Clinical Investigation Plan

Validation of Respiratory Rate with the MMT-CORSANO CardioWatch 287 Compared with Gold Standards

Clinical Investigation Plan Approval	
[redacted]	[redacted]
Coordinating Investigator: **Date**: [redacted]	Plan Author: [redacted] Date: [redacted]

1 Background and Introduction

This document outlines the MMT-CORSANO CardioWatch 287 Respiratory Rate clinical study, to show the feasibility, efficacy and performance of the MMT-CORSANO CardioWatch 287 for measuring respiratory rate.

According to the National Institute for Health and Care Excellence[1] "respiratory rate is the best marker of a sick patient and is the first observation that will indicate a problem or deterioration in condition". Respiratory rate is raised in respiratory conditions as well as in conditions with serious metabolic derangements.

The CardioWatch 287 is a non-invasive, continuous and wireless monitoring device based on photoplethysmography (PPG) technology. It measures several vital signs, including pulse rate, RR intervals and respiratory rate.

The CORSANO CardioWatch 287, embeds the CardioWatch 287, which provides a high-quality PPG sensor, a secured wireless BLE connection and data transfer. The PPG sensor uses a reference design and Vital Signs Optical software library powered by Philips Healthcare, that was clinically evaluated and validated against gold standards.[2]

Numerous studies showed that the Respiratory Rate can be measured from Photo-Plethysmography.[3] [4]

[1] NICE Guideline [CG50]: Acute Illness in Adults in Hospital: Recognising and Responding to Deterioration. National Institute for Health and Care Excellence (NICE); London, UK: 2007.

[2] Clinical Evaluation of the Measurement Performance of the Philips Health Watch: A Within-Person Comparative Study, Jos Hendrikx, MSc, Loes S Ruijs, MSc, PDEng, Lieke GE Cox, PhD, Paul MC Lemmens, PhD, Erik GP Schuijers, MSc, and Annelies HC Goris, PhD

[3] Charlton P.H., Bonnici T., Tarassenko L., Clifton D.A., Beale R., Watkinson P.J. An assessment of algorithms to estimate respiratory rate from the electrocardiogram and photoplethysmogram. Physiol. Meas. 2016;37:610–626 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5390977/

[4] Allen J. Photoplethysmography and its application in clinical physiological measurement. Physiol. Meas. 2007;28:R1. doi: 10.1088/0967-3334/28/3/R01.

Name	Validation of respiratory rate with the MMT-Corsano SmartWatch 287 compared with gold standards
Sponsor	[redacted]
Principal Investigator	[redacted]

2 Objectives

2.1 Primary objective

This study aims to evaluate the performance and efficacy of the MMT-CORSANO CardioWatch 287 in measuring respiratory rate at rest, as compared to golden standard and predicate device.
The main study endpoints are the Percentage of respiratory rates of matching the resting ECG recording.

- Percentage of respiration rate at rest ±2 BPM (beats per minute) matching the polygraphy device and manual counting.

2.2 Secondary objectives (where applicable)

Not Applicable

3 Study Design

The study is a single center, single arm prospective study.

4 Study population

The patients are selected from the patient population of Haaglanden Clinics, referred for an overnight Polygraphy exam for a suspicion of sleep-disordered breathing. Patients are scheduled for a Respiratory Rate measurement, independent of the proposed study. Patients that are scheduled for these examinations and meet the inclusion criteria (see below) are approached by their practitioner or specialized nurse supervised by the for participation in the trial.
The Study populations are:

- 26 subjects (at least 30% of each gender)

Inclusion criteria:

- People ≥ 18 years old

Exclusion criteria:

- Wearer of cardiac implanted electronic device (Pacemaker, ICD)
- CardioWatch 287 cannot be worn due to comprehensible reasons (allergic reactions, wounds, amputations, other)
- Unable or not willing to sign informed consent
- Significant mental or cognitive impairment
- Currently enrolled in another clinical investigation in which the intervention might compromise the safety of the subject's participation in this study

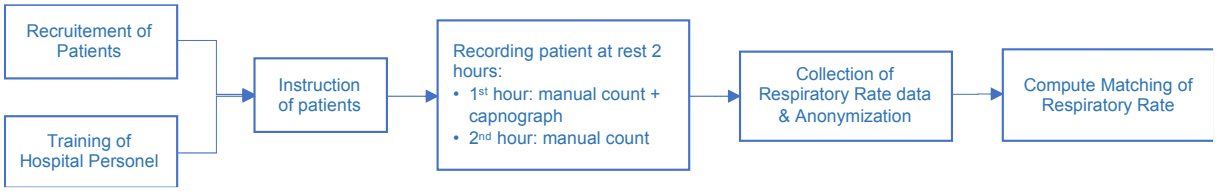
The sample size is calculated using previously collected unpublished data of CORSANO versus polygraph. The expected standard deviation in difference in average Respiratory Rate over a 15-min window between CardioWatch 287 and polygraphy was estimated to be 1.1 bpm. A 2-sided 95% CI for the mean of the differences between methods were constructed with a maximum length of 2 bpm. Assuming a dropout rate of 10% and at least 1 usable data point per patient, this requires the recruitment of 26 patients. Requested sensitivity is 90% to detect a difference of less than 5% between respiratory rate as measured by the capnograph and respiratory rate measured by the CardioWatch 287 at rest (Respiration Rate ±2 bprm MAD, ±5% MARD).
The primary endpoint will be analysed using a Bland Altman (BA) analysis to measure limits of agreement between methods.

5 Treatment of Subjects

The study will enroll 26 adult volunteers who will undergo a one-night in-lab sleep study. Study nurse hooks up the polygraph and places the Corsano device on the non-dominant

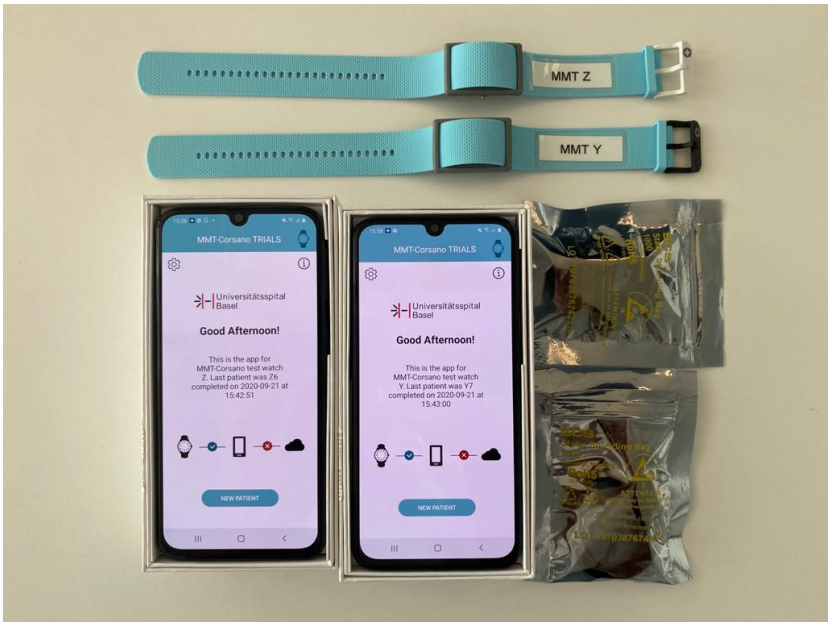
wrist. Overnight Polygraphy exam will be performed in the sleep laboratory. The next morning, the same study nurse removes the Polygraph and the device.

5.1 Flow chart



5.2 Trial Kit

CORSANO CardioWatch 287 Bracelets will be provided with paired smartphones:



With simple MMT-CORSANO Trials App, nurse can start and stop measurements. All data in the Bracelet will be saved on smartphone. Please note that it is not necessary to keep smartphone close to Bracelet during the night. Data is saved in the flash memory in the Bracelet and can be downloaded to smartphone in morning.

Charging is simple with magnetic cable. Battery life of the Bracelet is one week.

6 Study Execution

6.1 Procedure

The patients fulfilling the inclusion criteria will receive a wearable device (CORSANO CardioWatch 287) and a smartphone with the CORSANO Application. The CardioWatch 287 and the application on the smartphone are connected. Continuous monitoring of the respiratory rate will be conducted using photoplethysmography (PPG) and Philips Visual Sign Optical software library.

During the first hour, the patient respiratory rate will be measured using a capnography device. Simultaneously, a manual count of the respiratory rate will be recorded every 15 minutes for the two hours.
Data obtained with the MMT-CORSANO CardioWatch 287 will be saved on the smartphone and will be downloaded by the physician at the end of the monitoring procedure.
Data of the capnograph will then be analyzed by trained analysts and supervising physicians.
The Respiratory Rate data from the MMT-CORSANO CardioWatch 287 will be compared to the data measured by the capnograph device and to the manual counts.

6.2 Required resources

The study requires resources from CORSANO and the research center.
Cosrano provides:

- The measuring wrist wearables and corresponding software
- The App to record and download the data
- The technical support for the above items

The research center is in charge of:

- Requesting an exemption regarding the Medical Research Involving Human Subjects Act
- (WMO) through the medical ethical committee
- Suitable patients are selected and approached by the research center
- Instructing participants
- Applying the wearable to the participants
- Providing polygraphs and corresponding analysis software
- Acquiring raw data of polygraph and manual counting of the respiratory rate
- Analysis of results and writing of the articles

6.3 Proposed timeline

The proposed timeline is the following:

- First-Participant-In: October 2020
- Last-Participant-Out: December 2020

7 Methods and analysis

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

- Mean Average Error of PPG measured Respiration Rate and RR intervals compared to golden standards
- Correlation of PPG measured Respiration Rate and RR intervals compared to golden standards

7.1.2 Secondary study parameters/endpoints (if applicable)

Not applicable

7.2 Randomisation, blinding and treatment allocation

Not applicable

7.3 Study procedures

See paragraphs 6.

7.4 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.

7.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

7.5 Replacement of individual subjects after withdrawal

Subject who are withdrawn from the study will not be replaced

7.6 Follow-up of subjects withdrawn from treatment

Subject who are withdrawn from treatment will be followed according to the usual care at the participating hospitals.

7.7 Premature termination of the study

We expect no premature termination of the study, as the risk of participation is negligible.

7.8 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.

7.9 AEs, SAEs and SUSARs

7.9.1 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 / trial procedure/

the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

7.9.2 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.

7.10 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

8 Ethical considerations

8.1 Regulation statement

This study will be conducted in full accordance with the principles of the "Declaration of Helsinki" (most recent version, Fortalezea Brazil, October 2013) and with the laws and regulations of the Netherlands. The complete text of the Declaration of Helsinki is available to the investigators upon request.

8.2 Recruitment and consent

Only patients who are being treated in one of the participating cardiology outpatient Haaglanden Clinics are approached. All patients are selected and approached by the treating cardiologist or specialized nurse under supervision of the cardiologist. Patients first will receive an information letter informing them about the study and requesting their participation. The information provided is sufficient to understand the purpose and nature of the study and the potential (negligible) hazards and benefits. It will be stressed that the patient is completely free to refuse participation or to withdraw from the trial at any time, without consequences for his/her treatment, and that the physician or investigator can decide to withdraw a patient from the study for urgent medical reasons. The informed consent form is signed on the day of the inclusion. In all cases it is the responsibility of the research fellow to obtain written informed consent.

8.3 Benefits and risks assessment, group relatedness

In the current research project, we have the chance of investigating the of effect on early diagnosis and detection of a comfortable and aesthetically high level wearable (respiration rate). Any outcome of this study will play a considerable role in the future implementation of strategies in healthcare.
Potential disadvantages of participating in the research:

- Not applicable

Potential complaints will be monitored, patients can contact the research fellow at any time with questions. Thereby it is stressed in patients that quitting the research is possible at any moment. The risks of participation are in general limited.
No patients under the age of 18 years are included in the study.

8.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

8.5 Inventives (if applicable)

- Not applicable.

9 Administrative aspects, monitoring and publication

9.1 Handling and storage of data and documents

Patient anonymity is maintained, according to the General Data Protection Regulation (GDPR). On CRF's and other documents, patients are not identified by their names or dates of births but by randomly assigned identification codes. The investigator keeps a separate log of patient's codes, names and addresses, where only the research fellow will have excess to. The investigator maintains all documents in strict confidence.

9.2 Public disclosure and publication policy

The Investigators are entitled to disseminate the findings of the trial via publications in reputable scientific journals and via presentations at seminars or scientific conferences. The Investigators carry final responsibility for the scientific content of the publication on the main findings of the study. No limitations to the disclosure and publication of the findings have been imposed by the sponsor.