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Determination of SpO2 and PR accuracy specifications at rest
ACCURACY OF PULSE OXIMETERS WITH PROFOUND HYPOXIA NIHO 14
Pulse Oximeter Accuracy Evaluation Protocol

Study Site: The UCSF Hypoxia Research Laboratory, 513 Parnassus Ave San Francisco, CA 94133
Principal Investigator (PI): Philip E. Bickler, M.D
Study Period: March 16-17, 2022

Breathe-down Test at Rest

1. Objective

This study is intended to evaluate performance of the following pulse oximeter (test devices: recorded oximeters), shown in Table 1, manufactured by Nihon Kohden Corporation (1-31-4, Nishiochiai, Shinjuku-ku, Tokyo, 161-8560, Japan) sufficiently to support performance claims for an FDA 510K submission or ISO technical file. These claims include accuracy at rest.

Table 1. Test devices: *recorded oximeters

Device name	Model name
Pulse oximeter	OVL-4000 series, OLV-4202 (SW version: 01-12)
SpO_2 Connection Cord	JL-400T
SpO_2 Connection Cord	JL-030U1
*Multi-site probe	TL-220T
Attachment tape	- (option for TL-220T)
*Disposable probe	TL-271T3
*Disposable probe	TL-273TA
*Disposable probe	TL-535U
Attachment tape	XL (option for TL-535U)

Description of the tested devices is attached as Appendix A.

The following requirements are to be met at rest:

- SpO_2 value range 70% to 100%
- At least 10 subjects, with 2 of dark pigment
- At least 200 data points

Success criteria is as follows:

Primary outcome measure	
SpO_2 accuracy	Rms of within ±2 [%SpO_2] (70 to 100 [%])
Pulse rate accuracy	Rms of within ±3 [1/min.] (30 to 300 [1/min.])
Secondary outcome measure	
SpO_2 accuracy	Rms of within ±2 [%SpO_2] (80 to 100 [%]) Rms of within ±3 [%SpO_2] (70 to 80 [%])

Safety of the test devices will be evaluated by assessing adverse events occurred to subjects.

This test is designed in response to the 2013 FDA Guidance on Pulse Oximeters – Premarket Notification Submissions and by ISO 80601-2-61:2017 on Pulse Oximeters, specifically the sections listed below.

- 2013 FDA Guidance on Pulse Oximeters – Premarket Notification Submissions:
  - 4.1 Accuracy of Pulse Oximeters
  - 4.1.1 In vivo testing for SpO_2 accuracy under laboratory conditions
  - 4.1.5 Testing for Pulse Rate Accuracy claims
- ISO 80601-2-61:2017 Annex EE.2 and clause 201.12.1.101.2
  - 201.12.1.101 SpO_2 accuracy of pulse oximeter equipment
  - 201.12.1.101.2 Determination of SpO_2 accuracy
  - 201.12.1.104 Pulse rate ACCURACY

NOTE: This study has been designed per ISO 80601-2-61:2017, and it has been also designed to respond to the recommendations on subject safety added on ISO 80601-2-61:2011. Since ISO 80601-2-61:2011 has been updated as ISO 80601-2-61:2017 with no changes in the requirements for conducting the study and

demonstrating SpO_2 and PR accuracy, this study results can be referred for demonstrating SpO_2 and PR accuracy per ISO 80601-2-61:2011 as well as per ISO 80601-2-61:2017.

This study will be conducted in accordance with this protocol and the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155: 2011 and :2020. The study will not begin until the UCSF IRB approval is received. This study is funded by Nihon Kohden.

2. Subjects

This study is performed on volunteers who have previously been determined to be healthy enough for this study, have signed an informed consent form and met the following IRB requirements. These volunteers are compensated by the laboratory for their participation. Point of enrolment is defined as time at which subjects sign and date the informed consent form and screening based on subject demography and inclusion/exclusion criteria is complete. Expected enrolment period is 1 week. Expected duration of each subject's participation will be about 45 minutes. The total expected duration of this study is 2 days.

The inclusion criteria for the test subjects are:

1. Both male and female subjects who can give written informed consent
2. Healthy subjects capable of undergoing controlled hypoxemia to the levels outlined in the desaturation profile below
3. Meeting the demographic requirements listed above.

The exclusion criteria for the test subjects are:

1. Age below 18 or over 50
2. Pregnant women
3. Significant arrhythmia
4. Blood pressure above 150 systolic or 90 diastolic
5. carboxyhemoglobin levels over 3%
6. Subjects whom the investigator consider ineligible for the study.

At least 10 subjects will be recruited to complete the test. Of these 2 will be dark pigment. If the number of samples is less than the required 200 or if less than 2 of dark pigment successfully complete the test, subjects will be added to include 2 of dark pigment and at least 200 data points.

3. Desaturation

Each subject will have an arterial catheter inserted in the left or right wrist.

For each subject, a series of desaturation runs are performed. Run 1 starts with a stabilized period at room air and is followed by stabilized plateaus at various lower saturation levels. Run 2 starts with a stabilized period at 100% and is followed by stabilized plateaus at various lower saturation levels. The following are value targets:

Run 1	room air, 92%, 87%, 82%, 77%, 72%
Run 2	100%, 93%, 88%, 83%, 78%, 73%

The objective of these targets is to spread the data points evenly over the desired range. Achieving them exactly is not important, though every effort will be made to be within 2%.

The SpO_2 value is reduced by delivering a mixture of medical air and nitrogen, controlled by 2 manually controlled needle valve flowmeters. The operator controls the SpO_2 by observing the breath by breath arterial saturation, which is in turn computed from end tidal PO_2 and PCO_2. FiO_2 is reduced suddenly at first then adjusted to achieve a stable plateau value at the desired target. A plateau is defined as stable when the readings of the sponsor Control instruments have not changed more than 1 % for 20 seconds (they do not have to agree with each other). Each desaturation plateaus should not exceed 10 minutes. When the sponsor confirms that stability is achieved, a blood draw is taken to flush the tubing, then the first sample is taken using a 2.5 cc syringe. 30 seconds later, another sample is taken. The gas mixture is then changed for the next value. This is then repeated for each plateau value.

For each subject, this allows 24 samples to be taken when Room air sat is considered. So, with for example 12 subjects in the study, this produces 288 samples. This ensures that even if one or two subjects and some data points are thrown out, the results will meet the FDA norm of 10 subjects and 200 data points.

During this procedure, the subject is coached on breathing. If he/she appears to fall asleep, he/she is woken up. At any signs of distress, he/she is given 100% oxygen.

Each run should take Between 15 and 25 minutes. It is normal to schedule as many as 10 subjects per day.

Trained Nihon Kohden personnel will be present at the procedure. The role of the Nihon Kohden person is to give technical support relative to the use of the test pulse oximeters including applying the sensors to the subjects and to perform study monitoring. All these actions will be done under the careful direction of the investigator.

Data of the test devices will be automatically recorded simultaneously with measurement in an SD card inserted into the pulse oximeter OLV-4202. Subject's demographic data, time of blood draw, and Co-oximeter values will be collected using specific data collection forms.

4. Reference Data

The blood samples will be analyzed using a Radiometer ABL90 co-oximeter. The co-oximeter should be quality control checked and calibrated at the study site to be functioning properly before use.

The heart rate will be measured using a Nihon Kohden PVM-4763 as an ECG monitor. The monitor should be quality control checked at the study site to be functioning properly before use.

5. Sensor Placements

A 3-lead ECG will be taken on each subject with the sponsor Control instrument. The electrodes for the sponsor Control instrument will be the L-150X disposable ECG electrodes.

The probes for the primary test instruments will be the TL-220T multi-site probe for adults, children and neonates, the TL-271T3 disposable probe for adults, the TL-273TA disposable probe for adults and neonates, and the TL-535U disposable probe for neonates and preterm infants. Probes will be attached to the study subjects by Nihon Kohden engineers who are well trained to use the test devices under the supervision of PI or co-investigator. These probes will be arranged as follows:

On the left-hand side

	Subject 1 + 4 + 7 + 10	Subject 2 + 5 + 8 + 11	Subject 3 + 6 + 9 +12
TL-220T (Group 1)	Index	Middle	Ring
TL-220T (Group 2)	Pinky	Pinky	Pinky

On the right-hand side

	Subject 1 + 4 + 7 + 10	Subject 2 + 5 + 8 + 11	Subject 3 + 6 + 9 +12
TL-273TA	Index	Middle	Ring
TL-535U	Middle	Ring	Index
TL-271T3	Ring	Index	Middle

6. Subject Safety

The sensors will be isolated as follows

1. 500V between the sensor and earth ground

2. 4 KV between AC mains power and the low voltage power supply and 1.5 KV between the low voltage power supply and the sensor, OR 5 KV between AC mains and the sensor.

Non-invasive blood pressure will be measured at a screening. EtCO2, respiratory rate, and FiO2 of the subjects will be monitored. In addition, the laboratory maintains criteria for subject selection that have been proven to minimize the risk of any problems during the study.

Adverse event and serious adverse event will be assessed throughout the study by the PI and co-Investigator, or research nurse designated by the PI. If any adverse event occurs during the study, an appropriate medical treatment will be provided to the subject by a medical staff at the laboratory. Nihon Kohden may suspend or prematurely terminate the study when there are serious violations and deviations from the GCP which could adversely affect subject's safety and correct data recording.

The test will be discontinued when a subject requests to withdraw from the study, or the PI or co-investigator will terminate the desaturation procedure and/or a subject's participation in the study because of the reasons including: 1) the subject experiences unexpected oxygen desaturation or 2) the subject loses consciousness.

Risks and anticipated adverse device effects associated with participation in the study that are to be assessed include the following:

a. Risks of arterial cannulation include bleeding, infection, nerve injury and bruising at the site of catheter insertion. There are also remote risks of an allergic reaction from the lidocaine used for local anesthesia, or the development of arterial spasm, dissection, or thrombosis.
b. The risks of the brief exposures to hypoxia are include feeling short of breath, headache, and dizziness. Brief loss of consciousness may occur but is not expected at the levels of oxygen targeted for these tests.
c. The risks of hyperventilating include feeling light-headed or dizzy. The risks of breathing air with increased amounts of carbon dioxide include feeling short of breath and developing a headache.
d. The risks of burns and skin problems from poor blood circulation. Poor circulation can be avoided by not putting SpO_2 probes too tightly.

Nihon Kohden has determined that there is no residual risk associated with the test devices. Nihon Kohden will be responsible for maintaining the test devices.

Monitoring will be performed by Nihon Kohden. Any adverse events (serious and non-serious) and adverse device effects will be documented in case report forms and reported to Nihon Kohden by PI in a timely manner.

7. Data Analysis

Collected data used for data analysis will be reviewed by PI and Nihon Kohden. Data will be retained by the laboratory and Nihon Kohden per their SOPs and policies. Nihon Kohden has no access to subject's personal information.

Data from subjects who did not complete the protocol will be thrown out. Also, if subject's carboxyhemoglobin level is confirmed to be over 3% during or after the study, data from the subject will be thrown out. Missing data will not be supplemented.

Data points at a plateau where a co-oximeter output changes over 2% saturation will be thrown out.

Data from unstable pulse wave signal where the motion artifact red p-p amplitude is over the PPG p-p amplitude of the subject will be thrown out.

Data from unstable pulse wave signal where the respiratory artifact red p-p amplitude is over the PPG p-p amplitude of the subject will be thrown out.

SpO_2 data will be reduced using the ARMS method and accuracy will be reported as the ARMS deviation between the co-oximeter and the test instruments for all points gathered from each sensor.

$$A_{rms} = \sqrt{\frac{\sum_{i=1}^{n} (SpO_{2i} - S_{Ri})^2}{n}}$$

PR data points where heart rate changes over 4bpm for 10 seconds will be thrown out.

PR data points at a plateau where heart rate changes over 19bpm for 10 seconds will be thrown out.

PR data will be reduced using the ARMS method and accuracy will be reported as the ARMS deviation between the ECG monitor and the test instruments for all plateaus gathered from each sensor. Accuracy will be determined by comparing the noninvasive pulse rate measurement of the pulse oximeter (PRi) to the heart

rate obtained from an electrocardiography reference device (HRRi) and calculating the arithmetic root mean square (Arms) error value as follows:

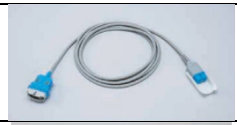
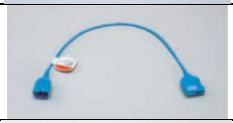
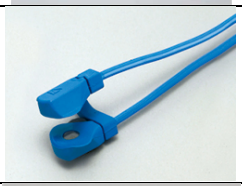
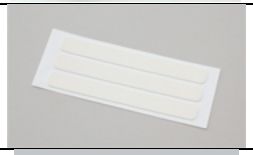
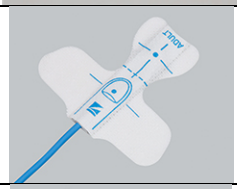
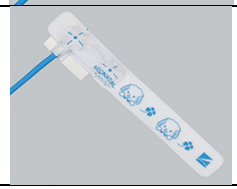
$$A_{rms} = \sqrt{\frac{\sum_{i=1}^{n} (PRi - HRRi)^2}{n}}$$

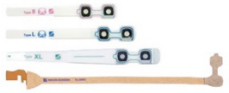
All records of this study related to TL-220T (Group 1), TL-220T (Group 2), TL-271T3, TL-273TA, and TL-535U will be retained by Nihon Kohden for at least 3 years after the date of release for commercial distribution of the test devices.

Data will be statistically analyzed by the laboratory per UCSF SOP. The laboratory will provide a summarized report for TL-220T (Group 1), TL-220T (Group 2), TL-271T3, TL-273TA, and TL-535U, using the data recorded by the sponsor suitable for FDA 510K submission. Any deviation from the protocol will be reported promptly using case report forms and reported in the report.

Appendix A Description of the investigational device

A.1. Test devices: *recorded oximeters

Device name	Model name	Quantity	Intended populations	Materials that will be in contact with subject's skin	Approved for market in Japan	Appearance
Pulse oximeter	OVL-4000 series, OLV-4202 (SW version: 01-12)	6	Adult/Child/Neonate	-	Yes	
SpO_2 Connection Cord	JL-400T	11	-	-	Yes	
SpO_2 Connection Cord	JL-030U1	1	-	-	Yes	
*Multi-site probe	TL-220T	2	Adult/Child/Neonate	-	Yes	
Attachment Tape	- (option for TL-220T)	24	Adult/Child/Neonate	Polyvinyl chloride	Yes	
*Disposable probe	TL-271T3	12	Adult	Polyester, acrylic adhesive	Yes	
*Disposable probe	TL-273TA	12	Adult/Neonate	Polyurethane, polyester, acrylic adhesive	Yes	

*Disposable probe	TL-535U	1	Neonate/Preterm infant	-	Yes	
Attachment tape	XL (option for TL-535U)	12	Neonate	Polyurethane, styrene-based elastomer	Yes	

The safety assessment per section 201.11 of ISO 80601-2-61:2011 has been conducted for all the test devices and confirmed that the test devices can be used on human subjects.

All test devices can be identified by serial number or lot number. Nihon Kohden will be responsible of keeping records documenting the delivery, use, return, and disposal of the test devices.