

different performance expectations related to reusable technologies. The impact of that has not been studied in the prospective clinical trials that Dr. Granelli mentioned. It is something I think further research will define the importance of that.

For Nellcor pulse oximetry we do offer this full line of adhesive or non-adhesive single-use or reusable, as well as specialty sensors. One of the characteristics we provide are sensors with defined accuracy at a very low saturation rate down between sixty and eighty percent. We do believe it's important to provide established accuracy data for neonates. These sensor portfolios include a variety of sensor choices to help hospitals meet their neonatal needs for monitoring and CCHD screening. Some of the features that our system provides is a digital memory chip that enables unique communication features that further enhance patient management when used with our full-featured OxiMax pulse oximeters.

As Dr. Granelli identified, it's important to really understand the system that's implemented, particularly in the multi-parameter monitor systems. We're all talking about our current generation pulse oximeters offering the best performance in this neonatal patient population. There are a variety of older multi-parameter monitors that provide either a Nellcor technology or a Masimo technology that may not contain current generation technology. Finally, our systems provide a variety of sensor messages that can help clinicians troubleshoot and provide additional tips for optimal sensor placement. Next slide.

I think it is important to always focus on the importance of proper sensor selection. We can imagine that, particularly for premature newborns or neonates, patient body weight is very important. Most of the sensors are identified for specific weight range. We heard the importance of patient activity, particularly movement in neonates, and how important that is. Duration of monitoring is a little bit different for a newborn screening examination where a simple five-minute examination may be sufficient. As hospitals think about screening a large number of babies, they have to identify what are the specific infection control concerns, or impact on skin integrity. Finally, as we heard, the importance of peripheral perfusion in newborns, particularly those newborns that may have critical congenital heart disease. Next slide.

In addition to choosing patient weight, it's important to identify that the right-sized sensor is utilized. The way these technologies are really operational is close alignment of the light source and the photo detector. In this schematic here, we see an example of proper application over a finger source. Particularly in neonates, quite often the hand and the foot ore utilized. It's important to have a proper-sized sensor so that there's good alignment between the light source and the photo detector. This is very important in getting highly accurate measurements which, as Dr. Granelli identified, is critical to successful utilization of the CCHD screening algorithm. Next slide.

It's no wonder, and I apologize I have a still photo here, but that the neonate is so frequently moving, particularly those lower extremities. The post-ductal location where we're trying to get a critical piece of pulse oximetry data to identify the vulnerable child. In general, a single patient use adhesive sensor would provide a more secure fit, which would be very important for long-term monitoring. I think as hospitals or doctors screening algorithms, they're going to have to balance this need for tight adhesion in active neonates versus what's the most effective method to screen the large number of babies. Next slide.

Similarly, it's important to identify the attempts that we can make as clinicians to avoid adhesive-related skin trauma, particularly in newborn infants, as well as a result of certain medications and illnesses that may go along in the newborn. We have to be concerned about the potential for skin integrity to be impaired. For longer-term use, there are specific recommendations to move sensors to new sites to minimize the risk of damage to skin integrity and, as identified here, use of non-adhesive sensors may be appropriate in many situations. Next slide.

We also have concerns about infection control. There are a variety of single patient use sensors that are optimally packaged in a sterile condition. They can be reused and moved to different sites in the same baby, but they are not labeled for use in different babies. For reusable sensors and, as identified in Dr. Kemper's recommendation, it's important that a routine cleansing process be used after use on each patient. Next slide.

As we enter this important phase of implementation of the CCHD screening recommendations, Covidien is very committed to providing ongoing educational support to clinicians around the world. I have a few

examples here. We've developed a very nice educational online training program that consists of both accredited CCHD training, as well as non-accredited CCHD training that is more specific for the use of the Nellcor technology. These are available via the Covidien website. It can be accessed by getting to what we call PACE, Professional and Clinical Education slides, so www.covidien.com\pace will take you to a variety of resources. It's very easy to navigate to our specific training that's supporting CCHD screening.

In addition to those online documents, on the lower right-hand panel you see an excerpt from a printed tool that we make available to our customers and other interested clinicians about how CCHD screening works, implementation of the screening algorithm, as well as a detailed review of the Nellcor pulse oximetry technology. In addition to these educational resources, as a company we provide clinical field-based clinical support, specifically at hospitals or doctor screening training programs, and then implement routine monitoring sensor use in their training systems. Believe it or not, just like today, the phone still works, so we provide product technical support by dialing 1-800-NELLCOR to get specific product technical support related to Nellcor oximetry. Next slide.

I believe the take-home message here is the clear evidence that pulse oximetry screening is quite effective in identifying these vulnerable babies that would otherwise potentially leave the hospital with undiagnosed critical congenital heart disease. As I stated earlier, Nellcor pulse oximetry technology provides the right degree of accuracy, motion tolerance, and use in neonates as identified in the recommendations. We are quite proud that this technology is having the impact around the world in identifying these babies.

As seen on this last slide here, in addition to myself, Nicole Malcolmson, who's the Product Manager supporting the Nellcor pulse oximetry product line, is available for additional detail, support, questions, as well as ongoing educational needs. With that, I'd like to turn it back to you. Again, just so appreciative that the organization has taken this effort to provide technology training to the interested parties.

Marci Sontag: Thank you, Dr. Kelley. That was great. I'm very relieved to know that the phone does still work. Sometimes I think we forget that. Thank you very much.

Now we'd like to move on a talk with the FDA to have a good understanding of what that pre-market review of the those pulse oximeters look like. With that, I'm very pleased to introduce Neel Patel and Sandy Weininger. Dr. Weininger is a Senior Electrical Biomedical Engineer in the Office of Scientific Technologies at the FDA Center for Devices and Radiological Health. He has been working on ensuring the safety and effectiveness of medical electronic equipment for more than twenty-five years working in the areas of understanding and characterizing why these devices malfunction and fail, safety and performance standards, and pre and post-market reviews.

Neel Patel is biomedical engineer, scientific reviewer in the Office of Device Evaluation in the FDA Center for Devices and Radiological Health. He is a senior member of the anesthesiology device branch and has over ten years of experience in performing pre-market reviews of pulse oximeters. He's also the primary contact for questions related to the review of pulse oximeters for the FDA guidance documents.

With that, Dr. Weininger and Mr. Patel, you can take it over.

Neel Patel: Hi. Can everyone year me?

Thalia Wood: We can. Thank you.

Neel Patel: Thank you, Marci and Thalia. I would also like to thank everyone for the opportunity to talk about how new modified pulse oximeters are geared for market in the US. Again, my name is Neel Patel. I'm a biomedical engineer with the anesthesiology devices branch. I'm joined by Dr. Sandy Weininger from the Office of Science and Engineering Laboratories. To begin, Dr. Weininger will provide a brief overview of how pulse oximetry works. Next slide in, Sandy.

Sandy Weininger: Sandy Weininger. Can you hear me?

Thalia Wood: We can. Thank you, Sandy.

Sandy Weininger: Just making sure the mute came off. I just wanted to take a few moments here to do a little education on what oximetry is actually doing, so what when we're making clinical measurements we have an appreciation for what the technology can and, most importantly, can't do. Remember I'm

an engineer. I'm not a clinician, so I don't make clinical recommendations. I make, if you will, device performance observations.

As Dr. Kelley showed in his slide, the oximeters have an [inaudible 00:41:10] detector. You can see that in the upper right picture. These have some field of view where the photons from two different color emitters bounce around inside the finger, the toe, whatever particular tissue is being imaged, and have to be collected by the detector. As you might imagine, if that emitter is not pointed in the right direction, that is at the detector, you start to get less signal and you get different tissue fields imaged.

Also importantly you will note that there is no way than you can get the emitter right back on the exact same place that you took it off. There are some differences when you take an oximeter off and put it back on, as well as from brand to brand based on how the oximeters are constructed. Just experimentally, and it's almost anecdotally, but there's a little more evidence, we've done some comparisons of one oximeter to another in adults in resting states, so that's not neonates, just at room air.

The differences are on the order of one or two percent SET. A lot of times those are traced back to the kind of co-oximeter, hemoximeter, that are used to caliber the particular devices. We've spent a lot of years trying to understand what the references are for these devices and how they compare in technology. Recognize that these are two wavelengths. That means that you can image two unknown quantities, in this case oxygenated and de-oxygenated blood which you see on the left-hand side. Based on the differential absorption of those two wavelengths, you can do some calculations to determine how many of the hemoglobin molecules are bound to oxygen. That gives us some indication of the percentage.

There's all kinds of great and wonderful theories, Beer's Law and different things, that try to predict how much light is going to come out the other side based on the concentration. Universally, all those different theories are violated when we deal with oximetry. Oximeters are calibrated empirically. Every time a manufacturer makes a new oximeter, or puts new materials in new emitters, they have to recalibrate their devices. Importantly, you as a user have no means of assessing calibration. It has to be done in a very controlled de-saturation environment. Next slide, please, and I'll turn it over to Neel.

Neel Patel: Thank you, Sandy. Before I begin with the rest of the slides, I just wanted to point out two documents that we rely upon [inaudible 00:43:53] pulse oximeters. The first document is the FDA Reviewer Guidance. This guidance document is available for the public on the FDA website. It relies heavily upon the second document which is International Standards for Basic Safety and Essential Performance of Pulse Oximeters. Next slide.

It's important to understand how pulse oximeters are classified as this is going to effect how they are reviewed. I want to quickly mention that this doesn't include sports-use oximeters. They haven't been evaluated by FDA. We are aware that these products are finding their way into the medical arena. Medical pulse oximeters are a Class II 510(k) devices, which means that the regulatory standard they must meet is one of substantial [inaudible 00:44:46], meaning as good or better than an existing pulse oximeter that's on the market.

They're also regulated as what the FDA refers to as tools. This is important to keep in mind. I will talk deployments again in a later slide, but being a tool means that the device has a claim that it can accurately measure a parameter, and a parameter that's generally well understood. It also means that it's up to the caregiver to use that information provided by device to the best of their knowledge. Next slide.

Now I will start to discuss what we as reviewers focus on when we review a new or modified pulse oximeter. A 510(k) has a number of sections and forms which should be provided by the manufacturer. I'll try to mention just the ones that are relevant to our discussion today. We want to know what is the intended use or the indications for use of the device are going to be of the pulse oximeter. They're are generally intended for noninvasive monitoring of arterial oxygen saturation and pulse rate. It's important to note that monitoring, whether continuous or spot checking, is viewed as a training use by the FDA. It's important to point that out when we're talking about screening use.

We also want to know the intended patient population, the settings of use, how the device works [inaudible 00:46:26]. The sensor application sites. Any other claims such as motion tolerance or a low perfusion performance, because all this is going to affect how the device is going to be tested, and then how it's going to be compared to an existing product device, and eventually evaluated by FDA. We also want to know if it's sterile or non-sterile, if it's going to be reusable, what the patient

contacting materials are, need to be evaluated for bio-compatibility. We review the wavelength to see if adequate directions for use are provided, and that there are no unsupported claims that have been made.

We focus on performance testing, both clinical and bench, to see how well the device measures SqO2 and pulse rate. Again, I want to mention that all this information is outlined in further detail in the pulse oximeter guidance. Next slide.

When we get a clinical test report from the sponsor, I'll go over what we look for in those reports. Just to mention in Section Four of the Pulse Oximeter Guidance, which also points to a number of clauses in the International Standards seen in a few slides above. Normally Sq02 is clinically validated. We look to see that invasive hypoxia testing using healthy adult volunteers was performed. Sometimes we see testing with exiting patients in the hospital, but this isn't going to allow the manufacturer to collect data over the range that we're interested in, seventy to one hundred percent, which is the range that oximeter accuracy section specification be ARMS where the [inaudible 00:48:20] applies to.

We look to see in the hypoxia testing with the healthy subjects that ten or more subjects were included, that from those ten or more subjects that two or more samples were taken and compared to a reading from a hemoximeter. We look to see that amongst the subjects there is variety of skin pigmentation. Studies have shown that that can affect how pulse oximeters perform. The samples that were taken should be as evenly spaced as possible over the range of seventy to a hundred because oximeters are known to perform well at the higher ranges.

The test reports should also provide all the data aligned with [inaudible 00:49:10] error plots of the data that we look at and rationale for excluding any data from their analysis. Next slide.

This is the formula in outline in the standard [inaudible 00:49:24] for ARMS. ARMS is a measure of bias and precision, so it combines the mean area and standard deviation into one metric. I'll let Sandy correct me if I've said anything wrong.

Sandy Weininger: Keep going. It's good.

Neel Patel: Next slide, please. Okay, there you go. Just as an example of de-saturation profile from the hypoxia testing, there's different profiles that you can use, but in this example the test subject would be saturated continuously down to seventy percent of the areas of saturation plateau where the data is collected. When the subject is on one of those saturation plateaus, you take simultaneous readings with a pulse oximeter and hemoximeter. You use the arterial blood samples. You want to make sure that you have a stable plateau when you're taking all your readings. Next slide.

Pulse rate performance. This is one thing I wanted to briefly mention. This is considered to be essential performance by International Standards. Pulse rate is tested on the bench using a functional tester or simulator that allows you to vary the signal strain, the Sq02, that the simulator produces and the pulse rate. As reviewers we look to see if the manufacturer tested their oximeter over the range of pulse rate that the device is labeled for, and that the other parameters that the simulator can change. That the signal strength or Sq02 are also varied, and that the pulse rate is within specification during that test. Next slide.

Motion and low perfusion. This have been discussed greatly the last couple of years in regards to CCHD screening. Motion tolerant oximeter is one that can distinguish the arterial pulsation from moving venous blood. In doing so, it can detect the true signal and reject motion artifact in the signal. When the manufacturer makes a motion tolerant screen for accuracy ... First, I have to describe the characteristics of motion including the [inaudible 00:52:20] the motion and the frequency of motion that they're going include in this clinical testing, because there's no standardized definition of motion. After they define what kind of motion they're going to test, they will perform the clinical testing that was described a slide or two earlier including that motion.

Low perfusion performance. That means that there is a reduced peripheral blood flow, and thus a detectable signal is weaker. Devices with good signal detection performance can still detect a weaker signal. If a manufacturer is making low perfusion claims, they can test their device on the bench using a simulator, as described in the pulse rate bench testing slide earlier. Where the signal aptitude on the simulator will be set to a level which again defined by the manufacturer as low perfusion for the oximeter. Next slide.

Marci Sontag: I want to do just a quick time check. I'd like to leave a few minutes for questions.

Neel Patel: Okay. I'll try to speak [inaudible 00:53:35].

Marci Sontag: Thank you.

Neel Patel: Clinical testing. Described as optimal to all pulse oximetry [inaudible 00:53:44] of the patient population. However, we know that neonates present unique challenges that adults and other pediatric populations don't. If the manufacturer wants to indicate their device for use in neonates, what they do is they provide the testing that I described in healthy adult volunteers, but they also provide additional clinical testing with sampling on neonates. The purpose of this is to verify the safe form, fit, and function of the device and the sensor. It actually observes how that specific oximeter and sensor are going to perform in neonates. As reviewers, we know that this additional testing is going to have limitations, and the number of test samples and subjects will be limited, but we recommend that manufacturers do this testing and they justify their sample size and their data collecting. Next slide.

This slide just outlines the additional testing that we look for. I just wanted to mention that. In the interest of time, we can go to the next slide.

For labeling there are a number of things we look for. All applicable warnings should be identified, anything that can affect the performance of the oximeter should be identified. Important instructions such as moving the sensor site after a number of hours to avoid burns should be included. Pulse rate accuracy specifications should be identified. We asked for Sq2 in the range of seventy to a hundred. We still ask for that, but we now ask for a breakdown, seventy to eighty, eighty to ninety, ninety to one hundred. That information is available for the user's reference if they need it.

If pulse oximeters are intended for neonates, then the labeling should disclose the important details of that testing that was performed in neonates. That's also available for reference, so you know how it actually performed in that population. Next slide.

When it comes to CCHD labeling, the guidance document that I mentioned does not comment on that. Pulse oximeters are generally reviewed in anesthesia devices branch. If there's any wavelength for CCHD, that's reviewed in a branch in the Division of Cardiovascular Devices. Currently, there are no pulse oximeters which are indicated for CCHD screening. The agency's view is that the pulse oximeters themselves do not provide CCHD diagnosis, so they use it as a tool during the screening process along with additional equipment and patient management.

We don't believe there are any regulatory barriers that prevent any pulse oximeter that is currently cleared for use in neonates in CCHD screening protocol. It's important for the caregiver to implement a protocol according to published literature and achieve diagnostic accuracy that was described the published literature. Next slide.

In summary, the take-aways are that pulse oximeter performance, [inaudible 00:57:05] in particular, is primarily evaluated in adults. Additional neonate data is collected to demonstrate neonatal performance. The agency believes that any oximeter cleared for use in the United States, can be used in CCHD screening protocol. Next slide.

This is just our, Sandy and my, contact info. If anyone has questions they can reach us.

Thalia Wood: Great. Thank you both very much.

Female: Excuse me. Is it possible if I can ask a question to FDA, Neel or Sandy?

Thalia Wood: Absolutely.

Anne Granelli: I had the pleasure of meeting both of you at the second stakeholders meeting. I clearly remember what we were discussing and our concerns. Then there was a genuine concern about recommending any device for screening, because the decision was made based by the Swedish and the UK research. Then, as I said in my presentation that the intention of FDA was to, and the key message, was to compare oximeters prospectively, and also to validate echoes in low saturation. For me as a scientist, if I'm going to measure CCHD babies, I absolutely took for granted that when you meant that you were going to do this prospectively and give clearance, like 510(k) clearance, I assumed it would be on CCHD babies.

If I am measuring CCHD babies and want to validate, I didn't assume that you had normal adults that were ... For me, when I do research, I compare the target group, I investigate the target group. Are you really saying that when you give the 510(k) clearance you haven't actually measured on the target CCHD screening, and still you say that the agency say there are no regulatory barriers against screening. You don't have any evidence-based prospective studies that was important, and still you say you can use any device. Am I clear in hearing what you're saying, or am I misunderstanding you?

Neel Patel: Sandy, do you want to ... I didn't clearly hear all the question.

Sandy Weininger: I think the question you're asking is, are clearances based on, 1) CCHD screening, and 2) actual neonatal evidence?

Anne Granelli: Yes, because that's more likely key things [crosstalk 01:00:01].

Sandy Weininger: In the interest of time, because I think we're already a few minutes over, let me briefly say that there are no claims for CCHD clearing as part of a 510(k) clearance. Neel stated that pretty clearly. As far as whether a pre-market submission contains neonatal data, it does contain neonatal data. It's possible some of those neonates have a defect, but it's very challenging to collect those kinds of convenience data and make real statistical information in it. What we recommend is that the manufacturers disclose the information that they do collect.

Anne Granelli: So basically, it's up to the person that wants to buy to review the literature and see if there has been extra studies on the target population before they decide.

Sandy Weininger: I'm trying not to make recommendations for or against any particular technology or manufacturer, only to say that my recollection of the conclusions of the committee were that any modern oximeter that can read through motion that has a decent accuracy specification, is [inaudible 01:01:31] to do these kinds of measurements. You pointed out that the saturation differences that you see are ten, fifteen, points. The differences in accuracy that we see of oximeters are on the order of a few points.

Anne Granelli: Yeah, compared on cyanotic babies in the seventy saturation, or hypoxia in adults. That's my concern.

Marci Sontag: I want to make sure that other people also have time to ask questions on this call. Are there other questions?

Daria: This is Daria. I actually had one question typed into the chat box. Do you recommend the wrist as an appropriate site for monitoring in the neonate? We hear that the right hand is the optimal pre-ductal site, but the wrist is often used in the [inaudible 01:02:19] and is included in the NRP recommendations. Would any of the speakers like to address that question?

Marci Sontag: Dr. Granelli, would you be able to answer that? The wrist versus the hand?

Anne Granelli: I haven't seen any of the large prospective on this study established recently that used the wrist. I think all of them has used the right hand, the palm of the right hand, and the sole of the foot. I think also perfusion index varies with the site. This is different from monitoring, and I know that as well, but I think it's like I want to see research as a recipe. If you follow the recipe, it works. If you don't follow the recipe, I would encourage do more studies, validate your own data, and don't diverge too much without having evidential backup. I wouldn't recommend the wrist. For monitoring, absolutely. For screening, I would not. That's from my point of view. I encourage more studies in that case, and to see [inaudible 01:03:42] evaluate that.

Marci Sontag: I think that's a key take-home here is that more research still needs to be done. We know a lot, but there's still much to learn. Any other questions?

Scott Kelley: It's Scott.

Marci Sontag: Go ahead, Scott.

Scott Kelley: I guess the only other thing is, particularly babies that are [inaudible 01:04:01], any type of symptomatic baby, is probably not going to follow the routine screening protocol for things like that. Even the large scale Chinese study, those patient's that were symptomatic in any way base on [inaudible 01:04:17] or other clinical signs really were routed directly to echocardiography to screen for the presence of a heart lesion. I think we're really talking about a simple screening examination in the vast majority of newborns that have no other clinical conditions.

Anne Granelli: Yes.

Thalia Wood: Thank you. Okay, we have one more question here that we want to go ahead and get answered before you get off the phone. Is there a way to check the FDA website to determine if a pulse oximeter is approved for use in neonate?

Neel Patel: Absolutely.

Sandy Weininger: Yes, you can-

Neel Patel: Go ahead.

Sandy Weininger: There's a 510(k) database on the external website where you can ... I think it might be difficult to search a key word by neonate, but you can look at a list of clearances of pulse oximeters and go through each one. You'd have to look at their indications for use statement or the 510(k) summary. It would mention the patient population in those documents.

Neel Patel: Frankly, it's just as easy to call the manufacturer and say, "Are you cleared?" If we find out they're lying, we don't take kindly to that.

Scott Kelley: No, I think that sage advice. On behalf of Covidien, we're very transparent with our clearance and indication for use for each of our monitors. Our submissions we want to provide technology that can serve, not only these patients, but a wide variety of patients. We are very clear on the indications for us for both our monitors. I think as Dr. Kemper ... It's the whole system to consider, not just the monitor but also what is the sensor that's being utilized. Is it age and weight appropriate?

Thalia Wood: [crosstalk 01:06:05]. The last question is somebody asked if they could get copies of the five presentations. I just want to let everybody know that's still on the call that, yes, this is recorded. The recording and the presentation will be on our website as soon as possible.

Marci Sontag: We'll have those up in the next week or two. We need to get them transcribed and we'll have them up on the NewSTEPs website, so that will be available for everyone. I'd like to take this time to really thank all of the speakers. You all put in a lot of effort to make sure we have the right information on this call. I very much appreciate that. I would encourage continued discourse either on the CCHD list serve or via emails. If we

have any additional information to share, we will absolutely share it with the community. Thank you all very much for your participation on the call. We apologize for going over a little bit, but I think that was lots of good information shared today.

Thalia Wood: Absolutely. Thank you everyone.