

Clinicaltrials.gov: NCT04144166

Title: Study Protocol and Statistical Plan for CS-011-004 IRB#: 19-0726

Date: 2 Aug 2019

# Clinical investigation plan

## EVALUATION OF CAPILLARY REFILL INDEX

Reference number: CS-011

Clinical investigation plan number: CS-011-004

Version number: 3.1    Date: August 2, 2019

Sponsor:

**Nihon Kohden Corporation**

1-31-4 Nishiochiai Shinjuku-ku, Tokyo, 161-8560 Japan

**Nihon Kohden Innovation Center**

237 Putnam Avenue, Cambridge, MA, 02139

**Nihon Kohden America**

15353 Barranca Parkway, Irvine, CA 92618

### Confidentiality

Information contained in this clinical investigation plan is owned by Nihon Kohden Corporation and is provided only to the principal investigator, other investigators of this clinical investigation and the Institutional Review Board. Recipients of this clinical investigation plan shall handle this material as confidential information. The recipients shall not disclose the information to any third party who are not involved in this clinical investigation without a prior written consent of Nihon Koken Corporation except for explaining this clinical investigation to subjects.

## Revision history

Date of revision	Version	Summary of revisions made
February 28, 2019	1.0	Initial version
June 26, 2019	2.0	The subject population additionally includes the ICU patients.
August 1, 2019	3.0	Remove CRF from the attachments
August 2, 2019	3.1	Add ICU in the section 1.3

## Synopsis

**Title:** Evaluation of Capillary Refill Index

**Study type:** Single-center, cross-sectional study

**Subject population:** Adult emergency department (ED) and intensive care unit (ICU) patients (both males and females without regards to ethnic and racial backgrounds) who meet the following eligibility criteria will be recruited.

### Inclusion criteria

- Individuals 18 years of age or older
- Patients who present to the ED or who are admitted to the ICU of North Shore University Hospital (NSUH)

### Exclusion criteria

- Pregnant
- Prisoners
- Finger, hand or forearm anatomical anomaly or disease that may interfere with attaching a pulse oximeter sensor
- Patients' deemed clinically unstable by the clinical team

**Number of subjects:** Total number of subjects is up to 60.

**Study duration:**

- Expected duration of each subject participation is approximately 15 minutes.
- The duration of subject recruitment is anticipated for 6 months.
- The total duration of the study (including data collection and analysis) is approximately 1 year.

**Investigational device:** This study will use a **non-significant risk** combination of two components to measure Capillary Refill Index (CRI):

- Non-FDA-cleared pulse oximeter (OLV-4201A, Nihon Kohden Corporation, Tokyo, Japan): OLV-4201A pulse oximeter is intended for use in monitoring SpO<sub>2</sub> and pulse rate (PR) using a finger sensor. It conforms to the safety standard of IEC 60601-1:2005+A1:2012, and the electromagnetic compatibility standard of IEC 60601-1-2:2007 and ISO 80601-2-61:2011 (clause202). The CRI measurement function is embedded in OLV-4201A.

- FDA-cleared SpO<sub>2</sub> sensor probes (TL-271T3, Nihon Kohden Corporation, Tokyo, Japan): The sensors are disposable and intended for single patient use.

**Note:** the pulse oximeter is a class II device and is not used for life support or as a life sustaining device, thus the risk of this investigational use is considered extremely low. Furthermore, the device will not be used for any clinical diagnoses and any data obtained from the device will be blinded from the treating physicians and thus will not have any impact on the patient's clinical care. Therefore, the investigational device qualifies as a **non-significant risk (NSR) device** and **does not require an Investigational Device Exemption (IDE) approval** from the FDA.

## Objectives:

### (1) Primary objective

The primary objective is to evaluate the capability of Capillary Refill Index (CRI) measured by the investigational device to predict altered peripheral perfusion determined with visual Capillary Refill Time (CRT) test. Predictive capability of CRI needs to be assessed to achieve a goal to provide clinicians with an alternative method to the traditional CRT test.

### (2) Secondary objective(s)

The secondary objective is to assess the correlation between CRI and CRT values. Although both CRI and CRT reflect time required for reperfusion of fingertip after the compression, measured absolute numerical values will be different since the mechanisms to assess peripheral perfusion are different between CRI and CRT.

## Endpoint(s):

### (1) Primary endpoint

The primary endpoint is the area under the curve (AUC) of the receiver operator characteristic (ROC) curve analysis on CRI values to predict the altered peripheral perfusion determined with the CRT test. A specific cutoff value for CRI has not yet been determined, then the AUC value will be used to summarize comprehensive capability of CRI to detect the altered peripheral perfusion.

### (2) Secondary endpoint(s)

The secondary endpoints include the followings:

- Sensitivity and specificity of CRI in differentiating altered peripheral perfusion determined with the CRT test. An optimal cutoff value for CRI will be

determined with the ROC analysis for the primary endpoint.

- Pearson's or Spearman's correlation coefficient to assess the correlation between CRI and CRT values.

## Table of Contents

Revision history .....	2
Synopsis.....	3
List of Abbreviations .....	9
<b>1 General</b> .....	10
1.1 Introduction .....	10
1.2 Sponsor.....	10
1.3 Principal investigator and investigation site(s) .....	10
<b>2 Investigational device</b> .....	11
2.1 Summary description of the investigational device and its intended purpose .....	11
2.2 Manufacture of the investigational device .....	12
2.3 Name or number of the model/type including software version and accessories.....	12
2.4 Traceability.....	12
2.5 Intended purpose of the investigational device in this clinical investigation .....	12
2.6 Populations and indications for which the investigational device is intended .....	12
2.7 Materials of the investigational device contacting with tissues or body fluids.....	13
2.8 Necessary training and experience needed to use the investigational device .....	13
2.9 Specific medical or surgical procedures involved in the use of the investigational device .....	13
<b>3 Justification for the design of the clinical investigation</b> .....	13
3.1 Evaluation of the results of the relevant pre-clinical testing/assessment carried out to justify the use of the investigational device in human subjects .....	13
3.2 Evaluation of clinical data relevant to this clinical investigation.....	13
<b>4 Risks and benefits of the investigational device and the clinical investigation</b> .....	14
4.1 Anticipated clinical benefits .....	14
4.2 Anticipated adverse device effects.....	14
4.3 Residual risks associated with the investigational device identified in the risk analysis .....	14
4.4 Risk associated with participation in the clinical investigation .....	14
4.5 Possible interactions with concomitant medical treatments .....	14
4.6 Steps that will be taken to control or mitigate the risks.....	14
4.7 Risk-to-benefit rational .....	15
<b>5 Objectives and hypotheses of the clinical investigation</b> .....	15
5.1 Primary and secondary objectives .....	15
5.1.1 Primary objective .....	15
5.1.2 Secondary objective(s) .....	15

5.2	Hypotheses to be tested by statistical data from the clinical investigations.....	15
5.3	Claims and intended performance of the investigational device that are to be verified .....	15
5.4	Risks and anticipated adverse device effects to be assessed .....	15
<b>6</b>	<b>Design of the clinical investigation .....</b>	<b>16</b>
6.1	General .....	16
6.1.1	Type of the clinical investigation .....	16
6.1.2	Measures to be taken to minimize or avoid bias, including randomization and blinding/masking .....	16
6.1.3	Primary and secondary endpoints.....	16
6.1.4	Methods and timing for assessing, recording and analyzing variables .....	17
6.1.5	Equipment to be used for assessing, recording and analyzing variables and arrangements for monitoring maintenance and calibration.....	17
6.1.6	Any procedures for the replacement of subjects .....	17
6.2	Investigational device(s) and comparator(s) .....	18
6.2.1	Description of the exposure to the investigational device(s) or comparator(s), if used .....	18
6.2.2	Justification of the choice of comparator(s).....	18
6.2.3	Other medical device or medication to be used during the clinical investigation.....	18
6.2.4	Number of investigational devices to be used.....	18
6.3	Subjects .....	18
6.3.1	Inclusion criteria for subject selection .....	18
6.3.2	Exclusion criteria for subject selection .....	19
6.3.3	Criteria and procedures for subject withdrawal or discontinuation .....	19
6.3.4	Point of enrollment.....	19
6.3.5	Total expected duration of the clinical investigation .....	19
6.3.6	Expected duration of each subject's participation .....	19
6.3.7	Number of subjects required to be included in the clinical investigation .....	19
6.3.8	Estimated time needed to select this number (i.e. enrolment period) .....	19
6.3.9	Subject compensation.....	19
6.4	Procedures.....	20
6.4.1	All the clinical-investigation-related procedures that subjects undergo during the study ...	20
6.4.2	Activities performed by sponsor representatives (excluding monitoring) .....	22
6.4.3	Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results.....	22
6.5	Monitoring plan .....	23
<b>7</b>	<b>Statistical considerations.....</b>	<b>23</b>
7.1	Statistical design, method and analytical procedures .....	23
7.2	Sample size .....	24
7.3	The level of significance and the power of the clinical investigation.....	24

7.4	Expected drop-out rates .....	25
7.5	Pass/fail criteria to be applied to the results of the clinical investigation .....	25
7.6	Provision for an interim analysis .....	25
7.7	Criteria for the termination of the clinical investigation on statistical grounds.....	25
7.8	Procedures for reporting any deviation(s) from the original statistical plan .....	25
7.9	Specification of subgroups for analysis .....	25
7.10	Procedures that take into account all the data .....	25
7.11	Treatment of missing, unused or spurious data, including drop-outs and withdrawals.....	25
7.12	Exclusion of particular information from the testing of the hypothesis.....	25
7.13	In multicenter clinical investigations, the minimum and maximum number of subjects to be included for each center .....	25
<b>8</b>	<b>Data management .....</b>	<b>26</b>
8.1	Procedures used for data review, database cleaning, and issuing and resolving data queries.	26
8.2	Procedure for verification, validation and securing of electronic clinical data system .....	27
8.3	Procedure for data retention .....	27
8.4	Specified retention period .....	27
8.5	Other aspects of clinical quality assurance .....	27
<b>9</b>	<b>Amendments to the clinical investigation plan .....</b>	<b>28</b>
<b>10</b>	<b>Deviation from the clinical investigation plan.....</b>	<b>28</b>
10.1	Statement specifying that the investigator is not allowed to deviate from the CIP .....	28
10.2	Procedures for recording, reporting and analyzing CIP deviations .....	28
10.3	Notification requirements and time frame.....	28
10.4	Corrective and preventive actions and principal investigator disqualification criteria .....	28
<b>11</b>	<b>Device accountability .....</b>	<b>28</b>
11.1	Labeling and packaging of the investigational device .....	28
11.2	Receipt of the investigational device .....	29
11.3	Identification of each investigational device (batch number, serial number or unique code).....	29
11.4	Expiry date of use .....	29
11.5	Use and storage of the investigational device.....	29
11.6	Subject identification .....	29
11.7	Investigational device which is returned/explanted from subject, if applicable .....	30
11.8	Return of unused, expired or malfunctioning investigational devices, if applicable .....	30
<b>12</b>	<b>Statement of compliance .....</b>	<b>30</b>
12.1	Declaration of Helsinki .....	30
12.2	International standard and any regional or national regulations.....	30
12.3	IRB and/or regulatory authorities .....	30
12.4	Insurance .....	31
12.5	Conflict of interest .....	31



<b>13</b>	<b>Informed consent process</b>	31
13.1	General process for obtaining informed consent	31
13.2	Informed consent process if the subject is unable to give it	32
<b>14</b>	<b>Adverse events, adverse device effects and device deficiencies</b>	32
14.1	Definitions of adverse events and adverse device effects	32
14.2	Definition of device deficiencies	32
14.3	Definition of serious adverse events, serious adverse device effect and unanticipated serious adverse device effects	32
14.4	Definition of unanticipated problems involving risk to subjects or others	33
14.5	Time periods for reporting adverse events and device deficiencies	33
14.6	Process for reporting adverse events and device deficiencies	34
14.7	Foreseeable adverse events and anticipated adverse device effects	36
14.8	Emergency contact for reporting serious adverse events and serious adverse device effects	36
14.9	Information regarding the data monitoring committee	36
<b>15</b>	<b>Vulnerable population</b>	36
<b>16</b>	<b>Suspension or premature termination of the clinical investigation</b>	36
16.1	Criteria and arrangements for suspension or premature termination	36
16.2	Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical investigation	37
16.3	Requirements for subject follow-up	37
<b>17</b>	<b>Publication policy</b>	37
<b>18</b>	<b>Bibliography</b>	37
<b>19</b>	<b>Attachments</b>	38

## List of Abbreviations

CRI	Capillary Refill Index
CRT	Capillary Refill Time
CIP	Clinical investigation plan
PI	Principal investigator
FDA	Food and Drug Administration
IDE	Investigational Device Exemption
NSR	Non-significant risk
°C	Degrees Celsius
°F	Degrees Fahrenheit
SpO <sub>2</sub>	Peripheral capillary oxygen saturation
PR	Pulse rate
NKC	Nihon Kohden Corporation
FIMR	Feinstein Institute for Medical Research
NSUH	North Shore University Hospital
IRB	Institutional Review Board
ED	Emergency department
ICU	Intensive care unit
AE	Adverse event
PHI	Personal Health Information
CRF	Case Report Form

## 1 General

### 1.1 Introduction

Capillary refill time (CRT) test is a simple and noninvasive method typically used to assess peripheral blood perfusion at the bedside. CRT is defined as the time required for a distal capillary bed (e.g., fingertip) to regain its color after having received enough compression to cause blanching [1]. A prolonged CRT (e.g. over 2 seconds) suggests a decrease in peripheral perfusion and is used to identify hemodynamically compromised patients in the critical care setting. Several observational studies have reported the clinical usefulness of CRT and the relevance between prolonged CRT and critical conditions. In intensive care patients, prolonged CRT was associated with diminished tissue perfusion as well as an increase in organ dysfunction with high blood lactate levels [2]. Prolonged CRT was also associated with the development of severe complications in patients following abdominal surgery [3]. However, the conventional CRT test has limitations in objectivity given that the measurement depends on clinicians' subjective visual assessment. Since the repeatability and inter-rater agreement of the CRT test has been questioned over the last few decades [4, 5], there is great demand for the creation of objective methods to assess peripheral blood perfusion [5, 6].

We developed a new analytic method to assess peripheral blood perfusion quantitatively using pulse oximetry waveforms to provide clinicians with an alternative method to the traditional CRT test. The method calculates the time it takes for blood to return to the fingertip after release from compression by algorithmically analyzing the light intensity waveform of a normal pulse oximeter sensor attached to a patient's fingertip [7,8]. Since the mechanisms to assess peripheral blood perfusion are different from the traditional CRT tests, we differentiate the calculated number by our method from CRT and named it Capillary Refill Index (CRI). The CRI measurement function is embedded in our investigational device OLV-4201A pulse oximeter.

### 1.2 Sponsor

- Nihon Kohden Corporation, 1-31-4 Nishiiochiai Shinjuku-ku, Tokyo, 161-8560, Japan
- Nihon Kohden Innovation Center, 237 Putnam Avenue, Cambridge, MA, 02139, USA
- Nihon Kohden America: 15353 Barranca Parkway, Irvine, CA 92618, USA

The sponsored research agreement for funding this study is to be made by and between Northwell Health and Nihon Kohden Corporation (NKC).

### 1.3 Principal investigator and investigation site(s)

- **Principal investigator:**

Timmy Li

Administrative Director of Clinical Research for Emergency Medicine

Northwell Health, 300 Community Drive, Manhasset, NY, 11030

- **Investigation site(s)**

Emergency Department (ED) and Intensive Care Unit (ICU)  
North Shore University Hospital (NSUH)  
Northwell Health, 300 Community Drive, Manhasset, NY, 11030

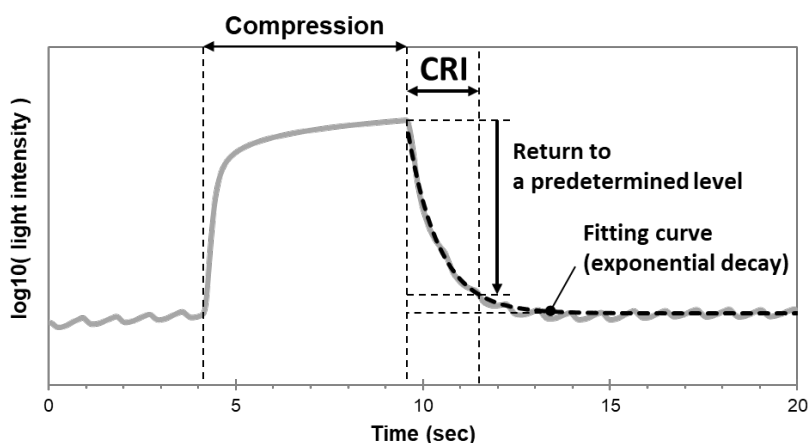
## 2 Investigational device

### 2.1 Summary description of the investigational device and its intended purpose

This study will use a **non-significant risk** combination of two components:

- Non-FDA-cleared pulse oximeter (OLV-4201A, Nihon Kohden Corporation, Tokyo, Japan): See *Attachment 1 Operator's Manual of OLV-4201*. OLV-4201A pulse oximeter is intended for use in monitoring SpO<sub>2</sub> and pulse rate (PR) using a finger sensor. It conforms to the safety standard of IEC60601-1:2005+A1:2012, and the electromagnetic compatibility standard of IEC 60601-1-2:2007 and ISO 80601-2-61:2011 (clause202). See *Attachment 2 and 3 Certificate of Safety/EMC Test*.
- FDA-cleared SpO<sub>2</sub> sensor probe (TL-271T3, Nihon Kohden Corporation, Tokyo, Japan; K151080, K120888, K080342, K001693, K946175, K945578, K043517, K082785): See *Attachment 4 Operator's Manual of SpO<sub>2</sub> sensor probe*. The sensor is disposable and intended for single patient use.

The investigational device passes light of two wavelengths (red: 660 nm, infrared: 940 nm) through the fingertip and measures the light intensity at each wavelength, allowing it to determine the different concentrations of two types of hemoglobin (oxy-hemoglobin and deoxy-hemoglobin). The CRI measurement uses a wavelength of infrared (940 nm) to trace change of blood volume in the fingertip. To measure CRI, a patient's fingertip with a pulse oximeter sensor probe attached is briefly compressed by an operator. The light intensity transmitted through the fingertip increases during compression as blood, which is the major absorber of the light, is squeezed out of the fingertip. The compression phase is followed by the release phase during which the light intensity decreases with return of blood to the fingertip. The curve describing the recovery phase of the intensity waveform is modeled as an exponential decay using the least squares method. The time for returning to a predetermined level of the intensity is calculated as CRI (Figure 1). The detailed operation of the CRI function of OLV-4201A is described in *Attachment 5 Operator's Manual of the CRI function*.



**Figure 1:** Calculation of CRI using a pulse oximeter waveform

**Note:** the pulse oximeter is a class II device and is not used for life support or as a life sustaining device, thus the risk of this investigational use is considered extremely low. Furthermore, the device will not be used for any clinical diagnoses and any data obtained from the device will be blinded from the treating physician and thus will not have any impact on the patient's clinical care. Therefore, the investigational device qualifies as a **non-significant risk (NSR) device** and **does not require an Investigational Device Exemption (IDE) approval** from the FDA.

## 2.2 Manufacture of the investigational device

Manufacture: Nihon Kohden Corporation

Address: 1-31-4 Nishiochiai Shinjuku-ku, Tokyo, 161-8560, Japan

## 2.3 Name or number of the model/type including software version and accessories

- (1) Model number: OLV-4201A
- (2) Name: Pulse Oximeter
- (3) Software version: 01-06
- (4) Composition

No.	Name	Model number
1	Pulse Oximeter	OLV-4201A

- (5) Accessories and disposables

No.	Name	Model number
1	Power cord	
2	SpO <sub>2</sub> connection cord	JL-400T
3	Disposable SpO <sub>2</sub> sensor probe	TL-271T3

## 2.4 Traceability

- OLV-4201A Pulse Oximeter: identify with assigned serial numbers
- TL-271T3 SpO<sub>2</sub> sensor probe: identify with assigned lot numbers

## 2.5 Intended purpose of the investigational device in this clinical investigation

- Measurement of CRI

## 2.6 Populations and indications for which the investigational device is intended

- Adult ED and ICU patients both males and females aged 18 years or older

## 2.7 Materials of the investigational device contacting with tissues or body fluids

Material of the investigational device that will be in contact with tissues is as follows:

TL-271T3 SpO <sub>2</sub> sensor probe	
Name of parts	Material
Sensor portion	Polyester

There is no material that will be in contact with body fluids.

## 2.8 Necessary training and experience needed to use the investigational device

Investigators will be trained by sponsor representatives about operations and cleaning of the investigational device following the operator's manual of the investigational device.

## 2.9 Specific medical or surgical procedures involved in the use of the investigational device

There is no medical nor surgical procedure involved in the use of the investigational device.

# 3 Justification for the design of the clinical investigation

## 3.1 Evaluation of the results of the relevant pre-clinical testing/assessment carried out to justify the use of the investigational device in human subjects

OLV-4201A Pulse Oximeter conforms to the safety standard of IEC60601-1:2005+A1:2012, and the electromagnetic compatibility standard of IEC 60601-1-2:2007 and ISO 80601-2-61:2011(clause202). See *Attachment 2 and 3 Certificate of Safety/EMC Test*. The part of the investigational device that will be in contact with the human subjects is the FDA-cleared TL-271T3 SpO<sub>2</sub> probe. There has been no issue regarding biocompatibility of the material of the SpO<sub>2</sub> probe described in the section 2.7. Therefore, the use of the investigational device in human subjects in this clinical investigation is considered to be justified.

## 3.2 Evaluation of clinical data relevant to this clinical investigation

*Attachment 6* is a report of a previous clinical study conducted at the ED of NSUH. In this preliminary clinical study, the term "Blood Refill Time (BRT)" was used, which is the same as CRI, and a prototype device was used to measure BRT. The prototype device is a non-FDA-cleared pulse oximeter (OLV-3100, Nihon Kohden Corporation, Tokyo, Japan) which is a previous model of OLV-4201A. OLV-3100 was used to record the pulse oximetry waveforms, and the recorded waveforms were analyzed thereafter. The calculation of CRI used in the analysis is the same as the CRI function embedded in the investigational device. A convenience sample of thirty adult ED patients were enrolled as subjects. Visual CRT values were measured by an ED physician using a stopwatch. Area under the receiver operator characteristic curve of BRT to predict whether the visual CRT was greater than 2.0 seconds was 0.84 (95% CI 0.70-0.98). There was a strong correlation between BRT and CRT ( $r=0.723$ ,  $p<0.001$ ). The results suggest that BRT measurements with the prototype device successfully identified subjects with altered peripheral perfusion determined by the conventional visual assessment of CRT.

## **4 Risks and benefits of the investigational device and the clinical investigation**

### **4.1 Anticipated clinical benefits**

This study is not expected to directly benefit the subjects, but it will provide information that may assist in improving the method to assess peripheral blood perfusion quantitatively.

### **4.2 Anticipated adverse device effects**

There is no particular anticipated adverse device effect since the applied part of the investigational device (TL-271T3 SpO<sub>2</sub> sensor probe) is equivalent to standard pulse oximeter sensors and has a FDA approval. A well-known potential adverse effect of pulse oximeters is thermal injuries due to temperature rise at the applied part of the sensor.

### **4.3 Residual risks associated with the investigational device identified in the risk analysis**

There is no residual risk associated with the investigational device which is judged unacceptable.

### **4.4 Risk associated with participation in the clinical investigation**

There is a potential risk of breach of confidentiality, which will be minimized by following the procedures set forth in the section 8 “Data management” of this CIP.

The study procedures are no greater than minimal risk. The pulse oximeter is a class II device and is not used for life support or as a life sustaining device, thus the risk of this investigational use is considered extremely low. Furthermore, the device will not be used for any clinical diagnoses and any data obtained from the device will be blinded from treating physicians and thus will not have any impact on the subject's clinical care. The application of the sensor probe on the subject's finger is not expected to cause pain. If the study procedure becomes too uncomfortable, the procedure will be stopped immediately. The investigator (qualified ED physician) will assess the clinical status of the subject prior to enrollment to determine eligibility when the subject is recruited.

### **4.5 Possible interactions with concomitant medical treatments**

There is no possible interaction with concomitant medical treatments.

### **4.6 Steps that will be taken to control or mitigate the risks**

All data and records generated during this study will be kept confidentially in accordance with policies of the study site(s) and HIPAA on subject privacy, and the investigator and other site personnel will not use such data and records for any purpose other than conducting the study. All subjects will be given a unique study number. The PI will be responsible for ensuring the safety of the subjects participating in this study. The study team will report to the PI any time that the sensor has to be removed prematurely, and the PI will track this information. Thermal injuries which are the potential adverse effect of the pulse oximeter will be assessed after the measurements with the investigational device.

#### 4.7 Risk-to-benefit rational

Based on the discussions above and the minimal risk involved with the study, the scientific benefits of this study outweigh the risks, even though no benefit for each individual study participant is expected.

### 5 Objectives and hypotheses of the clinical investigation

#### 5.1 Primary and secondary objectives

##### 5.1.1 Primary objective

The primary objective is to evaluate the capability of CRI to predict altered peripheral perfusion determined with the CRT test. Predictive capability of CRI needs to be assessed to achieve a goal to provide clinicians with an alternative method to the traditional CRT test. Receiver operator characteristic (ROC) curve analysis will be performed and area under the curve (AUC) will be calculated for this objective. An optimal cutoff value for CRI will be determined with the ROC analysis and the sensitivity and the specificity in differentiating altered peripheral perfusion will also be calculated.

##### 5.1.2 Secondary objective(s)

The secondary objective is to assess the correlation between CRI and CRT values. Although both CRI and CRT reflect time required for reperfusion of fingertip after the compression, measured absolute numerical values will be different since the mechanisms to assess peripheral perfusion are different between CRI and CRT. Pearson's correlation coefficient will be calculated to assess the correlation between CRI and CRT values. If the values are not normally distributed, Spearman's correlation coefficient will be used instead.

#### 5.2 Hypotheses to be tested by statistical data from the clinical investigations

CRI is capable to detect subjects with altered peripheral perfusion determined with the CRT test.

#### 5.3 Claims and intended performance of the investigational device that are to be verified

##### (1) Capillary Refill Index (CRI)

- Display range: 0.1 ~ 99.9 seconds

\*CRI will not be claimed as an intended for use in a regulatory application for FDA clearance of OLV-4201A Pulse Oximeter. CRI will be included in the regulatory application as an index intended for clinical research only, not for diagnosis.

#### 5.4 Risks and anticipated adverse device effects to be assessed

- ##### (1) Thermal injuries due to temperature rise at the applied part of the sensor probe



## 6 Design of the clinical investigation

### 6.1 General

#### 6.1.1 Type of the clinical investigation

Single-center, cross-sectional study:

In this clinical investigation, CRI and CRT measured at a same time point for each will be compared.

#### 6.1.2 Measures to be taken to minimize or avoid bias, including randomization and blinding/masking

- The investigator who will measure the visual CRT will be blinded from the CRI values measured with the investigational device.
- CRI and CRT measurements will be alternately repeated for 3 times each per a subject, and each averaged value will be used as measured CRI and CRT values for each subject.

#### 6.1.3 Primary and secondary endpoints

##### (1) Primary endpoint

The primary endpoint is the area under the curve (AUC) of the receiver operator characteristic (ROC) curve analysis on CRI values to predict the altered peripheral perfusion determined with the CRT test. A specific cutoff value for CRI has not yet been determined, then the AUC value will be used to summarize comprehensive capability of CRI to detect the altered peripheral perfusion. Procedures of the measurement of CRI and CRT, and statistical methods are described in the section 6.4 "Procedures" and the section 7 "Statistical considerations", respectively.

##### (2) Secondary endpoints

The secondary endpoints include the followings:

- Sensitivity and specificity of CRI in differentiating altered peripheral perfusion determined with the CRT test. An optimal cutoff value for CRI will be determined with the ROC analysis for the primary endpoint.
- Pearson's or Spearman's correlation coefficient to assess the correlation between CRI and CRT values.

#### 6.1.4 Methods and timing for assessing, recording and analyzing variables

The study team will perform assessments and measurements according to the following table:

Study Phase	Screening and registration	Study measurement at the bedside	Follow up
Review the inclusion and the exclusion criteria	X		
Informed consent/assent	X		
Assigning a unique study subject number	X		
Measurements for subject's basal characteristics		X	
Applying a SpO <sub>2</sub> sensor probe on the finger		X	
Measurements of CRI and CRT		X	
Adverse event assessment		X	
Medical record review for subject's basal characteristics			X

The study procedures listed in the table are described in the section 6.3 “Subjects”, the section 6.4 “Procedures” and the section 13 “Informed consent process”.

#### 6.1.5 Equipment to be used for assessing, recording and analyzing variables and arrangements for monitoring maintenance and calibration

Equipment to be used in this study are described in the section 2 “Investigational device” and the section 6.4 “Procedures”.

#### 6.1.6 Any procedures for the replacement of subjects

No replacement condition is foreseen. Subjects who withdraws early will not be replaced as we plan to recruit up to 60 subjects to achieve at least 54 subjects to be analyzed as described in the section 7.2 “Sample size”.

## 6.2 Investigational device(s) and comparator(s)

### 6.2.1 Description of the exposure to the investigational device(s) or comparator(s), if used

#### (1) Investigational device

The SpO<sub>2</sub> sensor probe will be applied to a subject's fingertip.

#### (2) Comparator

The comparator is the visual CRT. There is no physical exposure for the CRT test.

### 6.2.2 Justification of the choice of comparator(s)

The comparator is the visual CRT, which is typically used to assess peripheral blood perfusion at the bedside. The CRI measurement has been developed to assess peripheral blood perfusion quantitatively as an alternative method to the visual CRT test. Therefore, comparisons between CRI and CRT need to be performed.

### 6.2.3 Other medical device or medication to be used during the clinical investigation

A standard patient monitor used in the ED will be used to collect information of patient's basal characteristics as listed below:

- Noninvasive blood pressure
- SpO<sub>2</sub>
- Pulse rate or heart rate
- Respiratory rate (if available)
- Body temperature

There is no medication to be used during the investigation.

### 6.2.4 Number of investigational devices to be used

- OLV-4201A Pulse Oximeter: 1 unit
- TL-271T3 SpO<sub>2</sub> sensor probe: 1 sensor per subject

## 6.3 Subjects

### 6.3.1 Inclusion criteria for subject selection

Adult ED and ICU patients (both males and females without regard to diverse ethnic and racial backgrounds) who meet the following inclusion criteria will be recruited.

- Individuals 18 years of age or older
- Patients who present to the ED or who are admitted to the ICU of North Shore University Hospital (NSUH)

### 6.3.2 Exclusion criteria for subject selection

- Pregnant
- Prisoners
- Finger, hand or forearm anatomical anomaly or disease that may interfere with attaching a pulse oximeter sensor
- Patients' deemed clinically unstable by the clinical team

### 6.3.3 Criteria and procedures for subject withdrawal or discontinuation

All subjects are free to withdraw from the study at any time and for any reason. Subject safety will be monitored by the investigator who is a qualified ED physician. The primary safety concern is ensuring the patients are not distressed by the study procedures. All the procedures that subjects will receive are non-invasive, but if the subject reports any adverse effects during the course of the study, the investigators will immediately discontinue any procedures and remove any research instruments from the subject. Data collected up to the point of the subject's withdrawal will continue to be used and analyzed. No further data will be collected after the subject's withdrawal.

### 6.3.4 Point of enrollment

Adult patients who present to the ED of NSUH who meet the eligibility criteria will be recruited. Importantly, patients will only be approached who are physically available to participate in the study, as to not delay or interrupt the patient's care for recruitment. Informed consent will be obtained directly from the subject prior to all procedures. Then, a unique study subject number will be assigned, and the subject will be registered for this study.

### 6.3.5 Total expected duration of the clinical investigation

The duration of the study (including data collection and analysis) is approximately 1 year.

### 6.3.6 Expected duration of each subject's participation

Expected duration of each subject's participation is approximately 15 minutes.

### 6.3.7 Number of subjects required to be included in the clinical investigation

Total number of subjects is up to 60. Detail of the required sample size calculation is described in the section 7.2 "Sample size".

### 6.3.8 Estimated time needed to select this number (i.e. enrolment period)

The duration of subject enrollment is anticipated for 6 months.

### 6.3.9 Subject compensation

Each subject will receive a \$15 gift card as compensation for their participation in this study.

## 6.4 Procedures

6.4.1 All the clinical-investigation-related procedures that subjects undergo during the study

Adult ED patients aged 18 years and older will be recruited for this study. Informed consent will occur prior to the study enrollment. Patients will be assigned a unique study subject number. All data mentioned below will be recorded on paper forms. Raw data measured by the investigational device will be recorded digitally on a SD card inserted in the device. Data recoded on paper forms will be entered into REDCap so that it can be analyzed.

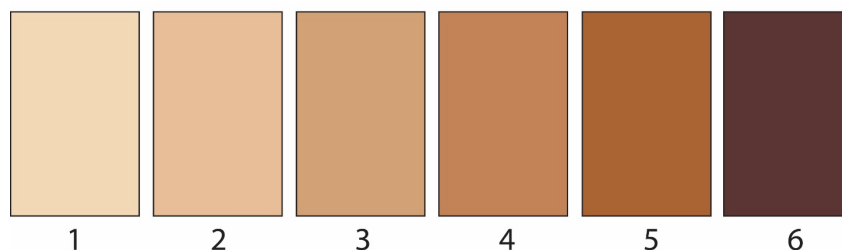
Patient's basal characteristics will be collected as shown below. Noninvasive blood pressure, SpO<sub>2</sub>, pulse rate, respiration rate and body temperature will be measured by a standard patient monitor used in the ED.

### Obtained from medical record:

- Age
- Gender
- Race
- Height
- Body weight
- Past general medical history (diabetes mellitus, hypertension, smoking, heart disease, lung disease, others)
- Initial vital sign data (blood pressure, SpO<sub>2</sub>, pulse rate/heart rate, respiratory rate and body temperature)
- Core body temperature (if available)
- Red blood cell count (RBC), Hematocrit (Ht) and Hemoglobin (Hb) (if available)
- Lab data: Blood lactate levels, Cre/BUN and TP/Alb (if available)
- Primary diagnosis
- Disposition (Discharged home, admitted, left against medical advice, skilled nursing facility, other hospital, expired, unknown or other)
- Time of events (ED arrival, ED encounter, ED discharge and admission, etc.)

### Obtained at the bedside:

- CRT
- CRI
- Noninvasive blood pressure
- SpO<sub>2</sub>
- Pulse rate or heart rate
- Respiratory rate (if available)
- Fitzpatrick skin tone scale



- Body temperature (axillary)
- Forearm and fingertip temperatures
- Room temperature

The surface temperature of the patient's hand will be measured by a non-contact infrared thermometer. To address the reliability of the subjective assessment of peripheral perfusion by the investigator, we will also measure forearm-to-fingertip skin temperature difference (T<sub>skin-diff</sub>), as well as central-to-fingertip temperature difference (T<sub>c-diff</sub>). The T<sub>skin-diff</sub> will be obtained from the index/middle finger temperature and the temperature on the radial side of the forearm, midway between the elbow and the wrist.

The CRT and the CRI measurements will be conducted with following methods for each subject in a relaxed position (seated or lying down) with relaxed hands. The subject's most accessible hand (right or left) will be used. Each measurement will be performed alternately and will be repeated three times each for a total of six compressions per subject. If the subject is wearing nail polish, the investigator will measure CRI/CRT after removing the subject's nail polish. If the subject is wearing a ring on their finger, CRI/CRT will be measured after removing the ring(s).

#### **Visual CRT measurement using a stopwatch**

An investigator (an ED physician) will compress the fingertip of the subject's index or middle finger for five seconds, signaled by "start compression" and "release compression" beep sounds. When the fingertip is released from the compression, the investigator will begin the visual CRT measurement. The investigator will hold a stopwatch in the hand that does not perform the compression and use this stopwatch to measure CRT.

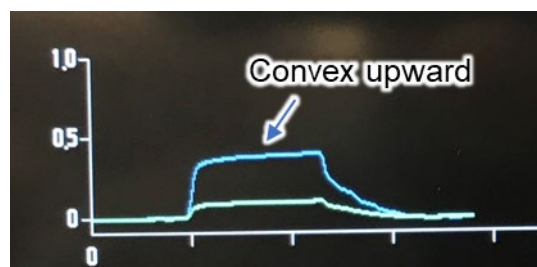
#### **CRI measurement by the investigational device**

The SpO<sub>2</sub> sensor probe will be applied to either the index or middle fingertip of the same hand of the subject used in the CRT measurement, depending upon which fingertip was compressed in the CRT measurement. For example, if the index fingertip was used in the CRT measurement, then the sensor will be applied to the middle fingertip. With the sensor on it, the investigator will compress the subject's fingertip for five seconds by the investigator's finger as same way of the traditional CRT test. The sensor is flexible and thus, the investigator is able to compress the fingertip by compressing the sensor (Figure 2). The compression will be performed with signals from the device, and then the device will measure CRI.



**Figure 2:** Compression for the CRI measurement

The investigator will confirm the sensor probe is properly applied to the fingertip by measuring CRI and checking whether the shape of the CRI measurement waveform is proper. With proper application of the sensor probe, the measurement waveform is convex upward as shown in Figure 3. If the sensor probe is not properly applied, the investigator will replace the sensor probe.



**Figure 3:** Proper shape of the CRI measurement waveform

The investigator will be blinded from the measured value of the CRI measurement.

All subjects are free to withdraw from the study at any time and for any reason. The investigators will immediately discontinue any procedures and remove any research instruments from the subject. Data collected until the subject's point of withdrawal from the study will be analyzed. The estimated duration of the subject's participation is approximately 15 minutes in total.

#### 6.4.2 Activities performed by sponsor representatives (excluding monitoring)

There is no activity performed by sponsor representatives.

#### 6.4.3 Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results

- Improper application of the sensor probe to the fingertip will cause inappropriate results of the measurement. The investigator will confirm the sensor probe is properly applied to the fingertip with the procedure described in the section 6.4.1. If the sensor probe is not properly applied, the investigator will replace the sensor probe.

## 6.5 Monitoring plan

Since this is a single site study, there is no plan for external site monitoring.

The principal investigator is tasked with ensuring the safety and data integrity of the study. The PI will continuously review the aggregate data to determine if any aspects of the study need to be changed or stopped. In addition, the PI will review any and all CIP deviations, adverse events, and unanticipated problems that may occur to determine their relatedness to the study, their severity, and whether they require study changes. Any unanticipated problems or instances of non-compliance will be reported to the IRB as per their reporting requirements. If any changes of CIP are needed, an investigator will submit a modification request to the IRB. CIP changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB will be promptly informed of the change following implementation.

The sponsor and/or representative may conduct periodic on-site monitoring visits during the course of the study, including study initiation and close-out to ensure appropriate documentation is present and completed. The investigator will permit study-related monitoring, audits, and inspections of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) by the IRB, the sponsor, government regulatory bodies, and compliance and quality assurance groups of the study site. The investigator will ensure the capability for inspections of applicable study-related facilities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices of the study site.

## 7 Statistical considerations

### 7.1 Statistical design, method and analytical procedures

In order to assess the study aims and hypotheses, we will describe the study sample using descriptive statistics such as frequencies, proportions, means, standard deviations, 95% confidence intervals, medians, and interquartile ranges. The mean of the three repeated CRI and CRT measurements will be considered as the values for each subject.

The primary and secondary endpoints are described in the section 6.1.3. Receiver operator characteristic (ROC) curve analysis will be performed and area under the curve (AUC) will be calculated to demonstrate capability of CRI to predict altered peripheral perfusion determined with the CRT test. An optimal cutoff value for CRI will be determined with the ROC analysis and the sensitivity and the specificity in differentiating altered peripheral perfusion will be calculated. Pearson's, or Spearman's correlation coefficient will be calculated to assess the correlation between CRI and CRT values.



## 7.2 Sample size

The primary endpoint of this study is an AUC of the ROC curve analysis on CRI values to predict altered peripheral perfusion determined with the CRT test. Sample size for subjects with altered peripheral perfusion required to obtain desired AUC is calculated with the following equation [9]:

$$n = \frac{\frac{Z_{\alpha}^2}{2} \times V(AUC)}{d^2}$$

where,  $Z$  is the standard normal deviate determined with probability of type I error:  $\alpha$ ,  $d$  is the desired width of one-half of the confidence interval (CI), and  $V(AUC)$  is variance of AUC which is derived from the following equation [10]:

$$V(AUC) = (0.0099 \times e^{-a^2/2}) \times \{(5a^2 + 8) + (a^2 + 8)/\kappa\}$$

where,  $a = \varphi^{-1}(AUC) \times 1.414$ ;  $\varphi^{-1}$  is inverse of standard cumulative normal distribution; and  $\kappa$  is the ratio of the number of subjects without the altered peripheral perfusion to the number of subjects with the altered peripheral perfusion. Based upon our preliminary data:

- The prevalence of the subjects with altered peripheral perfusion is expected to be 30%, and then  $\kappa$  is 2.33.
- We hypothesize that the AUC will be 0.84, and then  $a = \varphi^{-1}(0.84) \times 1.414 = 1.406$ .

Therefore,  $V(AUC)$  can be calculated as follow:

$$V(AUC) = (0.0099 \times e^{-1.406^2/2}) \times \{(5 \times 1.406^2 + 8) + (1.406^2 + 8)/2.33\} = 0.0816$$

To achieve an AUC of at least 0.70 which is considered as fair [11], one-half of the CI:  $d$  should be 0.14 with the hypothesized AUC of 0.84. At the significance level of 5% (probability of type I error:  $\alpha = 0.05$ ), the number of subjects with altered peripheral perfusion is derived as:

$$n = \frac{\frac{Z_{\alpha}^2}{2} \times V(AUC)}{d^2} = \frac{1.96^2 \times 0.0816}{0.14^2} = 15.99 \approx 16$$

The total number of required sample size given by  $n(1 + \kappa)$  is 54. Considering possible early withdrawals of subjects, we plan to recruit up to 60 subjects to achieve 54 evaluable subjects (10% of drop-out rate).

## 7.3 The level of significance and the power of the clinical investigation

All statistical tests will be assessed at the significance level of 5% (probability of type I error:  $\alpha = 0.05$ ).

#### 7.4 Expected drop-out rates

Although the drop-out rate for this study is unknown, relatively high drop-out rate can be expected since the study site is the ED and the subjects may need early withdrawals due to disposition (admission to the hospital or discharge). Therefore, we use 10% of drop-out rate and will recruit up to 60 subjects to achieve 54 evaluable subjects.

#### 7.5 Pass/fail criteria to be applied to the results of the clinical investigation

The hypothesis to be tested in this study is that CRI is capable to detect subjects with altered peripheral perfusion determined with the CRT test, as described in the section 5.2. A criterion to accept the hypothesis is that the AUC value described in the section 6.1.3 (1) "Primary endpoint" is at least 0.70 which is considered as fair [11].

#### 7.6 Provision for an interim analysis

No interim analysis is planned.

#### 7.7 Criteria for the termination of the clinical investigation on statistical grounds

As no interim statistical analysis is planned, no criteria for the termination of the study is defined.

#### 7.8 Procedures for reporting any deviation(s) from the original statistical plan

Any modification to the statistical analysis plan will be documented in the final study report if applicable.

#### 7.9 Specification of subgroups for analysis

Not applicable.

#### 7.10 Procedures that take into account all the data

Not applicable. This study is the observational study and no allocation of subjects is planned.

#### 7.11 Treatment of missing, unused or spurious data, including drop-outs and withdrawals

- Data collected up to the point of the subject's withdrawal will continue to be used and analyzed.
- If just one value of CRI/CRT out of the three repeated measurements is missing, the mean of the remaining two values will be used as the value for the subject.

#### 7.12 Exclusion of particular information from the testing of the hypothesis

- Data of a subject in which two or more values of CRI/CRT out of the three repeated measurements are missing will be excluded from the analysis.

#### 7.13 In multicenter clinical investigations, the minimum and maximum number of subjects to be

included for each center

Not applicable.

## 8 Data management

### 8.1 Procedures used for data review, database cleaning, and issuing and resolving data queries

#### (1) Identification of source document and source data

All data and information obtained in the study will be recorded on paper forms of case report form (CRF). The CRFs are considered as original source documents and the data recorded in the source documents is considered as original source data.

#### (2) Case Report Form (CRF)

The CRFs are the primary data collection instruments for the study. All data requested on the CRFs must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done, or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. **DO NOT ERASE OR WHITE OUT ERRORS.** For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

The PI is responsible for ensuring the data and information are properly recorded on each subject's CRF and related documents. The PI and an investigator who completes the recording will sign the CRF to validate that the data and the information are recorded on the CRF correctly and completely.

#### (3) Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

#### (4) Data review

The PI will continuously review the aggregate data to ensuring integrity of the study data. The PI is

responsible for identifying missing data and exclusion of data described in the section 7.11 and 7.12.

## 8.2 Procedure for verification, validation and securing of electronic clinical data system

The data and the information will also be input into the secure database REDCap, with access granted to study investigators only. There are procedures and processes in place by Northwell Health to safeguard the authenticity, integrity and confidentiality of the data in REDCap. And there are procedures for training, technical support, and auditing to ensure the system is functioning and being used in the manner intended.

## 8.3 Procedure for data retention

Signed consent forms and paper forms used to collect data will be stored in a locked research office at North Shore University Hospital and/or The Feinstein Institute for Medical Research. This data will also be input into the secure database REDCap, with access granted to study investigators only.

When data is sent out of the Northwell Health system to the sponsor, the data shall be de-identified and the data file will be encrypted. In this data file, each subject will be assigned a unique study subject number. No names or other direct identifiers will be included in the data file. The date when the data was collected and the information on past or current medical history are the only indirect identifiers that will be included in the data file. Only the PI will obtain a list that links the study subject numbers that are sent to the sponsor to the original subject information. This list will remain stored in the locked research office.

Any study records that identify subjects will be kept private. Participants will not be identified in publications disclosed outside of Northwell Health, except as detailed below. Investigators will share information collected from this research study with:

- Study sponsor and/or its agents,
- Other researchers,
- Regulatory agencies, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS), and
- Clinical staff not involved in the study who may be involved in the participant's treatment.

## 8.4 Specified retention period

The investigator and the sponsor shall retain all the records of the study during the study and for a period of 2 years after the latter of the following two dates:

- The date on which the study is terminated or completed
- The date that the records are no longer required for purposes of supporting applications for FDA clearance of the investigational device.

## 8.5 Other aspects of clinical quality assurance

Not applicable.

## 9 Amendments to the clinical investigation plan

If any changes on this CIP are needed, an investigator will submit a modification request to the IRB. CIP changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the study subjects. In such a case, the IRB will be promptly informed of the change following implementation.

## 10 Deviation from the clinical investigation plan

### 10.1 Statement specifying that the investigator is not allowed to deviate from the CIP

The Investigators are not allowed to deviate from the CIP, excepted under emergency circumstances, to protect the rights, safety and well-being of the subjects. In this case, such deviations shall be documented and reported to the sponsor and the IRB as soon as possible.

Any exceptions from the CIP must receive approval from both the sponsor and the IRB before they are initiated.

### 10.2 Procedures for recording, reporting and analyzing CIP deviations

Any CIP deviations initiated without the sponsor and IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be recorded and reported to the sponsor and to the IRB. If any CIP deviations are observed during the monitoring visit, all such observations must be documented in reports of the monitoring visits. All CIP deviations will be discussed during the data review which occurs before the data analysis, and then the discussion will be documented in the final study report.

### 10.3 Notification requirements and time frame

Any CIP deviations must be reported to the sponsor and the IRB as soon as possible, but no later than 5 working days after the CIP deviation occurs. If any CIP deviations are observed during the monitoring visit, all such observations must be documented in reports of the monitoring visits. An investigator shall report to the sponsor in a case of withdrawal of IRB approval as soon as a possible, but no later than 5 working days of the IRB notification of withdrawal of approval.

### 10.4 Corrective and preventive actions and principal investigator disqualification criteria

The PI will check whether the same deviation occurred in other subjects which are unreported. If other deviations are observed, all the deviations must be recorded and reported. The PI and/or the sponsor will warn the investigator of the importance to respect the CIP. An investigator who continuously violates the CIP despite the warnings could be excluded from the investigation after agreement of the sponsor.

## 11 Device accountability

### 11.1 Labeling and packaging of the investigational device

The study device or its immediate package will bear a label with the following information:

- The name and place of business of the manufacturer, packer, or distributor

- The quantity of contents, if appropriate
- The statement, "CAUTION -- Investigational device. Limited by Federal (or United States) law to investigational use."

The label will also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions, if applicable. The labeling of the device will not contain any false or misleading statements nor imply that the device is safe or effective for the purposes being investigated.

The study device will be packaged in accordance with the manufacturer's recommendations. The sensor probes will be shipped as bulk orders of 24 probes individually packaged. Only one probe will be used for each patient, and then it will be discarded.

### 11.2 Receipt of the investigational device

Upon receipt of the investigational device supplies, an inventory will be performed, and a device tracking log will be filled out and signed by the person accepting the devices from the manufacturer's carrier. Any damaged or unusable devices will be documented in the study files. The investigator will notify the sponsor of any damaged or unusable devices that were supplied to the investigator's site.

### 11.3 Identification of each investigational device (batch number, serial number or unique code)

Each investigational device will be identified with the following numbers as described in the section 2.4

"Traceability":

- OLV-4201A Pulse Oximeter: identify with assigned serial numbers
- TL-271T3 SpO2 sensor probe: identify with assigned lot numbers

### 11.4 Expiry date of use

Not applicable.

### 11.5 Use and storage of the investigational device

When in use, the device will remain in the possession of the study team. The device must be used only for the purpose of this study. The OLV-4201A Pulse Oximeter will be cleaned following the manufacturer's instructions (cleaned by hand with a mild detergent), and the standard hygiene and infection control procedure in the ED. The SpO2 sensor probes that come into contact with the subject's finger will be properly disposed after each use. The device will immediately be returned to the locked research office at NSUH and/or FIMR when not in use. The research team will follow product instructions and operator's manuals. There are no specific storage requirements nor special handling requirements during storage for the study device.

### 11.6 Subject identification

The serial number of the Pulse Oximeter and the lot number of the sensor probe which are used for each subject

will be documented in the CRF of each subject. With this record, the dates of using the device are also traceable.

#### 11.7 Investigational device which is returned/explanted from subject, if applicable

Not applicable.

#### 11.8 Return of unused, expired or malfunctioning investigational devices, if applicable

At the completion of the study, there will be a final reconciliation of the study devices. This reconciliation will be logged on the device tracking log. Any discrepancies noted will be investigated, resolved, and documented prior to returning the device to the manufacture.

## 12 Statement of compliance

### 12.1 Declaration of Helsinki

This study is to be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. These principles protect the rights, safety and well-being of human subjects, which are the most important considerations and shall prevail over interests of science and society. These principles shall be understood, observed, and applied at every step in the clinical investigation.

### 12.2 International standard and any regional or national regulations

This study is to be conducted in accordance with US and international standards of Good Clinical Practice: International Conference on Harmonization ICH E6, ISO 14155, the Code of Federal Regulations Title 21 parts 803 and 812, and other applicable government regulations and institutional research policies and procedures.

### 12.3 IRB and/or regulatory authorities

This CIP and any amendments on the CIP will be submitted to the Northwell Health IRB for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the CIP for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedures. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent. A waiver of documentation of consent will be used for any subjects that have a physical limitation preventing them from signing the consent form but have the ability to understand and express a reasoned choice. In this case, HIPAA authorization will be obtained verbally, and only in cases where there is a physical limitation preventing the subject from signing his/her name. Both the waiver of documentation of consent and the verbal HIPAA authorization will be documented in the enrollment note.

## 12.4 Insurance

The sponsor shall hold an insurance contract to cover the liability according to the arrangement of the sponsored research agreement for this study.

## 12.5 Conflict of interest

All Northwell Health Investigators will follow the Northwell Health Policy on Conflicts of Interest Related to Research.

# 13 Informed consent process

## 13.1 General process for obtaining informed consent

Adult patients who present to the ED of NSUH who meet the eligibility criteria will be recruited. Informed consent will be obtained directly from the subject prior to all procedures. Some individuals may be assessed to have difficulty writing but have the ability to understand and express a reasoned choice. For example, such limitations in writing may result from a broken arm, an infusion line causing pain when moving the arms or writing fingers, or a high fever that may induce feelings of lethargy that prohibits them from providing a written signature, etc. As such, we request a waiver of documentation of consent for individuals who have a physical limitation preventing them from signing the consent form. The consent process will be performed as follows:

- (1) The subject will be given consent forms to read and be given an opportunity to ask questions. If the subject has a visual impairment, the consent will be read to them.
- (2) One impartial witness will be present during the entire informed consent discussion.
- (3) After the written consent is provided to the subject, if capable of doing so, the subject will sign or mark an X to signify consent and will personally date the consent document. If that is not possible, the subject will provide verbal consent.
- (4) After consent has been obtained from the subject, the person obtaining consent and the impartial witness will sign and date the written study consent form with a statement that documents that an oral process was used and, if necessary, that the subject provided verbal consent. By signing the consent document, the witnesses attest that the information in the consent document and any other written information were accurately explained to the subject.
- (5) The consent process will also be documented in the medical record or in accord with the Institution's policy.
- (6) Signed copies of the consent form will be given to the subject.

HIPAA authorization will be obtained verbally, and only in cases where there is a physical limitation preventing the subject from signing his/her name. Both the waiver of documentation of consent and the verbal HIPAA authorization will be documented in the enrollment note.

If, at any point, the participant no longer wishes to be in this study, he/she may notify the study investigators (as outlined in the consent form) and be withdrawn from the study.



### 13.2 Informed consent process if the subject is unable to give it

Not applicable. If a patient approached for the study is assessed to have a cognitive impairment based on their inability to understand and express a reasoned choice, they will be unable to provide informed consent and thus will be excluded from participation in the study.

## 14 Adverse events, adverse device effects and device deficiencies

### 14.1 Definitions of adverse events and adverse device effects

#### (1) Adverse event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator, and events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

#### (2) Adverse device effect (ADE)

Adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

### 14.2 Definition of device deficiencies

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

### 14.3 Definition of serious adverse events, serious adverse device effect and unanticipated serious adverse device effects

#### (1) Serious adverse event (SAE)

Adverse event that:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
  - 1) a life-threatening illness or injury, or
  - 2) a permanent impairment of a body structure or a body function, or
  - 3) in-patient or prolonged hospitalization, or
  - 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to fetal distress, fetal death, or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

(2) Serious adverse device effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

(3) Unanticipated serious adverse device effects (USADE)

Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

NOTE: anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

#### 14.4 Definition of unanticipated problems involving risk to subjects or others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

#### 14.5 Time periods for reporting adverse events and device deficiencies

(1) Notifying the PI and the sponsor

Any adverse event that qualifies as a serious adverse event or a serious adverse device effect, and any type of unanticipated adverse device effect, regardless of seriousness or severity, must be reported immediately to the PI and to the sponsor **by telephone within 24 hours of the event. Within the following 48 hours**, the PI shall provide further information, as applicable, on the adverse event or the unanticipated problem in appropriate forms of a written narrative. This should include a copy of completed reporting forms, and any other diagnostic information that will assist the understanding of the event.

(2) Notifying the IRB

The Northwell Health IRB requires the investigators to submit reports of the following problems **within 5 working days** from the time the investigators become aware of any adverse event that occurs any time during or after the study, which in the opinion of the PI is:

- **Unexpected** (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

**AND**

- **Related** to the research procedures (An event is “related to the research procedures” if in the opinion of the PI or the sponsor, the event was more likely than not to be caused by the research procedures.)

The above is required regardless of whether the event is serious or non-serious, on-site or off-site.

All unanticipated adverse device effects and all serious adverse device effects reported by the investigator to the sponsor must also be reported to the IRB **as soon as possible, but within 5 business days.**

#### 14.6 Process for reporting adverse events and device deficiencies

##### (1) Notifying the PI and the sponsor

At each contact with the subject, the investigator must seek information on adverse events including adverse device effects by specific questioning and, as appropriate, by examination. Information on all adverse events including adverse device effects must be recorded immediately in the source documents, and also in appropriate adverse event case report forms. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source documents, though should be grouped under one diagnosis.

The clinical course of each event must be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events and serious adverse device effects that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse device effects that occur after the study period must be recorded and reported promptly.

The minimum initial information to be captured in the subject’s source documents concerning the adverse event includes:

- Study identifier
- Study subject number
- Model and serial number/lot number of the investigational device
- A description of the event
- Date of onset
- Investigator assessment of the association between the event and study procedure/treatment
- Current status

- Whether study procedure/treatment was discontinued
- Whether the event is serious and reason for classification as serious

## (2) Notifying the IRB

The investigators should report unanticipated problems to the Northwell Health IRB using the form: “Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events” or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation). Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator’s study file.

### <Other Reportable events>

For clinical studies with an investigational device, the following events are also reportable to the Northwell Health IRB:

- For device studies that include the delivery of investigational drugs, any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the protocol or the informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved

protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

#### 14.7 Foreseeable adverse events and anticipated adverse device effects

There is no particular anticipated adverse device effect since the applied part of the investigational device (the sensor probe) is equivalent to standard pulse oximeter sensors. A well-known potential adverse effect of pulse oximeters is thermal injuries due to temperature rise at the applied part of the sensor.

#### 14.8 Emergency contact for reporting serious adverse events and serious adverse device effects

##### **<Sponsor contact information for reporting purposes>**

Report adverse events including adverse device effects and any unanticipated problems by phone and email to the following representative of the sponsor:

Steve Weisner, CEO

Nihon Kohden Innovation Center

Phone: 617-318-5900

Email: Steve\_Weisner@nihonkohden.com

#### 14.9 Information regarding the data monitoring committee

Not applicable. There is no data monitoring committee for this study.

### **15 Vulnerable population**

Not applicable. The population for this study is not considered as a vulnerable population.

### **16 Suspension or premature termination of the clinical investigation**

#### 16.1 Criteria and arrangements for suspension or premature termination

The sponsor may suspend or prematurely terminate either a clinical investigation in an individual investigation site (if applicable) or the entire clinical investigation for significant and documented reasons. A principal investigator, IRB, or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigation sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the IRB or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed. The sponsor shall consider terminating or suspending the participation of a particular investigation site (if applicable) or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated CIP deviations.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties. The principal investigator and sponsor shall keep each other informed of any

communication received from either the IRB or the regulatory authority. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other investigators of other investigation sites (if applicable).

When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor shall inform the principal investigator, the IRB, and where appropriate, the regulatory authority of the rationale and provide them with the relevant data supporting this decision. Concurrence shall be obtained from the IRB and, where appropriate, regulatory authorities before the clinical investigation resumes.

#### 16.2 Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical investigation

Not applicable. The blinding in this study is used only when CRI and CRT measurements are performed at the bed side as described in the section 6.1.2: the investigator who will measure the visual CRT will be blinded from the CRI values measured with the investigational device.

#### 16.3 Requirements for subject follow-up

Any early withdrawal of subject must be fully documented in the case report forms. The subject must be followed up to state the reason for the withdrawal and to establish whether the reason is considered as an adverse event or not.

### 17 Publication policy

The result and the data obtained in this study will be used for applications for FDA clearance of the investigational device. A full publication policy is detailed in the sponsored research agreement for this study between Northwell Health and NKC. The guiding principles for this are based on the requirements of Northwell Health. Authorship and manuscript preparation will be done in accordance with accepted standards. In general, this publication policy allows for publication of the result and the data with the requirement that all publications and public release must be presented to the sponsor well in advance of any publication or presentation, time for the sponsor to respond to the data is encouraged and allowed per the publication policy.

### 18 Bibliography

1. Schriger DL, Baraff L: Defining normal capillary refill: variation with age, sex, and temperature. *Ann Emerg Med* 1988; 17:932-935
2. Lima A, Jansen TC, van Bommel J, et al: The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. *Crit Care Med* 2009; 37(3):934-938
3. Van Genderen ME, Paauwe J, de Jonge J, van der Valk RJP, Lima A, Bakker J, et al: Clinical assessment of peripheral perfusion to predict postoperative complications after major abdominal surgery early: a prospective observational study in adults. *Crit Care* 2014; 18(3): R114

4. Alisma J, van Saase JLCM, Nanayakkara PWB, et al: The Power of Flash Mob Research: Conducting a Nationwide Observational Clinical Study on Capillary Refill Time in a Single Day. *Chest* 2017; 151:1106-1113
5. Pickard A, Karlen W, Ansermino JM: Capillary refill time: is it still a useful clinical sign? *Anesth Analg* 2011; 113:120-123
6. Lima A, Bakker J: Noninvasive monitoring of peripheral perfusion. *Intensive Care Med* 2005; 31:1316-1326
7. Shinozaki K, Capilupi MJ, Saeki K, et al: Blood refill time: Clinical bedside monitoring of peripheral blood perfusion using pulse oximetry sensor and mechanical compression. *Am J Emerg Med* 2018; 36(12):2310-2312
8. Shinozaki K, Capilupi MJ, Saeki K, et al: Low Temperature Increases Capillary Blood Refill Time Following Mechanical Fingertip Compression of Healthy Volunteers: Prospective Cohort Study. *J Clin Monit Comput* 2018 [Epub ahead of print]
9. Hajian-Tilaki, K.: Sample size estimation in diagnostic test studies of biomedical informatics. *Journal of biomedical informatics* 2014; 48:193-204
10. Obuchowski, N. A., Lieber, M. L., & Wians, F. H.: ROC curves in Clinical Chemistry: Uses, misuses, and possible solutions. *Clinical Chemistry* 2004; 50(7)
11. E. A. Youngstrom. A primer on receiver operating characteristic analysis and diagnostic efficiency statistics for pediatric psychology: we are ready to ROC. *J Pediatr Psychol.* 2014;39(2):204-221.

## 19 Attachments

- Attachment 1: Operator's Manual of OLV-4201
- Attachment 2: Certificate of Safety Test of IEC 60601-1
- Attachment 3: Certificate of EMC Test of IEC 60601-1-2 and ISO 80601-2-61(clause202)
- Attachment 4: Operator's Manual of SpO2 sensor probe
- Attachment 5: Operator's Manual of the CRI function
- Attachment 6: Report of Collaborative Research at Northwell