

SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

ANESTHESIOLOGY DEVICES PANEL

November 1, 2022

8:00 a.m. EST

Attendees:**Chairperson**

Steven Nathan, M.D.
Professor of Education
Medical Director, Advanced Lung Disease
Chair, Transplant Program Inova Fairfax Hospital — Falls Church, Virginia

Voting Members

Hugh A. Cassiere, M.D, FCCP, FACP
Director, Critical Care Services, Sandra Atlas Bass Heart Hospital
Chief, Critical Care Division, Department of Cardiovascular & Thoracic Surgery
North Shore University Hospital — Manhasset, New York

Richard D. Branson, M.Sc., R.R.T.
Professor of Surgery, Director of Clinical Research
University of Cincinnati College of Medicine — Cincinnati, Ohio

Lonny B. Yarmus, D.O., M.B.A.
Director, Interventional Pulmonology
Johns Hopkins Hospital — Baltimore, Maryland

Temporary Non-Voting Members

Jeffrey R. Kirsch, M.D.
Professor of Anesthesiology and Pain Medicine
University of Washington — Seattle, Washington

Arlene J. Hudson, M.D.
Chair, Department of Anesthesiology, F. Edward Hébert School of Medicine
Uniformed Services University — Bethesda, Maryland

Robert G. Loeb, M.D.
Professor Emeritus of Anesthesiology
University of Florida — Gainesville, Florida

Andrea M. Kline, PhD, CPNPAC/PC, FCCM, FAAN
Nurse Practitioner Director Service Line A
University of Michigan Health — Ann Arbor, Michigan

Sean Hennessy, PharmD, Ph.D.
Founding Director, Center for Pharmacoepidemiology Research and Training (CPeRT)
University of Pennsylvania School of Medicine — Philadelphia, Pennsylvania

Jason Connor, Ph.D.
President & Lead Statistical Scientist
ConfluenceStat, LLC — Cooper City, Florida

Eliot Katz, M.D.
Assistant Professor, Harvard University — Cambridge, Massachusetts
Assistant in Medicine Pulmonary, Boston Children's Hospital — Boston, Massachusetts

Nancy Collop, M.D.
Professor of Medicine and Neurology, Division of Pulmonary/Critical Care Medicine
Emory University — Atlanta, Georgia

Jennifer Lynch, M.D.
Fellowship in Pediatric Cardiac Anesthesia
Children's Hospital of Philadelphia — Philadelphia, Pennsylvania

Murad Alam, M.D.
Professor of Medical Social Science
Northwestern University — Chicago, Illinois

Michael F. O'Connor, M.D.
Vice-Chair, Academic/Faculty Affairs and Faculty Development
University of Chicago — Chicago, Illinois

Industry Representative

William C. Wilson, M.D., M.A.
Senior Vice President, Chief Medical Officer, Clinical Researcher
Masimo — Orange County, California

Consumer Representative

Veverly M. Edwards, M.F.A.
Assistance Professor
University of Memphis — Memphis, Tennessee

Patient Representative

Joseph P. O'Brien, M.B.A.
President, Chief Executive Officer, and Patient
National Scoliosis Foundation — Stoughton, Massachusetts

Food and Drug Administration — Silver Spring, MD

Akinola A. Awojope, MPH, Dr.PH Designated Federal Officer

Jeff Shuren, M.D., J.D.,
Director, FDA Center for Devices and Radiological Health (CDRH)

Malvina B. Eydelman, M.D.
Director, Office of Ophthalmic, Anesthesia, Respiratory, ENT, & Dental Devices
OHT1 CDRH

RDML Richardae Araujo, PharmD, M.S.
Associate Commissioner, FDA Office of Minority Health and Health Equity (OMHHE)

Nilsa Loyo-Berrios, Ph.D., M.Sc.
Acting Associate Director
OHT1 CDRH

Food and Drug Administration Presenters

James Lee, Ph.D.
CDRH, OHT1

Sandy Weininger, Ph.D.
CDRH, OSEL

Allison O'Neill, Ph.D.
CDRH, OHT1

Mary Jung, Ph.D.
CDRH, OCEA

Kumudhini Hendrix, M.D.
CDRH, OHT1

Gene Pennello, Ph.D.
CDRH, OSEL

Josh Pfefer, Ph.D.
CDRH, OSEL

Invited Speakers

Rekha Hagen
Jessica Cocolin, CRNA
Bob Kopotic, RN, RRT
Paul Batchelder, LRCP, RRT, Clinimark

Amal Jubran, M.D., American Academy of Sleep Medicine
Eric Gartman, M.D., American College of Chest Physicians
Ann G. Rizzo, M.D., FACS, DABS, American College of Surgeons
Jesse Ehrenfeld, M.D., American Medical Association
Steven Gay, M.D., M.S., American Thoracic Society

Julian Goldman, M.D., Anesthesia Patient Safety Foundation,
Garrett Burnett, M.D., Society of Technology in Anesthesia
Elizabeth Bridges, Ph.D., RN, CCNS, FCCM, FAAN, American Association of Critical Care
Nurses

Michael W. Sjoding, M.D., University of Michigan Medical School
An-Kwok Ian Wong, M.D., Ph.D., Duke University
Ashraf Fawzy, M.D., MPH, Johns Hopkins University
Eric Raphael Gottlieb, M.D., M.S., Brigham and Women's Hospital
Phil Bickler, M.D., Ph.D., UCSF-CERSI
Christopher Almond, M.D., Stanford-CERSI
Michael Lipnick, M.D., University of California UCSF

Open Public Hearing Speakers

Dr. Veronica Hickson
Sam Ajizian
David Stricken
Grace Berson
Jeff Matthews
Dr. Steven Barker
Dr. Eve Calender
Dr. Michael Abrams
Renee Kohi

CALL TO ORDER INTRODUCTIONS

Panel Chairperson **Dr. Steven Nathan** called the meeting of the Anesthesiology Devices Panel to order at 8:00 a.m. He noted the presence of a quorum and stated that present members have received training in FDA device law and regulations. He stated the day's agenda: to discuss ongoing concerns that pulse oximeters may be less accurate in individuals with darker skin pigmentation and to discuss factors that may affect pulse oximeter accuracy and performance, the available evidence about the accuracy of pulse oximeters, recommendations for patients' health care providers, and amounts and type of data that should be provided by the manufacturer to assess pulse oximeter accuracy and to guide other regulatory actions as needed.

Dr. Nathan noted that 25 comments were submitted to the docket for this meeting, available at www.regulations.gov/docket/FDA/2022-N-210.

Chairperson Harris reminded the attendees that this is a non-voting meeting and asked members of the Committee and FDA participants to introduce themselves.

CONFLICT OF INTEREST STATEMENT

Akinola Awojope, Designated Federal Officer, announced the issue of a Conflict of Interest Waiver to Dr. Steven Nathan for his personal financial interests in health sector mutual funds that contain underlying assets potentially affected by firms invested in today's meeting. He also noted that **Dr. Christopher Almond**, an invited guest speaker, acknowledged his employer's interest in the form of a federally funded research grant. Similarly, **Mr. Paul Batchelder** and **Dr. Philip Bickler** acknowledged their employers' interests in the forms of research contracts and research studies, respectively.

He announced the participation of **Dr. William Wilson** of Masimo Corporation as the Industry Representative. She introduced **Dr. Sean Hennessy** as a temporary nonvoting members and Shauna Nelson as the press contact.

FDA OPENING REMARKS

Jeff Shuren gave opening remarks about the structure and purpose of the day's meeting.

- Discuss the impact of skin pigmentation on clinical performance of pulse oximetry technology, which could be indicative of racial disparities in the performance of these devices.
- Discuss and make recommendations regarding the design, conduct, and reporting of data for studies, assessing the accuracy of pulse oximeters and potential bias due to skin pigmentation.
- Promote transparency on this important public health issue and on the agency's activities to date.

- Provide a public forum for the many stakeholders impacted by this issue to express their views, patients, healthcare providers, professional societies, researchers, and industry.

The day's agenda:

- An overview of the current regulatory framework for pulse oximeters, including relevant standards, guidance documents, and pre-market study requirements.
- A summary of the currently available real-world evidence regarding the potential bias in pulse oximetry due to skin pigmentation.
- Invited speaker sessions, an open public hearing, and a panel discussion of FDA's questions.
- The panel's interpretation of the currently available real-world evidence on this issue, as well as
 - Recommendations regarding tools to assess skin pigmentation for future studies.
 - Recommendations regarding expectations of pulse oximetry accuracy across various clinical settings, arterial oxygen saturation ranges, and patient subpopulations of varying skin pigmentation.
 - Whether ARMS is the best metric to assess device accuracy.
 - Recommendations regarding device labeling to convey the potential inaccuracies due to skin pigmentation.
 - The content of labeling for lay users who may use pulse oximeters at home.

Richardae Araojo contributed that panelist remarks will inform FDA's final considerations on equitable approaches for the regulation of these medical devices.

FDA PRESENTATIONS

Pulse Oximeters: Technology, Accuracy Limitations, and Regulation

Dr. Lee presented uses, principles of operation, and regulatory categorization frameworks for Prescription Use Pulse Oximeters and Over the Counter (OTC) Pulse Oximeters. Prescription use pulse oximeters are Class II devices intended to measure blood oxygen saturation levels. Their accuracy can be impacted by skin pigmentation, dyshemoglobinemias, severe anemia, low perfusion, dyes, nail polish, and ambient light.

Dr. Lee went over Medical Device Reports (MDRs) for POs, which lacked sufficient information to assess association between use of device and adverse event, and the source for inaccurate readings. The top 3 reported health effects are inconsequential. The top 3 device problems relate to inaccurate readings.

Overall, pulse oximeters provide immediate, non-invasive estimates on oxygen saturation, but they have limits to their utility that have clinical implications

Standards for Pulse Oximeters: ISO 80601-2-61: 2017

Dr. Weininger provided historical background on PO clinical and engineering oversight as well as highly specific applicable safety standard codes. The intended use of pulse oximeter equipment includes, but is not limited to, the estimation of arterial oxygen hemoglobin saturation and pulse rate of patients in professional healthcare institutions as well as patients in the home healthcare environment and the emergency medical services environment.

Dr. Weininger defined ARMS, or Accuracy by Root-Mean-Square, which is currently used to assess PO accuracy. She detailed study parameters, inclusion criteria, factors influencing the performance of oximeters, and oximeter fidelity.

Overall, she presented the FDA Standard as one that provides definitions and requirements that address hazardous situations found in pulse oximeters, as well as establishes test methods, acceptance criteria, and rationale to verify risk control measures are in place and effective and acceptable. The Standard harmonizes with FDA's guidance document to support the regulation of pulse oximeters and assure reasonable safety.

A Systematic Literature Review of the Real-World Performance of Pulse Oximeters

Dr. O'Neill presented methodology and results from a literature review conducted by FDA that included 28 overall publications. 5 of 7 cross-sectional studies and 14 of 15 retrospective studies, but none of the lab studies, found a significant association between skin pigmentation and occult hypoxemia, showing that mounting real-world evidence from literature that suggests that pulse oximeter accuracy may vary by self-reported race, and skin pigmentation. **Dr. O'Neill** noted a need for prospective studies that utilize standardized measurement of skin pigmentation, capture simultaneous measurement of SaO₂ and SpO₂ paired data, and systematically collect data on important confounders.

Overview of Desaturation Studies in Pulse Oximeter 510(k) Submissions

Dr. Jung presented results of desaturation studies. For objective one, clinical studies, in comparing pre- and post- guidance submissions for clinical studies, there was greater: indication of skin pigmentation classifications; availability of patient line level data, use of Bland-Altman plots, and a wide variety of skin pigmentation categories was observed. Objective two investigated device labeling and found increases in reporting of factors that may impact accuracy observed from pre- to post-guidance. This objective also uncovered that an indication that skin pigmentation may impact device accuracy was not included in 73% of post-guidance 510(k) submissions included in the analysis.

Premarket Desaturation Studies for Pulse Oximeters

Dr. Hendrix presented the following topics: submissions requiring pre-market desaturation study; convenience sample verification in neonatal populations; data submission for FDA review; and limitations of pre-market desaturation study for clinical applications of pulse oximetry.

Dr. Hendrix posed questions given the limitations and purpose of pre-market desaturation testing, since currently, pulse oximeters are not diagnostic medical devices, rather for the interpretation and verification of SpO₂ levels from a clinician's perspective. Is the current indication adequate for clinical decision making? Are there clinically relevant ranges or thresholds where a greater degree of certainty is required, and what is the needed accuracy for these critical values and ranges? Additionally, can current pre-market desaturation studies be improved upon to provide clinically relevant pulse oximeter performance for all populations in the clinical setting?

Statistical Considerations in the Evaluation of Pulse Oximeters

Dr. Pennello detailed performance metrics, regression to the mean methods, box plots and their comparisons, and other statistical considerations in determining SaO₂ and SpO₂ levels. He discussed diagnostic accuracy from real-world data. Overall, he concluded that:

- Non-randomized comparisons of groups may be difficult to interpret without adjustment for potential confounders.
- Non-randomized comparisons of groups on occult hypoxemia rate are difficult to interpret because of confounding by hypoxemia prevalence.
- A pulse oximeter study may be difficult to interpret when paired measurements of SaO₂ and SpO₂ are not simultaneous, when data were excluded or not reported, and/or when limitations exist in study design, conduct, analysis, or reporting.

Methods for Assessing Skin Pigmentation in Pulse Oximetry Studies

Dr. Pfefer went over skin pigmentation assessment methods. These include, ordered from least to most objective and quantitative:

- Racial/ethnic self-identification.
- Skin color descriptors.
- Sunburn susceptibility/color scale (Fitzpatrick skin phototypes. I-VI)
- Color scales (Massey-Martin, Munsell)
- Optical methods (spectroscopy, colorimetry)
- Biopsy with histological/optical processing or HPLC

Subjective methods are common, inexpensive, and easy, but less accurate and repeatable. Objective optical methods are currently not standard approach in dermatology.

CLARIFYING QUESTIONS FROM PANEL TO FDA

Dr. Cassiere asked for clarification about desaturation studies, which **Dr. Hendrix** provided. **Dr. Alam** wondered what the FDA wants in terms of objective pigmentation; **Dr. Eydelman** clarified that all information is welcome. **Dr. Loeb** sees potential for the statistical methods to compensate for confounding factors. **Dr. Connor** wondered what **Dr. Pennello** missed in his data presentation, and **Dr. Pennello** responded that mean bias comparison adjustments may be incorporated to account for confounding by other factors.

Dr. Hennessy asked the engineers if potential error could be a function of device calibration, to which **Dr. Lee** responded that a trained algorithm is responsible for accounting for these types of data refinements. **Dr. Pfeffer** added that adding wavelengths can improve the robustness of pigmentation measurements. **Dr. Connor** requested extra data clarification, which **Dr. Lee** and **Dr. Pennello** provided. **Dr. Collop** wondered if there is any way to account for pulse variations over a sleeping period, and **Dr. Lee** responded that these measurements are taken epoch to epoch. **Dr. Weininger** commented that in medical grade pulse ox devices, clinicians can smooth out the data to account for variations at different time points.

Dr. Nathan asked if there is a half-life on the accuracy of pulse ox devices, and **Dr. Lee** expanded upon pre-defined device shelf lives. **Dr. Nathan** also wondered if there is a correlation between the distal fingertip and other parts of the body in terms of pigmentation differences, to which **Dr. Pfeffer** responded that that is an open question and objective approaches would need to be studied further for a sufficient response.

Dr. Connor wondered whether currently marketed devices account for skin color in their algorithm; **Dr. Eydelman** responded not to her knowledge and said she will follow-up on this question. **Dr. Hennessy** asked about standardized preclinical testing data and what is included in that, and **Dr. Lee** emphasized that clinical testing is most desirable, but in initial phases, sensitivity to spectra and light are decent criteria. Finally, **Dr. Bickler** commented that skin perfusion is a complicated issue that goes beyond selecting a button indicating dark/medium/light skin pigment.

OPEN PUBLIC HEARING

Dr. Awajope read the Open Public Hearing Disclosure Process Statement. **Dr. Nathan** announced the receipt of nine requests to speak, the final three of which were delivered live.

Dr. Veronica Hickson of the Electrode Company provided a clinician's perspective, stating that practitioners must take pulse oximetry as a general guide to be used in conjunction with other diagnostic protocols and not as a stand-alone metric. She emphasized the importance of accuracy in medical devices to ensure the best outcomes for vulnerable patient populations that often rely on PO technology for diagnostics. She called for devices not confirmed within 3% at any SpO₂ level to be removed from market.

Sam Ajizian of Medtronic asserted that he stands with the effort to improve standards for POs and reduce health disparity. He presented data from his company suggesting that Nucor POs function slightly better in lighter-skinned individuals, but still function within FDA requirements

in darker-skinned individuals. He called for collaboration between public and private research and underscored his company's commitment to achieving health equity.

David Stricken, a physician at the University of Wisconsin, highlighted main points of the Hospital Medicine Re-Engineering Network's letter to the FDA on this issue. He proposed

- Extensive subgroup analyses on the basis of skin pigmentation, on the basis of race, and on the basis of gender, all separately
- Prohibiting race correction factors to avoid changing the devices themselves
- Pre-market testing in hospitalized patients, not just healthy patients
- More stringent approval requirements for prescription and OTC pulse oximeters, keeping separate requirements for OTC devices
- Proactive searches for racial bias
- Inter-agency collaboration
- Additional safeguards from FDA to detect and prevent biases in other diagnostic tools, perhaps instituting a dedicated committee
- Investing in independent research to uncover other sources of bias inherent to these devices

Grace Berson delivered a statement on behalf of the Federation of American Scientists and their partners at the University of Maryland Medical System. In her state of Maryland, an estimated 1,012 African Americans have occult hypoxemia when discharged from the System's Emergency Departments in the last year. She emphasized the negative impact of inaccurate pulse oximeter readings on patient outcomes, particularly in COVID-19 cases. She and her partners believe that FDA should

- require publication of testing data for current pulse oximeters to inform clinician use,
- reconsider which models of POs can be used as 510(k) predicates,
- only allow devices that have been tested on a diverse range of skin tones,
- employ both subjective and objective skin pigmentation assessments,
- require manufacturers to ensure their devices work in critically ill patient populations to mirror real-world usage,
- set a greater standard for accuracy for OTC PO devices, especially during the pandemic,
- fund research into low-bias and bias-free tools in collaboration with NIH and NSF,
- establish accelerated approval pathways for technologies proven to work in diverse populations.

Jeff Matthews of the Electrode Company expressed concerns that the market is becoming overwhelmed with inaccurate devices, largely because of inaccurate sensors and replacement sensors. He argued that it makes no sense to try to fix racial bias, as any adjustments will be swamped with manufacturing errors. He closed by claiming that the first step here is to insist that sensors are at least as accurate as they used to be.

Dr. Steven Barker, on behalf of pulse oximeter manufacturer Masimo, pointed out holes in some of the previous presenters' data. He referenced ambiguity towards manufacturer and device model and mixed models present in the studies, an approximately 10-minute time delay between blood gas analyses and SpO₂ pulse oximeter value readings, failure to account for dishemoglobins, under-reporting of low perfusion and patient motion, and under-reporting of illness severities and the presence of other hemoglobinopathies. He asserted that Masimo's recent research will be published in the Journal of Clinical Monitoring and Computing in confirmation of Masimo's accuracy across all individuals of all skin types. He noted that Masimo believes in prospective clinical studies and is pursuing these with mind to ethical considerations.

The full summary of Masimo's recommendations to the FDA panel was submitted as comments in the docket.

Dr. Eve Calender spoke on behalf of the National Center for Health Research, reporting no conflicts of interest. She advocated that marketable products should be proven to be accurate and reliable for everyone and called upon the FDA to require manufacturers to test devices in a higher percentage of individuals of dark pigment. She further asserted that objective skin pigmentation assessments are the only acceptable assessments, calling for more regulatory scrutiny in efforts to minimize biases.

Dr. Michael Abrams of Public Citizen's Health Research Group identified two major challenges that the FDA faces: first, racial equity; and second, deficiencies in the 510(k) pathway for clearing medical devices as it concerns racial equity. He urged a recall of all existing pulse oximeters with demonstrable racial bias and those without evidence for lack of bias. He also called for the 510(k) pathway standards to be revised to ensure that devices will only be marketed after they demonstrate reasonable safety and effectiveness in sufficiently minority-enriched populations.

Renee Kohi of the Consumer Technology Association reported no conflicts of interest. She posed a question: how do we help to prevent these types of issues from occurring in the future? She recounted CTA's work in developing a repository of work dedicated to fixing equity issues with healthcare devices. She emphasized the importance of inclusive design of studies and more diverse research teams. She implored the FDA to consider how to incorporate these factors into decision-making so to better satisfy diverse stakeholders. She also made a point to ask the FDA to look at reviews that encompass devices' entire life cycle to ensure similar inequities are not present in other categories of medical devices.

CLARIFYING QUESTIONS FROM PANEL TO OPEN PUBLIC HEARING SPEAKERS

No pertinent clarifying questions were able to be answered. **Dr. Nathan** prompted the beginning of the invited speakers' presentations.

INVITED SPEAKERS' PRESENTATIONS

Adult Patients' Perspective About Pulse Oximetry

Rekha Hagen spoke on the importance of accuracy for at-home pulse oximetry devices, as regular people – like her multiracial family – use them to inform their actions, particularly whether or not to seek medical attention. She mentioned that ease of use and insurance eligibility lend to the devices' credibility in a layperson's mind. She offered these suggestions to the FDA: include a skin tone color chart on the box of oximeters available over the counter or sell the device behind the pharmacy counter so the pharmacist can explain the device's limitations.

Ms. Hagen emphasized that she feels awareness of the issue is very limited in her community.

Pediatric Patients' Perspective About Pulse Oximetry

Jessica Cocolin cited literature reporting that pulse oximeter technology is known to be biased in currently marketed PO products and urged FDA to reassess device standards for testing and certification. She stated that there is great risk to delicate populations whose next steps are often confirmed by home-grade PO readouts that give a false sense of security. She is especially concerned about lower accuracy in individuals with darker skin.

Industry Perspective on Pulse Oximetry

Bob Kopotic presented an industry perspective on behalf of AdvaMed. He advocated for PO usefulness as convenient and noninvasive estimates and expressed a commitment to improving healthcare standards in this area.

Researcher Perspective on the Conduct of Pulse Oximeters Desaturation Studies

Paul Batchelder, Chief Clinical Officer of Clinimark, shared patient data, described conventional pulse oximeter statistics, and presented data from controlled clinical lab testing that found, when comparing to light skin over the range of 70 to 100%, the bias in dark skin is less than 1% SpO₂ for pulse oximeters. He reported that this indicates that the source of patient-reported bias may be something other than the basic design and engineering of the pulse oximeter.

Professional Society Perspectives on Pulse Oximetry

Dr. Amal Jubran of the American Academy of Sleep Medicine presented data showing that pulse oximeters are less accurate in darker-skinned patients.

Dr. Eric Gartman of the American College of Chest Physicians presented data that argues there are worse clinical outcomes for patients with dark skin for hidden hypoxemia. He highlighted challenges with PO accuracy overall and called the FDA to recognize test devices and ask manufacturers who they're testing these devices on, and to ensure those are the people that the devices are being used on.

Dr. Ann Rizzo of the American College of Surgeons stated that the College supports treating all patients equally and accounting for any disparities in equipment with blood testing and blood gases. She supports the effort to improve pulse oximetry's accuracy, especially considering sicker patients have disproportionately more inaccurate readings.

Jesse Ehrenfeld of the American Medical Association applauded the FDA for taking action on the disparities of PO technology. He called for warning labels to end users and more extensive real-world data collection and post-market surveillance to mitigate potential bias. He also strongly recommended that all healthcare providers be made aware of the limitations of this technology.

Dr. Stephen Gay of the American Thoracic Society made five points:

- POs can offer valuable clinical information to guide clinical care in the outpatient and inpatient settings.
- The medical and scientific community is aware that differences in skin pigmentation affect and impact pulse oximetry results and that such affects may adversely impact clinical decision- making.
- The COVID pandemic and increased reliance on pulse oximetry monitoring to initiate and adjust treatment for patients with COVID expose the problems clinicians see when treating patients with darker skin pigmentation when they must rely on pulse oximeter readings for decisions on care.
- Unless the skin pigmentation pulse oximeter issues are resolved, interim guidance on the appropriate use of pulse oximeter monitoring for patients with darker skin pigmentation should be developed.
- The pulmonary community in partnership with medical device industry and federal agencies must collect appropriate data to understand how skin pigmentation impacts pulse oximetry monitoring and must develop approved methods to ensure accurate interpretation of pulse oximetry saturation levels for all patients, including patients with darker skin pigmentation.

Julian Goldman of the Anesthesia Patient Safety Foundation announced that the APSF supports the renewed attention to the accuracy of pulse oximeter, which has revolutionized medical care and augmented patient safety, and she called for closer examination to improve pulse oximetry performance and its use in collaboration with clinicians, manufacturers, and regulators.

Garrett Burnett of the Society of Technology in Anesthesia expressed that the influence of dark skin pigmentation on pulse oximeters may impact clinical care and outcomes disproportionately, yet pulse oximeters will continue to be a vital tool for the practice of anesthesiology. This limitation should be recognized by clinicians and future technologies to adjust for this impact may be necessary. Evidence has shown that pulse oximeters have varying degrees of bias across all manufacturers, and while not every manufacturer has the same level of discrepancy, it's imperative that device manufacturers be held accountable for the performance of their product across patients of all ethnicities. Finally, considerations for increasing diversity of FDA validation and premarket testing should be considered to further address these disparities.

Elizabeth Bridges of the American Association of Critical Care Nurses noted that AACN was the signatory to the CCSC letters in 2021 and 2022 urging the FDA to direct developers and manufacturers of FDA-regulated pulse oximeters to test all devices to ensure accurate and reliable readings for patients with diverse degrees of skin pigmentation. She urged FDA to partner with professional societies, journal editors and organizations responsible for the development of guidelines and guideline standards to ensure bias is not perpetuated through dissemination efforts.

CLARIFYING QUESTIONS FROM PANEL TO SPEAKERS

Dr. O'Brien asked **Ms. Hagen** why her friend wanted an oximeter; she did not know. **Dr. O'Brien** also wondered if any instructions came with the oximeter she bought from CVS, to which she responded that she did not look. **Dr. O'Brien** asked **Mr. Batchelder** if skin pigmentation is really the cause of all the variance that is seen in the data, to which **Mr. Batchelder** responded that there are many combinations of conditions that influence device output, but skin pigmentation has proven an egregious issue thus far.

Dr. O'Connor pointed out to **Ms. Cocolin** that preemie data may require a different standard than for neonates and for adults.

Dr. Collop wondered if **Mr. Batchelder** would comment on if and how probes themselves should be analyzed; she also wondered if skin thickness has an impact on accuracy. **Mr. Batchelder** responded that skin thickness has an impact and that sensor placement, application, background, light injection, and detector sensitivity are all complex aspects of the probes that do not have stringent parameters at the moment.

Dr. Nathan requested clarification on whether obesity and tightness of grasp influence readings; **Mr. Batchelder** responded affirmatively.

Dr. Loeb asked if **Dr. Ehrenfeld**, from a clinical perspective, has changed his thought regarding accuracy in light of recent studies. **Dr. Gay** responded instead, stating that he believes clinicians have always assumed noninvasive devices are not fully accurate. **Dr. Rizzo** affirmed this.

Mr. Branson probed all the speakers for their thoughts on how to discuss what accuracy is so that laypeople are better informed. **Dr. Loeb** wondered why occult hypoxemia was chosen

as a benchmark indicator in many studies. **Mr. Goldman** answered the prior question by saying that clinicians are inherently suspicious of device readings.

With that, **Dr. Nathan** ensured there were no other questions and prompted more speaker presentations.

INVITED SPEAKER PRESENTATION: REAL-WORLD EVIDENCE AND PULSE OXIMETRY

Dr. Michael Sjoding presented nuanced research and put forth these recommendations: manufacturers must report pulse oximeter performance across racial groups; pulse oximeter studies must be powered to be able to detect small but clinically important performance differences across these groups; and pulse oximeter testing must align with clinical practice.

Dr. Ian Wong presented data and urged FDA to reevaluate accuracy standard and posed recommendations based on machine learning and artificial intelligence algorithms.

Dr. Ashraf Fawzy of Johns Hopkins University spoke on consequences of racial bias in pulse oximetry on clinical decision-making, highlighting his group's recently published research regarding patients infected with COVID-19. He emphasized that it is imperative to ensure that pulse oximeters perform equitably before further expanding their use because data currently suggests there is a significant clinical impact of these inequities.

Dr. Eric Gottlieb shared research from Harvard Medical School that further supports a racial bias of PO devices. He reported that minority patients received less supplemental oxygen than white patients for a given hemoglobin oxygen saturation, but not for a given pulse oximeter reading. He conjunctively showed that the gap between the pulse oximeter reading, the SpO₂, and the hemoglobin oxygen saturation mediates the observed racial disparities.

Dr. Phil Bickler of the EquiOx Study Group at UCSF described a study from his facility that is currently underway. The study aims to measure bias in PO performance in hypoxemic patients of varying skin pigmentation, determine what skin pigmentation metrics best correlate with pulse oximeter bias, and determine if POs perform at a regulatory standard level in clinical use.

Dr. Christopher Almond spoke of the launch of a prospective clinical study for PO accuracy evaluation by UCSF and Stanford, including a detailed list of limitations and procedures.

Dr. Michael Lipnick shared information about the UCSF Hypoxia Lab. He delineated these objectives: developing a research agenda for both regulatory and technology standpoints. We hope to not only identify but also test them and view data in real-time with the group. As well as to account for international perspective and attention to communities at risk in the U.S. and as well as globally. The group hopefully will account for total product lifecycle, design,

distribution, utilization. This would include not just the performance, but also procurement guidance as well as education and communication and implementation guidance. He also emphasized promoting clear and consistent communication, not only in the education piece and advocacy pieces, but also as it relates to data collection, definitions, best practices for data, doing so in a way that doesn't unnecessarily erode confidence in this essential patient safety tool. He discussed data sharing and inter-facility collaboration strategies.

CLARIFYING QUESTIONS FROM PANEL TO SPEAKERS

Dr. Nathan first inquired about the reference group for the hidden hypoxia study, and **Dr. Wong** replied that the reference group was the intervention group or the case group with hidden hypoxemia and gave technical specifications for these groupings.

Dr. Yarmus asked everyone if they had ideas for working solutions and clinical parameters the help adjudicate issues, and **Dr. Almond** weighed in that the scope of the problem is still being defined and gave a brief example from prospective trials for heart conditions.

Dr. Loeb asked **Dr. Wong** for clarification on the absorption spectra for melanin and water, and **Dr. Wong** elaborated on his graph. **Dr. Loeb** also asked **Dr. Bickler** if the ratio between red and infrared absorptions is accounted for; **Dr. Bickler** responded that it is. **Dr. Collop** furthered this by requesting details on calculations behind the perfusion index, which **Dr. Bickler** also provided.

Dr. O'Brien requested that **Dr. Bickler** address perfusion index errors, and **Dr. Bickler** commented that other parts of the body are often used if the oximeter is not producing reliable readings on the fingertip. **Dr. Nathan** asked if different anatomical sites are ever compared to gain insight into the effects of perfusion. **Dr. Bickler** responded that a study to that effect is currently underway with considerations for clinical aspects of the decision to use alternate body parts for pulse ox readings, rather than just moving the device around on an individual. He also added that baseline used is whatever the patient's reading is, and not a standardized measure.

Dr. O'Connor expressed that he finds comorbidity data collected prospectively for a full understanding of device limitations. **Dr. Bickler** noted that a wealth of information is collected in the studies, and **Dr. Almond** noted that moving the probe around is common practice in pediatrics. **Dr. Klein** announced he looks forward to the results of this work.

Dr. Nathan asked about patients who are not responsive to pulse oximetry due to the lack of pulsatile flow, and **Dr. Bickler** responded that, indeed, with some patients, one is simply out of luck if they do not have enough pulsatile activity. **Dr. O'Connor** added that LVAD cases are generally handled with a blood pressure cuff, and he also asked **Dr. Almond** what will be done with hemoglobin F in very young patients. **Dr. Almond** responded that the study is still in its early phases and information is being collected about hemoglobin F presently. To this, **Dr. Kopotic** added that studies show there is no effect from fetal hemoglobin, and he also added that in cases with medical conditions present such as polycythemia, reduced flow to peripheral sites warrants playing with sensor placement.

Dr. Hennessy finally inquired if higher rates of occult hypoxemia are seen in Black patients compares to white patients due to a higher presence of hypoxemia in Black patients, or if it's all due to the pulse oximeter functioning worse in that population. **Dr. Sjoding** responded

that the study accounted for prevalence in the populations, and he added that he believes residual occult hypoxemia is likely related to the fact that oxygen is titrating to SpO₂ rather than SaO₂. **Dr. Hennessy** also asked if **Dr. Wong** has a hypothesis on why Black patients had lower use of arterial blood gas, but **Dr. Wong** responded that they are unable to distinguish why this happened.

Dr. Gottlieb made final comments, noting that his study found that Black patients had lower SaO₂ but have higher SpO₂ than white patients, meaning that Black patients weren't necessarily more hypoxemic. **Dr. Gottlieb** also added that there is upcoming technology that can auto-titrate oxygen according to SpO₂, so disparities in this area could be seriously amplified with approaches like that.

PANEL DELIBERATIONS/DISCUSSION

Dr. Alam voiced a few comments to start. He first noted that skin pigmentation is inherently imprecise and can vary in a given individual between days, saying that it is a bit paradoxical to strive for precise measures of this. He further commented on the complexity of having device mechanics account for skin tone, and he supported the use of corrective algorithms. **Dr. Alam** finished by stating that OTC devices should not be neglected in the regulatory conversations but should not, in the name of public accessibility, be blanket-labeled as insufficient or medically useless.

Ms. Edwards contributed a personal anecdote and agreed that OTC oximeters should come with a warning or be made available behind the counter where a pharmacist can explain the device's limitations to a layperson.

Dr. O'Connor offered a few suggestions: 3% ARMS is too permissive, and the goal should be 1.5% or 2%. Further, he finds it necessary to have a statistically significant dataset between the saturation of 75 and 92%, because that's the domain where pulse oximetry will inform decisions. **Dr. O'Connor** suggested implementing Phase 3 trials in ICUs and ORs to get data from hypoxemic patients. He added that 2 light sources are almost definitely insufficient, and that devices need better signal processing on the signals they do incorporate. He underscored precision issues with met hemoglobin and carboxyhemoglobin. Finally, he expressed a desire to see designs that mitigate the influence of ambient light. He also vouched for a positive predictive value provided by manufacturers for every point between 92% and 77%. **Dr. O'Connor** also relayed that as a clinician, if he sees a saturation of 65% read out on an oximeter, he feels this is necessarily actionable information, and as such, it is not always practical to say that oximeters are to be used in conjunction with other tools.

Dr. Wilson concurred with all of **Dr. O'Connor's** points. He underscored the necessity of keeping parameters (1.5%, 2%) consistent between saturation levels, such as between 70% and 80%, between 80% and 90%, etc. **Dr. Wilson** also elaborated on the pros and cons of the different subjective pigmentation assessment types, which he finds necessary to employ, but is not sure which one is the most beneficial. **Dr. O'Connor** added that the classifications do not seem to accurately represent a realistic variety of skin colors. **Dr. Alam** contributed that Fitzpatrick typing is meant to assess how easily a person sunburns, not necessarily pigmentation; he further noted that different ethnicities may present as the same skin color, but their skin

structure and its ability to transmit light may be very different. To this, **Dr. Alam** suggested expanding the concept beyond just color to include other refractive qualities, like keratinocyte density, etc.

Dr. Nathan added that in this situation, equal representation of skin tone in a study means equal chance of having accurate measurement, and that the 15% minority standard employed historically may not be fully appropriate here.

Dr. Cassiere expressed a contrary view to his peers, that subjective scales are not as effective as self-reporting but concedes that there is not hard data to determine this. **Dr. Nathan** furthered this by saying scales may be unnecessary and manufacturer use of self-reported information is their responsibility to prove efficacy. **Dr. Cassiere** expressed a desire to see a 1.5% or 2% boundary for accuracy, calling it a ‘reliability index.’

Dr. O’Connor expressed a need for a statistically significant number of patients of darker skin color, calling the 15% “the wrong metric.” **Dr. Nathan** agreed.

Dr. Loeb advocated for nuanced gradients in individual skin tone that are beyond the ability to self-report, which **Dr. Wilson** seconded. He suggested using equal numbers of darkly and lightly pigmented individuals for studies and found it pertinent to perform studies under conditions of good perfusion only. **Dr. Nathan** contributed that the phase 3 population will likely need to be real-world and not a highly selected population.

Dr. Kirsch celebrated all the great comments thus far and emphasized that there are disparities with weight/BMI across different populations, encouraging the FDA to account for this. **Dr. Nathan** affirmed this.

Dr. Collop reminded that there is variability in oxygen saturation during sleep, and **Dr. Nathan** found this point relevant to knowing whether or not to burden patients with transportable oxygen.

Mr. Branson stated that self-identification of race is too subjective to be clinically meaningful.

Ms. Edwards inquired how FDA defines “darkly pigmented” since even within a given ethnicity, pigments vary vastly. **Dr. Nathan** seconded this. **Ms. Edwards** ascertained that, if the issue lies with darker pigmented individuals, that a study containing exclusively darker pigmented individuals may elucidate device issues. **Dr. Eydelman** added that the FDA is having this discussion in part because of the absence of a hard definition for “darkly pigmented” and seeks the panel’s input on this cutoff. **Dr. Nathan** suggested that there should be a scale.

Dr. Yarmus brought up the issue of how the devices are accessed and regulatory concerns surrounding access, highlighting a need for providers to know the difference between medical-grade POs and a drugstore PO.

Dr. Hudson and **Dr. O’Connor** agree with the above about outpatient devices. **Dr. O’Connor** wondered about the feasibility of an intermediary device between medical grade and drugstore grade, which **Dr. Eydelman** said is what they consider a take-home prescription device.

Mr. O’Brien chimed in from a patient perspective and suggested audiovisual learning aids to educate patients and providers in the digital era.

Dr. Cassiere asserted that consumer devices have their merit provided users understand the limitations. **Dr. Nathan** agreed, provided there is accessible and meaningful labeling, and he

prompted the panel for their ideas on how to label such that a consumer will read the information. **Dr. Hudson** disagreed and felt that it harms the public to have access to these devices, since no one is using them recreationally, but rather medically, and their medical merit is questionable. **Dr. Nathan** suggested, when questioned by **Dr. Eydelman**, that the verbiage on layperson-focused devices should center that it is not for medical usage.

Dr. Nathan inquired whether wearable devices are regulated differently; **Dr. Lee** responded that, yes, those fall under sports and aviation.

Dr. Hennessy said that patients will tend to always assume the readings are accurate.

Ms. Edwards agrees that there needs to be a warning that OTC PO devices are not for medical use. **Dr. Klein** worried that low literacy consumers will be missed by educational information enclosed in the device packaging. **Dr. Klein** also worried that it is the probe and not the device itself that causes many issues with at-home use.

Dr. Alam does not see these devices as health and wellness devices and asserted that reclassification of the OTC devices is essential. **Mr. O'Brien** echoed this.

Dr. Nathan reminded the panel that PO devices had mediocre performance across all populations and prompted the panel to make recommendations on improving overall accuracy.

Dr. Hudson stated it should not be hard for a manufacturer of a medical-grade device to curate their standards to a more effective OTC device, as the manufacturers of these two product types are often the same companies.

Dr. Yarmus added that inpatient and outpatient use should be treated equally.

Dr. Loeb then contributed that the main problem with both medical and OTC devices is the signal to noise ratio, aka profusion index. In OTC devices, the signal to noise ratio can be less sensitive because it can be assumed relatively healthy individuals are using the device. He supported an external display of signal to noise ratio on the devices when they make their readings.

Dr. Pfefer contributed some thoughts: the priority here is to make sure individuals with the darkest skin pigments are not missed, and additionally, melanin is the main contributor to pulse oximeter discrepancies per the literature, not race/ethnicity. He briefly elaborated on some of the subjective pigmentation scales, which **Dr. Nathan** still found too ambiguous and subjective, favoring objective assessments.

Dr. Connor disagreed with home use of these devices, arguing that not having pulse ox information available OTC would not be that detrimental to the general public.

Dr. O'Connor thinks that LED technology is advanced enough to roll out high-grade PO devices to the public within a few years if the racial bias can be rectified. **Dr. Alam** agreed and added that FDA should not decommission any of the currently available devices. **Dr. Nathan** added that it is expensive and takes time and money for manufacturers to adapt to newly implemented standards.

Dr. Yarmus suggested that there should be a very strict and straightforward message to inpatient care providers about the limitations of the devices since that is where they are used most critically.

Dr. Wilson suggested that the FDA could send out a notice warning to physicians and patients that if the patients are being monitored at home for a medical condition, it should be with a medical grade pulse oximeter. **Dr. Nathan** agreed but pondered whether patients could guarantee they are going to get a medical grade device if they have a prescription. **Mr. O'Brien** voiced concerns over patient ability to pay for the devices if they need a prescription.

Dr. Kirsch noted that bad results from an at-home device can lead to costly and potentially harmful further testing once a patient visits their physician on those concerns.

Dr. Lynch agreed with the prior comments and underscored that the primary issue is where the guidelines are set to say that the reading is problematic for different skin types.

Dr. Katz noted some holes in the preemie studies and contributed that a false sense of comfort given by the devices can be dangerous.

Dr. Cassiere commented that desaturation studies under low perfusion states are the critical piece of information needed to inform regulatory decisions. **Dr. Nathan** agreed that prospective studies do not need to be detailed here and that the important part is the performance threshold. **Mr. Branson** agreed and also said he wanted to see better ARMS parameters.

Dr. Wilson added that not all PO devices are created equal and holding all manufacturers to a higher standard should be the goal. He cautioned the FDA against allowing warming of extremities and advised very rigid guidelines for how well the extremity is perfused.

Ms. Edwards finished the discussion by reminding the participants that the disparity in care for African Americans is how this whole discussion started.

Dr. Nathan adjourned the deliberations and moved on to the FDA questions to the panel.

FDA QUESTIONS TO PANEL

Question One

Please discuss the clinical evidence from the scientific literature about the accuracy of pulse oximetry among patients with darker skin pigmentation. In your deliberations consider the strengths and limitations of the studies, including study design, outcome definitions, and potential confounding factors that can impact interpretation of the evidence. Specifically, please address the following:

- a. Does the currently available clinical evidence demonstrate disparate performance in patients with darker skin pigmentation? If so, do you believe such disparate performance may lead to increased risks? Please include prescription use and OTC pulse oximeters (when used for medical purposes) in your deliberations.
- b. Do you believe the reported disparate performance or increased risks may be explained by factors other than darker skin pigmentation such as perfusion index, motion artifacts?

Dr. Nathan summarized the panel’s contributions from **Dr. Loeb, Dr. Hennessy, Mr. Branson, Dr. Connor, Dr. Collop, Dr. Cassiere,** and **Dr. Yarmus.**

“The panel believes clearly there is a disparate performance in patients with darker skin pigmentation, and this increases the patient’s risk for their given disease outcome. Even though we didn't see data on over the counter usage, we know that these are used by patients on the outside to gauge whatever illness they might have, so we believe that this effect that we are seeing from the numerous studies on inpatients probably has ramifications for the outpatient use of over the counter devices as well.”

“With regards to a, we do believe that other factors, and clearly perfusion, plays a role. Not just pigmentation, but perfusion, and perhaps demographic factors in terms of the width of the finger, the breadth of the finger, and obesity. And so there are factors beyond pigmentation, but certainly pigmentation is the main reason why there is this disparity. As the FDA looks at this, we would encourage the FDA to consider these other issues as well that can perhaps be addressed in some fashion at the same time.”

Question Two

There are several tools to assess skin pigmentation, including but not limited to, colorimetry, spectrophotometer, melanosome volume fraction, and skin color scales (e.g., Fitzpatrick scale, von Luschan color scale). Please provide recommendations for studies evaluating pulse oximeters, for the following:

- a. Standardization of skin pigmentation assessment.
- b. Categorization and reporting of skin pigmentation data.

Dr. Nathan summarized the consensus of **Dr. Cassiere, Dr. Loeb, Dr. Hennessy, Dr. Yarmus, Ms. Edwards, Dr. Collop, Dr. Connor,** and **Mr. Branson.**

“The panel generally believes that yes, there should be standardization of skin pigmentation assessment, which should include an objective measure ideally, but can also include one of these more subjective measures, like the Fitzpatrick scale. It should be easy enough to include both.”

“Identified race should be included as part of the demographics captured, and there should be equal representation across the spectrum of skin pigmentation.”

“Categorization should ideally be based on objective measures but also can include these visual analog scales to complement that.”

“The reporting of skin pigmentation can be categorized by all the mechanisms, including the subjective color scales, as well as subgroup analyses based on race.”

Question Three

FDA currently recommends assessment of the effectiveness of pulse oximeters using Arms [Root mean square of pooled data pairs], and adherence to the currently recognized

ISO 80601-2-61:2017 standard. For this variable (Arms), currently, pulse oximeters are expected to have accuracy within 1 standard deviation (SD) (66% of the time), and within 2 SD (95% of the time). Please address the following:

- a. Please discuss how accurate pulse oximeters should be for clinical use. In your discussion, please address whether the accuracy varies based on:
 - (i) the clinical setting or
 - (ii) the levels of SaO₂.
- b. Please discuss your recommendations for pulse oximeters performance across sub-groups of subjects with different skin pigmentation.
- c. Please discuss if Arms is an appropriate measure of device effectiveness for clinicians and users. If you do not believe Arms is appropriate, please discuss alternative methods to assess the accuracy of a pulse oximeter.

Dr. Nathan summarized the consensus that the parameters should be tightened to 1.5% or 2% and that everyone is generally uncomfortable with the lack of clinical data in manufacturer development reports, especially as it relates to hypoperfusion and oxygen saturation, which should be validated across the SpO₂ spectrum from 70% to 100%. As such, no one feels quite comfortable throwing out a number how best to define accuracy.

For b, **Dr. Nathan** stated that the panel believes there should be equal representation across different skin pigmentations.

For c, the panel stuck with an ARMS of 1.5 O₂, saying that it is up to the companies to translate that marker into something that's more clinically meaningful.

Question Four

Current labeling for prescription uses pulse oximeters is intended for clinicians and generally it does not address inaccuracies that may be associated with skin pigmentation. In your deliberations, please discuss:

- a. Labeling modifications to address inaccuracies that may be associated with skin pigmentation.
- b. Recommendations for the content of labeling for lay users who may use pulse oximeters at home.

The panel unanimously endorsed **Dr. Nathan's** proposal to use language that says, simply, "Not approved by the FDA for medical use." The panel agreed that there should be a maximum degree of transparency around labeling modifications and potential skin biases.

Dr. Nathan addressed part b by saying that the prescribing physician holds a large level of accountability for the weight placed on the results of a take-home pulse oximeter and that the clinician/pharmacist should provide detailed instructions.

FDA SUMMATION

Dr. Alderman thanked the invited speakers and the Open Public Hearing speakers for their opinions, thanked the panel members for their deliberations, and thanked the FDA for their participation, and pronounced the panel meeting complete.

ADJOURNMENT

Dr. Nathan thanked the FDA, panel, speakers, and Open Public Hearing participants and adjourned the meeting.

I approve the minutes of this meeting as recorded in this summary.



Steven Nathan, M.D.,
Chairperson

12/01/2022

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November 14, 2022

I certify that I attended this meeting on November, 01, 2022 and that these minutes accurately reflect what transpired.

Akinola Awojope
Designated Federal Officer