Clinical Investigation Plan

MULTI-VITAL Study

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Independent experts	Not applicable
Laboratory sites	Not applicable
Pharmacy	Not applicable

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1 Summary

This trial regards testing wrist band performance for clinical monitoring.

Impact, data handling and practical proceedings have been previously evaluated by the non-WMO MDR article 82 trial, currently underway in Reinier de Graaf, called “To test superiority of Bracelet derived PPG blood pressure measurements versus cuff measured blood pressure in relation to invasive blood pressure”.

The trial as proposed by this clinical investigation plan, is an MDR article 62 study with the aim to validate the Corsano CardioWatch 287-2.

Rationale: Today, continuous monitoring of vital signs remains a challenge since it generally requires the patient to be connected to multiple wired sensors, which restricts patient mobility in the intra-mural setting and complicates home monitoring in the extra-mural setting. Wearable devices on the wrist, although emerging, are often not clinically validated or limited to the monitoring of one or two vital signs.

Primary objective: This study aims to validate the Corsano CardioWatch 287-2 for the continuous monitoring of heart rate at ≤ 4 bpm root mean squared error (RMSE); breathing rate at ≤ 2 brpm RMSE; peripheral oxygen saturation at ≤ 3 percentage point RMSE; and non-invasive blood pressure at ≤ 10 mmHg RMSE against a reference device.

Secondary objective: This study aims to validate the Corsano CardioWatch 287-2 for the measurement of non-invasive blood pressure according to ISO 81060-2:2018.

Study design: The study is a single center, single arm prospective study

Study population: Study participants will be drawn from patients undergoing monitoring, including invasive arterial monitoring, as part of clinical routines, in the Reinier de Graaf Gasthuis, Delft, The Netherlands.

Intervention (if applicable): Summarizing, in patients being monitored intra-arterially, the Corsano CardioWatch 287-2 wristband will be placed on the patient’s wrist, enabling the comparison between wristband-data and data from routine monitoring.

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Measurements for the trial encompass standardized hemodynamic measurements.
These consist of invasive and non-invasive blood pressure recordings, peripheral oxygen saturation, heart rate and respiration rate by a reference device.
Main study parameters/endpoints: Root mean squared error between measurements recorded by Corsano CardioWatch 287-2 and reference device.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients will be asked for informed consent. If consent is provided, the patient will be put on the Corsano CardioWatch 287-2 during invasive arterial monitoring like heart catherization examination. Besides, the patient will be connected to sensors from a reference monitoring device. When the procedure is finished, the Corsano CardioWatch 287-2 and the sensors will be removed. There will be no follow-up.
The risks carried by this study are very low, considering the non-intrusiveness of the investigative device and the conventional sensors of the reference device. Study participants will have no direct benefit from participating to the trial. However, when the Corsano CardioWatch 287-2 has been validated, the patient population involved in this trial will benefit from a continuous monitoring device that is considerably less intrusive than conventional monitoring devices. This will facilitate long-term continuous intra- and extramural monitoring of vital signs.

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2 Background and Introduction

This document outlines the MULTIparameter VITAL signs monitoring validation (MULTI-VITAL) study.

Continuous monitoring of vital signs is of great importance in healthcare. While spot checks are labor intensive and can only provide a limited scope on the patient's health, continuous monitoring provides a more detailed and real-time status of the patient's vital signs. Still, today, continuous monitoring remains a challenge since it mostly requires the patient to be connected to multiple wired sensors, which restricts patient mobility and complicates home monitoring. Wearable devices, although emerging, are often not clinically validated or limited to the monitoring of one or two vital signs.

The Corsano CardioWatch 287-1 is a CE-MDR certified and clinically validated vital signs monitoring bracelet. It is able to continuously measure pulse rate [1], inter-beat intervals [1], breathing rate [2], sleep and activity. The Corsano CardioWatch 287-2 adds electrocardiogram (ECG), oxygen saturation (SpO_2), galvanic skin response (GSR), core body temperature and non-invasive blood pressure (NIBP).

Pulse rate, respiratory rate, SpO_2, GSR, temperature and ECG will be submitted to laboratory tests against internationally recognized standards. Additionally, the MULTI-VITAL study intends to provide clinical evidence by validation the Corsano 287-2 in a healthcare setting. More specifically, a total of 65 patients will be monitored during heart catheterization simultaneously with gold standard measurement devices and the Corsano 287-2.

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3 Objectives

3.1 Primary objective

This study aims to validate the Corsano CardioWatch 287-2 for the continuous monitoring of

- heart rate at ≤ 4 bpm root mean squared error (RMSE);
- breathing rate at ≤ 2 brpm RMSE;
- oxygen saturation at ≤ 3 percentage point RMSE;
- non-invasive blood pressure at ≤ 10 mmHg RMSE.

3.2 Secondary objective

This study aims to validate the Corsano CardioWatch 287-2 for the measurement of non-invasive blood pressure according to ISO 81060-2:2018.

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4 Study Design

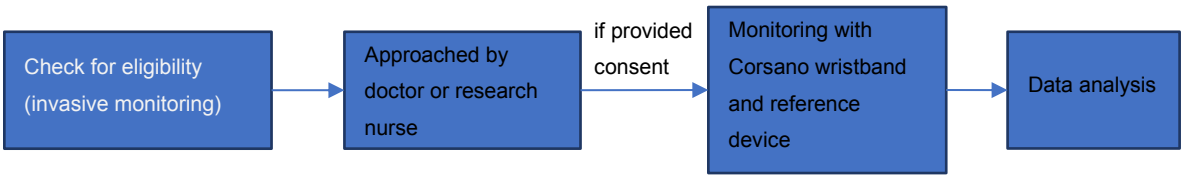
The study is conducted as a single center, single arm prospective study. The patients are selected from the patient population undergoing invasive hemodynamic monitoring. More specifically, patients undergoing cardiac examination in the catheterization laboratory who meet the inclusion criteria (see section 5) will be approached by their practitioner or by a research nurse for participation in the trial.

The study will take place at the catheterization laboratory of Reinier de Graaf Gasthuis Delft, starting after approval by CCMO and the hospital (estimated March 2021) until the intended number of participants has been reached (estimated June 2021).

Measurements will take place by the Corsano CardioWatch 287-2 and a reference device.

A control group is not applicable, since an intra-patient analysis will be conducted on the measurement data from different devices connected to the same patients.

After data collection, the measurements by the Corsano CardioWatch 287-2 and the measurements by the reference device will be statistically compared. Accuracy of the Corsano CardioWatch 287-2 for several vital signs will be assessed.



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5 Study population

5.1 Population base

Study participants are patients undergoing invasive hemodynamic monitoring during heart catheterization exam in the Reinier de Graaf Gasthuis. On average, weekly, 20 patients are scheduled for an exam. It is our intention to include 5-8 patients admitted for heart catheterization each week. A higher amount would place a burden on the care workflow that is too big for personnel and time resources.
If on schedule, the inclusion period will be finished within ±10 weeks.

Adults study shall include ≥30% males and ≥30% females, and shall have

- ≥5% of the reference systolic BP readings ≤100 mmHg,
- ≥5% with ≥160 mmHg,
- ≥20% with ≥140 mmHg

  and
- ≥5% of reference diastolic BP readings ≤60 mmHg,
- ≥5% with ≥100 mmHg,
- ≥20% with ≥85 mmHg

5.2 Inclusion criteria

Patients

- ≥ 18 years old;
- having an arterial line as part of standard care;
- able to provide consent.

5.3 Exclusion criteria

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Patients

- who cannot wear the Corsano CardioWatch 287 due to reasons such as allergic reactions, wounds, amputations etc.;
- unable or not willing to sign informed consent;
- with significant mental or cognitive impairment;
- who do not have a suitable entry site for the invasive arterial line.

5.4 Sample size calculation

Sample size calculation for this study is based on heart rate, since the hypothesized RMS error between the investigational device and the reference device (≤ 4 bpm) is small with respect to the measurement range (30-220 bpm).

Furthermore, sample size calculation for this study is based on comparing mean vital parameters measured by the Corsano CardioWatch and a reference device in one-sample equivalence testing accepting 80% power, a significance level of 0.05 and a bidirectional 4 bpm cutoff to indicate equality.

In a previous study with the Corsano CardioWatch 287-2 conducted by Haaglanden Clinics, The Hague, a mean heart rate of 62±10 bpm was found.

This yields a sample size of 54 patients. We plan to enroll 65 patients because of expected drop-out and expected difficulties with obtaining valid measurement pairs in the case of short and dynamic catheterization exams.

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6 Treatment of subjects

The MULTI-VITAL is not an interventional study in the sense that the investigator intervenes in the catheterization exam. The patients will be subjected to an investigational product, i.e. the Corsano CardioWatch 287-2, but this will have no effect on the catheterization exam. The investigational product itself is described in chapter 7 and the way how the investigational product is applied is described in chapter 9.

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7 Investigational product

7.1 Name and description of the investigational product

The Corsano CardioWatch 287-2 will be investigated in this study.

The CardioWatch 287-2 is a wireless remote monitoring device intended for continuous collection of physiological data in home and healthcare settings. This includes heart rate, heart rate variability (R-R interval), respiration rate, activity, sleep, ECG, SpO2, core body temperature and blood pressure. Data is transmitted wirelessly from the device via a mobile phone application or gateway to a server or health cloud where it is stored and made available for further analysis.

The CardioWatch 287-2 consists of the following parts:

a) PPG sensor. The PPG sensor is located at the back of the watch and measures the watch-wearer's heart rate at the wrist of the wearer. The PPG sensor includes green, red and infrared LEDs and two photodiodes.
b) Accelerometer. The accelerometer is an activity tracker that records all activities, such as hiking, running or cycling, and sends the data to the CardioWatch Module 287-2
c) ECG and GSR sensor. It consists in 3 electrodes, one on the top frame or the enclose, 2 on the bottom part of the case.
d) Casing. The casing contains all parts of the device and protects them against the environment. Because especially the backside of the casing is in direct contact with the wearer's skin care should be taken for allergic reactions. The lenses for the PPG sensor and the electrodes for ECG ad GSR are integrated in the enclosure case.

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e) Strap. The strap is used to connect the device to the wearer's wrist. Because the Corsano CardioWatch 287-2 will be certified as a medical device also the strap has to meet the relevant medical regulations.
f) MMT CardioWatch Module 287-2, produced by Manufacture Modules Technologies (MMT). The CardioWatch Module 287-2 contains the electronics for connection with the Corsano Trials App using Bluetooth Low Energy (BLE) and has enough internal storage capacity to store data when the device is out of connection.
g) Corsano Trials App on a suitable smartphone (Android or iOS). The Corsano Trials App collects the data from the Corsano CardioWatch 287-2 and stores it on the CardioWatch cloud. In the Corsano Trials App no interpretation of data is done, i.e. the data is directly forwarded to the CardioWatch cloud. Alternatively, the CardioWatch 287-2 can be connected directly to a hospital data, device and patient management system via a BLE Gateway.
h) CardioWatch cloud. The measured data is collected and stored in the CardioWatch cloud system. The CardioWatch cloud APIs enables the data to be transferred, to and from the cloud. This enables third-party medical applications to use the data for further analysis. The data are visible through a web interface via secure login.

7.2 Summary of findings from clinical studies

7.2.1 Cardiologie Centra Nederland

Heart rate and RR-interval measurement accuracy was assessed in a clinical trial conducted by Cardiologie Centra Nederland (CCN). In this trial, the Corsano CardioWatch 287-1 was tested against ECG. 180 cardiology patients with the following characteristics were included:

- Age 60 ± 15
- BMI 27.0 ± 5.0
- Skin type I-VI

7'880 heart beats were recorded and included in the analysis.

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Root mean squared error (RMSE) for heart rate (Figure 2) was 1.96 bpm. Limits of agreement were between -3.89 and 3.77 beats per minute.

RR-intervals (Figure 3) yielded a correlation of 0.891 (95%CI 0.886-0.895). 89.2% (95%CI 88.5-89.9) of the recorded RR-intervals were within ± 50 ms of the concurrent ECG RR-interval. 94.6% (95%CI 94.1-95.1) of the recorded RR-intervals were within ± 100 ms of the concurrent ECG RR-interval.

The results were published in the Journal of Electrocardiology: https://doi.org/10.1016/j.jelectrocard.2021.06.009

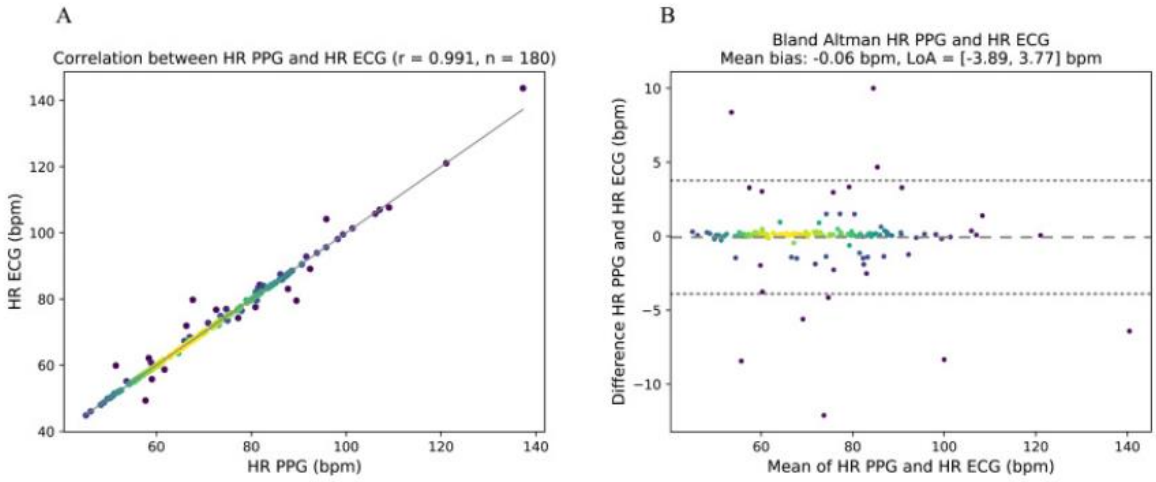

Figure 2 Accuracy of heart rate measurement by the Corsano CardioWatch 287-1

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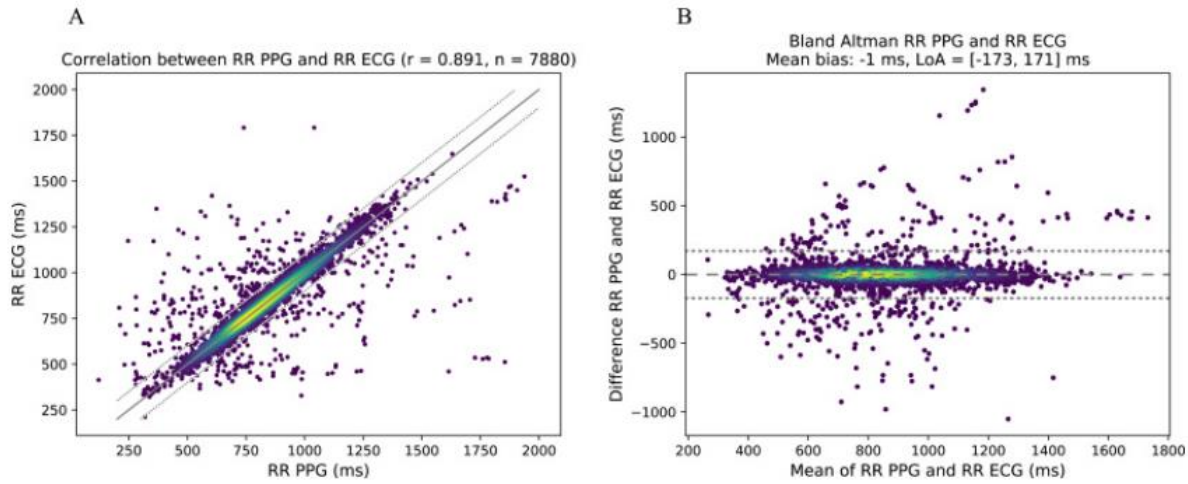

Figure 3 Accuracy of RR-interval measurement by the Corsano CardioWatch 287-1

7.2.2 Haaglanden clinics

Heart rate and respiration rate measurement accuracy was assessed in a clinical trial conducted by Haaglanden Clinics. In this trial, the Corsano CardioWatch 287-1 was tested against a pulse-oximeter for heart rate and a chest-worn belt for respiration rate. 26 patients were included, with the following characteristics:

- 18 suspected for Obstructive Sleep Apnea
- 8 healthy
- Age 47±16 years old
- BMI 28.6±7.4 kg/m2
- Skin type II-V

10’962 minutes were recorded, yielding 38’693 heart rate measurement pairs and 31’083 respiration rate pairs. Measurements were averaged over a window of 60 seconds.

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Heart rate accuracy was 0.95 bpm (RMSE). 95% Limits of Agreement were –2.09 to 1.17 bpm (mean bias -0.46 bpm).

Respiration rate accuracy was 0.60 brpm (RMSE). 95% Limits of Agreement were -1.28 to 1.71 brpm (mean bias -0.14 brpm).

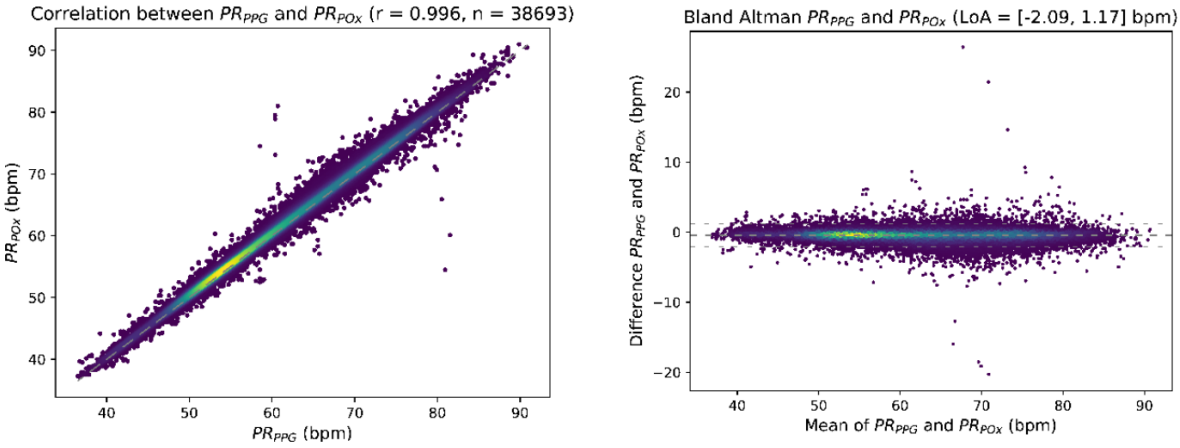

Figure 4 Accuracy of heart rate measurement by the Corsano CardioWatch 287-1. PR: pulse rate. PPG: photoplethysmography. POx: pulse-oximetry. bpm: beats per minute.

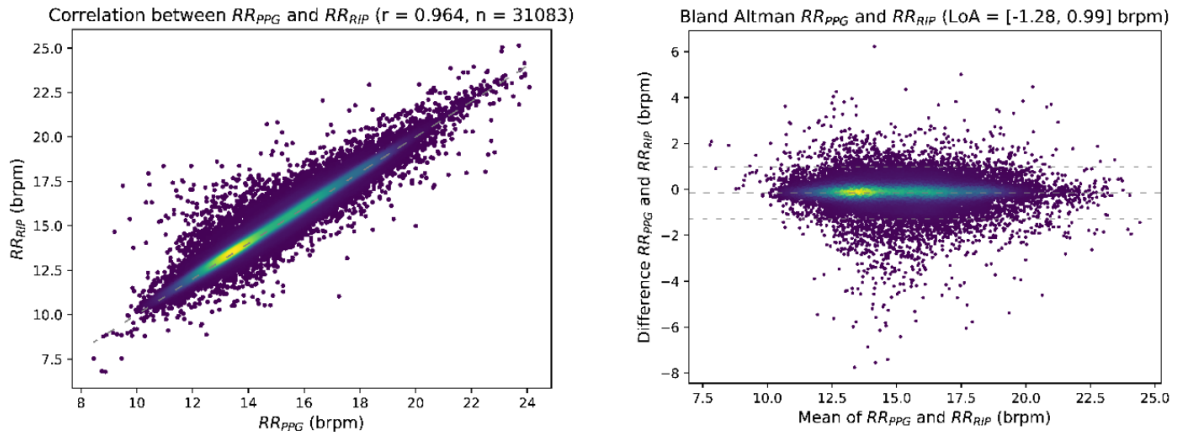

Figure 5 Accuracy of respiration rate measurement by the Corsano CardioWatch 287-1. RR: respiration rate. PPG: photoplethysmography. RIP: respiratory inductance plethysmography. brpm: breaths per minute.

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7.3 Summary of known and potential risks and benefits

Risks were assessed according to ISO 14971:2019. The risk management report states: All risks were reduced to a minimum by design, protection and warning methods. The mitigation measures were verified. All residual risks are acceptable. The benefit/risk ration is very high. The overall residual risk was assessed. The stress due to false positive is a well-known risk for this kind of products. Nevertheless, the device does not give a direct diagnosis to the user. Moreover, in this respect, a warning is given to the user in the IFU. Another risk is to cross user data. This risk was reduced by design. In practice this problem never happens. The overall residual risk is perfectly acceptable.

A detailed exploration of the risks can be found in the supplementary file 'D-RD-04-00 Risk Management File CW287-1 v1.0.xlsx'

7.4 Description and justification of route of administration and dosage

Not applicable

7.5 Dosages, dosage modifications and method of administration

Not applicable

7.6 Preparation and labelling of Investigational Medicinal Product

Not applicable

7.7 Drug accountability

Not applicable

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8 Non-investigational product

8.1 Name and description of non-investigational product(s)

The Fysicon QMAPP Hemodynamic Monitoring module will be used for the recording of invasive blood pressure, non-invasive blood pressure, heart rate, respiration rate and oxygen saturation. The device is CE and FDA approved.

A detailed description can be found in the supplementary file 'fysicon_description.pdf'.

A detailed technical specification list can be found in the supplementary file 'fysicon_technical_specifications.pdf'.

8.2 Summary of findings from non-clinical studies

Not applicable

8.3 Summary of findings from clinical studies

Not applicable

8.4 Summary of known and potential risks and benefits

Risks

Using the Fysicon QMAPP in this study will require the patient to be connected to multiple extra sensors, besides the already applied sensors. These are 3 extra ECG electrodes, a pulse oximeter and a non-invasive blood pressure cuff. We consider the placement of these sensors to carry very low risk.

Besides, between the arterial catheter and the pressure system, an extra pressure monitoring set will be installed . Specifically, the Edwards TruWave 3 cc system will be installed. Unfamiliarity with this system carries the risk of incorrect installing and treating this system. While we consider the probability of this risk to be low, the severity of the risk is high. For example, allowing air bubbles to enter the catheter will likely lead to air embolism. We

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mitigate this risk by proper and extensive training of the personnel by an experienced cardiologist. All personnel involved are experienced staff and are experienced with invasive monitoring. Training will be done according to education material provided by Edwards Lifesciences. Training of the personnel will be recorded in the training log.
Another risk of using the QMAPP system is that the personnel will use the sensor readings for monitoring the patient's condition. While the QMAPP system is CE certified and FDA approved as a medical device, we consider it undesirable to use the system to this end. After all, the equipment normally used to monitor the patient's condition is subjected to regular calibrations. We cannot guarantee the QMAPP system's accuracy and reliability to the same degree. For this reason, the personnel will be carefully instructed only to use the readings for the purpose of confirming correct placement of the sensors.

Benefits

The major benefit of using the QMAPP system is the fact that it will provide all raw data and high sampling frequency. The existing equipment in the operating room will not allow for this.

8.5 Description and justification of route of administration and dosage

Not applicable

8.6 Dosages, dosage modifications and method of administration

Not applicable

8.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

8.8 Drug accountability

Not applicable

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9 Methods

9.1 Study parameters

In this trial, the following parameters will be studied:

- heart rate root mean squared error (RMSE) between Corsano CardioWatch 287-2 and reference device;
- breathing rate RMSE between Corsano CardioWatch 287-2 and reference device;
- oxygen saturation RMSE between Corsano CardioWatch 287-2 and reference device;
- non-invasive blood pressure RMSE between Corsano CardioWatch 287-2 and reference device.

9.2 Randomisation, blinding and treatment allocation

Not applicable. All patients included in the trial will receive monitoring with Corsano CardioWatch 287-2 and reference device.

9.3 Study procedures

Blood pressure measurements will be performed according to ISO 81060-2:2018. This includes the following steps:

1. Determine the subject's blood pressure using the CardioWatch 287-2
2. Clear the memory of the CardioWatch 287-2 and wait at least 3 minutes. Do not use data points obtained in point 1. in the calculation of accuracy.
3. In each measurement session of interest, start recording the invasive reference blood pressure at least 40 s before the CardioWatch 287-2 measurement. Stop the recording of the invasive reference blood pressure when at least 40 s have elapsed after the CardioWatch 287-2 measurement. Continues reference monitoring is also allowed.

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a. When the reference recording is not interrupted due to cuff inflation, the reference blood pressure ranges will be determined from the recording of the invasive blood pressure for a duration of at least 30 s that includes the period of the determination of the CardioWatch 287-2.

4. Wait at least 60s between determinations.
5. Repeat point 3 and 4 until the required number of recordings, with a maximum of 10, have been performed.

The implementation of the study requirements within the catheterization exam will be as follows:

First, informed consent is obtained. Patients admitted for heart catheterization exams are generally capable of providing informed consent. They will be approached at least one hour before the catheterization exam, providing enough time to decide on their participation.

Secondly, several study measurements will take place in a preparation room prior to the catheterization exam. A nurse (from now nurse 1) will be appointed who will do all actions related to the study in the preparation room. Nurse 1 will start with filling in the by Corsano provided case report form (CRF) and measuring the patient's arm circumference. Furthermore, nurse 1 will calculate the lateral difference between both arms by measuring the blood pressure 3 times in both arms simultaneously by means of two identical automated non-invasive sphygmomanometers. The resulting systolic BP and diastolic BP measurements will be averaged and patients will be excluded from the study when the measured lateral difference is larger than 15 mmHg for the systolic BP and/or larger than 10 mmHg for the diastolic BP. Finally, nurse 1 will perform 2 measurements, one Corsano CardioWatch 287-2 measurement and one initialization measurement using an automated non-invasive sphygmomanometer on the same arm as the CardioWatch 287-2. To make this possible nurse 1 will attach the Corsano CardioWatch 287-2 to the patient’s wrist that is not

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going to be used as an access point for the catheterization exam. The CardioWatch 287-2 measurement will be performed prior to the initialization measurement by starting the measurement on the smartphone belonging to the CardioWatch 287-2. This measurement will have a minimal duration of 60 seconds. After ending the CardioWatch 287-2 measurement on the smartphone nurse 1 will perform a single initialization measurement using an automated non-invasive sphygmomanometer.

Thirdly, after finalizing the initialization measurement the patient will be transported to the catheterization laboratory. The same or a second nurse (from now nurse 2) will be appointed who will do all actions related to the study when the patient arrives at the catheterization laboratory. Nurse 2 will not do any sterile actions for the purpose of the invasive monitoring, like the catherization procedure. Nurse 2 connects the various sensors of the reference device to the patient. If or when 3 minutes have elapsed after the first CardioWatch 287-2 measurement nurse 2 will start the second measurement on the smartphone belonging to the CardioWatch 287-2 and the reference measurements on the computer belonging to the Fysicon QMAPP system.
The nurse who will aid the operating cardiologist with the procedure (from now nurse 3), and who will move within the sterile field for this reason, will connect and zero the TruWave pressure transducer. This is the only task that nurse 3 will do regarding the trial. Consequently, nurse 3 can fully focus on the monitoring procedure.

At fourth, the measurements begin. Before the official start of the catheterization exam there will be one full minute of no action by the members of the sterile team, this time represents the first study measurement. Somewhere during the intervention there will be another one minute pause by the members of the sterile team to allow for a second study measurement. The cardiologist will decide which moment is appropriate for this. At the end of the catheterization exam there will be a three minute pause by the members of the sterile team,

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this time represents the third and fourth study measurement as well as a one minute pause between both final measurements. After these final measurements nurse 3 will disconnect the blood pressure transducer. Nurse 2 will remove the Corsano CardioWatch 287-2 and disconnect all reference device sensors. Finally, nurse 2 will stop the measurements on the Corsano smartphone and the reference device computer.

9.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

9.5 Replacement of individual subjects after withdrawal

For patients with data that is not analysable (due to excessive noise in the invasive or non-invasive measurements), or for those who retract from trial participation, each patient involved will be replaced by another patient.

9.6 Follow-up of subjects withdrawn from treatment

Follow-up is not part of this trial and thus not applicable.

9.7 Premature termination of the study

Not applicable, due to the non-intrusive character of the trial. If unforeseen logistic or financial reasons form a reason to terminate, the relevant bodies will be notified.

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10 Safety reporting

10.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

10.2 AEs, SAEs and SUSARs

10.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

10.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

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The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will be contacted by e-mailing the SAE details to Arthur van Nieuw Amerongen, clinical trials coordinator of Corsano, via ar.vannieuwamerongen@corsano.com.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

10.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable since the investigational product is not a medicinal product.

10.3 Annual safety report

Not applicable since the investigational product is not a medicinal product.

10.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

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11 Statistical analysis

For each vital parameter that is measured in this trial, each measurement point obtained by the Corsano CardioWatch will be compared with the simultaneously recorded measurement by the reference device. The frequency rate of the reference device is higher compared to Corsano CardioWatch's frequency rate. This means that for every Corsano CardioWatch measurement point, a measurement point acquired by the reference device with very short time distance should be available. In some cases, reference device's signal quality will be too low to obtain a valid measurement point. Then, a measurement point with maximum time distance of 30 seconds will be searched. If this measurement point is not available, the Corsano CardioWatch measurement will be excluded from analysis.

Comparison will be done using three statistical methods and will yield three outcome parameters accordingly.

11.1 Primary study parameter

The primary study parameter is the **root mean squared error** (RMSE) between the Corsano CardioWatch and the reference device.

11.2 Secondary study parameters

The secondary study parameters comprise the correlation coefficient and the bias with limits of agreement.

Correlation coefficient will be obtained by calculating the covariance between measurements obtained by the Corsano CardioWatch and reference device. The covariance will then be divided by the product of the standard deviation of the measurements obtained

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by the Corsano CardioWatch and the standard deviation of the measurements obtained by the reference device.

Bias and limits of agreement will be obtained by Bland Altman analysis [3]. Guidelines for Bland Altman applied to multiple measurements per patient [4] and for calculation of confidence intervals [5] will be followed.

12 Ethical considerations

12.1 Regulation statement

The MULTI-VITAL study will be conducted according to the following principles and guidelines:

- Declaration of Helsinki, 64th WMA General Assembly, Fortaleza, Brazil, October 2013
- Good Clinical Practice
- ISO 14155:2020
- GDPR

12.2 Recruitment and consent

Patients will be recruited by regular screening of the list with scheduled patients. The cardiologist (dr E Ronner, dr Monnink, drs Constandse, Dr Van Vliet, Dr Hoftijzer and Dr Bech and residents (‘in opleiding”) when applicable) in charge of the catheterization procedure or a dedicated research nurse will inform the patient and ask for consent. The patient will be given time to consider the decision until the moment of the procedure.

12.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

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12.4 Benefits and risks assessment, group relatedness

The patient does not receive any direct benefit from participating to the study. However, when the Corsano CardioWatch 287-2 has been validated, the patient population involved in this trial will benefit from a continuous monitoring device that is considerably less intrusive than conventional monitoring devices. This will facilitate long-term continuous intra- and extramural monitoring of vital signs.

The risks as summarized in sections 6.4 and 7.4 are very low and are outweighed by the potential benefits of the related patient population.

12.5 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Please consult the attached certificates:

- Reinier de Graaf - Verzekeringscertificaat MA 2020.pdf
- Reinier de Graaf - WMO Verklaring 2021.pdf
- Corsano Health - Insurance Corsano Health.pdf

12.6 Incentives (if applicable)

Not applicable

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13 Administrative aspects, monitoring, and publication

13.1 Handling and storage of data and documents

Handling of data, coding of data, access to data and data security have been described in the data management plan:

- Datamanagementplan_indiening corsano MULTI-VITAL studie.docx

13.2 Monitoring and Quality Assurance

Monitoring of the trial has been described in the monitoring plan:

- Monitoringplan_indiening corsano MULTI-VITAL studie.docx

13.3 Ammendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

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13.4 Annual progress report

The sponsor will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

13.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

13.6 Public disclosure and publication policy

The trial will be registered at clinicaltrials.gov. A report of the study will be published in a peer reviewed journal.

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14 Structured risk analysis

14.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The Corsano CardioWatch 287-2 makes use of photoplethysmography. This comprises the emission of low energy green light by a diode. This mechanism is not associated with bodily harm. The
power supply of the wrist band is low energy/low voltage, and approved by authorized bodies

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

PPG is widely used in medical devices (oxygen saturation sensors) and consumer devices (smartwatches)

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

Not applicable

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable

e. Analysis of potential effect

Since the green light emitted by the diode carries very low energy, no effect on the patients skin is to be expected.

f. Pharmacokinetic considerations

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Not applicable

g. Study population

Only patients that are hemodynamically stable are admitted to heart catheterization exams. Informed consent will be obtained according to GCP.
Data will be handled according to GCP and GDPR. Data leaks will be handled according to Reinier de Graaf Standard Operating Procedures.

h. Interaction with other products

PPG light is emitted very locally into the patient's wrist. Multiple PPG devices in close proximity may interfere with each other. However, if a finger pulse oximeter is connected to the patient, the distance between the CardioWatch and the pulse oximeter will be to large for this interference to occur.

i. Predictability of effect

Not applicable

j. Can effects be managed?

Not applicable

14.2 Synthesis

PPG light emitted by the Corsano CardioWatch 287-2 carries very low energy and does no bodily harm. Connecting the CardioWatch to the patient can be considered as very low risk.

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15 References

1. Blok S, Piek MA, Tulevski II, Somsen GA, Winter MM. The accuracy of heartbeat detection using photoplethysmography technology in cardiac patients. J Electrocardiol. 2021 Jul-Aug;67:148-57.
2. Gehring JM, Saeijs-van Niel LC, Ten Bosch-Paniagua LP, Frank MH. Continuous respiration rate monitoring using photoplethysmography technology in patients with Obstructive Sleep Apnea. *Under peer review*
3. DG Altman and JM Bland, Measurement in medicine: the analysis of method comparison studies. The Statistician 1983; 32:307-317.
4. C Hamilton and S Lewis, The importance of using the correct bounds on the Bland-Altman limits of agreement when multiple measurements are recorded per patient, Journal of Clinical Monitoring and Computing 2010: 24:163-175.
5. GY Zou, Confidence interval estimation for the Bland-Altman limits of agreement with multiple observations per individual, Stat Methods Med Res 2013; 22: 630-642.

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