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1 Introduction

1.1 Purpose

The purpose of this document is to report the SpO2 clinical investigation results of the viQtor device, after performing a controlled desaturation study.

1.2 Scope

This document has the following scope:

- Describe the procedure used to acquire data for the validation of the performance of the SpO2 algorithms on the viQtor device according to EN-ISO 80601-2-61:2019
- Results analyzed according to EN-ISO 80601-2-61:2019
- Discussion, such as inclusion criteria of samples and test subjects
- Conclusion

1.3 Study details

investigational devices and their identification numbers	3x viQtor devices, see chapter 3.3 for ID's and software version used
CIP number	Protocol NL78476.058.21 v1.1 date 08-07-2021 PRD1339-4-2153
Coordinating investigators	Rutger van der Schrier, MD (Leiden University Medical Center)

Principal investigators	Prof. Albert Dahan, PhD (Leiden University Medical Center)

2 Investigation Summary

EN-ISO 80601-2-61:2019[2] Medical electrical equipment — Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment [2] is the ISO standard used by the EU for the evaluation of safety and performance requirements for medical pulse oximeter equipment. Compliance of the viQtor device to this standard is analyzed in the Compliance guidance document [5]. The standard contains (among others) the to be used method for the validation of SpO2 performance in a clinical trial.

The viQtor SpO2 measurement has been calibrated and validated against a co-oximeter according to this standard during a clinical trial at LUMC. This specific study was a secondary study goal in a larger clinical trial named “Carotid body dysfunction in type 2 diabetes” (NL78476.000.21). The principal investigator was Prof. Albert Dahan, anesthesiologist at LUMC. Approval for this clinical trial was given by the institutional review board of LUMC on October 8, 2021. The trial was a two arm pre-post study, in which the difference in chemosensitivity during baseline and euglycemic hyperinsulinemia between patients with type 2 diabetes and healthy controls was investigated. During the baseline measurement and the euglycemic hyperinsulinemia, the study subjects were desaturated in a controlled manner to study the hypoxic ventilatory response, enabling the validation of the viQtor SpO2 sensor at the same time.

The trial consisted of two parts. During the first part, calibration of the viQtor was performed. During the second part, validation of the viQtor was performed. For both parts the same measurement protocol was used, using controlled desaturation of subjects in several plateaus between 100% and 70%. A co-oximeter analyzing SaO2 in blood samples was used as a gold standard for SpO2. This report describes the results of the controlled desaturation study to validate the SpO2 performance of the viQtor device.

The following results were obtained:

SaO2 Range [%]	Used samples	A_{rms} [%]
All samples	**779**	**1.74**
90-100	332	1.21
80-90	246	1.66
70-80	201	2.44

Table 1: Summary of results

A total of 1187 samples were obtained during the trial, of which 779 unique SaO2 samples.

SaO2 samples were excluded when there were no SpO2 samples from the ViQtor device that passed the inclusion criteria (see chapter 5) close to the time of recording for the SaO2 sample, leading to 779 samples that were used for accuracy calculations.

The measurements included in this SpO2 performance assessment where from 07-dec-2021 to 4-feb-2022. The investigation for this SpO2 performance assessment has not been terminated early, nor was it temporarily halted or suspended.

One subject had a vasovagal reaction during a measurement, which required a Trendelenburg position and a single dose of atropine 0.5 mg. The subject was discontinued, subject did not withdraw consent. Measurements up to this point were used for analysis. Otherwise no adverse events occurred.

The conclusion of this investigation is: the SpO2 performance of the viQtor complies with the EN-ISO 80601-2-61:2019[2] standard, with a demonstrated accuracy of **1.84%** Arms (1.74% as seen from the table above plus 0.1% error from the reference data accuracy[3]), which is within the 4% Arms requirement of subclause 201.12.1.101.1.

3 Setup

3.1 Summary of clinical investigation plan

Objective:

Main objective: Evaluate the difference in chemosensitivity during baseline and euglycemic hyperinsulinemia between patients with type 2 diabetes and healthy controls.

Secondary objective:

- Assess differences in heart rate variability during baseline and euglycemic hyperinsulinism between patients with type 2 diabetes and healthy controls.
- Assess whether isocapnic hypoxic ventilatory response differs significantly from the Dejours test in evaluating carotid body chemosensitivity.
- Assess whether the degree of insulin resistance is correlated to chemosensitivity and/or heart rate variability
- Calibrate and validate a new wearable pulse-oximeter (SQ1 / viQtor)

Study design: a two arm pre-post study

Study population, sample size and selection criteria: The study population consists of 15 adult subjects diagnosed with type 2 diabetes that are non-insulin-dependent (NIDDM) and 15 healthy age and BMI matched controls. For a complete overview of the inclusion and exclusion criteria, see the study protocol [1]

Intervention (if applicable): The intervention is an hyperinsulinemic euglycemic clamp, as described by DeFronzo et al. [1], and consists of both a constant intravenous infusion of insulin to create an artificially constant hyperinsulinemic state and a variable glucose infusion to maintain a euglycemic state.

Treatment schedule: The experiment is to be performed in a single visit and consists of three episodes of controlled desaturation: a baseline measurement, a measurement under hyperinsulinemia, and finally a measurement under normoglycemia.

Follow-up duration: There is a follow-up of 2 hours after the protocol is completed.

Concomitant treatments: Controlled desaturation is achieved using the Leiden Gas Mixer (built in-house).

Statistical plan: The sample size was calculated based on the primary objective. A Repeated Measures ANOVA will be used to determine whether there is a significant interaction between the change hypoxic ventilatory response due to the euglycemic hyperinsulinemia between diabetics and healthy controls. A correction for non-sphericity will be applied based on previous studies using the hypoxic ventilatory response in our laboratory (non-sphericity correction score of 0.8). The analysis of the effect measured over three timepoints between two groups assuming an effectsize of 0.75, power = 0.9 (alpha = 0.9) results in 28 subjects. Considering that the correction for non-sphericity is an estimation that could result in underpowering if it is underestimated we propose a further 2 subjects to be added, resulting in a total sample size of 30 subjects.

> For the secondary objective of validating the viQtor SpO2, the EN-ISO 80601-2-61:2019 [2] standard recommends a minimum of 10 subjects and 200 datapoints. We expected that 20 included subjects would suffice for the validation. A justification of the included subjects and datapoints in the validation part can be found in chapter 3.2 (needed sample size estimation).

Ethical aspects: Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The study requires a screening visit during which a physical examination, vital signs and ECG will be performed. The experiment will require a single visit. Fasting is required for the experiment, which will refrain the subjects that are on oral antidiabetic medication from using this medication on the day of the experiment and the evening before the experiment. The study requires placement of intravenous and arterial access. During the experiment ECG measurements will be performed in order to acquire heartrate variability data. Three hypoxic ventilatory response measurements are acquired. Three Dejours tests [2] (hyperoxia during two breaths) will be performed. A hyperinsulinemic euglycemic clamp will be performed.

All subject will be monitored by a qualified physician and research nurse using ECG, pulse oximetry, invasive and non-invasive blood pressure ensuring participant safety during the experimental procedures. Placement of the arterial line will be performed following an Allen's test, and application of a local anaesthetic. The isocapnic hypoxic ventilatory response is the golden standard to evaluate carotid body chemosensitivity and is performed routinely by research groups around the world. Our research team has ample experience performing hypoxic ventilatory responses. We ensure that the hypoxic steps do not last longer than required and the lowest SpO2 will be 70% for 2 min. The isocapnic hypoxic ventilatory responses are accompanied by hyperventilation which could be experienced as uncomfortable by some subjects. The measurement takes approximately ten to fifteen minutes and ventilation returns to baseline within a minute. Hypoxia is not infrequently experienced as pleasant. All precautions are in place to ensure no harm will come to the participant while the hypoxia is being induced and a hyperoxic gas mixture can be administered at all times. The hyperinsulinemic euglycemic clamp is the golden standard for determining insulin resistance in patients with diabetes and is a procedure familiar to the research team. Monitoring on an onsite blood gas analyser ensures this procedure can be both performed efficiently and safely. The overall risk of the study is low, the burden is relatively low compared to other studies performed in our laboratory. The aim of the study is to find whether the carotid body is a key organ in sympathetic overactivity in patients with type 2 diabetes and could contribute to the number of patients with type 2 diabetes affected in the COVID-19 pandemic. Patients and healthy controls do not stand to benefit from this study other than financial recompense, they were recruited via posters and online advertisements.

Monitoring and quality measures: Subjects are measured under continuous supervision of the study staff, monitoring includes blood pressure, continuous ECG and continuous SpO2 (with a second CE marked fingerclip SpO2 sensor (Masimo Radical 7)). The viQtor SpO2 sensor is validated against a gold standard, which is a CE marked co-oximeter (Siemens RapidPoint 500, calibrated just before the start of the study). The quality of the data is analyzed as described in the discussion (chapter 5 - Exclusion of SaO2-SpO2 datapairs).

3.2 Needed sample size estimation

The following input criteria have been used for the estimation of the required samples size:

1. 2/3 of our SpO2 samples to be within 4% of our SaO2 samples (This is the basis for the derivation of Arms in the EN-ISO 80601-2-61:2019 - subclause 201.12.1.101.1 [2] standard).
2. A (default) 80% statistical power for our study (i.e. the probability that we find a significant effect, if there is one, with our amount of samples).

The requirement of having 80% statistical power means for our sample size requirement that we must assume that we want to prove significance for our SpO2 accuracy with an additional 0.84 standard deviation on top of the 1.0 standard deviation that roughly corresponds to the definition of Arms.

Then we also need define our H0 and H1 hypotheses.

For our H0, lets assume that SpO2 and SaO2 should be identical, we can transform this to a probability p = 0.5 that any error between the two samples is positive.

For H1, lets take a scenario in which there is a systematic (positive) error in our data (i.e. a bias) with a value of 0.4%, the probability that our error is now positive can be calculated assuming that our error is normally distributed by integrating the formula for the normal distribution:

$$P(X >= 0)|_{\mu=0.4,\sigma=4} = \int_0^\infty \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}(\frac{x-\mu}{\sigma})^2} \approx 0.54$$

So to acquire enough significance considering our required statistical power and confidence intervals (1 sigma) we must be able to show this difference in probabilities of 0.54 - 0.5 = 0.04.

$$(1 + 0.84)s.e. = 0.05$$

using our H0 probability we can convert the standard error (s.e.) to a estimated number of samples:

$$s.e. = \frac{\sqrt{p(1-p)}}{\sqrt{n}} = \frac{0.5}{\sqrt{n}}$$

We can substitute the above 2 equations in one another and calculate an estimate of the number of required samples:

$$n = (\frac{0.5(1+0.84)}{0.04})^2 = 529$$

3.3 Data acquisition procedure

Protocol *Carotid body dysfunction in type 2 diabetes (Protocol ID: NL78476.058.21 v1.1; date: 08-07-2021; Document ID: PRD1339-4-2153)* [1] was used for the data acquisition. A summary of the study procedure is given:

1. Prepare subject and equipment setup:
    a. The subject is checked in and vital parameters are assessed to check subject health
    b. An arterial cannula (*BD arterial canula 20G*) is placed in the radial artery of the non-dominant arm.
    c. The viQtor device is placed on the ipsilateral arm as the cannula
        i. Optionally, a second viQtor device is placed on the contralateral arm.
    d. The subject is connected to standard monitoring devices including an ECG, SpO2 and arterial blood pressure monitoring device.
    e. The subject is placed in semi-recumbent position and a mask is placed over the nose and mouth which is connected to the Leiden Gas Mixer.
2. During hypoxic ventilatory response measurements isocapnic conditions are maintained and the fraction of inspired oxygen is decreased to an FiO2 of 8%. As a result the subject will desaturate and the ventilatory response is measured.
    a. Gasses administered to the subject are medical-grade mixtures of O_2, CO_2 and N_2 produced by Linde gas
3. Once the subject is comfortable, decrease the oxygen saturation in a stepwise manner in the subject
4. Before a blood gas sample was obtained a 30-second plateau of SpO2 was maintained.
    a. a plateau is an area where the oxygen saturation does not change significantly, according to the Masimo radical-7 pulse oximeter which was placed on the contralateral index finger.
5. Extract an arterial blood gas sample from the subject.
    a. One researcher performs the sampling, a second reseacher registers the data (time of extraction, SpO2 value from the Masimo device and SaO2 value from the Rapidpoint (see chapter 3.3)) to the datasheet.
    b. A 4-eyes principle was used and an Excel macro was used for entering the timestamp.
    c. Data from the viQtor device is recorded automatically and no manual action is required.
6. Increase the oxygen saturation in the subject in a stepwise manner and repeat step 3 and 4.
7. Multiple measurements were performed during the experiment in accordance with the protocol, repeating Step 2-5.
8. Subject is disconnected from the equipment, the arterial cannula is removed.

3.4 Device information

The Device Under Test is the viQtor device, a wearable which is part of the viQtor Solution. Besides the viQtor device, there is a backend, Web Portal and Mobile App.

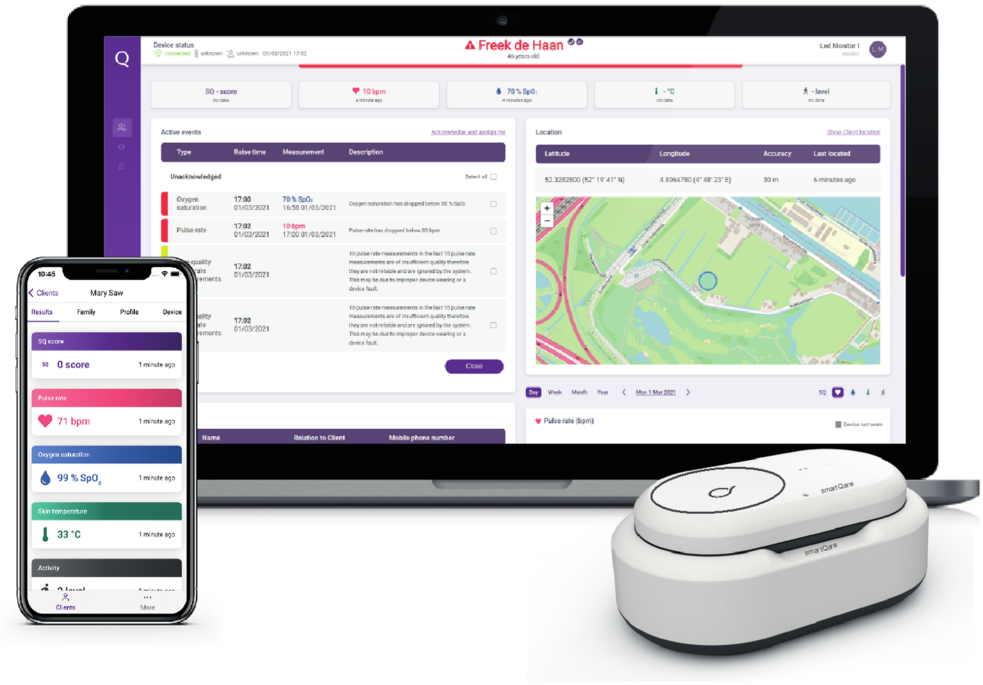

Figure 1: (from left to right) the mobile app, the web portal and the viQtor device on it's charger.

The following Device Under Test (viQtor devices) were used :

Device under test	Hardware version	Software version
SQ-07	SQ1	0.10.4
SQ-33	SQ1	0.10.4
SQ-35	SQ1	0.10.4

Table 2: Used viQctor devices

Used setup and equipment:

Item	tool/equipment number	Calibrated
Masimo radical 7 saturatiemeter	SN 256376	N/A
Siemens RapidPoint 500e	system ID 0500-599221	1. From factory 2. On installation 3. Device performs full calibration 3x per 24 hour *
Leiden Gas mixer	LUMC inventarisnr. 21-800-1420	N/A
Masimo ISA capnograaf	SN 939790	N/A

Table 3: Other devices used during data acquisition

* For more details on the Siemens RapidPoint 500e calibration, see Appendix A: Rapid Point 500e calibration assurance.

4 Results

4.1 Subject information

A total of 20 subjects have been included in this SpO2 Validation study. One subject was discontinueod following a vasovagal reaction during the measurement. The subject did not withdraw informed consent and recorded data up to discontinuation has been included for analysis.

In the table 4 below a description of the relevant biometrics is given per subject:

ID	Sex	Age	Weight [kg]	Height [m]	BMI	Fitzpatrick skin type	Diabetic
1	M	58	95	1.81	29.0	Type 2	N
2	M	48	86	1.83	25.7	Type 2	N
3	M	72	96	1.81	29.3	Type 2	Y
4	M	52	101	1.93	27.1	Type 2	N
5	F	21	54.4	1.58	20.5	Type 2	N
6	F	72	58.8	1.74	19.4	Type 2	N
7	M	24	94.6	1.91	25.9	Type 2	N
8	M	71	86	1.83	25.7	Type 2	N
9	M	29	71.8	1.89	20.3	Type 2	N
10	M	72	62	1.67	22.2	Type 2	N
11	M	29	110	1.80	34.0	Type 2	Y
12	F	21	59	1.60	23.1	Type 2	N
13	F	75	53	1.54	22.4	Type 2	N
14	M	70	84	1.74	27.7	Type 2	N
15	M	69	64.0	1.78	20.2	Type 2	N
16	M	36	83.3	1.78	26.3	Type 3	N
17	F	67	72.0	1.80	22.2	Type 2	N
18	M	78	72	1.75	23.5	Type 2	N
19	M	23	71.3	1.75	23.3	Type 5	N
20	M	65	71	1.77	22.7	Type 2	Y

Table 4: Test Subject characteristics

The subjects had a median age of 61.5 years, with a range of 21-78 years and inter-quartile range of 42.25 years. BMI varied between 19.4 and 34, with a mean of 24.5 and SD of 3.7. Five of the 20 subjects were female, and three of the 20 subjects were diabetic. The included subjects show a large variation in age and weight, as required by the EN-ISO 80601-2-61:2019 [2] standard. Note that in the CIP [1] only subjects with skin type 1 or 2 could be included. However, one subject with skin type 3 and one subject with skin type 5 were added to also increase the variation in skin color, increasing the number of healthy subjects to 17 instead of the 15 subjects as specified in the CIP [1].

4.2 Data Pairs

In total there were 650 unique SaO2 samples collected during the validation procedures. The SaO2 samples were correlated in time to the viQtor SpO2 value.

Most measurements were made using two viQtor devices simultaneously, which means that a single SaO2 sample can be matched with (at most) two SpO2 samples, one from each device. This leads to a total of 1187 potential SaO2-SpO2 pairs, out of which a total of 779 pairs passed the inclusion criteria. For more details on the data pair exclusion methods see topic "Exclusion of SaO2-SpO2 datapairs" in chapter 5 "Discussion"

The samples are in a range between 70% to 100% SaO2, the EN-ISO 80601-2-61:2019 [2] standard requires that the samples measured during validation must include samples that are at most 3% removed from the boundaries of the claimed range (in our case, our claimed range is 70%-100% therefore our sample set should contain samples that at least span the range 73%-97%, Subclause 201.12.1.101.2), and we fullfill this condition.

The data pairs are distributed as presented in figure 2 below:

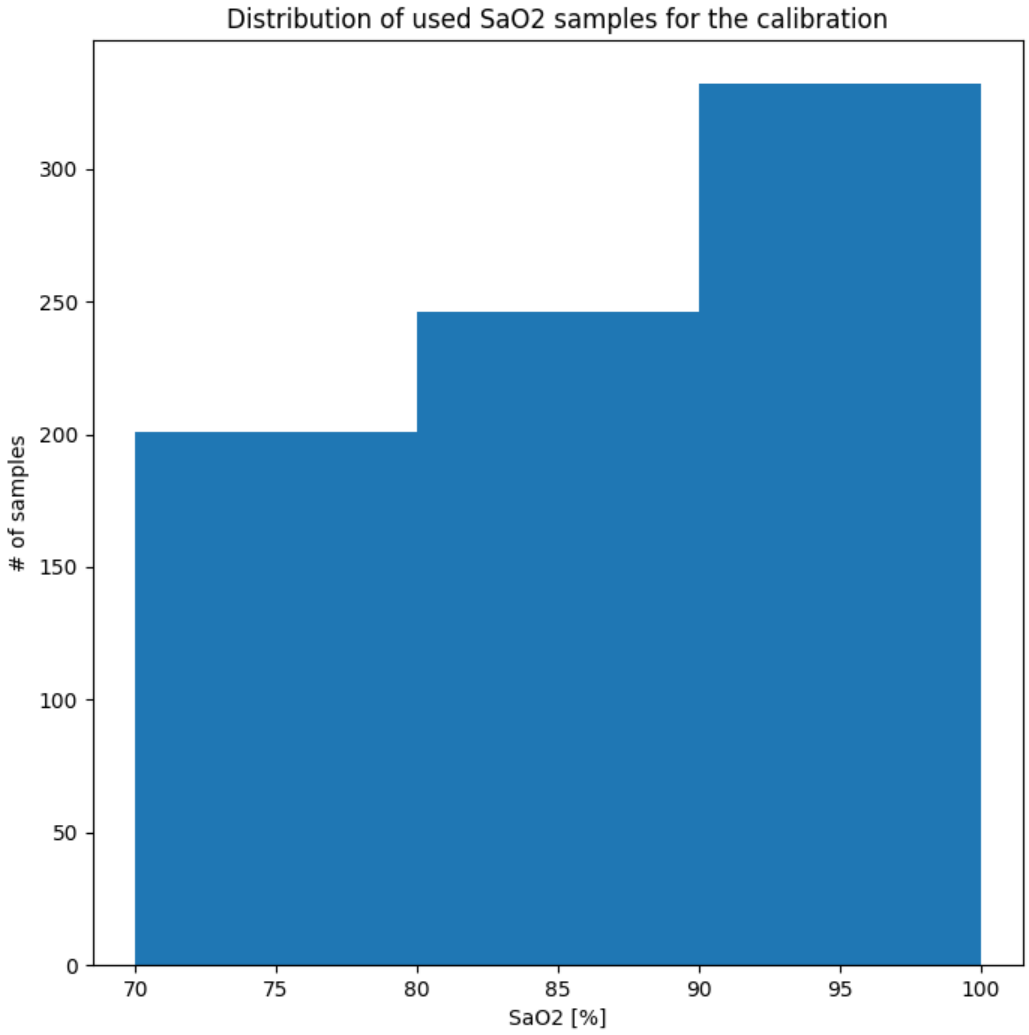

Figure 2: Amount of SpO2 samples per SaO2 range.

For more details on the distribution of samples per SaO2 range see topic "Inequality between SaO2 ranges" in chapter 5 "Discussion"

4.3 Calculated SpO2 accuracy

For the calculation of our statistics and plotting of graphs we use the builtin statistics framework within our Data Processing Library software tool[6], which is validated according to the SmartQare management system.

The following formula is used for the accuracy calculation of SpO2 (as defined in the standard: EN-ISO 80601-2-61:2019 [2] subclause 201.12.1.101.3):

$$A_{rms} = \sqrt{\frac{\sum (S_pO_2 - S_aO_2)^2}{n}}$$

where A_{rms} stands for Root Mean Square error Accuracy, S_pO_2 for the oxygen saturation sample from the ViQtor device that was paired with the sample from the reference Pulse Co-Oximeter, S_aO_2 the sample from the reference Pulse Co-Oximeter and n the number of used samples.

The resulting accuracies calculated are as follows:

SaO2 Range [%]	Used samples	A_{rms} [%]
All samples	**779**	**1.74**
90-100	332	1.21
80-90	246	1.66
70-80	201	2.44

Table 5: Summary of results

The Standard deviation of the Rapid Point 500 for FO2Hb is 0.1% (see The Rapid point user manual page E-16[3]) which we add to our accuracy estimate:

Final accuracy of the SpO2 measurement is 1.74 + 0.1% = 1.84% Arms.

In case we would assign an equal weight to the 3 SaO2 ranges, the SpO2 accuracy is 1.77%. No subgroup analysis is performed.

4.4 Bias

Another important factor for the analysis of the data collected during the SpO2 validation procedure is the presence of a (local) bias in the data, for this we create a scatter-plot and a modified Bland-Altmann plot of the samples:

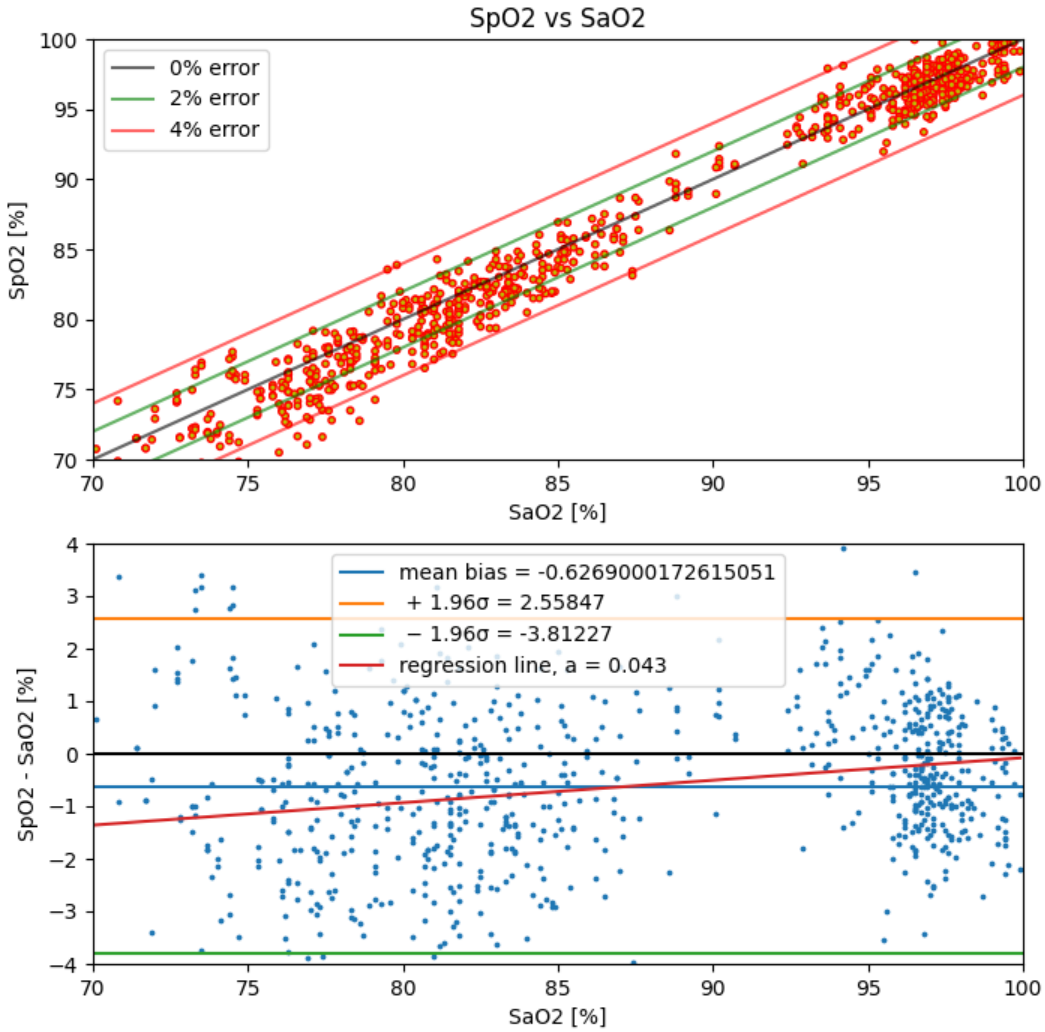

Figure 3: a scatter-plot (top) and Bland-Altmann plot (bottom) of the SaO2-SpO2 pairs used in the calculation of the accuracy of the viQtor device.

There is a bias (mean, average) overestimation of 0.63% SpO2 over the entire dataset. For the 90%-100% range, which is most prevalent in daily practice, this bias is quite small (the regression line passes 0.51% overestimation at 90% SaO2). The bias is larger for lower saturation ranges but still within acceptable range (as per ISO 80601-2-61:2019[2]) with a significant margin: The amount of samples within a 4% error is 99.7%, 100% and 99.5% for the ranges 90%-100%, 80%-90% and 70% -80% respectively.

5 Discussion

Using 2 measurements from Firmware V0.10.3

Subject 1 and 2 were measurements obtained with firmware version 0.10.3, This version included an error in the parameters for the conversion of the Ratio-of-Ratios to SpO2. Compared to firmware 0.10.3, the only change made in 0.10.4 was a minor adjustment to these parameters[4]. As this conversion formula is a simple formula (S_pO_2 = a*RoR + b), we have included the data extracted from these subjects by converting the SpO2 values reported by the viQtor devices back to the Ratio-of-Ratios and then to the SpO2 values according to the adjusted parameters before including these measurements in the SpO2 performance validation. This is a minor correction and thus will not affect the outcome.

Alignment of SaO2 samples and SpO2 samples using correlation

The internal clock of the devices used in the data acquisition procedure is not aligned to UTC time, so we cannot directly compare the results recorded during the procedure. Correlation is a standard method for the alignment of 2 datasets from devices measuring the same phenomenon simultaneously (Annex EE 2.3.3 k[2]).

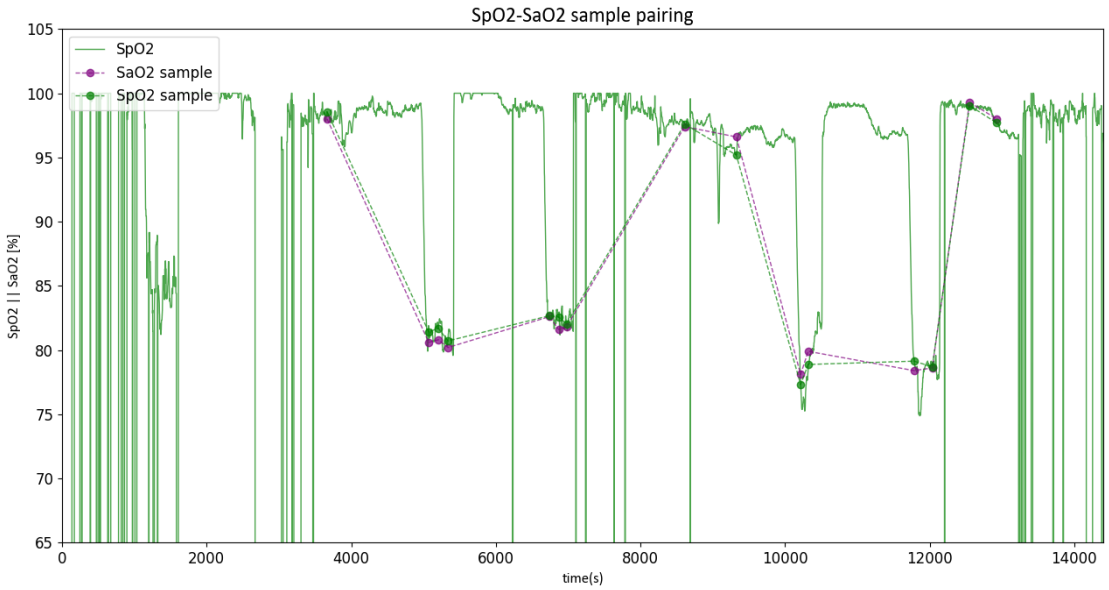

Figure 4: Example of alignment of SaO2 and SpO2 data. Only valid (see below) SpO2-SaO2 pairs are shown. Note: Values which are considered unreliable by the viQtor are given a value of 0.

Exclusion of SaO2-SpO2 datapairs

Selection of samples is done by:

1. SaO2 values of the data pairs must be in range 70% < SaO2 < 100%.
2. Exclude samples which are excluded by viQtor device based on estimation of data reliability using a proprietary algorithm of smartQare.
3. Transient exclusion

The viQtor SpO2 algorithms contain a quality indicator which is calculated for every reported SpO2 sample. Only samples with a high quality indication are considered reliable and are included in the validation procedure. Low quality samples are recorded, but are not used (excluded) and are not visible to the patient or healthcare professional during normal operation.

The EN-ISO 80601-2-61:2019 [2] requires that the data pairs are obtained at saturation plateaus (periods in which the saturation is relatively stable). Besides short and unstable plateaus, small alignment/timing errors of the SpO2-SaO2 data pairs might introduce large errors when the SpO2 transient of the area around the SaO2 sample is large. For instance this can happen when a SaO2 sample is taken at the edge of an SaO2/SpO2 plateau and there is a small temporal alignment error. Alignment errors can originate from the data correlation methods, timing errors can originate from variation in physical conditions and data entry timing variation.

To improve the reliability of the data, the data pairs with large transients are excluded. This is implemented by excluding data pairs where the mean absolute difference of a SpO2 sample (of a data pair) with respect to its neighboring SpO2 samples is above a certain threshold (a mean absolute error of 0.5% with 4 neighboring samples was chosen, as this provided a decent trade-off between removal of wrongly aligned data pairs and number of samples kept). In figure 5 the transient of the SpO2 values is visualized.

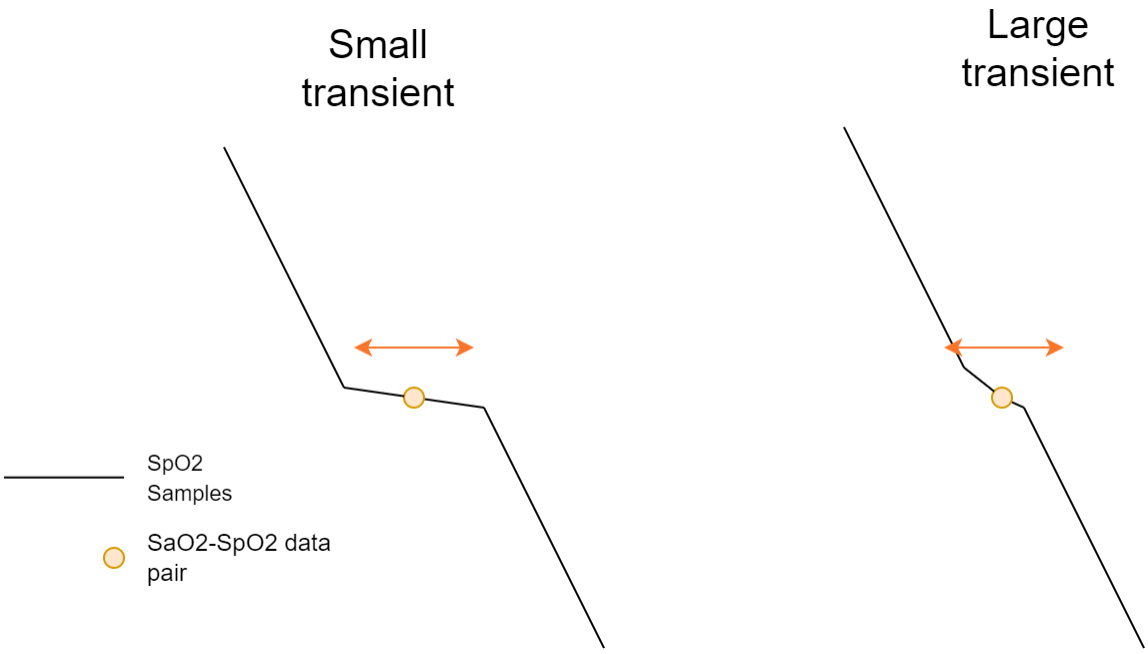

Figure 5: Transient exclusion example: (left) The SpO2 samples is located in the middle of a reasonably flat and lengthy plateau, a small time-shift of the sample will lead to at most a small change in the SpO2 value. (right) The sample is located on a short and slanted plateau, a small time-shift can cause a large change in SpO2 value.

After excluding SpO2 samples with large transients or unstable plateaus, the approach to creating SaO2-SpO2 data pairs is as follows:

Match every SaO2 sample to the closest (in time) SpO2 sample which has passed the exclusion criteria above. If no SpO2 samples can be found within 5 seconds (past or future) of the SaO2 sample, the sample is not used. If multiple viQtor devices were used it is possible a suitable SpO_2 sample was obtained from either one of the devices.

This approach excludes the following amount of samples by the different methods (a sample can be excluded by multiple methods):

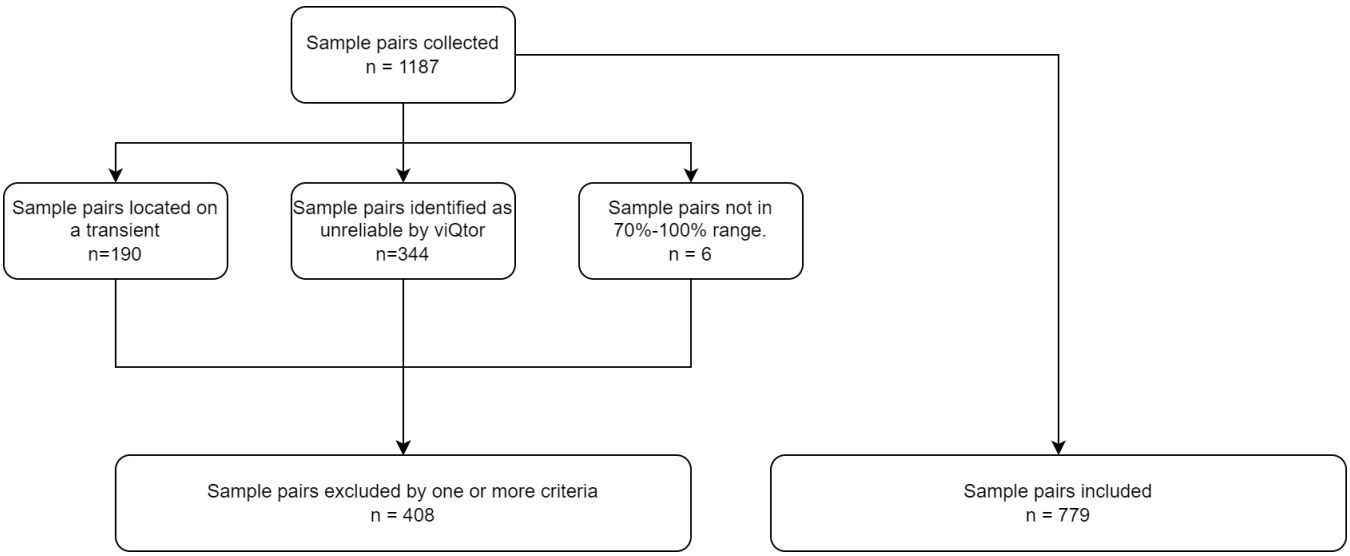

Figure 6: STARD diagram of sample pair inclusion/exclusion

Method	excluded data pairs	Percentage of total

Sample outside 70 to 100% SaO2 range	6	0.51%
Samples excluded by viQtor device (unreliable samples)	344	28.98%
Transient exclusion**	190	16.01%
Total excluded*	**408**	**34.37%**

Table 6: Sample exclusions

* Some samples quality for multiple exclusion criteria, therefore the total is less than the sum of the different methods.

** To assess if the amount of transient exclusions were due to a structural problem of the study or due to device performance, we used the data pairs which have continuous SpO2 data from the Masimo radical 7 available (this is not available for all measurements because continuous data was not needed to detect plateau's). From these selected data pairs was assessed how many of pairs would be rejected if the Masimo data were to be used instead of the viQtor data for pairing samples. On this subset of data pairs, using the viQtor: 13% of data pairs is excluded due to transients, while using the Masimo: 20% of data pairs is excluded due to transients. Therefore we concluded the rejection of data pairs due to transients is due to SpO2 plateaus not being stable enough in those cases.

Inequality between SaO2 ranges

More SaO2 samples were acquired in the 90-100% range wit respect to the 70-80% and 80-90% ranges due to frequent sampling in order to maintain the euglycemic hyperinsulinemic clamp. Therefore more samples were acquired in the higher SpO2 range. The standard requires an equal division of data pairs over the three SaO2 ranges (70%-80%, 80%-90%, 90% -100%). Based on the recommended 200 samples noted in EN-ISO 80601-2-61:2019, and the fact that there are >200 data pairs in both the 70-80% and 80-90% range, we have included the additional data pairs in the 90-100% range. Therefore, we feel the this unequal division over the three ranges does not affect performance validation. In addition, the higher number of samples in the 90%-100% range results in higher validity in the range where alarm fatigue is most relevant, especially for continuous monitoring.

Rejection of two measurements

During 2 experiments no PPG sensor data was acquired, The devices used for these measurements likely had a PPG sensor that was disconnected from the internals of the device. In normal usage this is not to be expected since production is quality controlled and the device identifies disconnected PPG sensors.
These experiments were excluded from the analysis, as we cannot calculate SpO2 values without PPG data.

SaO2 samples relation to SpO2

In most cases there are two SpO2 samples recorded for each SaO2 sample (2 viQtor devices were collecting data simultaneously), meaning that every SaO2 sample can be paired with up to two SpO2 samples. Because the rejection or acceptation of a SaO2-SpO2 data pairs depends on the SpO2 samples (as the inclusion criteria are applied to these) it is possible for a SaO2 sample to form a data pair with an SpO2 sample in one device but not in the other and vice versa. This makes it difficult to quantify the actual number of unique SaO2 samples used for the SpO2 validation, however considering that an SaO2 sample can be responsible of a maximum of two data pairs, we can be certain that at least half (rounded up) of all used SaO2-SpO2 data pairs (779/2 = 390) must be unique samples, this exceeds above the recommended minimum number of 200 data pairs[2], the use of 2 devices providing multiple sample pairs per SaO2 sample also ensures that enough samples were obtained in accordance with the power calculations.

Test subject inclusion

The inclusion criteria for a controlled desaturation study in healthy subjects defined in subclause 201.12.1.101.2 of the standard EN-ISO 80601-2-61:2019[2], are as follows:

- Healthy subject between 18 and 50 years old
- Subject falls in ASA 1 category
- Positive Allen's test

These strict criteria are set to ensure that the residual risk inherent in a controlled hypoxia study and arterial line placement in healthy adult volunteers, after suitable mitigation by following these additional procedures, can be reduced to a non-significant level (subclause 201.12.1.101.2).

Within our pool of test subjects we thread outside this standard for healthy subjects, as our study is a part of a larger study which also uses diabetic patients and thus the standard for healthy subjects is not applicable. The study also includes subjects of a higher age, which is a benefit for our SpO2 validation as the intended target group for the viQtor includes elderly.

The study protocol was evaluated and approved by the institutional review board*, which means that the board decided that the residual risks for the subjects was acceptable.

*International review board is the METC LDD, the study has been registered under P21-082 and is also registered at the NTR with ID NL0769.

Physical variation of test subject group

We have the following variation the test subject group:

- Age varies between 21 to 78 years. 10 subjects have an age of 65+ years.
- 5 women, 15 men
- BMI between 20.2 to 34.
- 3 diabetic patients
- 2 subjects with darker skin pigmentation

The characteristics of the subject group shows a large variation in age, gender and BMI, as prescribed in EN-ISO 80601-2-21: 2019 [2] Annex EE.2.3.1. In addition, diabetic patients and subjects with a darker skin pigmentation were included.

Statistical justification

The standard[2] requires that attempts should be made at least to achieve a measured SaO2 within 3% SpO2 of the stated range of SpO2 ACCURACY, including at least ten subjects and at least 200 data points (Subclause 201.12.1.101.2). In order to fulfill this requirement, the clinical trial aimed to include at least 15 subjects in the SpO2 validation study, recognizing that it might be difficult to obtain 20 samples in each subject.

At the end of the trial, a total of 20 subjects were included, and a total of **650** SaO2 datapoints were measured, which after combining with our SpO2 datapoints and applying our exclusion criteria provides us with **779** data pairs. When we look at the results, the measured Arms is **1.84**%, which is well within the required accuracy of 4% as stated in clause 201.12.1.101.1. In addition, only 0.3% of the measured datapoints is outside the range of ±4 error, which is acceptable according to the same clause. The Bland-Altman plot shows that 95% of the datapoints are within a range of **+2.6** error and **-3.8** error, which is also within the required accuracy of 4%. The bias is **-0.63**%, which is not clinically relevant and therefore acceptable.

Based on the obtained results in the trial, we can conclude that the **650** datapoints in 20 subjects substantiate the claim that the device fulfills the accuracy requirements from the standard. Based on the obtained results in the trial, we can conclude that the **650** datapoints in 20 subjects substantiate the claim that the device fulfills the accuracy requirements from the standard.

6 Conclusions

With regards to the relevant requirements of EN-ISO 80601-2-61:2019[2] standard, the following can be concluded:

Performance

- The accuracy of the SpO2 measurement of the viQtor device is 1.8% Arms, which is within the 4% Arms requirement of subclause 201.12.1.101.1.
- The included number of data pairs 779, which is more than the recommended number of 200 samples as well as sufficient according to our power analysis (chapter 3.2), acceding to the requirement in Annex EE.2.3.4f.
- The included test subjects is 20, which is above the recommended minimum of 10 persons, acceding to the requirement in Annex EE.2.3.4f.

Therefore we comply with the requirements for the EN-ISO 80601-2-61:2019 standard[2].

Safety, precautions, implications

No serious adverse events occurred during the study. Therefore, no new risks have been identified to update risk management. In additions, no results were found that implicate specific precautions for specific patient populations or implications for the investigational device.

Clinical benefits and clinical relevance

As this clinical trial was aimed only at the performance of the viQtor SpO2 sensor according to the EN-ISO 80601-2-61:2019 [2], no assessment of risks and clinical benefits or clinical relevance in accordance with clinical state of the art can be done based on the obtained results. However the same standard states an accuracy <4% Arms is clinical relevant. The instructions of use of the viQtor provide a list of (public known) warnings which could affect the SpO2 accuracy.

Limitations of the investigation

There were no limitations of the investigations. Investigators are not advisors of the company, nor do they or their families possess shares in the company. The LUMC (not the investigators) was compensated by SmartQare for performing the study.

7 Document Info

7.1 References

References are by default to the last version of a document. Specific versions maybe indicated when needed.

Ref.	Document Title	Doc. ID.
[1]	Carotid body dysfunction in type 2 diabetes (See Appendix B)	N/A
[2]	EN-ISO 80601-2-61:2019	N/A
[3]	Rapid Point 500e Operator's Guide (See Appendix B)	N/A
[4]	Software Release - WeQare - Algo subsystem V1.1.1	PACSQ1-099
[5]	Compliance guidance 80601-2-61 Pulse oxy equipment v1.0	PRD1339-5-19
[6]	Sw-Tool STL-38: Data Processing Library (DPL)	STL-38

7.2 Document Version History

Version	Date [dd Mmm yyyy]	Author [First Last Name]	Status	Description of Change
0.1	12-jan-2022	René Verhoef	Draft	Initial draft
0.2	13-jan-2022	René Verhoef	Draft	Processed review of Frank Boon
0.3	18-jan-2022	René Verhoef	Draft	Processed review of Rutger van der Schrier (Leiden University Medical Center)
0.4	20-jan-2022	René Verhoef	Draft	Processed review of Esther Spanjer (DEMCON)
0.5	4-feb-2022	Frank Boon	In Review	Processed review feedback from Job van der Palen (Clinical Epidemiologist at Medisch Spectrum Twente)
0.6	9-feb-2022	Frank Boon	In Review	Updated statistics and processed review feedback from Esther Spanjer (DEMCON)

0.7	7-mrt-2022	René Verhoef	In Review	Updated after review with Prof.Dr. Wim (W.A.) Buurman.
0.8	14-mrt-2022	René Verhoef	In Review	Updated after review of Rutger van der Schrier, MD (Leiden University Medical Center) and Prof. Albert Dahan, PhD (Leiden University Medical Center)
1.0	14-mrt-2022	René Verhoef	Approved	Approved version

8 Appendix A: Rapid Point 500e calibration assurance

To assure the Blood gas analyzer (model: Siemens RapidPoint 500e with system ID 0500-599221) is fully calibrated during the data collection for this investigation, the following has been done or implemented:

1. The RapidPoint 500e is calibrated in the factory by Siemens (report is available on request)
2. On installation of the RapidPoint 500e in the LUMC site, a full calibration is done during installation (report is available on request)
3. The device performs a full calibration after an *x* number of quality controls per day and 3x per 24 hours.
   When the device deviates from the setpoints, and the calibration is not achieved, the deviceuse is discontinued and analysis must take place.
   In practice, this means that the cartridges are replaced. All sensors are present in a test cartridge which can make 250 determinations.
   The Cartridges were replaced a number of times during the study (because they were used up or because they were no longer valid (can last for 30 days)).

According to Siemens, making a post-investigation calibration is not useful, since full calibrations are performed before use and at regular intervals during the usage.

At no point during the data collection for this SpO2 investigation, the RapidPoint 500e calibration failed. Hence all blood gas samples analyzed had a passing device calibration before and after each analysis.

From the above we conclude all blood gas data collections included in this SpO2 performance study are made with a fully calibrated Siemens RapidPoint 500e.

9 Appendix B

9.1 Data collection protocol

9.2 Rapid Point 500e Operator's Guide


RP500e_OG_RevA_EN.pdf