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Determination of SpO2 and PR accuracy specifications during motion
ACCURACY OF PULSE OXIMETERS WITH PROFOUND HYPOXIA NIHO12

Pulse Oximeter Accuracy Evaluation Protocol During Controlled Motion

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Study Period: March 25, 2021

Breathe-down Test During Motion

1. Objective

This study is intended to evaluate performance of the following pulse oximeter:

Device name	Model name	Quantity	Intended populations	Materials that will be in contact with subject's skin
Pulse oximeter	OVL-4000 series, OLV-4202 (SW version: 01-11)	4	Adult/Child/Neonate	-
Disposable probe	TL-273TA	5	Adult/Neonate	Polyurethane, polyester, acrylic adhesive
Disposable probe	TL-535U	1	Neonate/Preterm infant	-
Attachment tape	XL (option for TL-535U)	5	Neonate	Polyurethane, Styrene-based elastomer
Multi-site probe	TL-220T	1	Adult/Child/Neonate	-
Attachment tape	- (option for TL-220T)	5	Adult/Child/Neonate	Polyvinyl chloride
Multi-site Y probe	TL-260T	1	Adult/Child/Neonate/ Preterm infant	-
TL-260T clip adapter	- (option for TL-260T)	1	Adult	Silicone

SpO_2 probe, TL-281-IB will be used for monitoring SpO2 for reference. Bedside monitor, PVM-4763 (SW version 01-10) will be used for monitoring heart rate for reference. 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.

The following requirements are to be met during motion:

- SpO2 value range 70% to 100%
- 5 subjects, with 2 of dark pigment

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 SpO2 accuracy under laboratory conditions
  - 4.1.3 Testing for SpO2 accuracy for oximeters making motion performance claims
  - 4.1.5 Testing for Pulse Rate Accuracy claims
  - 4.1.6 Testing for Pulse Rate Accuracy for oximeters labeled with motion performance claims
- ISO 80601-2-61:2017 Annex EE.2 and clause 201.12.1.101.2
  - 201.12.1.101 SpO2 accuracy of pulse oximeter equipment

- o 201.12.1.101.2 Determination of SpO2 accuracy
- o 201.12.1.102 Accuracy under conditions of motion
- o 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 the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155:2011 and :2020.

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 duration of each subject's participation will be about 45 minutes.

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. Subjects whom the investigator consider ineligible for the study.

5 subjects will be recruited to complete the test. Of these 2 will be dark pigment.

3. Desaturation

Each subject shall have their right arm positioned on a motion generating machine. The right hand is called the motion hand, the left is called the control hand.

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, 90%, 80%, 70%
Run 2	100%, 95%, 85%, 75%

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, the plateau is held for 90 seconds. The gas mixture is then changed for the next value. This is then repeated for each plateau value.

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 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 obtained in an SD card inserted into the pulse oximeter OLV-4202. Subject's demographic data will be collected using specific data collection forms.

4. Reference Data

The reference SpO2 will be measured using a Nihon Kohden OLV-4202 as a secondary standard pulse oximeter equipment. The equipment should be quality control checked 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. Motions

This study evaluates the effect of several motions. The main attributes are rubbing and tapping. For each subject one run will use tapping and the other rubbing. Motion types will be arranged as follows:

On the motion-hand side

	Subject 1 + 3 + 5	Subject 2 + 4
Run 1	rubbing	tapping
Run 2	tapping	rubbing

Each of these motions can be driven in the following ways.

- 2Hz sine (2Hz)
- 4Hz sine (4Hz)
- Sequence of moves of a pseudo random distance from 1mm to 30mm (Rand)
- The amplitude of the sine motion and the maximum slope of the random motion will be determined at the beginning of each Desaturation Run.
- For 2Hz sine and 4Hz sine, motion artifact red p-p amplitude will be equal to the PPG p-p amplitude of the subject. For Rand, the largest motion artifact red p-p amplitude will be equal to the PPG p-p amplitude of the subject.

In each plateau, the motion drive type will be sequentially changed in the following ways.

- 30 seconds' no motion
- 30 seconds' 2Hz
- 30 seconds' 4Hz
- 30 seconds' Rand

6. Sensor Placements

A reference SpO2 will be taken on each subject with the sponsor Control instrument. The SpO2 probes for the sponsor Control instrument will be the TL-281-IB disposable SpO2 probes. These probes will be arranged as follows:

On the control-hand side

	Subject 1 + 4	Subject 2 + 5	Subject 3

TL-281T-IB	Middle	Ring	Index

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-273TA Neonatal and Adult disposable probe, the TL-535U Neonatal disposable probe, the TL-220T Multisite reusable probe. These probes will be arranged as follows:

On the motion-hand side

	Subject 1 + 4	Subject 2 + 5	Subject 3
TL-273TA	Index	Middle	Ring
TL-535U	Middle	Ring	Index
TL-220T	Ring	Index	Middle

7. 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 Principal Investigator and Co-Investigator or research nurse designated by Principal Investigator. 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 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 associated with participation in the study include the following:

a. 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.

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.

8. Data Analysis

Data from subjects who did not complete the protocol will be thrown out. Missing data will not be supplemented.

Data points at a plateau where the equipment output for TL-281-IB changes over 2% saturation will be thrown out.

Data from unstable pulse wave signal due to the uncontrolled motion will be thrown out.

SpO2 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:

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