Validation of the performance of the COBOX solution for measuring heart rate and respiratory rate

Clinical investigation protocol under article 62.1 of regulation 745/2017 relating to a class IIa medical device: COBOX

Version 1.0.0

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Sponsor :

- Ø Sponsor name: QUANTIQ.IO
- Ø Developer's address: 4 allée Jacques Prévert - 92500 RUEIL-MALMAISON
- Ø Contact details of the Sponsor: 06.50.89.39.29

Head of research acting on behalf of the sponsor / and authorized to sign the protocol and its possible modifications on behalf of the sponsor: Fabien Niel

Coordinating investigator (multicentric research): Laure Abensur Vuillaume, MD, PHD

HISTORY OF PROTOCOL UPDATES

VERSION	DATE	REASON FOR UPDATE
1	05/23/2022	Document creation
2	05/27/2022	Modification of the section: Ethical and regulatory considerations - type of study MR001
3	05/31/2022	Modification of the title of Arnaud Depil Duval: elimination of the PhD title
4	06/15/2022	Accuracy of the approximate start and end date of the investigation. Addition of signatures: Sponsor and coordinating investigator.
5	07/19/2022	Accuracy of CPP South-East VI. Modification of the parts: research summary as well as in the rest of the document of the following points: 1: Changing study dates 2: Duration and timing of the research 3: Elimination of the medico-economic study Modified recruitment methods.

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SUMMARY

Contents

ABREVIATIONS LIST

ANSM	National Agency for the Safety of Medicines and Health Products
ARC	Clinical Research Associate
CPP	Committee for the Protection of Persons
CNIL	National Commission for Computing and Liberties
CRF	Case Report Form
SAE	Serious Adverse Event
EIGI	Serious Unexpected Adverse Effect
IOA	Reception organization nurse
MR	Reference Methodology
TEC	Clinical Study Technician
API	Application Programming Interface
SAUV	Reception room for vital emergencies
SaaS	Software as a Service
PPG	Photoplethysmography
rPPG	Remote Photoplethysmography
HR	Heart rate
EN	Respiratory rate

1. Research Summary

Sponsor	Quantiq.io
REFERENCE	2022-A00818-35
Coordinating/Principal Investigator	Laure Abensur Vuillaume, MD, PhD CHR METZ-THIONVILLE Mercy Hospital 1 Castle Driveway - CS 45001 57085 METZ Cedex 03
Title	Validation of the performance of the COBOX solution for measuring heart rate and respiratory rate
Acronym	COBOX
Goals	The main objective is to validate the performance of the measurement of the heart rate (HR) measured by the COBOX medical device compared to a measurement carried out by applying the reference processes for taking measurements via a CE marked device. The concordance between the two measurement methods is sought here. The secondary (ranked) objectives of the study are: - Evaluate the performance of the measurement of the respiratory rate (RR) measured by the COBOX medical device compared to a measurement carried out by a reference method of manual counting . - Establish and verify the clinical safety of COBOX and detect any adverse side effects under normal conditions of use of the device and assess whether these constitute an acceptable risk in relation to the expected benefits of the device concerned.
Research scheme	Clinical, prospective and observational investigation
Inclusion criteria	- Adult patient (18 years and over) And

	-Patient consultant in the emergency department of a participating center And - Patient having constant FC and FR taken by the reception organizing nurse (IOA) in the area dedicated to the reception of patients And. - Patient having given their consent to participate in the study.
Non-inclusion criteria	- Patient in a state of vital emergency with direct entry into SAUV or intensive care. - Patient who did not consent to participate in the study. - Patient unable to express consent. - Patient unable, for health reasons, to face the COBOX solution. - Patient unable to stand for 30 seconds facing the COBOX solution . - Patient with skin stigma over more than 50% of the face (burn, graft). - Patient having the face covered or not allowing access to the entire face (clothing).
Treatments/Strategies/ research procedures	The patients included in the study will have their HR and HR constants taken simultaneously at the reception of the emergencies by a reference medical device and by COBOX.
Judgment criteria	The main judgment criterion for the HR will be the evaluation of the concordance between the measurements obtained following the application of the reference technical processes of non-operator dependent measurement taking via a CE marked device and via COBOX. The secondary judgment criterion associated with the measurement of the RR will also be the subject of an evaluation of the concordance between the measurements obtained via a reference method of manual counting

	according to the good practices of the medical or paramedical nursing staff (or arc or tec) and via COBOX. For each of the parameters measured, we will establish the repeatability of the measurement and its accuracy (comparison of the relative error expressed as a percentage between the two types of measurement).
Study size	323 patients
Planned number of centers	4
Search duration	Duration of participation for each patient: less than 30 minutes Total research duration: 3 months Approximate study start date: mid-July 2022 Approximate study end date: mid-October 2022
Statistical analysis of data	The performance of the tool will be estimated by the concordance between the measurements obtained from the application of the reference technical process via a CE marked device and with the measurements obtained by COBOX. An intraclass correlation coefficient (ICC) with its 95% confidence interval (95% CI) will be calculated. Measurement errors will be calculated and expressed as a percentage (root mean square error, etc.). The two study samples will be compared by Student's t test and Fischer's F, with a desired significance for P value = 0.05, for all the analyses. A DIXON test will be performed to assess the presence of statistically outliers within the samples.
Expected benefits	These data will enable the COBOX tool, a class IIA medical device, to be validated in terms of measurement performance compared to a CE-marked device used in a reference technical process for taking measurements and a reference method for manual counting. Applications for taking constants without contact have a wide field of application in

	the field of routine care, saving medical time, increasing quality by limiting manual copying errors, better quality with a tool without contact, limiting the risk of contamination and better accessibility to vital sign measurements thanks to its purely software side which only requires a camera.
Provisional schedule of the study	– Start of inclusions: Mid-July 2022 – Duration of the inclusion period: 2 months – Duration of participation of each patient: The time of their passage in the IOA box (less than 30 minutes) – Total research duration: 3 months
Obtaining authorization from the CNIL	Certificate of compliance with MR001

2. Definition of the medical need addressed: the overload of the healthcare system

The overload of an Emergency Department (SU) is considered a threat to the quality and safety of care, and leads to an increase in morbidity and mortality during hospitalization [1-4]. This overload also generates negative effects for caregivers and their quality of life at work [5]. It would seem that inappropriate recourse to emergencies is from 13.5% to 27.4% [6]. Many patients turn to emergencies and this is partly linked to a need felt to be urgent and to the limited nature of the devices available to guide home routes.

In this global context, the care access service (SAS) was created and is currently being tested. The SAS aims to improve the conditions of access to the healthcare system by developing an information and orientation center in addition to the medical regulation of the SAMU-15 based in part on city medicine. It is a medical orientation device, in response to a request for care and / or information, answering health questions. This system will be accessible at any time and by various means such as telephone calls and teleconsultations. It will be conducted by the staff of the professional territorial health communities (CPTS) and the SAMU-15 of each of these territories [7]. The call, through a single number for the management of unscheduled care (SNP) and emergencies, will initially be taken into account by a medical dispatch assistant (ARM) in charge of identifying the place of distress, the caller and the nature of the call. This call is then redirected either to an ARM in the urgent medical aid sector in the face of a medical emergency, or redirected to a liberal regulatory doctor in the SNP sector. Currently being deployed in 22 pilot sites (including SAMU 10), the system covers more than 40% of the French population and ensures the widest possible territorial coverage, in mainland France and overseas, concerning both urban poles than less dense territories which are experiencing problems of medical desertification.

Other care systems already use models that include initial patient orientation contacts. Sweden has also equipped itself with an innovative tool based on artificial intelligence technologies to help with the role of Gatekeeper, allowing pre-orientation of patients. However, this type of tool available to the patient at home must prove its safety in terms of sorting performance. To date, the most reproducible and controlled sorting is carried out in emergency services by reception and orientation staff. Also, a tool comparing the performance of a tool versus this reference process would make it possible to show all its interest, particularly in France.

3. Identification and description of the experimental medical device

General description

"COBOX" by Quantiq.io is Class IIa stand-alone software pursuant to Rule 11 of Regulation 745./2017. It is an API (Application Programming Interface) put into service through a SaaS solution (Software as a Service) whose technology is based on remote photoplethysmography, allowing the physiological parameters of a patient to be measured without contact by a healthcare professional or lay user. The SaaS API is accessible from a smartphone, a computer or a health post equipped with an optical camera.

The technology at the heart of "COBOX" is remote photoplethysmography (or remote photoplethysmography in English, abbreviated as rPPG). rPPG is a technique derived from photoplethysmography (PPG). Photoplethysmography is an optical technique used to detect blood volumetric changes in the peripheral circulation. It is an inexpensive and non-invasive method that performs measurements on the surface of the skin. The technique provides valuable information related to our cardiovascular system. Recent technological advancements have revived interest in this technique, which is widely used in clinical physiological monitoring and measurement.

The PPG uses a low intensity red and infrared (IR) LED. When light passes through biological tissues, it is absorbed by bones, skin pigments, and venous and arterial blood. Since light is more strongly absorbed by blood than surrounding tissue, changes in blood flow can be detected by PPG sensors as changes in light intensity. The electrical voltage signal from the PPG is proportional to the amount of blood flowing through the blood vessels. Even small changes in blood volume can be detected using this method.

A PPG signal has several components, including an AC component of volumetric changes in arterial blood that are associated with cardiac activity, changes in venous blood volume that modulate the PPG signal, and a DC component showing the optical property of tissues and bones in the body. Changes in blood flow occur mainly in the arteries and not in the veins).

The PPG can operate in 2 main configurations: either by transmission, where the light is transmitted through the finger and captured on the opposite photodetector, or by reflection where the photodetector and the LED are on the same side and the light is transmitted then reflected on the finger towards the photodetector (see figure 1).

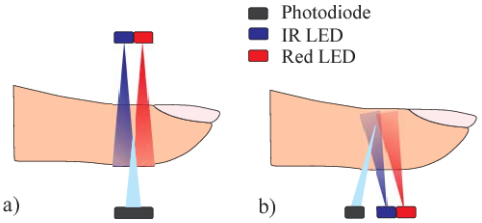

Figure 1. Pulse oximetry modes. a) Transmission b) Reflection

Source: *AT Ayance, HS Ramírez, JMR Pérez and CGT Palacios, "Low-cost microcontrolled based wireless heart rate and oxygen saturation monitor," 2018 International Conference on Electronics, Communications and Computers (CONIELECOMP), 2018, pp. 176-180, doi: 10.1109/CONIELECOMP.2018.8327195.*

The rPPG on the other hand works on the same basic principle as the PPG in reflection except that the ambient light plays the role of the LED and the camera the role of the photodetector (see figure 2).

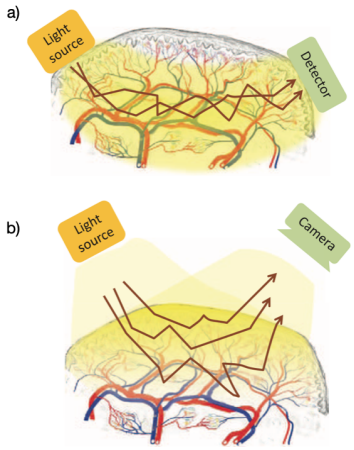

Figure 2. Light path in skin for
a) contact PPG b) remote PPG

Source: *Verkruysse, Wim PhD*; Bartula, Marek MSc†; Bresch, Erik PhD‡; Rocque, Mukul MSc†; Meftah, Mohammed BSc†; Kirenko, Ihor PhD† Calibration of Contactless Pulse Oximetry, Anesthesia & Analgesia: January 2017 - Volume 124 - Issue 1 - p 136-145 doi: 10.1213/ANE.0000000000001381*

In its current version, the technologies embedded in this SaaS platform (COBOX) allow remote tracking, calculation and processing of several biological markers (cardio-respiratory rate). The idea is therefore to transform any camera into a medical device. From this camera. It is a SaaS platform type product that can be integrated and integrated into any other existing or future device. The data can be sent to the patient and the practitioner or managed in real time by trained and qualified nursing staff.

Finally, for its operation, the SaaS API requires a high-speed internet connection and an image capture device by optical camera.

The objectives of this solution are multiple:

- Standardization & reproducibility of the measurement :

Taking the constant “manually” by observation is today the reference method for measuring the respiratory rate. According to good training practices for medical or paramedical nursing staff, this method consists of counting the respiratory movements (inspiration and expiration) of the rib cage for 30 seconds extrapolated to 1 minute (by multiplying the value by two). This technology makes it possible to standardize the measurement of the respiratory rate by a reproducible and repeatable method with considerably reduced operator bias.

- Save time by automating vital signs measurements

The measurement of vital parameters is essential for: assessing the patient's health status; follow the evolution of his state of health; check the effectiveness of the treatments; assist in medical diagnosis. In the state of this taking of vital signs includes the measurement of heart rate and respiratory rate.

Taking constants manually is now the reference in the hospital context, it consists of auscultating the patient by performing all the measurements manually with the help of tools such as a blood pressure cuff, a saturometer or another thermometer. It is a time-consuming operation for the healthcare professional and may involve risks depending on the patient's profile, in particular the risk of infection and the risk of error.
Excluding respiratory constants, the taking of electronic constants is the most used by the medical profession, it is carried out thanks to multiparametric monitors in the vast majority of cases. A multi-parameter monitor is a medical device for monitoring a patient's vital parameters. Typically, basic models monitor heart activity, blood pressure, respiration, oxygen saturation, and temperature. They display the value of the parameters while presenting their evolution curves over time.

- Risk limitation

This solution differs from its competitors thanks to a feature that makes it its strength: the user has no physical contact with the camera, which is the only measurement tool. Nosocomial infections, or "care-associated infections", are infections contracted in a healthcare establishment such as a hospital or clinic. Santé Publique France estimates that approximately one hospitalized patient in 20 was confronted with it in France in 2017. The World Health Organization estimates on its website at 1.4 million the number of people who have contracted an infection with 'hospital. The Ministry of Health estimates that nosocomial infections are responsible for 4,000 deaths each year in France.

Other objectives are also targeted:

• Relieve medical and paramedical staff thanks to automated metrics taking.

• Secure and reassure patients through constant monitoring of their state of health

• Facilitate taking metrics without human intervention.

Details of the manufacturer of the investigational medical device

Name: Quantiq.io

Head office address (Kbis): 4 allée Jacques Prévert - 92500 RUEIL MALMAISON

Model/type name or number, including software version and accessories, if applicable, for complete identification.

The name of the SaaS API is COBOX, a software-only solution.

As part of this study, we will use "COBOX" version 1.0.0.

During the clinical investigation, this API will be integrated into the "DemoCOBOX" version 0001 application in order to allow its use by medical personnel (or arc or tec) . This application will be installed on a Samsung S6 tablet. The tablet will be placed on a tablet support equipped with an anti-theft device.

Description of how traceability should be ensured during and after the clinical investigation, for example by assigning batch, batch or serial numbers.

During the clinical investigation, Quantiq.io will keep an identical model of the tablet with the same version of COBOX installed in order to be able to reproduce any possible deviation in a measurement and to investigate whether it comes from the tablet or the clinical trial conditions. The reference of each tablet distributed for the trial as well as the DemoCOBOX application version installed on it will be stored on our servers. The use of the application may be monitored on our servers. Quantiq reserves the right to make extremely minor patches to the API as well as the demo application during the trial, in order to meet a potential request from medical staff (or arc or tec) and/or patients. In the event of a bug fix, or non-substantial modification, the server may be put on hold. A system for updating the version on the "device" side can be used (telephone, pc).

The traceability of the software version used during the clinical investigation will be recorded on secure databases for the duration of the study and for a period of 10 years from the end of the study.

1. The populations and indications for which the experimental device is intended

COBOX is a medical software intended for the measurement of clinical parameters of heart rate and respiratory rate, in a medicalized or non-medicalized environment. COBOX is a solution intended to be used by healthcare personnel and lay users. As part of this test and in order to validate its performance, the COBOX device will be used by health professionals in real conditions of use.

As part of the study, the COBOX device is intended to be used:

- For measuring HR and HR in a clinical setting or at home for regular pathology monitoring or teleconsultation.
- In the context of reception and emergency care by trained personnel .
- On patients defined by the inclusion or exclusion criteria of this protocol.

Description of the experimental device, including any material that will be in contact with tissues or body fluids

The COBOX device and the equipment that supports it do not come into contact with the patient. The COBOX solution is purely software-based and poses no danger to the patient.
COBOX is an autonomous software type medical device. It consists of a SAAS API that works on devices equipped with a camera such as smartphones, computers or tablets with an operating system described as compatible in the user manual.

Summary of training and experience required to use the experimental device.

The use of this solution does not require specific training, beyond becoming familiar with the user manual prior to its use and following the indications present on the user interface respecting the specifications of Quantiq.io. The user manual is the same for the patient and the nursing staff (or arc or tec).

Description of the specific medical or surgical procedures involved in the use of the investigational device.

The measurement of Heart Rate and Respiratory Rate are usual and routine elements necessary for the diagnosis and management of patients. The measurement of these two physiological constants will be made using the COBOX solution in addition to the reference measurement processes and methods. As a result, there is no heavy interventional procedure added to the care of the patient at the emergency department.

4. Risks and benefits of the experimental device and the clinical investigation

Clinical benefits

The clinical advantages of COBOX are:

- Measurements are simplified via a single tool thanks to the solution.
- They do not require any particular medical procedure.
- They are non-invasive.
- They are contactless and do not require disinfection after use.
- They make it possible to measure the Respiratory Rate in an automated and reliable way.
- It offers an opportunity to standardize the measurement of respiratory rate.
- It allows more regular monitoring and possible continuous monitoring:
    - Faster identification of decompensation and/or acutisation of a pathology – Tachypnea/Polypnea.
    - Monitoring of risky drug intake (morphinics and derivatives – Bradypnea)

In current practice, measurements of respiratory rhythms and frequencies are taken visually by identifying the movements of the rib cage: The operator (nursing staff or arc or medical or paramedical tec) in current practice counts the complete respiratory movements (inspiration + exhale) for 30 seconds and multiply by 2 to extrapolate the result to 1 minute (Cycles per minute).

This medical decision-making can therefore vary according to these results, 2 to 3 cycles per minute varying around a "risk zone" (Above 20 cycles/minute or below 12/minute) can decide to whether or not to put on oxygen (these results are always interpreted with the oxygen saturation). Beyond the lack of robustness and reproducibility of this measurement in routine care, the purely human intervention makes its regular or continuous monitoring complex and time-consuming.

Finally, this data without a real monitoring standard is data that is almost unusable in epidemiological and/or clinical research.

Potential side effects

There are no direct or indirect adverse effects for the patient identified to date.

Residual risks associated with the experimental device, as identified in the risk analysis report

After implementation of risk reduction actions (in accordance with document REC-M2-016 Product risk analysis of the Technical File), all the residual risks assessed are deemed acceptable.

Risks associated with participating in the clinical investigation

No associated risk has been identified, the non-inclusion measures having been identified in this regard. The data collected for the evaluation will be observational and the information provided by COBOX will not be used in clinical decision-making.

Possible interactions with concomitant medical treatments

No interactions have been identified.

Measures that will be taken to control or mitigate the risks

The COBOX application poses no risk to the patient.

Justification of the risk/benefit ratio

As stated previously, the implementation of the risk management process led to the absence of unacceptable residual risks for the conduct of this study. Furthermore, the assessment of the benefit/risk is the subject of provisions documented within the PRO-M2-004 Risk Management procedure.

It follows that the absence of unacceptable residual risk and the identification of expected clinical benefits, established on the basis of preclinical performance verification trials, are such as to establish a favorable benefit/risk ratio for the conduct of the study. .

5. Objectives and hypotheses of the clinical investigation

Research hypotheses and expected results

In order to meet safety and quality standards, new health technologies require rigorous clinical validation with measurement performance at least equivalent to that obtained through the application of reference measurement processes using marked devices. CE, as well as those obtained via the manual counting reference method.

In this context, we hypothesize that the COBOX device will take measurements of heart and respiratory rates consistent with those obtained through the application of reference processes for taking measurements via CE marked devices, as well as those obtained via the manual counting reference method.

We also make the assumption of an economic superiority by a release of time allowed by the automation of these catches, and the suppression of the protocols of decontamination allowed by the taking of measurement remotely.

The tool (COBOX) will reduce the cognitive load of caregivers in favor of a higher quality of care. It will also allow greater access to vital sign measurements thanks to its purely software nature and requiring only a smartphone or tablet (or a computer or any other device with a camera).

Primary objective

The main objective is to validate the performance of the measurement of the heart rate (HR) measured by the COBOX medical device compared to a measurement carried out by applying the reference processes for taking measurements via a CE marked device. The concordance between the two measurement methods is sought here.

Secondary objectives

The secondary (ranked) study objectives are:

- Evaluate the performance of the measurement of the respiratory rate (RR) measured by the COBOX device compared to a measurement carried out using the manual counting reference method. The concordance between the two measurement methods is sought here.
- Evaluate the additional parameters allowing to establish the clinical performance of COBOX for the measurement of HR and RR:
    - Measurement repeatability.
    - The accuracy of the measurement: concordance within a tolerated margin between the measurement taken by the COBOX device and current practices.

- Establish and verify the clinical safety of COBOX and detect any adverse side effects under normal conditions of use of the device and assess whether these constitute an acceptable risk in relation to the expected benefits of the device concerned.
- Evaluate ergonomics and user feedback.
- Evaluate the ease of use of the device (assessed by an ad-hoc questionnaire completed by the caregivers (or arc or tec), one questionnaire per caregiver and per type of device).

Justification of methodological choices

We are carrying out an observational, multicenter, prospective clinical investigation, evaluating the performance of the COBOX device in the context of and within the framework of usual care. Heart rate and respiratory rate are two physiological parameters measured when a patient arrives at the emergency room, so, given the high attendance of these services, it seemed to us to be an excellent place for this study. This measurement is carried out as part of the patient's care pathway using reference technical processes for taking measurements via a CE marked device and a reference method of manual counting. The inclusions of patients consulting in the emergency department make it possible to quickly obtain both a large number of inclusions, and on the other hand, a great variability of the constants noted due to the various pathological states. This approach allows great reproducibility in all clinical situations and thus makes it possible to validate performance in different contexts. In addition, a medico-economic study of the tool will be carried out.

Hypotheses

- H_0 :Routine care measurements in French care services, taken by the COBOX solution are different from measurements obtained through the application of reference technical processes and a manual counting reference method.
- H_1 :The current care measurements in French care services taken by the COBOX solution are consistent with the measurements obtained via the application of the reference technical processes and a reference method of manual counting.

Claims and expected performance of the investigational device that need to be verified.

COBOX is a tool for measuring cardiac and respiratory rhythm in routine clinical practice for patients outside intensive care and outside continuous monitoring. We expect a correlation coefficient of more than 0.7 between the COBOX measurements and those obtained using the reference method. Regarding the secondary endpoints, we expect average standard deviations

between COBOX and the reference methods of 5 bpm for the heart rate and 3 bpm for the respiratory rate.

Expected benefits

These data will validate the COBOX tool in terms of measurement performance compared to the results obtained through the application of reference processes for taking measurements using CE marked devices, as well as those obtained using the reference method of counting. manual. Applications for taking physiological constants without contact have a wide field of application in the field of routine care and save medical time, increase quality by limiting manual copying errors and the risk of contamination.

6. Research design

Research scheme

This is an observational study, responding to Article 62.1 of the European medical device regulations, prospective, comparative.

Primary endpoint

The main judgment criterion will be the intra-class correlation coefficient between the measurement by COBOX and the measurement obtained thanks to the application of the reference processes for taking measurements via a measurement by a CE marked tool (for HR).
In order to ensure the repeatability of the device, three successive comparative measurements (each spaced 5 seconds apart) on the same patient will be carried out.

Secondary endpoints

The additional secondary judgment criteria will be:

- For RF (ranked criterion): comparison with a manual measurement following a reference method of manual counting according to good training practices for healthcare personnel trained in taking measurements (ide, as, internal external).
- The reliability of the reproducibility of the measurement
- The time in seconds dedicated to taking the parameters with and without the COBOX tool (time for installing and removing the tool if applicable, time for completing the medical file if applicable, effective time for taking the HR constants and FR).
- Assessment of treatment costs:
    - Pick-up times / delays
    - Total treatment costs (direct medical and non-medical costs)

Inclusion criteria

- Adult patient (18 years and over)
  AND
- Patient consulting in the emergency department of a participating center
  AND
- Patient having constant FC and FR taken by the nursing staff (or arc or tec) of emergency reception
  AND
- Patient who did not express his opposition to participate in the study
  AND

- Patient affiliated to a social security scheme

Non-inclusion criteria

- Patient in a state of vital emergency with direct entry into SAUV or intensive care.
- Patient unable to express consent.
- Patient unable, for health reasons, to face the COBOX tool.
- Patient unable to stand for 30 seconds facing the COBOX solution.
- Patient with skin stigma over more than 50% of the face (burn, graft)
- Patient with the face covered or not allowing access to the entire face (clothing)

Recruitment methods

In order not to delay the care of patients in the emergency room, recruitment is carried out by the IOA (or arc or tec) at the time of their usual care. She communicates oral information to the patient on the use of the tool during the measurements and presents the consent letter in electronic format in the tablet. If the patient gives consent, the test is performed. In case of opposition, the COBOX device will not be used.

It is therefore a serial recruitment, without selection of the participants.

7. Experimental device(s) and comparator(s)

Description of exposure to comparators

In order to standardize the measurements of the four hospital centers, QUANTIQ will provide each center with a CMS60D digital pulse oximeter from the Contec brand. This device is CE marked and commonly used in hospitals. This device will be used at the same time as the CE marked device used during the reference technical process of the hospital center, without modifying the practices of each center . The comparison of results will be between the Contec CMS60D and the COBOX tool.

Device	Acquisition cost	Trolley (300 to 700 Euros)	Whip Set and Monobase Cables	Lifespan (Year)	Annual Maintenance Cost	Annual cost for 1 technical platform
Contec CMS60D Digital Pulse Oximeter (SpO2 - Heart Rate)	242.50 €	N / A	N / A	2 YEARS (AVERAGE)	Replaced/No Maintenance - PURCHASE Management (12.1 €)	133.4 €

List of any other medical device or drug that will be used during the clinical investigation.

The Contec CMS60D reference DM will be provided by Quantiq while COBOX will be installed on a Samsung S6 tablet also provided by Quantiq.

Number of experimental devices to be used, along with a rationale

3 reference Contec CMS60D oximeters will be provided per center.

Treatment(s)/ management of experimental devices

QUANTIQ provides users with one tablet per site per physician. Delivery of a functional tablet in the event of a malfunction within 5 working days. Bug fix within 3 days in case of software malfunction with continuous information for professionals.

8. Research process

Research timeline

- Start of inclusions: Mid-July 2022
- Duration of the inclusion period: 2 months
- Duration of participation of each patient: The time of their passage in the IOA box (less than 30 minutes)
- Total research duration: 3 months

Summary of patient follow-up

- Oral information by the IOA. If necessary, an investigating physician can complete the information at the patient's request.
- Informed consent with electronic signature.
- Collection of the patient's age, gender and Fitzpatrick phototype.
- Collection of patient identification number.
- The nursing staff (or arc or tec) installs the oximeter on the patient's finger.
- The nursing staff (or arc or tec) starts COBOX and begins to count the breaths in parallel.
- After 15s, a first measurement is made by COBOX. The pulse oximeter reference result is acquired in parallel, associated with the patient ID number and stored with the COBOX result at the same time on an electronic database.
- After 20s (5s after the previous measurement), a second measurement is made by COBOX. The pulse oximeter reference result is acquired in parallel, associated with the patient ID number and stored with the COBOX result at the same time on an electronic database.
- After 25s (5s after the previous measurement), a third measurement is made by COBOX. The pulse oximeter reference result is acquired in parallel, associated with the patient ID number and stored with the COBOX result at the same time on an electronic database.
- After 30s, the nursing staff (or arc or tec) enters the number of breaths counted since the start. This result is converted into a respiratory rate (RR) then associated with the patient number and stored in the database.

The data is blocked on the database until the end of the study. At the end of the study, they will be sent to the coordinating centre.

In order not to disrupt the general operation of the emergency department and patient care, the usual patient circuit is not modified. The COBOX tool is used by the reception staff in a contemporary way to their usual collection of input parameters.

Collection of consent

The information is compiled by the IOA and if necessary completed by a doctor. This information must make it possible to answer all the patient's questions concerning the objective, the nature of the constraints, the foreseeable risks and the expected benefits of the research. It also specifies the patient's rights in the context of a clinical investigation and verifies the eligibility criteria. A copy of the information note and the electronic consent form are then given to the patient by the investigating physician.

The consent form is electronic and must be signed before data can be collected for research. After electronic acceptance of the consent, a copy of the consent form is sent to the patient with his identification number allowing him at any time to ask the Sponsor to delete his data. For his part, the Sponsor only has access to the patient's identification number but his email address is not stored.

The data will include:

- Taking FC and FR by the reference method
- HR and FR taken by the COBOX tool at the same time as those of the reference tool.
- The patient's age, sex and Fitzpatrick phototype.

The different copies of the information notice and the consent form are then distributed as follows:

- A copy of the information note and the signed consent is given/sent by email to the patient.
- The original copy is kept by the investigating physician (even if the patient moves during the duration of the research) in a safe place inaccessible to third parties.
- When accepting the patient's participation on the electronic form. This is automatically sent to the Sponsor.

Search stopping rules

The temporary stoppage of the research can be pronounced by technical problems concerning the evaluated tool. The research stops definitively when the necessary number of subjects is reached and all the data allow the analysis.

Constraints related to research and possible compensation of subjects/patients

Patients can simultaneously participate in another research. No compensation is provided for in this study. The patient will not be registered in the national file of people who lend themselves to biomedical research.

9. Management of adverse events and new facts

In accordance with article 2 of regulation 745/2017, the following terms mean:

Adverse Event: Any harmful manifestation, unintended illness or injury, or untoward clinical sign, including an abnormal laboratory finding, in Participants, Users, or others, in a clinical investigation, related or no to the medical device that is the subject of a clinical investigation.

Serious adverse event: any adverse event resulting in: a) death; b) a serious deterioration in the Participant's state of health, which results in: i) an illness or injury endangering the life of the Participant; ii) a permanent impairment of an anatomical structure or function; (iii) hospitalization or prolongation of the participant's hospitalization; (iv) medical or surgical intervention to prevent any life-threatening illness or injury or permanent impairment of anatomical structure or function; (v) chronic illness; (c) fetal distress, fetal death, congenital physical or mental impairment or birth defect.

Defectiveness of a medical device: any defect in the identity, quality, durability, reliability, safety or performance of a medical device under investigation, including any malfunction, error of use or any defect in the information provided by the manufacturer

In accordance with article 80 of regulation 745/2017 as well as "MDCG-2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745" and "MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation",

Sponsor :

A/ records the following events:

The sponsor records the following data sent to it by the investigator within the time limits specified in point C/ of this document: a) any adverse event defined in the protocol as decisive for the evaluation of the results of the clinical investigation. B) any serious adverse event; c) any defect in an MD which could have led to a serious adverse event in the absence of appropriate measures or intervention, or if the circumstances had been less favourable; d) any new element concerning an event referred to in points a) to c).

B/ declare to the authorities

The sponsor notifies the authorities according to the procedures described in the following sections: a) any serious adverse event with a proven or reasonably foreseeable causal link with: - the MD subject to the investigation, - or the comparator MD - or the investigation procedure which precedes it; b) any defect in an MD which could have led to a serious adverse event in the absence of appropriate measures or intervention, or if the circumstances had been less favourable; c) any new element concerning an event referred to in points a) and b).

C Reporting deadlines

C.1 Deadlines for reporting by the investigator to the sponsor

The events and defects are declared to the sponsor by the investigator without delay (immediately) and no later than within 3 calendar days from the moment when the investigator became aware of them.

C.2 Deadlines for reporting by the Sponsor to the competent authority

All events and defects resulting in death or risk of imminent death, serious injury or illness and which require prompt corrective action for participants/patients, users or other persons, or any new information relating to these events: Without delay (immediately), and no later than 2 calendar days from the day on which the Sponsor becomes aware of the event to be declared or of new information concerning an event already declared.

Other events and defects or any new information/update concerning them: Without delay (immediately), and no later than 7 calendar days from the day on which the Sponsor becomes aware of the event to be declared or of new information concerning an event already declared.

All safety reports in clinical investigations of medical devices under Regulation (EU) 2017/745 will be carried out in accordance with MDCG 2020-10/1 and MDCG 2020-10/2.

10. STATISTICAL ASPECTS

Study size calculation

Considering the results of the performance verification tests of the medical device under study, we have established the study hypotheses in connection with the calculation of the size of the study set out below:

Minimum acceptable value of the ICC correlation coefficient (ρ0)	0.6
Expected value of the ICC correlation coefficient (ρ1)	0.7
The number of observations per subject k	3
Two-sided significance level (α)	0.05
Power (1 - β):	90%
Minimum size (n)	226
Size at 30% safety margin	**323**

A final study size of 323 patients is retained; taking into account a rate of unusable data of 30% in order to maintain the statistical power of the study in the event of exclusion of outliers.

Statistical methods used

The analysis will carry an initial descriptive part. The qualitative variables will be expressed in frequencies (with their 95% CI), and the quantitative variables expressed in means (with their standard deviation) if the distribution is normal. Otherwise, the quantitative variables will be expressed as the median (with their interquartile range).

Then, we will perform a comparative analysis, using chi 2 tests (or Fisher's exact) for the qualitative variables and student test (or Mann-Whitney test if applicable) for the quantitative variables. For performance estimation, we will determine the intra-class correlation coefficient with its confidence interval and we will perform a graphical analysis of Bland and Altman. In addition, we will calculate the mean square errors between the measurement with COBOX and the reference measurements, and they will be expressed as a percentage.

All our analyzes will be carried out at the 5% significance level.

An analysis of the repeated and compared measurements between COBOX and the CE marked device (used during the technical reference process for taking measurements) for the heart rate will make it possible to evaluate the reproducibility of the COBOX on repeated measurements in the

same individual. A secondary statistical analysis will be done for the measurement times T+5s and T+10s.

We will use imputation methods or sensitivity analysis for the management of missing data.

11. Access rights to source data and documents

Access to data

The sponsor is responsible for obtaining the agreement of all the parties involved in the clinical investigation in order to guarantee direct access to all the places where the research is carried out, to the source data, to the source documents and to the reports in a purpose of quality control and audit by the Sponsor.

The investigators will make available the documents and individual data strictly necessary for the monitoring, quality control, audit of the clinical investigation and available to persons having access to these documents in accordance with the legislative and regulatory provisions in force (articles L.1121-3 and R.5121-13 of the public health code).

Source data

Any original document or object that proves the existence or accuracy of data or a fact recorded during the research is defined as a source document.

List the type of source document as part of the research (medical record, original biological examination result, imaging examination report, etc.).

Data Privacy

In accordance with the legislative provisions in force (articles L.1121-3 and R.5121-13 of the Public Health Code), persons having direct access to the source data will take all the necessary precautions to ensure the confidentiality of the information. relating to the research, to the persons who take part in it and in particular with regard to their identity as well as to the results obtained. These people, like the investigators themselves, are subject to professional secrecy.

During the clinical investigation or at its end, the data collected on the people who agree to it and transmitted to the sponsor by the investigators (or any other specialized contributors) will be made anonymous. Under no circumstances should they clearly show the names of the persons concerned or their addresses.

The Sponsor will ensure that each person who lends himself to the research has given his written consent for access to the individual data concerning him and strictly necessary for the quality control of the research.

12. Quality control and assurance

Guidelines for data collection

All the information required by the protocol must be recorded in the tablet in the boxes dedicated to this purpose. Data should be collected as it is obtained.

Research follow-up

The clinical investigation will be monitored by a clinical research technician. He will be responsible, alongside the coordinating investigator, for:

- Research logistics and monitoring,
- Reporting on its progress,
- Verification of data collection with the tablet,
- The transmission of SAEs to the Sponsor.

He will work in accordance with standard operating procedures, in collaboration with the clinical research associate delegated by the Sponsor.

Quality control

A clinical research associate mandated by the sponsor visits each investigating center on a regular basis, during the setting up of the research, one or more times during the research depending on the rate of inclusions and at the end of the research. During these visits, the following elements will be reviewed:

informed consent,

Compliance with the research protocol and the procedures defined therein,

Quality of data collected in the tablet: accuracy, consistency of data with source documents (medical records, appointment books, original laboratory results, etc.),

Any visit will be the subject of a monitoring report in written form.

Data managment

Data processing will be carried out under the responsibility of Fabien Niel.

The data will be entered automatically and stored in the tablet reserved for the study and provided by the sponsor.

The data validation and freezing processes will be carried out according to the procedures in force.

Auditing and inspection

An audit may be carried out at any time by persons appointed by the Sponsor and independent of the research managers. Its objective is to ensure the quality of research, the validity of its results and compliance with the law and regulations in force.

Investigators agree to comply with the requirements of the sponsor and the competent authority with respect to an audit or inspection of the research.

The audit may apply to all stages of the research: from the development of the protocol to the publication of the results and the classification of the data used or produced within the framework of the research.

13. Ethical and Regulatory Considerations

The sponsor and the investigator(s) agree that this research will be carried out in accordance with the Public Health Code, as well as in accordance with Good Clinical Practice (ICH version 4 of May [1] 1996 and decision of November 24, 2006) and the Declaration of Helsinki (which can be found in its integral version on the site http://www.wma.net) and according to the MDR 745/2017.
The research is conducted in accordance with this protocol. Except in emergency situations requiring the implementation of specific therapeutic acts, the investigator(s) undertake(s) to respect the protocol in all respects, in particular with regard to the collection of consent. .
This research received an ID-RCB number on the ANSM website: https://ictaxercb.ansm.sante.fr/Public/index.php .

Assurance QUANTIQ – Sponsor of the study

As part of this research, subject to Law No. 2018-493 of June 20, 2018 on the protection of personal data, the data recorded during this research is subject to computerized processing by Quantiq. io in order to analyze the results of the research with regard to the objectives of the latter. In accordance with the General Data Protection Regulation (RGPD 2016/679 of the European Parliament and of the Council of April 27, 2016), health data will be processed for scientific research purposes in compliance with the fundamental rights and interests of the person. suitable for research (Article 9 §2, paragraph i and j).

The data controller for this study is Fabien Niel.

People participating in the research have a right of access to their data, a right of rectification, erasure of their data, a right to limit processing as well as a right of opposition. to the processing of their personal data. These rights are exercised with the Investigator, who will inform the sponsor of the research as soon as possible.

People taking part in the research also have the right to lodge a complaint with the supervisory authority in France, namely the Commission Nationale de l'Informatique et des Libertés (CNIL).
The personal data will only be accessible to the persons concerned (those participating in this research) and to the persons charged by the sponsor with controlling the quality of the study. These data will be pseudonymised: they will be marked by a code number comprising an inclusion number (corresponding to the chronological order of their inclusion and the center number) as well as the 1st letter of the name and the 1st letter of the first name of each concerned person. The correspondence table will be kept separately from the entire data set by the only persons authorized by the Sponsor, who will not be data operators. If necessary, they may also be transmitted to the authorized health authorities, under the legal conditions provided. In all cases, they will be used under conditions guaranteeing their confidentiality.

This data processing may be part of the reference methodology MR001 according to article 62.1 of the MDR.

For comfort, the company Quantiq.io filed a request for CNIL authorization on December 24, 2021, supported by a PIA.

Protocol amendment

Changes to the protocol will be managed in accordance with the requirements of Regulation 2017/745.

Any substantial modification, i.e. any modification likely to have a significant impact on the protection of persons, on the conditions of validity and on the results of the research, on the quality and safety of the products tested, on the interpretation of the scientific documents that support the progress of the research or the methods of conducting it, is the subject of a written amendment which is submitted to the sponsor; the latter must obtain, prior to its implementation, a favorable opinion from the CPP and inform the ANSM.

Non-substantial modifications, ie those having no significant impact on any aspect of the research whatsoever, are communicated to the CPP for information.

All amendments are validated by the sponsor, and by all the research stakeholders concerned by the modification, before submission to the CPP.

All amendments to the protocol must be brought to the attention of all investigators participating in the research. Investigators undertake to respect its content.

Any amendment that modifies the care of patients or the benefits, risks and constraints of research is the subject of a new information note and a new consent form, the collection of which follows the same procedure as the one mentioned above. .

Deviation from protocol

Any deviation from this protocol, the signed agreement, applicable regulations and any condition of approval imposed by an EC or by applicable regulatory authorities, which affects the rights, safety and well-being of the subjects or the scientific integrity of the clinical investigation, must be documented (including the date and reason for the deviation). Site staff must identify and report deviations to the sponsor within 5 working days.

In emergency circumstances, deviations from this protocol to protect the rights, safety, or well-being of participants are permitted without the prior approval of the sponsor and investigators. The site must document and report these emerging deviations to Fabien Niel and Nicolas Desrumaux and to the EC within 5 working days of the occurrence of the emergency.

Where appropriate, measures to ensure compliance may be taken by the data controller. These actions may include discontinuation of device shipments, removal/disposal of devices from the investigator, or termination of the investigator's participation in the study.

Declaration of conformity

A) This clinical investigation will be conducted in accordance with the ethical principles which have their origin in the Declaration of Helsinki, the ISO 14155:2020 standard (Clinical investigation of medical devices for human subjects - Good clinical practice).

B) This clinical investigation will be conducted in accordance with this International Standard and any regional or national regulations, where applicable, including Regulation 2017/745.

C) This clinical investigation will not commence until the required approval/favourable opinion has been obtained from the EC or the regulatory authority, as the case may be.

D) Any additional requirements imposed by the EC or regulatory authority will be followed, as applicable.

14. Preservation of documents and data relating to research

The following documents relating to this research are archived in accordance with Good Clinical Practice:

- By the medical investigators:

  - for a period of 15 years (research relating to drugs, medical devices or in vitro diagnostic medical devices or research not relating to a product mentioned in Article L.5311-1 of the Public Health Code) ,

    • The protocol and any amendments to the protocol
    • Observation notebooks (copies)
    • The electronically signed informed consents of the participants
    • The source files of the participants who signed a consent
    • All other documents and letters relating to the research

  All these documents are the responsibility of the investigator for the regulatory archiving period.

- By the Sponsor:

  - for a period of 15 years (research relating to drugs, medical devices or in vitro diagnostic medical devices or research not relating to a product mentioned in Article L.5311-1 of the Public Health Code) ,

    • The protocol and any amendments to the protocol
    • The original observation notebooks
    • A copy of the electronically signed informed consents of the participants
    • Documents relating to serious adverse events
    • All other documents and letters relating to the research

All these documents are under the responsibility of the Sponsor for the regulatory archiving period. No displacement or destruction can be carried out without the agreement of the Sponsor. At the end of the regulatory archiving period, the Sponsor will be consulted for destruction. All data, documents and reports are subject to audit or inspection.

15. Posting Rules

Scientific papers

The data provided by the investigating centers are centralized by the coordinating center and sent to Quantiq.io for statistical analysis (statistical analysis is done by Quantiq.io). This analysis gives rise to a written report which must then be sent to the Committee for the Protection of Persons and to the competent authority.

Any written or oral communication of the results of the research must receive the prior agreement of the coordinating investigator and, where applicable, of any committee set up for the research.

The publication of the main results mentions the name of the sponsor, of all the investigators who included or followed patients in the research, of the methodologists, biostatisticians and data managers who participated in the research, of the members of the committee(s) set up(s) for research and funding source(s). International rules for writing and publication will be taken into account (The Uniform Requirements for Manuscripts of the ICMJE, April 2010).

Communication of results to patients

In accordance with law n°2002-303 of March 4, 2002, patients are informed, at their request, of the overall results of the research.

Transfer of data

Data collection and management are handled by the coordinating centre. The conditions for the transfer of all or part of the research database are decided by the research sponsor and are the subject of a written contract.

Sponsor		**COORDINATING INVESTIGATOR**	
Last name	**Date and signature**	**Last name**	**Date and signature**
Fabien Niel	07/19/2022 	Laure Abensur Vuillaume	07/19/2022 

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