Official Title: SpO2 Accuracy of Noninvasive Disposable Pulse Oximeter Sensor

NCT Number: NCT05245526

Date of Protocol: January 19, 2022

General Information

1.0 Purpose

1.1 The purpose of this clinical study is to validate the SpO2 accuracy of the Stryker Sustainability Solutions pulse oximetry sensors during non-motion conditions over the range of 70-100% SaO2 as compared to arterial blood samples assessed by CO-Oximetry. The end goal is to provide supporting documentation for the SpO2 accuracy validation of the reprocessed sensors.

In this study, the level of oxygen within the blood will be reduced in a controlled manner by reducing the concentration of oxygen the study volunteer breathes. The accuracy of a noninvasive pulse oximeter sensor will be assessed by comparison to the oxygen saturation measurements from a laboratory blood gas analyzer.

It is required that the Accuracy Root Mean Square (ARMS) performance of the Stryker pulse oximetry sensors will meet a specification of +/-3% with a target of +/-3% or better in non-motion conditions for the range of 70 - 100% SaO2 (typically, saturation is determined once with air breathing and then at three or six levels [redacted], thereby demonstrating an acceptable SpO2 accuracy performance specification. [redacted]

1.2 This study is being conducted to support regulatory body approval of pulse oximeter probes sterilized and/or decontaminated [redacted].

2.0 Scope

This procedure applies to the following Stryker Sustainability Solutions location(s):

☒ Tempe ☒ Tijuana

2.1 This study has been designed to include the subject devices listed in Table 1.

Study Device:			
OM	SKU	Minimum Quantity	Cycle Count
[redacted]	[redacted]	20	[redacted]
[redacted]	[redacted]	20	[redacted]

Table 1: Subject devices

3.0 Associated References

3.1 Pulse Oximeters – Premarket Notification Submissions [510(k)s] Guidance for Industry and Food and Drug Administration Staff Document issued on: March 4, 2013

3.2 ISO 80601-2-61:2017 Medical Electrical Equipment — Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment

4.0 Related Documents

[redacted]

[redacted]

5.0 Key Terms

Refer to CQM-02, Stryker Corporation Quality and Regulatory Master Glossary, for definitions to the Key Terms used within this document.

5.1 Allocation: A method used to assign participants to an arm of a clinical study. The types of allocation are randomized allocation and nonrandomized.

5.2 Arm: A group or subgroup of participants in a clinical trial that receives a specific intervention/treatment, or no intervention, according to the trial's protocol.

5.3 Eligibility criteria: The factors that allow someone to participate in a clinical study are called inclusion criteria, and the factors that disqualify someone from participating are called exclusion criteria. They are based on characteristics such as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions.

5.4 Intervention/treatment: A process or action that is the focus of a clinical study. Interventions include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include noninvasive approaches, such as education or modifying diet and exercise.

5.5 Masking: A clinical trial design strategy in which one or more parties involved in the trial, such as the investigator or participants, do not know which participants have been assigned which interventions. Types of masking include: open label, single blind masking, and double-blind masking.

5.6 Primary outcome measure: In a clinical study's protocol, the planned outcome measure that is the most important for evaluating the effect of an intervention/treatment. Most clinical studies have one primary outcome measure, but some have more than one.

5.7 Study type: Describes the nature of a clinical study. Study types include interventional studies (also called clinical trials), observational studies (including patient registries), and expanded access.

6.0 Roles and Responsibilities

6.1 Divisional

6.1.1 R&D Engineering in collaboration with Regulatory Affairs is responsible for the preparation and execution of this protocol, analysis of the test results, and the preparation of the summary report.

6.1.2 R&D Engineering, Regulatory Affairs and Principal Investigators are responsible for ensuring adherence to the Clinical Trial Agreement associated with the study outlined in the protocol.

6.1.3 The external facilities that may be used in the execution of this protocol are listed in Table 2.

Service	Name and Location
Clinical Study	UCSF (University of California San Francisco) [redacted]

Table 2 – External facility information

Study Design

7.0 Summary

Study Design:	
Study Type:	Interventional Non-significant Risk Lab Test
Enrollment:	A typical study will include at least 10 subjects (up to 24 if needed to reach the 200 necessary data points to meet the ISO 80601-2-61:2017).
Allocation:	Non-randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Subjects will recline for the study. Reference sensors will be placed on each subject to evaluate the SpO_2 accuracy and performance. Shield material may be used between any adjacent finger sensors to prevent optical crosstalk. Simultaneous data collection will be set up for devices under test. The data from the test devices will be collected by the sponsor or trained UCSF staff. Data will be collected for 1 second intervals data analysis. The SpO_2 accuracy of the test devices will be evaluated over the oxygen saturation range between 70-100%.
Masking:	None (Open Label)
Primary Purpose:	Device Validation
Study Start Date:	January 19-20th 2022

Arms and Interventions:	
Experimental: [redacted] Reference sensors from the reprocessed oximeter device will be placed on each subject to evaluate the SpO2 accuracy and performance.	Device: Stryker Sustainability Solutions [redacted] Pulse Oximetry Sensors An oximeter is a device used to transmit radiation at a known wavelength(s) through blood and to measure the blood oxygen saturation based on the amount of reflected or scattered radiation. Pulse oximetry monitoring is considered a standard physiological measurement and is used by clinicians in everyday situations to estimate arterial oxygen saturation. Because an arterial sample of blood is not required to make the measurement, the pulse oximeter can provide non-invasive real time information.
Sham Comparator: Radiometer ABL-90 multi-wavelength oximeter A whole blood analyzer (CO-Oximeter) is used as the reference standard device for obtaining the functional SaO2 value from arterial blood samples obtained during the study.	Device: CO-OXIMETRY SENSORS A whole blood analyzer (CO-Oximeter) is used as the reference standard device for obtaining the functional SaO2 value from arterial blood samples obtained during the study.

Primary Outcome Measures:	
1. Accuracy of Sensor by Arms Calculation [Time Frame: 1-5 hours]	Percentage of SpO2 (oxygen saturation by pulse oximetry) measured by the Reprocessed Oximeter pulse oximetry sensors during non-motion conditions over the range of 70-100% SaO_2 as compared to arterial blood samples assessed by CO-Oximetry.

	The Accuracy root mean square (ARMS) between measured SpO_2 and reference SaO2 (arterial oxygen saturation) must meet the 3% specification for each Stryker Sustainability Reprocessed pulse oximetry sensor style. Accuracy will be determined by comparing the noninvasive blood oxygen saturation measurement of the pulse oximeter to that obtained from a blood sample and calculating the arithmetic root mean square error (Arms) value. In order to obtain the Arms value, the blood oxygen saturation measurement is subtracted from the pulse oximeter oxygen saturation measurement for a number of samples, the average of this difference is computed as the bias. The standard deviation of the differences is computed as the precision. The square root of the sum of the squares of bias and precision is computed as the Arms Error value. For each range specified, *Sp*O2 ACCURACY of the PULSE OXIMETER EQUIPMENT shall be stated in terms of the root-mean-square (rms) difference between measured values (SpO_{2i}) and reference values (S_{Ri}), as given by the following formula. $A_{rms} = \sqrt{\frac{\sum_{i=1}^{n} (SpO_{2i} - S_{Ri})^2}{n}}$
Eligibility Criteria:	
Ages Eligible for Study: ≥18 and <50 (Adult) Sexes Eligible for Study: All Accepts Healthy Volunteers: Yes	
Inclusion and Exclusion Criteria	Inclusions: • The subject is male or female, aged ≥18 and <50 • The subject is in good general health with no evidence of any medical problems. • The subject is fluent in both written and spoken English • The subject has provided informed consent and is willing to comply with the study procedures Exclusions: • The subject is obese (BMI>30) • The subject has a known history of heart disease, lung disease, kidney or liver disease • Diagnosis of asthma, sleep apnea, or use of CPAP • Subject has diabetes • Subject has a clotting disorder • The subject a hemoglobinopathy or history of anemia, per subject report or the first blood sample, that in the opinion of the investigator, would make them unsuitable for study participation • The subject has any other serious systemic illness • The subject is a current smoker

	• Any injury, deformity, or abnormality at the sensor sites that in the opinion of the investigators would interfere with the sensors working correctly • The subject has a history of fainting or vasovagal response • The subject has a history of sensitivity to local anesthesia • The subject has a diagnosis of Raynaud's disease • The subject has unacceptable collateral circulation based on exam by the investigator (Allen's test) • The subject is pregnant, lactating or trying to get pregnant • The subject is unable or unwilling to provide informed consent, or is unable or unwilling to comply with study procedures • The subject has any other condition, which in the opinion of the investigators would make them unsuitable for the study
Contacts and Locations:	
Locations	United States, California University of California San Francisco
Sponsors and Collaborators	Stryker Sustainability Solutions, [redacted]
Investigators	[redacted]

8.0 Product Description

8.1 Intended Use: Reprocessed [redacted] Pulse Oximeter Sensors are indicated for single patient use for continuous noninvasive arterial oxygen saturation and pulse rate monitoring.

8.2 Principle of Operation: The principle of operation of pulse oximetry is based upon the fundamental principle that hemoglobin bound to oxygen (oxyhemoglobin) and hemoglobin unbound to oxygen (deoxyhemoglobin) vary in the absorption of different wavelengths of the light and the absorptions can be used to estimate SpO2 and PR. The mechanism by which this process occurs is the use of red and infrared wavelengths of light delivered by an emitter and the detection of the signal from the light absorption of oxygenated blood and deoxygenated blood to determine functional oxygen saturation of hemoglobin (SpO2).

8.3 Mechanism of Action for Achieving the Intended Effect: The Reprocessed Pulse Oximeter Sensor provides the intended effect equivalent to the previously cleared pulse oximeter sensor in that it utilizes an optical sensor that is applied to the patient's finger or toe through which light is transmitted to the photodetector that detects the signal transmission. The signal transmission is processed by the Pulse Oximeter to provide SpO2 and PR.

[redacted]	[redacted]

9.0 Worst Case Justification

9.1 The pulse oximeter sensors which are identified in Table 1 as subject devices [redacted].

10.0 Sample Size Designation

10.1 A typical study will include at least 10 subjects (up to 24 if needed to reach the 200 necessary data points to meet the ISO 80601-2-61:2017). Per FDA guidance, at least 2 or 15% of the subjects will have dark skin pigmentation. Skin pigmentation will be assessed using the Fitzpatrick scale by UCSF study personnel.

10.2 Each study subject will have two reprocessed sensors attached to their fingers. Two Reprocessed [redacted] sensors should be placed on one side of the subject; however, sensors may be placed opposite sides. Digits selected should be two of the three middle fingers on each hand avoiding the thumb or pinky fingers as test sites.

11.0 Preliminary Investigations and Justification of the Study

11.1 Stryker Sustainability Solutions has developed a process to reprocess pulse oximeters that cleans and disinfects the devices active element components and device cord and replaces all patient contacting tapes. The foam covering the cable is cleaned and disinfected but not replaced during reprocessing.

11.2 The manufacturing process for reprocessing includes 100% visual inspection and functional assessment.

11.3 As part of the product development and validation phases of this project, Stryker has performed or is currently performing the following studies:

- Cleaning
- Disinfection
- Biocompatibility
- Performance
- Functionality

12.0 Study Devices

12.1 Device Accountability

12.1.1 Receipt of Device will be conducted by the study monitor.

12.1.2 Use of Study Device

12.1.2.1 Use of devices will be documented electronically as case reports for each subject.

12.2 Packaging and Labeling

12.2.1 Research conducted for this study will utilize investigational devices. The Sponsor is responsible for packaging and labeling of the devices for delivery to the study site. Investigational devices or its immediate package shall bear a label with the following information:

"CAUTION – Investigational device. Limited by Federal (or United States) law to investigational use".

13.0 Procedure

13.1 If the principal investigator deems it necessary, the subject may be asked to run hot water over hands and arms for 5 minutes to improve perfusion. After injection of a local anesthetic, a 22-gauge catheter is inserted in one radial artery. Pulse oximeters are attached to fingers with adequate spacing between fingers or shielding to minimize device cross-talk. Subjects are in a comfortable semi-recumbent position. Subjects then breathe air mixtures containing reduced amounts of oxygen to produce the desired level of hypoxemia. Stable, safe and controlled hypoxia is adjusted manually by an anesthesiologist that permits the inspired gas mixture to be adjusted to achieve a level of lung alveolar gas that will achieve the desired degree of saturation.

13.2 Typically, saturation levels involve one period with air breathing and then at one of three or six levels[redacted]. Each level of saturation is held for 30-60 seconds or 60-90 seconds respectively. At appropriate intervals and when oxygen levels are stable, arterial blood samples are obtained from the radial arterial catheter. The operator then changes the inspired oxygen concentration to attain the next desired stead-state level of hypoxia. [redacted] A "run" consists of several stable steady-state hypoxia [redacted]. Each run is terminated by a breath of 100% O2 followed by room air. [redacted]. Saturation of each arterial blood sample is determined by direct oximetry in a Radiometer ABL-90 multi-wavelength oximeter. The precise target levels of saturation can be adjusted to suit the sponsor, but typical testing is done to satisfy ISO and FDA standards for testing, which is 70% to 100%.

13.3 The study takes about 1 hour of each subject's time. Analysis of the data requires several days. Manufacturer's representatives (Stryker) will be present for these tests, and to mount the probes.

14.0 Sponsor Pulse Oximeter Study Data

14.1 Data from test pulse oximeters for comparison to blood values can be obtained in several ways. In every case, the goal is to obtain a reading from the oximeter that corresponds to the associated blood sample or a reference oximeter. Because of circulation delays and instrument averaging time, attempts will be made to create steady state conditions at each level of oxygenation. Therefore, a means should be provided to record the instrument reading at each blood sample. This instrument reading may be obtained with several different approaches. Some instruments have no digital or analog output and the instrument reading may be recorded manually or recorded by a video of the instrument display. Other instruments may have an analog output. The laboratory can record analog data by use of LabView. Digital recording of output can also be obtained via LabView but this requires information from the sponsor concerning the structure of the digital signal.

14.2 If a manufacturer prefers to collect and analyze the data, the continuous digital signal of each oximeter should be read, for comparison with the blood sample, 9 seconds before the record shows a sudden fall or rise in oxygen saturation, not at the time of blood sampling. This procedure accounts for the delays of finger circulation and uses the estimated delay from the lung to the sample site. There is no useful correlation between the actual time of blood sampling and

the oximeter recording because of the variability of tissue blood flow lag. As mentioned, steady-state hypoxia avoids the concern that oximeter reading is not aligned with a blood sample reading.

15.0 Statistics

15.1 The number of subjects and the number of comparisons (paired pulse oximeter readings and arterial saturation values) is determined by current FDA guidance requirements. This is a minimum of 200 data points and 10 subjects. In the course of this type of study, some subjects may drop out, some readings can be lost due to motion or other interference and occasionally some do not consent.

15.2 The following demographic data will be collected on the subjects:

- **15.2.1** Gender (male, female, other)
- **15.2.2** Age
- **15.2.3** Skin pigmentation (dark, medium, light) [redacted]
- **15.2.4** Height (cm)
- **15.2.5** Weight (kg)
- **15.2.6** Wrist circumference (cm)
- **15.2.7** Dominant hand (left or right)

16.0 Data Analysis

16.1 In all cases, the blood analysis data are provided, including the SaO2, MetHb, COHb and Hgb concentration.

16.2 The data analysis report will consist of the following:

- **16.2.1** A Table of the oximeter readings versus corresponding blood SaO2 values.
- **16.2.2** Graphic plots of the bias between the oximeter reading and the SaO2 measured by the hemoximeter (on the blood sample, i.e Modified Bland-Altman plots for each instrument or instrument probe combination).
- **16.2.3** Regression equations for the bias of each instrument.
- **16.2.4** Tables of the mean error or bias, its standard deviation, standard error, 95% confidence interval, maximum and minimum and root mean square error, all computed both overall and by several sub-ranges of desaturation.
- **16.2.5** A table of the demographics of the subject population is provided.

17.0 Subject Safety

17.1 Pulse oximeter sensors are typically considered non-significant risk medical devices. The LED light energy utilized in typical test measurements is within the same range as other cleared marketed devices and introduces no further risks. An LED light emits light that passes through the tissue. A light detector then measures how much light was absorbed by the tissue. Based on the ratio of absorbance of different wavelengths of light, the device calculates the oxygen saturation.

18.0 Risks and Benefits of the Investigational Device and Clinical Investigation

18.1 Breathing a very low oxygen mixture may cause dizziness and might cause loss of consciousness for a few seconds. It may make one feel very short of breath during the test and for a few seconds afterwards. There is a remote possibility that if the subject loses consciousness he/she might have muscular twitching or convulsions. This study will not seek to reach saturations below 70%.

Hypoxia may cause tachycardia and increased blood pressure during the test, and might cause headache. In all the years of the lab conducting the study no subject has mentioned headache. Much more severe and prolonged lack of oxygen could cause brain injury or death, but the duration and depth of hypoxia is limited by the test protocol to short intervals. The needle catheter used to take blood may hurt when it is inserted despite the use of local anesthesia, and there may be a black and blue spot afterward. It is remotely possible the artery might be damaged or clot, or a tendon sheath near it be injured by the needle, resulting in some soreness. These risks are unlikely because none of the enrolled 2000+ subjects has ever had a serious complication. Hyperventilating during the part of the study requiring reduced PCO2 may make subjects lightheaded or dizzy. Breathing air with added CO2 may make subjects feel short of breath and cause a headache. Some subjects feel faint when they arrive for the study, apparently related to the thought of having an arterial line. These subjects will likely be excluded from the study.

18.2 Currently the FDA defines pulse oximeters as Class II devices which transmit radiation at a known wavelength(s) through blood and to measure the blood oxygen saturation based on the amount of reflected or scattered radiation and may be used alone or in conjunction with a fiberoptic oximeter catheter. All oximeters being used in this study work by transmittance of radiation at known wavelength(s) through tissue to measure blood oxygen saturation based on the amount of reflected and scattered radiation. The devices under test and this study procedure are considered Non-Significant Risk (NSR).

[redacted]

The device and use of the device under test does not meet the definition of a significant risk device. Under 21 CFR 812.3(m), an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

19.0 Invasive Laboratory Testing on Healthy Volunteers

19.1 The risk determination is based on the use of the device in an investigation in addition to the device itself. Generally, the FDA believes pulse oximeters as addressed in the FDA Guidance Document for Pulse Oximeters (March 4, 2013) are non-significant risk devices. Further, the recommendation is to conduct the study in accordance with Clause 201.12.1.101.2 and Annex EE.2 of ISO 80601-2-61:2011, where Annex EE.2 describes the procedure for invasive laboratory testing on healthy volunteers.

20.0 Risk Mitigations

Subjects are all monitored with accurate reference oximeters and continuous end-tidal gas analysis to prevent the risk of more profound hypoxia than desired. Investigators are experienced anesthesiologists adept at assessing breathing and in maintaining appropriate airway conditions. The study room is set up like an OR with all resuscitation equipment immediately available.

21.0 Informed Consent

21.1 Written informed consent is obtained before any study interventions. In discussions with the study coordinator before the day of the study, potential subjects will be offered the consent form to

review. On the day of the study subjects are given the consent form which they read and sign if they wish to participate. A study doctor is present to answer questions.

21.2 Only subjects clearly able to understand and read English will be enrolled. Subjects will be asked if they have any questions and are told they can withdraw at any time.

22.0 Investigational Review Board (IRB)/Independent Ethics Committee (IEC)

22.1 Prior to the start of subject enrollment, the investigator will be responsible for obtaining approval from the authorized IRB/IEC for the institution at which the proposed clinical investigation is to be conducted. Written approval from the IRB/IEC should specifically refer to the investigator, the protocol title and date, and subject informed consent date.

22.2 Written IRB/IEC approval and any conditions of approval imposed by the IRB/IEC was obtained by the sponsor/investigator.

22.3 Protocol amendments must also undergo IRB/IEC review and approval at each clinical site. The written approval from the IRB/IEC for the amendment should specifically refer to the investigator, the protocol version number and title, and any amendment numbers that are applicable.

22.4 [redacted].

23.0 Monitoring Arrangements

23.1 A representative from the sponsor and study monitor will provide all monitoring. The Monitor shall be responsible for maintaining a record of the findings, conclusions, and actions taken for the results of monitoring the study ensuring that:

23.2 The monitoring requirements for an NSR device study is identified in 21 CFR 812.2(b) Abbreviated requirements. For monitoring an NSR device investigation, the requirement is to comply with 21 CFR 812.46 with respect to monitoring investigations: (a) Securing Compliance, (b) Unanticipated adverse device effects, (c) Resumption of terminated studies

- Compliance to the signed agreement between the Investigator and sponsor
- The study follows the protocol and any amendments that apply
- Compliance to any conditions of the approval imposed by the IRB or FDA

23.3 Sponsor will assess any new hazards/harms identified during a clinical investigation (i.e., pre- or post-market study) [redacted].

24.0 Data Storage

24.1 Identifiable subject information is always stored securely following all applicable rules and regulations. Consent forms and other study related documents are retained following UCSF data retentions policy.

25.0 Acceptance Criteria

25.1 The statistical results of the data will be reviewed for the following pass/fail criteria:

[redacted]

26.0 Protocol Revision History

Revision	Change Order Number	Description
A	ECO134294	Establishment of a new protocol.
B	ECO134868	Updated document to reflect study parameters allowing for 3 plateaus as well as 6 plateaus.

[redacted]