Prospective Clinical Study to Evaluate the Accuracy of Pulse Oximeters in Pediatric Patients with Increased Skin Pigmentation

UCSF-Stanford Center of Excellence in Regulatory Science and Innovation (CERSI)

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Objectives

1. To review briefly the study design/rationale of the pediatric pulse oximetry study and to provide an update on the status of the pediatric study.

2. To review the baseline characteristics of the study cohort including the distribution of skin pigment using subjective and objective scales

3. To examine the correlation between individual typology angle (ITA) or colorimeter and pigment scales

4. To review some of the challenges and lessons learned from conducting a pediatric study in pulse oximetry.

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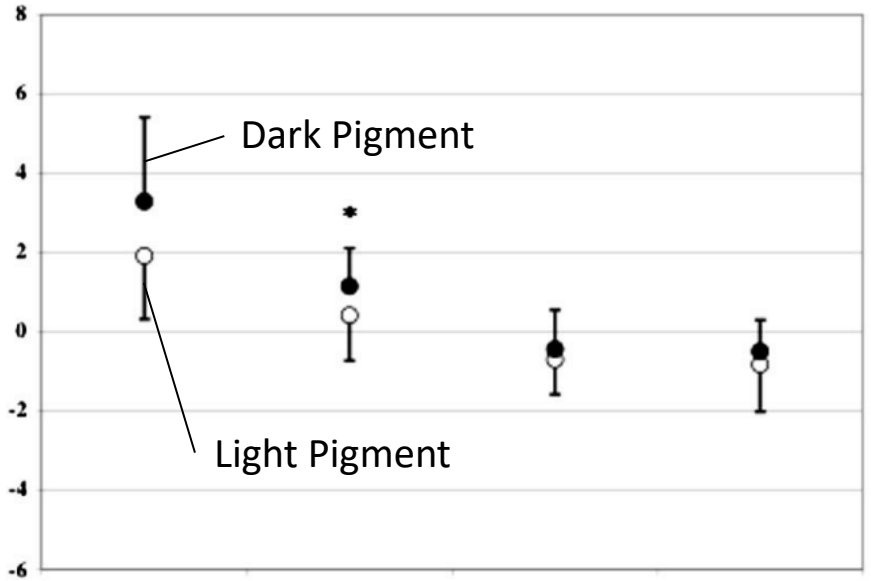
BACKGROUND/RATIONALE

- In infants and children, pulse oximetry is widely used to determine whether a patient is adequately oxygenated. Studies suggest that pulse oximetry systematically overestimates the true oxygen saturation in patients with darker skin pigment
- This error—or bias—puts children with darker skin pigment at considerable risk by failing to detect important levels of hypoxemia that drive critical treatment decisions like medications (COVID), hospital admission, ICU transfer, intubation and ECMO.
- Prior studies have understandable limitations r/t their retrospective design:
  1. Use of race/ethnicity as a proxy for skin pigment
  2. Oxygen saturations extracted from the EHR may not be simultaneous (S_p02 and S_a02) or drawn at steady-state
  3. EHR has limited information on factors like motion artifact, perfusion quality, & temperature difficult that directly impact measurement validity.
- The purpose of this prospective real-world study is to address these limitations

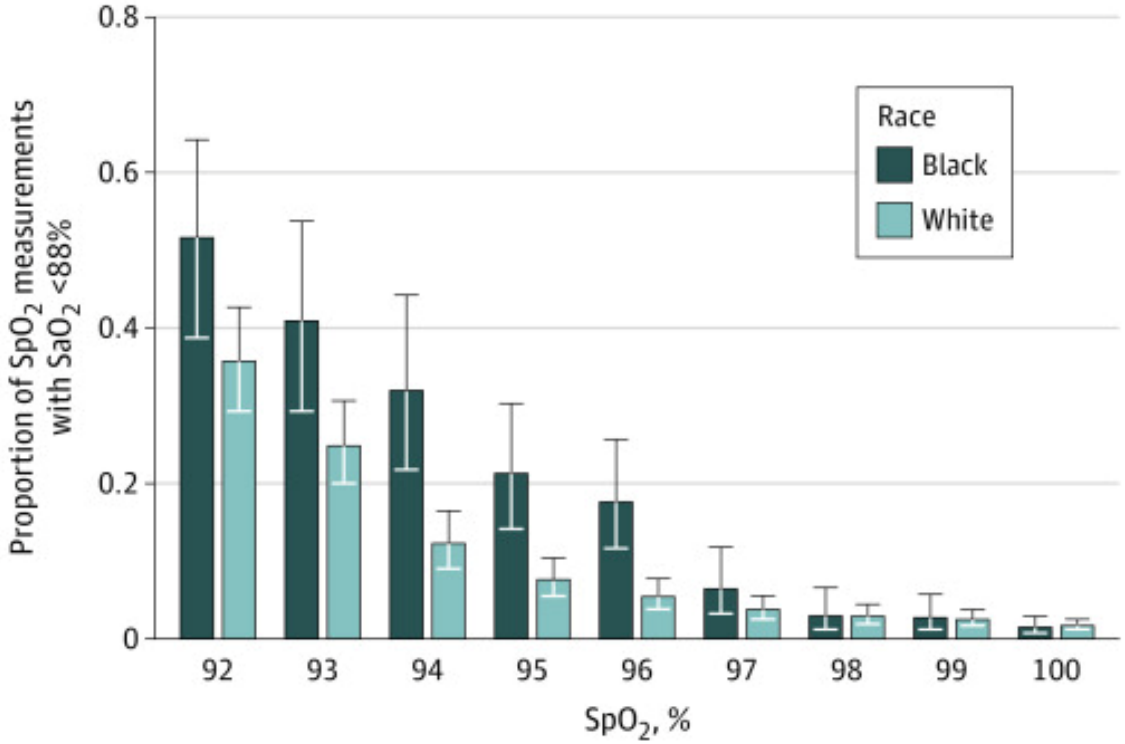
BACKGROUND

2005



PE Bickler, et al. Anesthesiology, V 102, No 4, Apr 2005

2022 (COVID era)



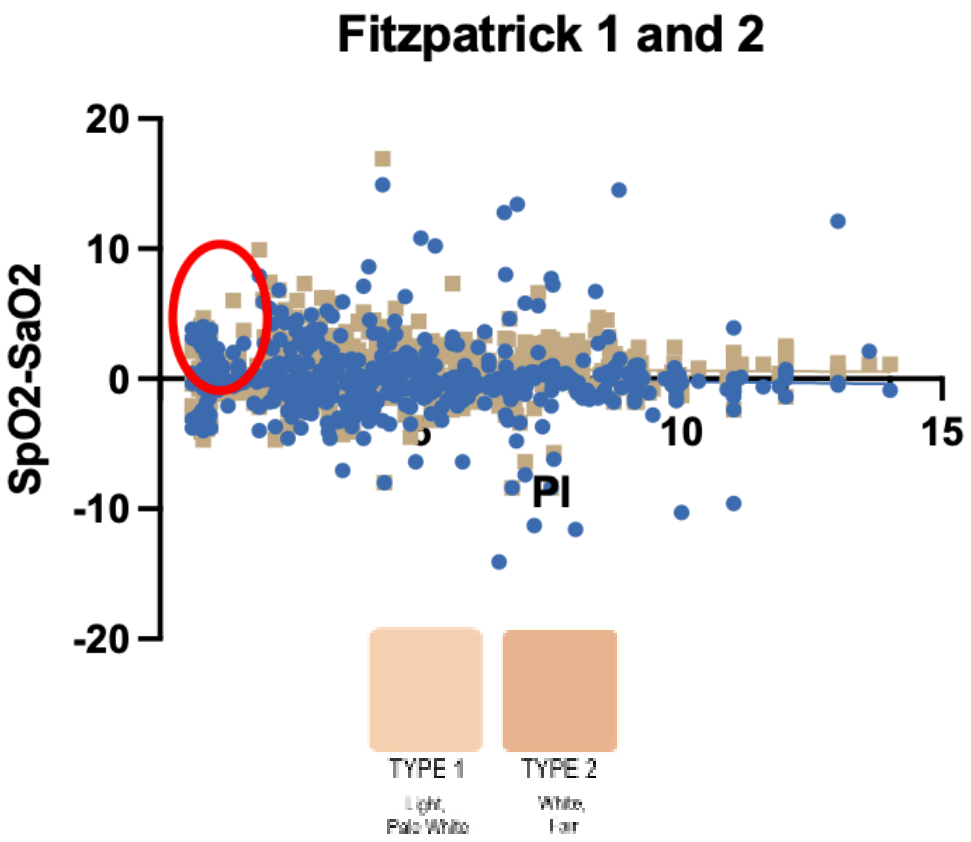
Sjoding et al, NEJM, 2020
Andrist et al, JAMA Pediatrics, 2022 (N=1061)
Ruppel et al, JAMA Pediatrics, 2023 (N=774)

STUDY DESIGN

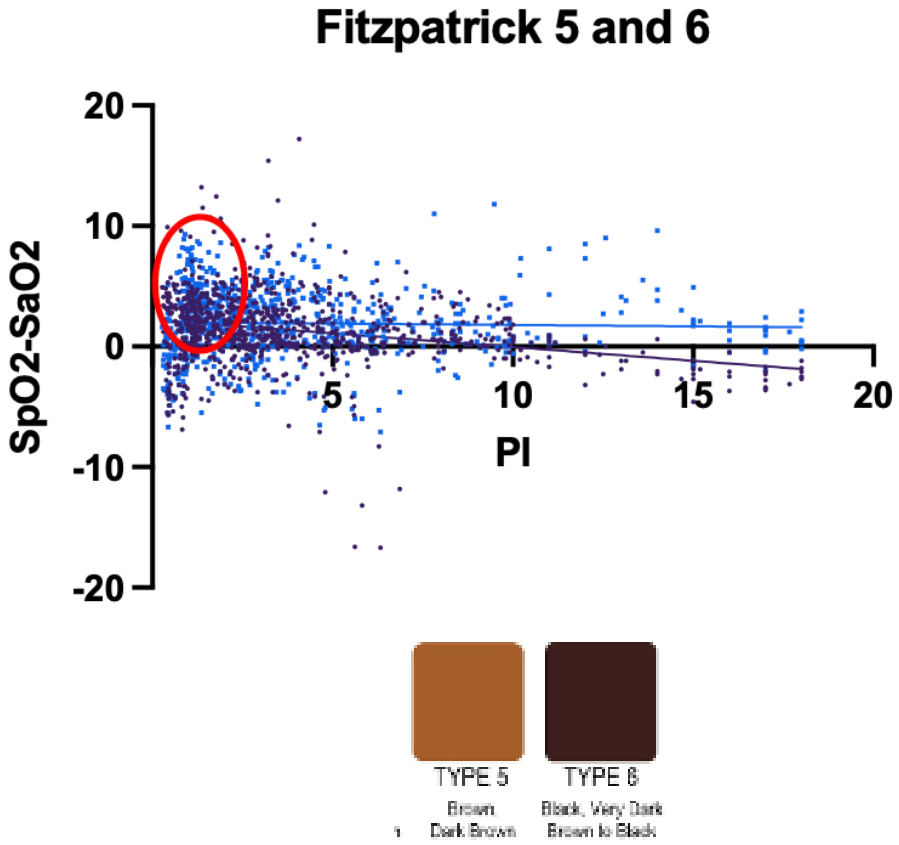
- **Study Design**: Prospective single-center study (now multicenter)
- **Eligibility Criteria**: Non-anemic children age ≤21 years with an arterial line where written informed consent obtained from patient or LAR
- **Setting**: Hospitalized children—cardiac catheterization laboratory, Cardiac ICU, Cardiac Operating Room
- **Exposure variables**: skin pigment as measured by the Von Luschan (VL) scale, Monk Skin Tone (MST) scale, Fitzpatrick Scale. Individual typology angle (ITA) as measured by Konica Minolta (CM-700d) and Delfin colorimeters.
- **Outcome variables**: Sp02 (Masimo RD) and Sa02 (Radiometer ABL90 Flex)
- **Secondary variables:** perfusion index (PI), age, self-report race/ethnicity, location, carboxyhemoglobin, temperature, diagnosis, medications.
- **Sample Size:** 154 subjects (evenly divided across 4 VL categories, N~38 each)
- **Data Monitoring Committee:** interim look to re-estimate sample size.

The error may be magnified at low perfusion (Bickler et al, UCSF)

Mean bias not evident at PI < 2 (red circle) in adult subjects with lighter skin pigmentation as defined by Fitzpatrick 1-2 skin pigment.

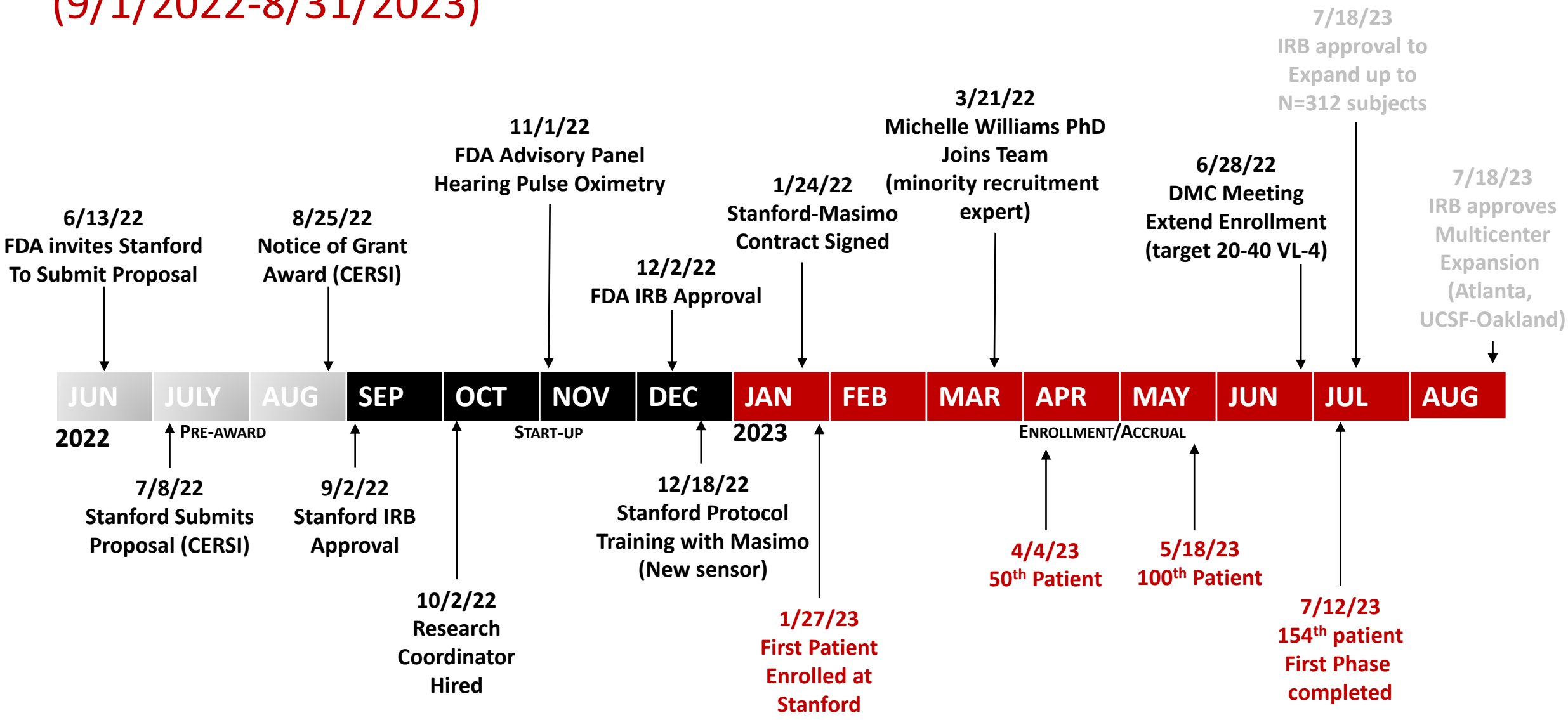


Mean bias evident at PI <2 (red circle) in adult subjects with darker skin pigmentation as defined by Fitzpatrick 5-6 skin pigment.

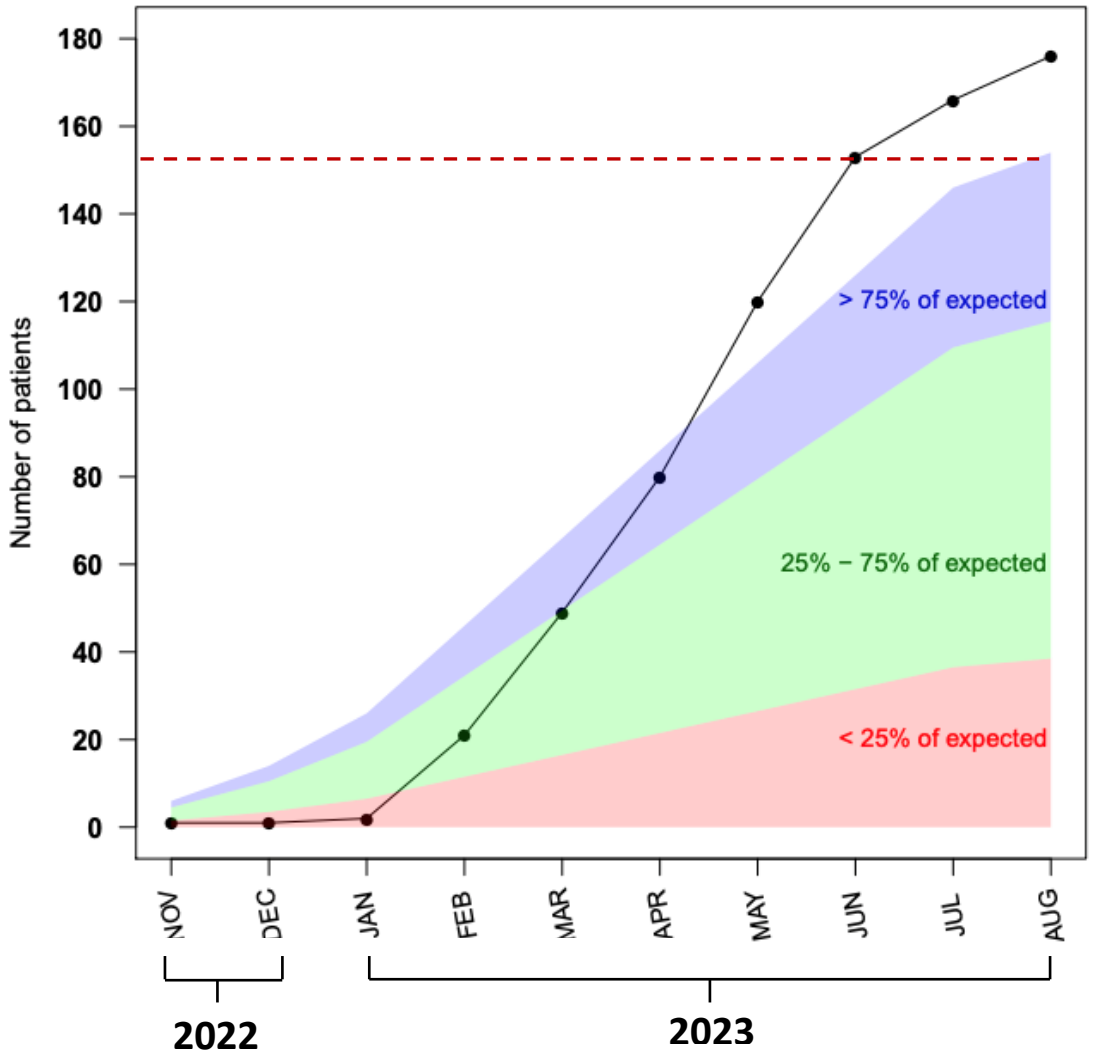


Update on the status of the pediatric pulse oximetry study

Study Timeline
(9/1/2022-8/31/2023)



Trial Enrollment (Year 1)
(9/1/22-8/31/23)



N=176 (actual)

N=154 (target)

Total Children Eligible
N=194

Declined Consent
N=18 (9%)

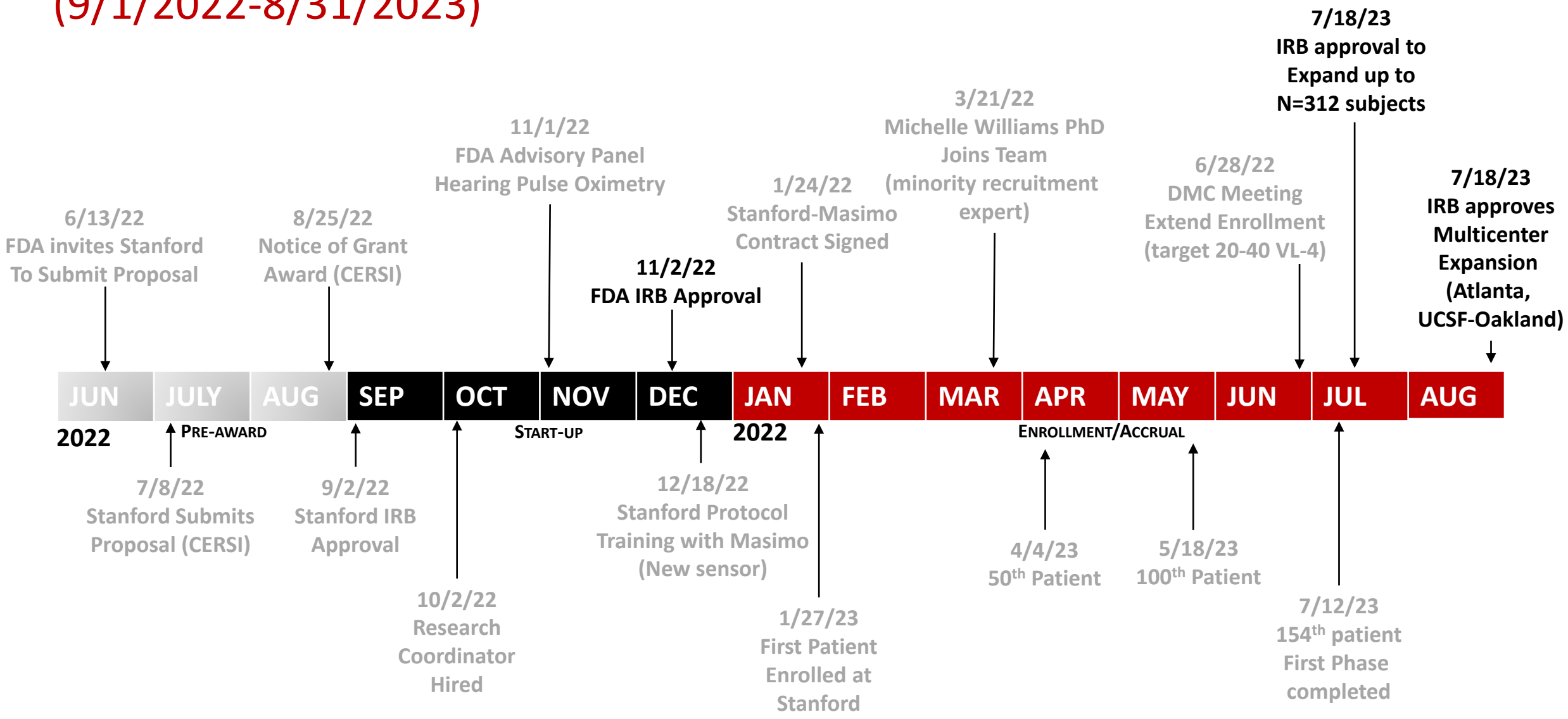
Total Patients Eligible
N=176

(91% consent rate)

VL Category 4 patients underrepresented in enrollment leading the DMC to expand enrollment to N=312 with goal of 20-40 VL Category 4 patients

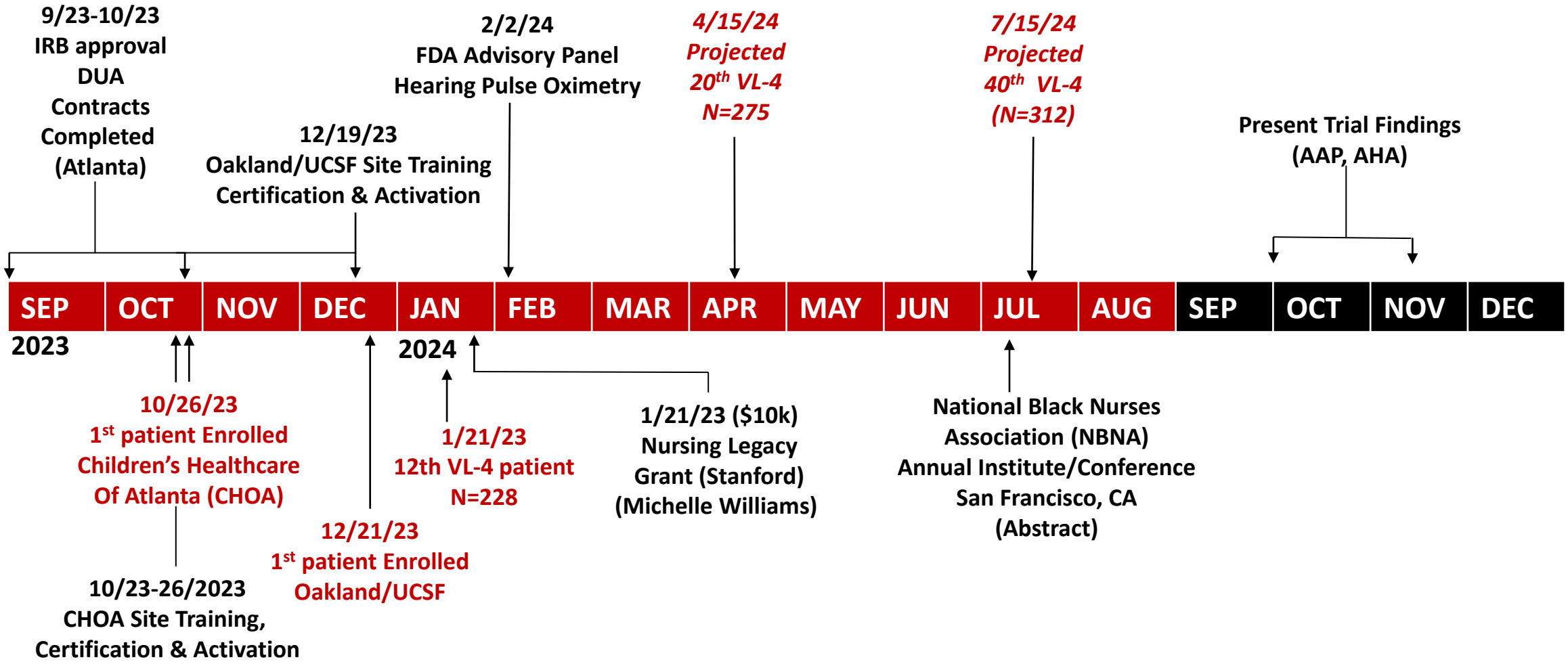
Courtesy Weiguang Yang, PhD (Engineer, Stanford Dept of Pediatrics)

Study Timeline
(9/1/2022-8/31/2023)



Study Timeline

(Year 2 Expansion, 9/1/2023-present)



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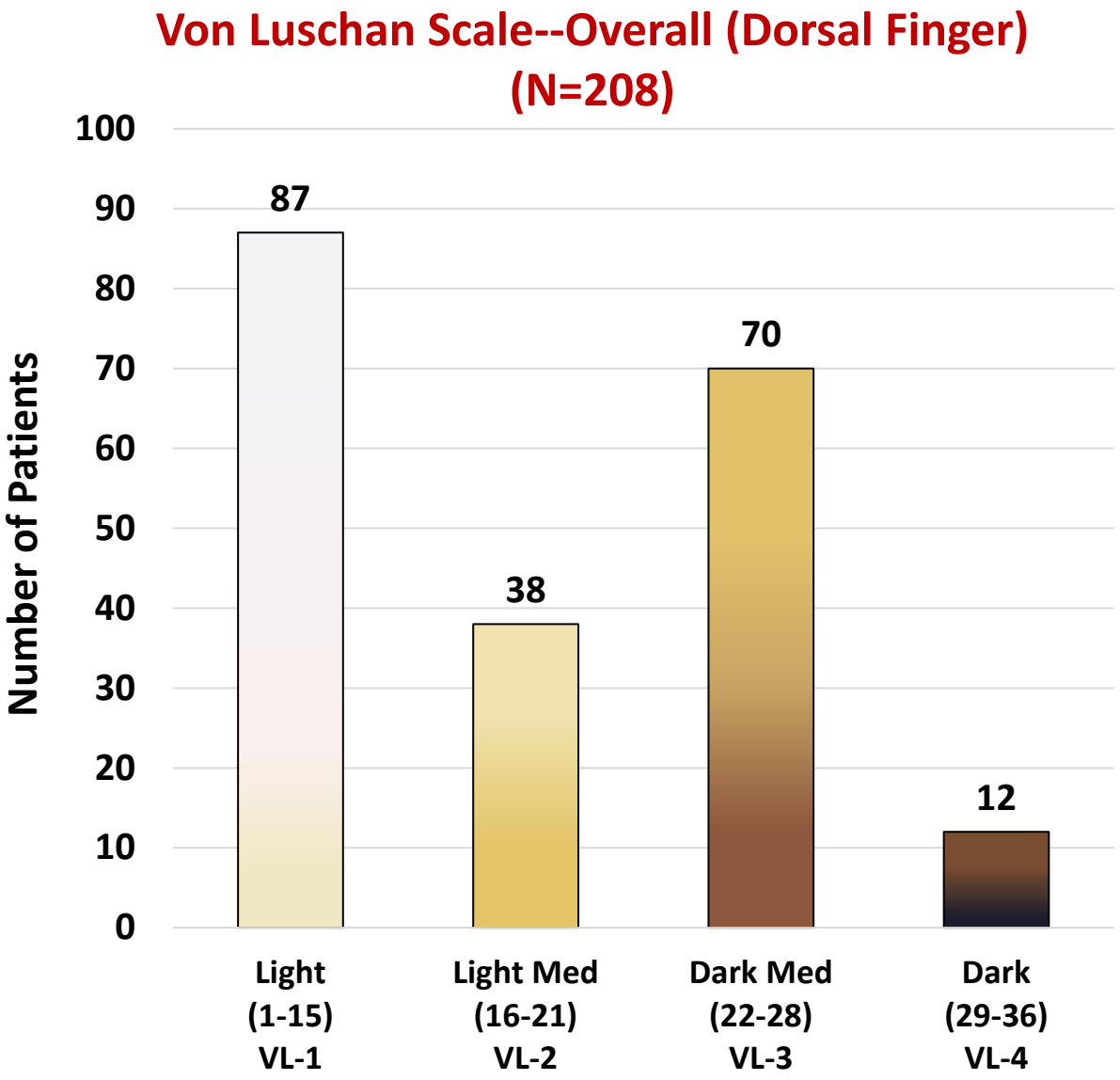
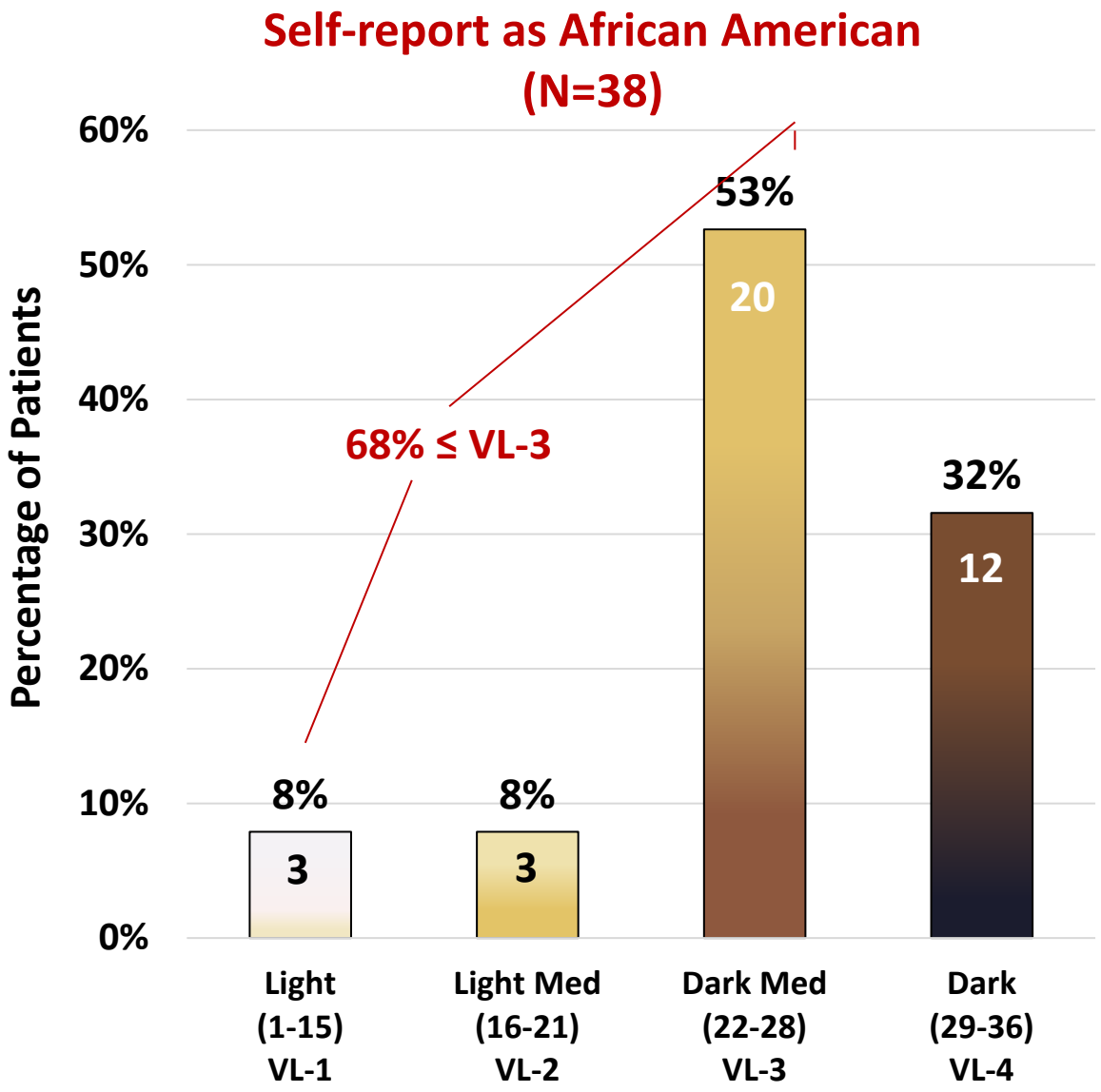
Baseline Characteristics (N=228)

Characteristic	N (%) or Median (range)
Age—years	4.9 years (4 days to 21.8 years)
<2 years	76 (33%)
2-12 years	70 (31%)
12-22 years	82 (36%)
Female sex (%)	114 (50%)
Hispanic/Latino ethnicity (%)	78 (34%)
Race categories (self-reported)	
White	77 (34%)
African American	38 (17%)
Asian	30 (13%)
Hawaiian/Pacific Islander	5 (2%)
Other	75 (31%)
Baseline $Sp0_2$ <90%	29%
80-89%	16%
70-79%	12%
60-69%	1%

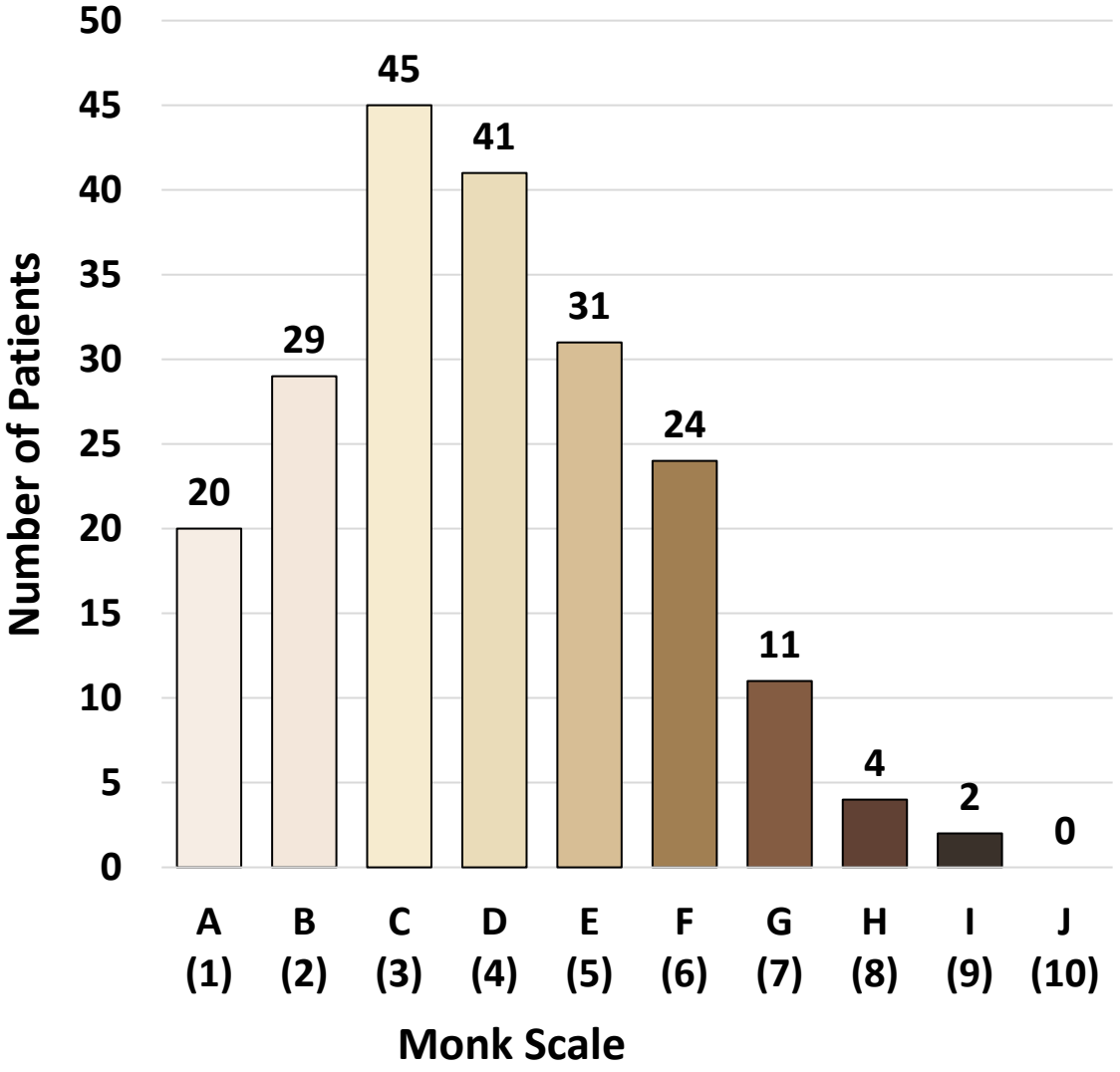
Enrollment by 4 Von Luschan Categories



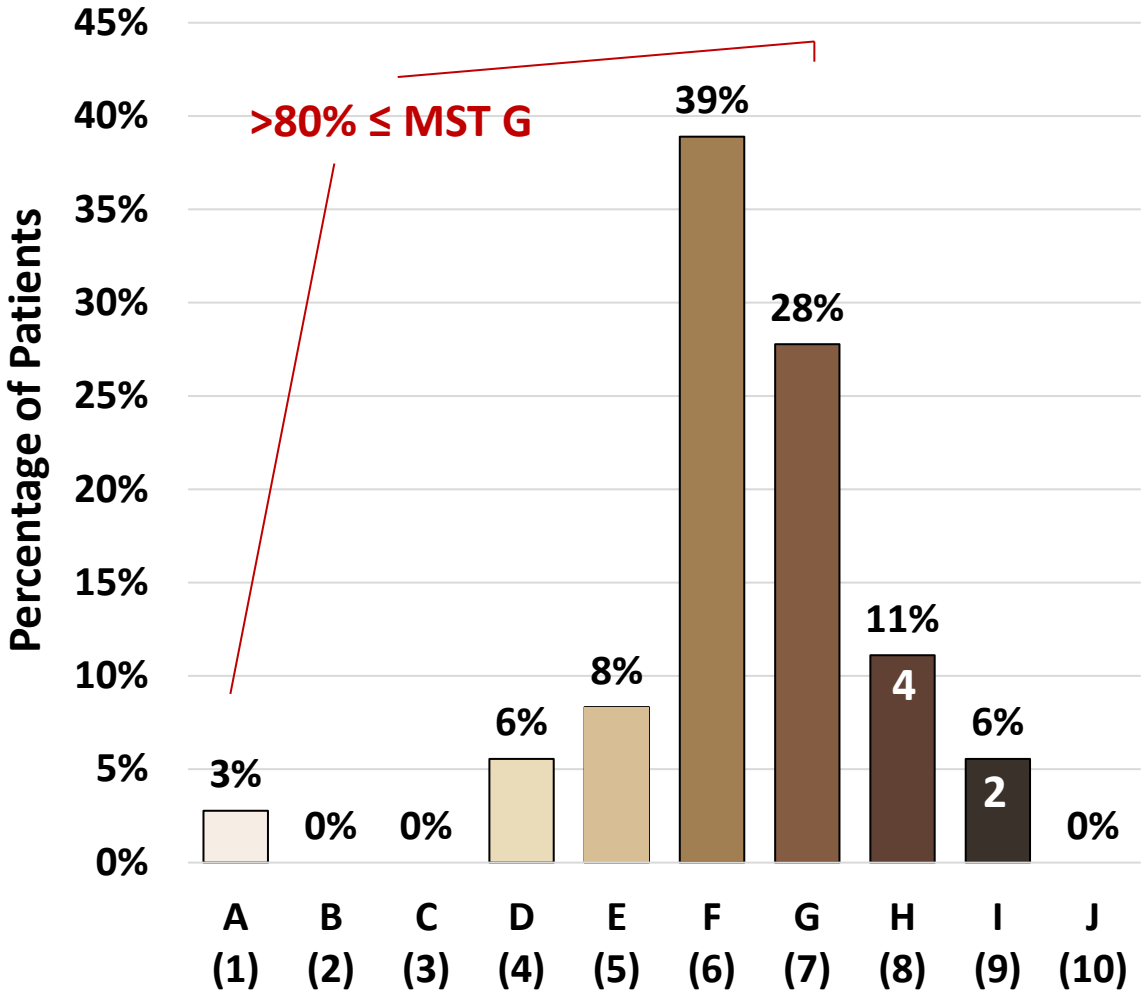


Pediatric Enrollment by Monk Skin Tone Test

Monk Scale—Overall cohort (N=208)



Monk Scale—Self-report African American (N=38)



Among 36 African American children enrolled, >80% had an MST scale ≤7

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Spearman correlation Statistics between Pigment Scales in Children

Skin Pigment Scale	Monk Skin Test-10 ρ (Overall)
Von Luschan-36 (DF)	0.89 (0.86 to 0.93)
Von Luschan-4 (DF)	0.86 (0.82 to 0.89)
Fitzpatrick-6 (DF)	0.87 (0.83 to 0.91)

Spearman Correlation between Pigmentation Scale and ITA (Colorimetry) in Children

Skin Pigment Scale	ITA (Colorimetry) Location	Konica Minolta Spearman's ρ (95% CI)	Delfin Spearman's ρ (95% CI)
Von Luschan-36 (DF)	DF	0.72 (0.63 to 0.81)	0.79 (0.72 to 0.86)
Von Luschan-4 (DF)	DF	0.69 (0.50 to 0.78)	0.77 (0.71 to 0.83)
Monk-10 (overall)	DF	0.69 (0.60 to 0.78)	0.76 (0.70 to 0.83)
Fitzpatrick-6 (DF)	DF	0.70 (0.62 to 0.78)	0.76 (0.70 to 0.82)

ITA Categories: (1): ≥50, (2) 26 to 49, (3) -34 to +25, (4) -44 to 35, (5) ≤-45

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#1. Strategies to enhance minority recruitment can be effective

1. Prioritized VL-4 category patients for approaching and enrollment
2. Favored minority concordance b/w investigators & patient/family where possible.
3. Developed a weekly dashboard to track minority recruitment/enrollment
4. Recruited Michelle Williams PhD to the team to identify strategies to enhance minority recruitment
5. Developed a study brochure that is demographically diverse
6. Enhanced communication strategies (i.e., highlight in the introduction that study is *designed to identify racial bias in hopes of addressing it)*
7. Expanded recruitment to include electronic consent (i.e., for families that must work while their child is hospitalized) and hospital-wide.
8. Expanded study to 2 additional sites (Atlanta/Emory, Oakland/UCSF) (i.e., a multicenter study)

Study Expanded to Two Additional Sites

CHILDREN'S HOSPITAL OF ATLANTA (CHOA)

Emory University

PI: Dr. Laura Downey (peds cardiac anesthesia)

Co-PIs: H Bauser-Heaton (cath), M Mills (CVICU)

OAKLAND CHILDREN'S HOSPITAL

University of California-San Francisco

PI: Dr. April Edwell (Pediatric Intensive Care)

Co-PI: Patrick McQuillen (PICU, Research)

…Other Lessons Learned

Other Challenges	Lesson Learned
2. No widely accepted pigment scale available at study launch	• Collecting data on 3 common scales for comparison • Collecting ITA data for objective comparison
3. Children's fear of Colorimeter (Konica) b/c it has appearance of large weapon	• Involved Child Life experts in smaller, non-sedated children
4. Reduce the impact of pre-analytic factors (handling, processing, timing) on Sa02 measurement	• Used a validated portable blood gas analyzer (Radiometer ABL90 Flex) for all study patients rather than sending to the clinical lab
5. In cardiac OR, oxygen saturations too dynamic to assess reliably, while on CPB, no pulse	• Shifted enrollment from OR to cath lab and Cardiac ICU.
6. Parents may not be available at the bedside because of need to work or other children	• Obtained IRB approval for remote consent (Adobe-Sign)

Conclusions

1. The SPOT BIAS study is designed to determine whether racial bias exists in a contemporary FDA-approved oximeter in children across a wide range of ages.
2. The study has enrolled >225 children across 3 children's hospitals to date and is expected to complete enrollment in the coming months
3. The correlation between the Monk Skin Tone Scale and older pigment scales appears reasonably strong. Initial studies suggest pigments scales correlate moderately with ITA values using two colorimeters.
4. While we've encountered a variety of challenges in conducting the study, most have been addressable and should allow us to answer the study question while also helping to inform the design and conduct of future pediatric oximetry studies.

Pediatric Pulse Ox Collaborators

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Michelle Tarver (FDA Co-Lead)

Malvina Eydelman (Collaborator/Oversight)

Allison O'Neill (Safety Signal Coordinator)

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Rebecca Torguson (Statistician)

Rebecca Ward (Epidemiologist)

Vasum Peiris (Pediatric Cardiologist)

Damia Jackson (FDA PM)

Thank You!

US Food and Drug Administration

UCSF EquiOx Study Team
Children's Health Care of Atlanta
Oakland Children's Hospital

Patients and their families