CLINICAL INVESTIGATION PLAN

Study Title:	***PROSPECTIVE STUDY FOR THE CLINICAL VALIDATION OF SOUNDI WEARABLE MEDICAL DEVICE***
AcronymmodelStudio:	***STUDIO SOUNDI***
Reference number or identification code of the clinical investigation:	*EUDAMEDSNR:IT-MF-000031905*
Protocol Version Number:	v.1.0
Issuing date:	*February 15, 2023*

Confidentiality statement

GENERAL INFORMATIONS

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APPROVAL OF THE PROTOCOL

Study Title:	***PROSPECTIVE STUDY FOR CLINICAL VALIDATION OF THE SOUNDI WEARABLE MEDICAL DEVICE***
CodeEUDAMEDSNR:	IT-MF-000031905
Protocol Version:	v.1.0 dated 15 February 2023

The Scientific Manager and Principal Investigator:

- approves this Protocol;
- declares that the study will be conducted in accordance with Good Clinical Practice and ISO 14155:2020, according to national and local regulatory requirements and in accordance with this protocol and its procedures.

_____ _____

Prof.CarolinaLombardi Date

Synopsis

Promoter:	BiocubicaSrl
Title of the study:	PROSPECTIVE STUDY FOR THE CLINICAL VALIDATION OF THE WEARABLE MEDICAL DEVICE SOUNDI
Acronym:	StudioSOUNDI
Version and date of the synopsis: v.1	0 of 15 February 2023
CodeEUDAMEDSNR:	IT-MF-000031905
Medical device:	SOUNDI wearable medical device
Directions for use:	Continuous monitoring of vital parameters for the diagnosis and follow-up of breathing and sleep disorders in adult subjects.
Background Rationale:	Obstructive Sleep Apnea Syndrome (OSA) is a highly prevalent sleep disorder and is characterized by repeated episodes of obstruction of the sleep apnea during sleep which accompanies intermittent anxiety and sleep fragmentation. ment of this pathology with numerous serious repercussions on the health of the individual, various technologically advanced systems are being developed which aim to minimize the bulk of the sensors on the patient, increase the comfort of the examination and reduce the need for multiple hospital visits. Among the recently developed systems is Soundi, a small, lightweight medical device that allows non-invasive monitoring and continuous recording of vital parameters. The results obtained so far on healthy subjects are very encouraging, but for the market introduction of SOUNDI as a certified medical device its clinical validation on patients is necessary.
Study design:	This is a pre-marketing, single-center, prospective clinical investigation to compare the effectiveness and safety of the SOUNDI medical device compared to polysomnography in detecting parameters for the diagnosis of OSA in subjects suspected of having a sleep disorder. All eligible subjects will be placed with the Sound device at the same time as a traditional polysomnography machine. The signals will be acquired for approximately 8 hours during a single night with both systems simultaneously and will then be calculated, via automatic analysis software, with subsequent manual correction by a doctor expert in sleep medicine, the indices used, according to international guidelines, for the diagnosis of breathing and sleep disorders. No further follow-up is planned for subjects.

Goals:	**Primary objective:** Evaluate the effectiveness of the SOUNDI system in detecting parameters necessary for the diagnosis of OSA compared to polysomnography (gold standard) in subjects with suspected diagnosis of sleep disorders. **Secondary objectives:** • Evaluate the safety and tolerability of the SOUNDI system • Evaluate the level of patient satisfaction in using the SOUNDI system.
Endpoints:	**Primary endpoint:** Equivalence between the detection of parameters useful for the diagnosis of OSA using the SOUNDIV system and standard polysomnographic methods. **Secondary endpoints:** • evaluation of satisfaction with the use of SOUND I after the night of recording the parameters, by completing a questionnaire. • safety and tolerability of the SOUNDI device using it recording of adverse events.
Estimated enrollment:	50 subjects
Study population:	Adult subjects belonging to the clinical centre, to carry out a polysomnography for suspicion of a breathing disorder sleep.
Inclusion criteriaed exclusion:	**Inclusion criteria:** • Signature of informed consent • Patients of both sexes, of any ethnicity • Age between 20 and 70 years • Prescription, from clinical practice, to carry out a polysomnography on suspicion of a breathing disorder in sleep. **Exclusion criteria:** • Women during pregnancy • Insufficient cooperation/degree of collaboration in following the procedures required by the study • Participation in another clinical study. • Allergy to one of the materials in the device • Pacemaker users.
Procedures:	Some data will be collected during a visit anthropometric devices will be positioned simultaneously for polysomnography: - a traditional polysomnigraph, as prescribed - the experimentalSoundi device. During the night, at the patient's home, the following parameters will be acquired for at least 8 consecutive hours: oro-nasal flow, thoracic and abdominal respirogram, snoring, ECG, arterial oxygen saturation, body position. The following morning the subject will return to the clinics to return the two systems and complete a simple satisfaction questionnaire prepared for the study.

Statistical considerations:	Efficacy analyzes will be carried out on all patients who have completed the evaluation and whose data will be considered evaluable. For each parameter, the agreement between the measurement carried out with the SOUNDI method and the one carried out with polysomnography will be evaluated using the Bland-Altman graph and the Concordance Correlation Coefficient (CCC). Descriptive statistics will be used to evaluate the subject's satisfaction with using SOUNDI. The safety analyzes will be carried out on all patients to whom the Sound device and the polysomnography device have been applied, regardless of the validity of the data collected. The safety analyzes will be of a descriptive nature. A sample of 50 analyzable patients will guarantee a power of 90% in determining six values of the parameters detected with the SOUNDI method which are in agreement with those measured by polysomnography.
Study duration:	The expected duration of enrollment of all subjects is approximately 6 months. The expected duration of the study for the subject is a maximum of 24 hours. The overall duration of the study will be 1 year.

Summary

1. Abbreviations

HADES	Adverse effect of the device
ASADE	Serious and expected adverse effect of the device
AE	adverseevent (AdverseEvent)
OUCH	ApneaHypopneaIndex
BMI	BodyMassIndex
CPAP	ContinuousPositiveAirwayPressure
CRF	CaseReportForm
ECG	Electrocardiogram
EEG	Electroencephalogram
GCP	GoodClinicalPractice
MAD	Mandibular advancement system
OSA	Obstructive Apnea Syndrome
SADE	Serious adverse effect of the device
SAE	SeriousAdverseEvent
SaO2	Arterial oxygen saturation
USADE	Serious and unexpected adverse effect of the device
VOC	VolatileOrganicCompounds

2. Erational background

2.1 Background

Obstructive Sleep Apnea Syndrome (OSA) is a highly prevalent sleep disorder and is characterized by repeated episodes of obstruction of the upper arteries during sleep which are accompanied by intermittent anxiety and sleep fragmentation. OSA, being associated with excessive daytime sleepiness and increased cardiovascular risk, significantly increases mortality and morbidity in the affected population, constituting a public health problem. These consequences are significantly reduced by the early and appropriate implementation of specific treatments for apnea such as Continuous Positive Airway Pressure (CPAP), weight loss, surgery or mandibular advancement systems (MAD).

The diagnosis at the moment is carried out by carrying out polysomnographic tests which can be carried out at home or in a hospital environment. Polysomnography is based on the nocturnal collection of various vital parameters capable of providing an objective quantification of the number, characteristics and intensity of apneas.
The parameters that are acquired during complete polysomnographies are: Electroencephalogram (EEG), eye movements, muscle tone of the mylohyoid muscle and tibial muscles, nasal, thoracic and abdominal respirogram, body position, oximetry, Electrocardiogram (ECG).

For cardiorespiratory polysomnography, the number of parameters is smaller (nasal, thoracic and abdominal respiration, body position, oximetry, ECG).
In both cases, however, the patient must be prepared with the positioning of the sensors in the hours preceding the examination, he must keep them worn throughout the night and have them removed in the morning by expert technicians who also proceed to download the data from the memory on which they are collected during the night. Some tests are carried out at home and therefore the patient must access the hospital in the evening and one in the morning for toes dismantle the equipment, or are carried out in the hospital and in this case the patient remains sleeping inside the
structure.

2.2 Rational

To facilitate easier access to the diagnosis and therefore treatment of this pathology with numerous serious repercussions on the health of the individual, various technologically advanced systems are being developed which aim to minimize the bulk of the sensors on the patient, increase the comfort of the examination and reduce the need for multiple hospital visits. Among the recently developed systems is Soundi.

Soundi is a small, lightweight medical device that allows non-invasive monitoring and continuous recording of blood pressure, without the use of a cuff, and a whole series of physiological parameters including temperature, ECG, ejection fraction, blood pressure, respiratory rate, flow, oxygen saturation, apnea/hypopnea index. This innovative device can completely revolutionize the concept of monitors sleep aid, currently carried out using invasive instrumentation methods. Soundi will allow the patient, once worn, to carry out all his normal daily activities without any discomfort.

Simultaneous collection of a number of parameters using a single vital sign detection device can provide close, long-term, low-cost and shareable health status monitoring, with the potential to improve health management and quality of life, promote both early intervention and proactive care and reduce healthcare costs.

The results obtained so far on a population of healthy subjects are very encouraging (2-3-4-5), but its production and introduction on the market as a certified medical device requires its clinical validation on patients.

3. Information about the medical device

Soundi is a wearable medical device for the continuous monitoring of vital parameters capable of collecting useful information for the diagnosis and follow-up of breathing disorders in sleep.

The SOUNDI medical device is produced by the Biocubicasrl company. The measurement unit is made of plastic material (PA12 food grade), the ECG connector cover is made of food grade silicone, ECG cables (Spes Medica SpA) are made of Cu/Ag with PVC insulation and the medical double-sided adhesive (MED6364R) is made up of a double coating, thin, conformable, with transparent and moisture-resistant polyester film on both sides.

The current prototype of the Soundi device was developed on the basis of a technology patented by Biocubica (Italian patent no. 102016000052588 “Physiological monitoring device” and European patent EP3.248.541 “Physiological monitoring device”)(1) and is equipped with the ability to listen, through a particular bell shape, to all the sound evidence nothing from our body and generated at different frequencies by different organs and/or muscles and tissues, and transduce them, through a series of sensors and with appropriate algorithms, into different vital signals.

Specifically, the parameters Sound detects are:

- Temperature
- Heart rate
- ECG
- Oxygen saturation
- Respiratory rate
- Flow
- Snoring
- Nocturnal posture
- Numeropassi.

Soundi is also able to record environmental parameters in which the individual lives, in particular it detects temperature, relative humidity, pressure, CO2 equivalent, Volatile Organic Compounds (VOC) produced by human breathing (for example CO) and by the environment (for example formaldehyde).

Soundi is a small (diameter of 60 m and height of 12 mm), lightweight, which is applied with a double-adhesive medical patch on the left hemithorax and can record the parameters over 24 hours for up to 15 consecutive days. Equipped with a rechargeable battery, it is capable of providing continuous measurement of the main physiological parameters.

Soundi is made up of the following components (Figure 1):

1. multi-sensor measuring unit (Figure 2)
2. ignition key

3. a double-adhesive medical plaster.

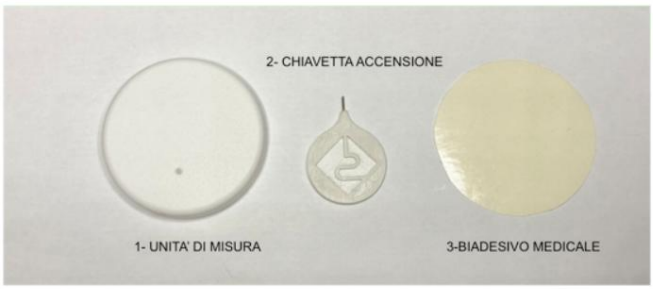

Figure 1. SOUNDI:1.Measurement unit;2.Ignition key;3.Double-sided medical tape.

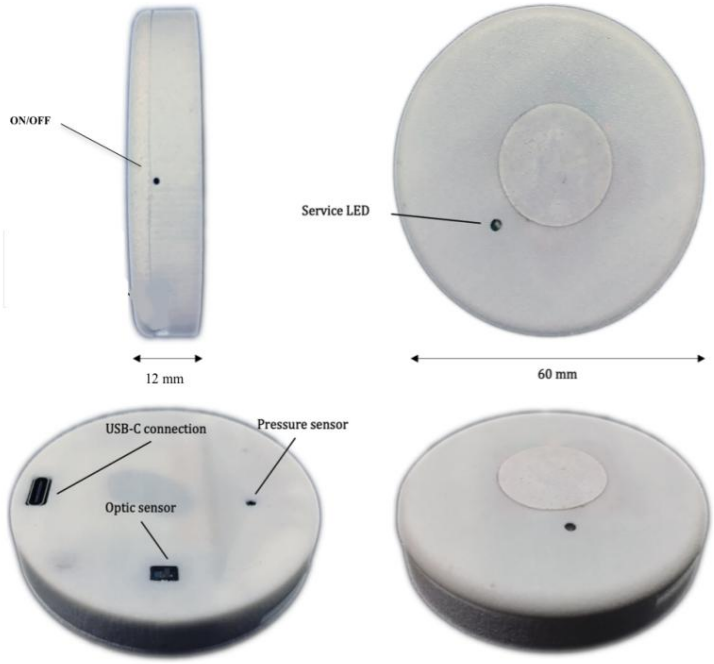

Figure2. Image of the SOUNDI multisensor measurement unit

Soundi is supplied with the following accessories: • 1-
channel ECG cable • USB
cable to allow charging of the rechargeable battery and connection to the PC • power supply

• softwarepcSOUNDIDOC.

The device will be used for full cardiorespiratory monitoring.

Being a wearable device also intended for non-hospitalized patients, SOUNDI is also intended to be used in a home environment.

The SOUNDI device records in internal memory the physiological data of the monitored person. The data is then downloaded, via USB cable, to the PC to be converted into a file with standard edf, the same format as the file returned by the standard polysomnography device.
SOUNDIDOC is the software for managing the SOUNDI device. It is a desktop software mainly composed of two sections/functionalities:

1. Examination programme
2. DownloadExam.

The recording file downloaded onto the experimenter's PC will then be analyzed with the Remlogic software already in use at the center for the analysis of polysomnographic signals.

Figure 3 shows the SOUNDI system diagram.

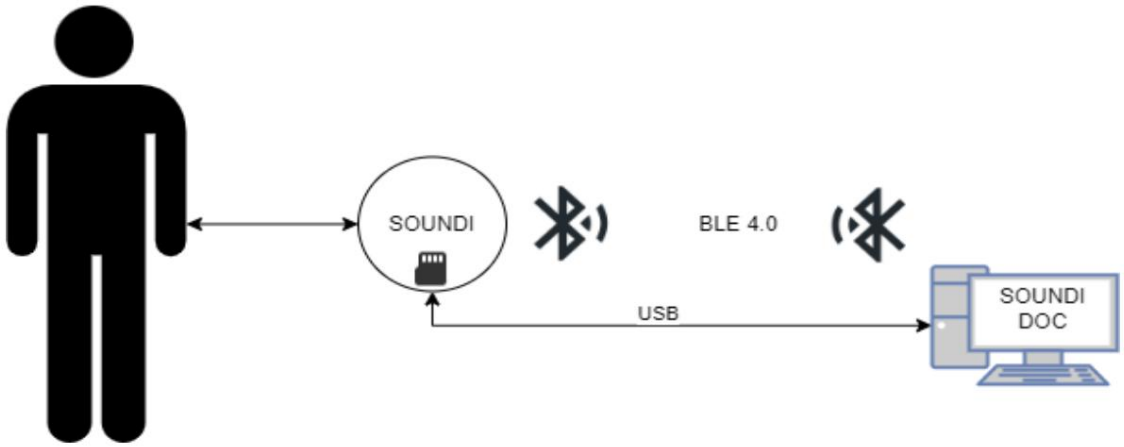

Figure3. SOUNDI system

Figure 4 shows the block diagram of the hardware part of the device.

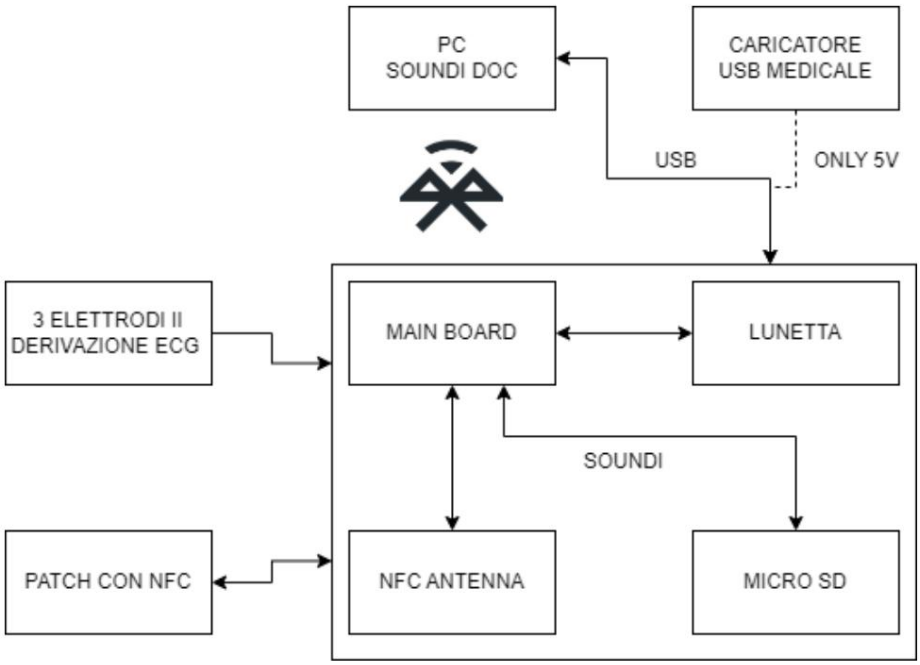

Figure4. Block diagram

The SOUNDI medical device will be provided to the Investigator together with the current version of the User manual.

The Experimenter will be required to carefully read the manual before using the device so as to be aware of important information such as safety warnings, dangers, precautions, calibration, use, contraindications, maintenance and storage etc...

The SOUNDI device does not require any particular maintenance if the following conditions are met:

- o Cleaning the device: The SOUND In device should never be immersed in any liquid. The unit should be cleaned with a neutral soap solution with a soft cloth. Never use a sharp tool to remove dirt, as it will scratch the surface.

- o Storage: The SOUNDI device must be stored in a dust-free environment, at a temperature between -25°C and +70°C and at a relative humidity of less than 93%.

The SOUNDIDOC software package will be installed by sponsor personnel on a PC indicated by the experimenter. A sufficient number of SOUNDI device samples to conduct the investigation clinic will be provided at the center.

3.1 Pre-clinical tests

The preclinical evaluation of the SOUNDI device concerned:

- verifying compliance of the SOUNDI medical device with the European Medical Device Directive using biocompatibility and electromagnetic compatibility testing
- electrical safety carried out at the MTICINTERCERT certified laboratory (annex 9 _SOUNDI_06_FT_01_Proveditipo).
- the verification and validation of the software reported in the Technical File, in the file 11_FT_01_VerificaRequisitiSW.

3.2 Tests on healthy volunteers

The results obtained so far on a population of healthy subjects are very encouraging (2-3-4-5).
Marzoratietal (2) demonstrated in a court of 20 healthy subjects that the use of Sound for non-invasive measurement of blood pressure produces results with accuracy comparable to that of a normal blood pressure monitor.

Furthermore, Marzoratietal (3) have proposed an innovative algorithm to improve the accuracy in the detection of signals recorded by Soundi during 24 hours.
Based on measurements taken in five male volunteers who had no previous signs of cardiovascular disease, Rossietal (4) suggested a robust deep learning model to improve the estimation of the variables extractable from the signals acquired by the Soundi.

Rossietal (5) used Soundi on a group of 20 healthy subjects to carry out acquisitions of physiological signals during sleep. Through an algorithm based on artificial intelligence they extracted the main parameters linked to respiratory disorders in sleep with an accuracy of approximately 97%.

3.3 Risks and benefits

The main risks associated with the use of the SOUNDI device by the subjects included in the clinical investigation are:

- Discomfort associated with positioning/removing the measurement unit using double-sided adhesive medical
- Allergic reaction to double-sided adhesive components

These risks will be minimized by the training of the personnel who will place and remove the device from the subject and by the exclusion from the study of subjects with a known allergy to the components of the double-sided adhesive.

The intrinsic risks most related to the design of the device (explosion/fire of the battery, electrocution linked to electrical leakage, emission of electromagnetic radiation, etc.) were evaluated and minimized in the design phase and verified through laboratory tests (electrical safety and electromagnetic compatibility).

The simultaneous collection of vital signs may allow for an early diagnosis of OSA in subjects suspected of having a sleep disorder.

Furthermore, the clinical validation of the SOUND I device on patients will allow the marketing of a small, handy and inexpensive device for the continuous monitoring of vital parameters, capable of collecting useful information for the early diagnosis or follow-up of breathing disorders in sleep.

4. Study design

This is a pre-marketing, single-center, prospective clinical investigation to compare the effectiveness and safety of the SOUNDI medical device compared to polysomnography in detecting parameters for the diagnosis of OSA in subjects suspected of having a sleep disorder.

The study expects to enroll 50 patients.

All patients belong to the Sleep Medicine Center of the Italian Auxological Institute IRCCS-
San Luca Hospital in Milan.

After signing the informed consent, the Sound device will be placed in all eligible subjects and at the same time as a traditional polysomnography device the activation of the devices for the acquisition of the parameters will be programmed so that it begins when the subject lies down.
The signals will be acquired for approximately 8 hours during a single night with both systems simultaneously and will then be calculated, via automatic analysis software, with subsequent manual correction by a doctor expert in sleep medicine, the indices used, according to international guidelines, for the diagnosis of breathing and sleep disorders.

No further follow-up is planned for subjects.

4.1 Comparison

As a comparison to evaluate the effectiveness of the SOUND In device in detecting the parameters for the diagnosis of OS, an Embletta polysomnography machine (Natus) will be used. This device is already in use at the clinical center and will be used according to clinical practice for polysomnography.

5. Objectives of the study

5.1 Primary objective

Evaluate the effectiveness of the SOUNDI system in detecting parameters necessary for the diagnosis of OSA compared to polysomnography (gold standard) in subjects with a suspected diagnosis of sleep disorders.

5.2 Secondary objectives

- Evaluate the safety and tolerability of the SOUNDI system
- Evaluate the level of patient satisfaction in using the SOUNDI system

6. Study population

6.1 Number of patients

The study involves the enrollment of 50 patients belonging to a single Italian centre: Sleep Medicine Center of the Italian Auxological Institute IRCCS - San Luca Hospital in Milan.

To document the patient selection bias, all reasons for non-participation in the study will be recorded on a specific form (Screening Log).

Patients will be identified by a unique alphanumeric code which will be assigned at the time of enrollment based on the center code and enrollment sequence (e.g. Aux-001).

6.2 Inclusion criteria

- Signature of informed consent
- Patients of both sexes, of any ethnicity
- Age between 20 and 70 years
- Prescription, from clinical practice, to carry out a polysomnography on suspicion of a sleep breathing disorder.

6.3 Exclusion criteria

- Women during pregnancy
- Insufficient cooperation/degree of collaboration in following the procedures required by the study
- Participation in another clinical study.
- Allergy to one of the materials in the device
- Pacemaker users.

7. Study procedures

All subjects enrolled in the study will undergo polysomnography (monitoring

nocturnal cardiorespiratory for the diagnosis of apnea in sleep) with traditional polysomnography (Embletta, Natus) according to normal clinical practice and at the same time as data acquisition with the Soundi system.

On the afternoon before the night of the evaluation, at the Sleep Medicine Service clinic, each object will be placed

- a traditional polysomnigraph, as prescribed
- theSoundiexperimentaldevice.

The patient will be instructed by the Investigator on the correct management of the devices.
During the visit, the following anthropometric data will be collected: age, BodyMassIndex (BMI), neck circumference and abdomen.
Furthermore, the Experimenter will program the devices to begin recording the parameters at the moment the subject expects to recharge and continue for at least 8 consecutive hours.
During the night, at the patient's home, the following parameters will be acquired with two systems: oro-nasal flow, thoracic and abdominal respirations, snoring, ECG, arterial oxygen saturation (SaO2), body position.

The following morning the subject will return to the clinics to return the two systems which will be detached by the medical staff. There, the subject will be asked to fill out a simple satisfaction questionnaire prepared for the study.

The signals acquired with both systems simultaneously will be processed by the software RemLogic, via automatic analysis software, with subsequent manual correction by a doctor expert in sleep medicine, the following indices used, according to international guidelines, for the diagnosis of respiratory and sleep disorders:

- ApneaHypopneaIndex(AHI)totalandsupine
- AHIcentral
- AHIobstructive
- OxygenDesaturationIndex(ODI)
- Average arterial oxygen saturation (SaO2).
- Minimum SaO2
- TimewithSaO2<90%
- Average heart rate
- Minimum heart rate
- Percentages of time spent in different body positions.

The anthropometric data (age, BMI, neck and abdomen circumference), the parameters deriving from the analysis of the acquisitions of the instrumental polysomnographic signal and the responses to the questionnaire provided by the subject will be reported in the electronic data collection form (CRF).

7.1 Compliance with procedures

All tests without artifacts invalidating the interpretation of one or more signals acquired for at least 4 hours of sleep will be considered valid.

7.2 Follow up

Unless particular problems are reported to the patient (adverse events or effects related to the use of the device in the study) which will be followed by specific assessments, a follow-up will not be necessary.

8. Duration of the study

The expected duration of enrollment of all subjects is approximately 6 months.

The expected duration of the study for the subject is a maximum of 24 hours.

The start of the study is defined by the date of signing the consent of the first patient and the end of the study by the last data analysis of the last patient.

The overall duration of the study will be 1 year.

8.1 Interruption and withdrawal of subjects from the clinical investigation

Each patient is free to withdraw from the study at any time or his participation may be interrupted by decision of the trial for safety, behavioral or reasons
administrative.

Reasons for discontinuing a patient's participation in the study may include:

- withdrawal of consent by the patient
- the change in the patient's clinical-functional conditions that do not allow participation

- lack of adherence to the procedures required by the study protocol on the part of the patient
- an adverse event (related or unrelated to the study device) which, in the opinion of the Principal Investigator, does not allow the continuation of the study itself.

If the study is interrupted for any of the reasons listed above, the measurements taken will not be considered in the statistical analysis.

The reasons for stopping the study will be recorded in CRF.

Unless particular problems are reported to the patient (adverse events or effects related to the use of the device in the study) which will be followed by specific assessments, a follow-up will not be necessary.

Patients excluded from the study and who cannot obtain the data required by the study protocol will be replaced to reach the required number.

8.2 Early closing or suspension of the study

The Promoter reserves the right to interrupt or suspend the study at any time for reasonable medical, safety, or administrative reasons.

The Sponsor will notify the Ethics Committee and the Principal Investigator of the decision to suspend or interrupt the study with the reasons. It will also provide the trial with specific instructions to inform the patients and indications on the procedures to be followed.

Circumstances that may justify interruption or suspension of the study:

- Determination of an unexpected, significant or unacceptable risk to participants
- Any serious or persistent case of non-compliance with the legislation
- Suspension or termination of Ethics Committee approval
- The feedback from the data is excessively different from that expected.

In the event of suspension, the study may be resumed once issues of safety, protocol compliance or data quality have been resolved to the satisfaction of the Sponsor and the Ethics Committee.

9. Evaluation of effectiveness

9.1 Primary endpoint

The primary endpoint of the study is the equivalence between the detection of parameters useful for the diagnosis of OSA using the SOUNDIV system and standard polysomnographic methods.

9.2 Secondary endpoint

The secondary endpoint of effectiveness of the clinical investigation is the evaluation of satisfaction with the use of SOUND I after the night of recording the parameters, through the patient's completion of a questionnaire prepared for the study.

10. Evaluation of the safety and vigilance of the medical device

The clinical investigation also aims to evaluate the safety and tolerability of the SOUNDI device by recording adverse events (secondary safety endpoint).

10.1 Recording of adverse events

The investigator is responsible for detecting and documenting in the patient's medical records all twenty that occur during the study, regardless of their severity and relationship to the device and their recording in the dedicated section of the CRF.
Adverse events (AEs) will be collected by signing informed consent at the end of the study procedures or until they are resolved or stabilized or until follow-up is no longer possible.

10.2 Definitions

Adverse Event (AE)

AE means any harmful clinical event, disease, unintentional injury or favorable clinical sign (including an abnormal laboratory result) that occurs in subjects, users or other persons as part of a clinical investigation, whether or not the event is related to the device under investigation

Note 1: This definition includes events related to the wearable wireless device (SOUNDI), polysomnography and any other procedures covered by the study protocol.

Note2: For users or other persons this is limited to events relating to the SOUNDI medical device.

Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any adverse event that has one of the following consequences:

- undeath;
- a serious worsening of the subject's health conditions which resulted in:

(i)a life-threatening illness or injury;
ii) a permanent damage to a body structure or function; iii) the need for hospital admission of the patient or its prolongation;

• fetal distress, fetal death or a malformation or physical or intellectual disability congenital

Note 1: A planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered an SAE.

Adverse Device Effect (ADE)

Adverse device effect (ADE) means an adverse event related to the use of the SOUNDI wearable wireless device.

Serious Adverse Device Effect (SADE)

Serious adverse device effect (SADE) means a serious adverse effect related to the use of the SOUNDI device.

Serious and Expected Adverse Device Effect (ASADE)

Anticipated serious adverse device effect (ASADE) means an adverse effect of the device already identified in the risk analysis.

Adverse Device Effect Serious and Expected (USADE)

Serious and unexpected adverse effect (USADE, unanticipated serious adverse device effect) means an adverse effect of the device not identified in the updated version of the risk analysis.

Device defect

Device defect means any deficiency in the identity, quality, durability, reliability, safety or performance of a device under investigation, including malfunction, errors in use or inadequacy of information provided by the manufacturer.

10.3 Classification of adverse events

The investigator and/or the Promoter will provide an assessment of the seriousness, severity of the event and the causal relationship with the device under study and will also record the duration, outcome and actions taken.

10.3.1 Evaluation of the severity of the event

The intensity of the AE will be characterized as follows:

O mild: transient discomfort or mild; no activity limitations; no intervention doctor/therapyrequired.

O moderate: from mild to moderate limitation of activity; some assistance may be necessary; none or minimal medical intervention/therapy required.

O severe: marked limitation of activity, usually requires some assistance; intervention doctor/therapy required, hospitalization possible.

10.3.2 Evaluation of the relationship to the medical device

The relationship between the use of the medical device and the occurrence of each adverse event must be evaluated and classified. During the evaluation of causality, the investigator must use clinical judgement, including all relevant factors such as time course and latency, known properties of the device and alternative explanations (e.g. medical history, concomitant diseases) and must Please consult relevant documents, such as instructions for use, clinical protocol or risk analysis report, as all foreseeable serious adverse events and potential risks are listed and assessed in these documents.

The Investigator and the Sponsor will separately evaluate and document the relationship between an adverse event and the experimental device or procedure, according to the following classification criteria:

- causal relationship: event is associated with the medical device or a procedure beyond any reasonable doubt
- probable: the relationship with the use of the experimental device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information can be obtained.
- possible: the relationship with the use of the device is weak, but cannot be completely ruled out. Alternative causes are possible (e.g. a concomitant disease, a treatment, another device, etc.). Cases in which the relationship cannot be established or sufficient information is not available should be classified as possible.
- unlikely: the relationship to the use of the device does not appear relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- not related: the relationship with the medical device or procedure can be excluded.
- unclassifiable: clinical event for which the information received is inadequate and/or contradictory and do not allow reasonable ascertainment.

10.3.3 Duration of the event

For both AE and SAE, the experimenter will record the start date and time and the end date and time of the event.

10.3.4 Outcome of the event

The clinical outcome of the AE or SAE will be recorded as follows:

- death
- resolved: the patient has returned to the condition prior to the event
- ongoing: the patient has not recovered and the symptoms continue
- resolved with consequences: the patient recovered from the event, but with clinical consequences.

10.3.5 Actions Undertaking

The treatment or action taken following the onset of an AE or SA will be recorded as follows: o

pharmacological treatment: e.g. inflammatory drugs
or non-pharmacological treatment: e.g. physiotherapy
or none: no treatment or action taken.

10.4 Predictable/expected adverse events and effects

Predictable potential adverse effects are exclusively linked to the use of double-sided medical adhesive and may include skin irritation, inflammation or other negative reactions.

More information on expected adverse effects and their management is available in the investigator's dossier.

10.5 Reporting of adverse events

The reporting of adverse events will comply with what is reported in the national reference legislation (DLvo37/2010), in the UNIENISO14155 technical standard and in the MEDDEV2.7/3 guidelines.

All adverse events (serious and non-serious) and medical device defects will be collected, carefully evaluated and documented in the medical record and in the CRF by the Principal Investigator.

The Investigator must immediately communicate to the Sponsor of the clinical study and in any case no more than 3 days after the event:

a) any SAAnd b)
any defect in a device which could have caused a serious adverse event in the absence of appropriate measures or intervention or if the circumstances had been less favourable;

c) any new conclusions relating to each event referred to in letters from a) to c).

The communication will be made using the appropriate form to be sent to:

dario.bovio@biocubica.it.

Furthermore, the Investigator will have to do what is necessary for the safety and well-being of the subject, until recovery or clinical stabilization.

If/when additional information is available, the Investigator will send a follow-up SAE in the same manner and timing as the initial SAE.

10.6 Notification to the Competent Authorities

Events will be reviewed by the Promoter to determine any reporting obligations. Reporting will take place within the time limits described in the applicable regulations.
In the case of USADE, the Sponsor or its delegate will report the results of the evaluation to the Competent Authority and the Principal Participating Investigator in accordance with the applicable regulations.
The following events must be reported by the Promoter to the Competent Authorities (Ministry of

Health):

- any serious adverse event (SAE) for which there is a causal relationship, even if only reasonably possible, with the device under investigation, the comparison product or the investigation procedure;
- any defect in a device that could have caused a serious adverse event in the absence of appropriate measures or intervention or if the circumstances had been less favourable;
- any new conclusion relating to each event referred to in the previous 2 points.

The Promoter must forward the events specified above to the Ministry of Health and the Ethics Committee with the following deadlines:

- immediately and no later than 2 days in the case of SAE with imminent danger to life, death;
- immediately and no later than 7 days in other cases SAE.

10.7 Consequences on risk analysis

If serious adverse effects occur, defects in the device which could have produced a serious adverse effect, the Promoter will evaluate, together with the Principal Investigator, whether to update the risk analysis and implement preventive or corrective actions.

11.Statistics

11.1 Effectiveness analysis

The continuous variables will be reported as the mean value and standard deviation or as the median and interquartile range in the case of non-normally distributed data. Therefore, for each parameter the agreement between the measurement carried out with the SOUNDI method and the one carried out with polysomnography (gold standard) will be evaluated using the Bland-Altman graph and the Concordance Correlation Coefficient (CCC) [6]. In short, this graph represents the value of the differences of the measurements carried out with two methods differ from their average[7]. The CCC varies between -1 and 1, values between 0.61 and 0.80 indicate substantial agreement while values greater than 0.81 almost perfect agreement according to the Landisand Koch scale [8].

Descriptive statistics will be used to evaluate the subject's satisfaction with using SOUNDI.

11.2 Securityanalysis

The safety analyzes will be carried out on all patients to whom the Sound device and the polysomnography device have been applied, regardless of the validity of the data collected.
In general, safety analyzes will be descriptive in nature. The frequency, severity, severity and causal relationship of adverse events will be tabulated.
Both the number and percentage of events and patients experiencing an event will be presented. Additionally, adverse events that led to study suspension and device defects reported.

Sample size.
A sample of 50 analyzable patients will guarantee a power of 90% in determining six values of the parameters detected with the SOUND I method are in agreement with those measured by polysomnography. The estimate was made considering: i) a z-head and a tail with a significance level of 5%; ii) a value of the CCCparia 0.60 below H0; iii) a value of the CCCparia 0.81 below H1 .Sample sizing was performed using PASS2021(PowerAnalysisandSampleSizeSoftware(2021).NCSS,LLC.Kaysville,Utah,USA).

11.3 Analysis set

Efficacy analyzes will be carried out on all patients who have completed the evaluation and whose data will be considered evaluable.

The following will be excluded from the statistical evaluation:

- all measurements lasting less than 4 ha cause the malfunction/ malposition of the device
- data obtained from measurements of patients excluded from the study.

The safety analyzes will be carried out on all patients to whom the Soundi device and the polysomnography device (safety population) have been applied, regardless of the validity of the data collected.

11.4 Systematic errors - bias

Any distortions will be prevented by deriving the indices used for the diagnosis of respiratory and sleep disorders from both methods (Polysomnigraph and Soundi) using the same automatic analysis software (RemLogic).

This will then be followed by manual correction by the operator expert in sleep medicine who is blind to: the identity of the subject under examination, the device with which the data are obtained and the outcome of the same parameters obtained with the comparison device.

To document the patient selection bias, all reasons for non-participation in the study will be recorded on a specific form (Screening Log) and considered in the subsequent statistical analysis.

Impairment of the results or interpretation of the results may be caused by malposition or malfunction of the device.

Specifically, a check of all the sensors when the device is started was included in the design phase. In the event of a malfunction of one of them, it is signaled by a flashing red LED. In this case the measurement can be repeated with another device supplied.

In the event of bad positioning, the measurement results may be compromised and the signal may be incomparable with that acquired by the polysomnography machine. In this last case the measurement is unusable for the study and the patient data will not be included in the effectiveness analysis.

How to minimize these biases is further detailed in the dossier for the investigator.

12.Medical device

It is planned to use 2 experimental devices (SOUNDI system, Biocubica) and 1 product

comparison (polysomnograph, Embletta, Natus).

The experimental SOUNDI devices will be supplied by the Promoter and will be identified by a batch number and a serial number.

The Investigator will be responsible for keeping track of the experimental devices from their delivery to the center until they are returned to the Sponsor at the end of the study.

The devices will be stored centrally in a secure location where only authorized personnel can access them and at a temperature between -25°C and +70°C and a relative humidity of less than 93%, as indicated by the manufacturer, until delivery to the patient.

If a device is lost or damaged, the Investigator will notify it
immediately to the Promoter.

The polysomnograph (Embletta, Natus) is already present at the center as it is used for clinical practice.

13. Ethical and regulatory aspects

13.1 Ethical management of the clinical investigation

The clinical investigation will be conducted in full compliance with the provisions of international legislation and its national transposition regarding clinical trials and the principles of the Helsinki Declaration with the aim of ensuring maximum protection of the subjects involved.
and in accordance with the Medical Devices Regulation (EU) 2017/745 and ISO14155:2020.
The Principal Investigator is responsible for the correct conduct of the clinical investigation in accordance with the provisions of this protocol, any future amendments, the other procedures envisaged by the Sponsor and the Good Clinic Practice (GCP).

13.2 Regulatory aspects

The clinical investigation is subject to review and approval by the Competent Authority and the Ethics Committee.

The written approval of the relevant Ethics Committee must be obtained before the start of any study-related procedure and must be documented through official communication to the Investigator.

If during the course of the trial, substantial changes to the study protocol become necessary, the Sponsor will submit an appropriate request for an amendment to the Ethics Committee and the Competent Authority. The authorization of the Ethics Committee and/or the Competent Authority will be necessary before their application.

13.3 Method of obtaining informed consent

Before recruitment, each subject will be informed of the nature and purpose of the clinical investigation, procedures, duration and risks and benefits.

The Investigator will inform the subject that participation in the study is completely voluntary and that in no way would refusal jeopardize future treatment or relationships with his doctor.
Furthermore, withdrawal from study is possible at any time without the need for any explanation.

An information sheet written in non-technical language and containing all the most important aspects of the study will be given to the subject and he will be given the opportunity to ask questions to clarify any doubts.
The patient must be given adequate time to reflect before signing the informed consent.

Before any study procedure, the subject will express his or her written consent in a specific document approved by the Ethics Committee.
The informed consent to the study, signed in the original, must be archived by the Investigator after having delivered a copy to the patient.
Any modification to the informed consent must be approved by the Ethics Committee.
The informed consent process will be documented in *the source documents.*

13.4 Participant confidentiality

It is the Investigator's responsibility to ensure that the confidentiality of all subjects participating in the study and all their medical information is maintained throughout the study.
The subjects will be identified by a unique alphanumeric code which will be used in CR and in any other study document. The identifying information will be kept separate in a secure location with access limited to study personnel.

The personnel authorized by the Promoter, or the Ethics Committee or the Regulatory Authority who will have direct access to the study documentation and medical records of the participating subjects for verification purposes, will be bound by the obligation of confidentiality.

13.5 Data processing

Written authorization for the same amount of personal data will be obtained from each subject before recruitment into the study in accordance with EU Regulation 2016/679 and the applicable privacy regulations. Failure to sign the consent to data processing will preclude the possibility of participating in the study.

13.6 Deviations from the clinical investigation plan

The investigator must not deviate from the protocol unless necessary to eliminate an immediate danger to patients in the study.

Any deviation from the clinical protocol will be grounds for exclusion of patients from the study.

Any deviations from the study protocol must be notified to the Sponsor, documented on the appropriate form and communicated to the Ethics Committee, if required by local regulations.

13.7 Study monitoring

Monitoring of the study will be carried out by the Promoter's staff.
Monitoring activities will be carried out periodically at the center, according to the monitoring plan.

The aim of the monitoring is to verify that the rights and well-being of patients are protected, that the study data reported is accurate, complete and verifiable on the basis of the original data and that

the study is conducted in accordance with the protocol, the study procedures, the ICH-GC and the requirements regulatory.

The Investigator must give the monitors direct access to the original study documents (provided that the confidentiality of the subjects is protected) and provide adequate space and time to carry out monitoring.

13.8 AuditedInspections

To ensure compliance with the protocol, study procedures, ICH-GCP and all applicable regulatory requirements, the Sponsor may conduct an audit at the participating centre.

The Regulatory Authority may carry out an inspection of the study. The Principal Investigator must promptly inform the Sponsor if an inspection by the Regulatory Authority has been scheduled at his site.

Such audits/inspections may be carried out at any time during or after the completion of the study.

In the event of an audit, the Principal Investigator and the Institution agree to allow the auditor/inspector direct access to all relevant documents and to ensure that time is available to discuss the results of the audit/inspection and any findings in the presence of the Sponsor, if required or necessary.

14. Ownership and Data Publication Policy

The Promoter is the exclusive owner of all information arising from the clinical investigation, including resulting data, results, discoveries, inventions, know-how and similar.

The results deriving from the clinical investigation may be the subject of joint publication in the name of the Promoter and the Principal Investigator. These results may be published in national and international journals or presented at similar congresses, conferences, seminars.

15. Data management and storage

15.1 Sourcedocuments

The Investigator must keep adequate and accurate documentation to allow the execution of the study to be fully documented and to subsequently verify the clinical investigation data.

Source documents are generally the documents on which information or data were recorded for the first time and may include patient medical records, questionnaires, as well as diagnostic test results.

The Investigator is responsible for ensuring the reliability, accuracy, completeness, originality and readability of the data reported in the source documents.
If requested, the Investigator will provide the Sponsor and the Regulatory Authority with direct access to the source documents.

15.2 CaseReportForm

An electronic Case Report Form (eCRF) will be used in this study to meet regulatory requirements, ensuring system validation, traceability and audit trail, preservation, protection, reproducibility and recovery of experimental data, control of access to information and electronic signature.

Center staff will receive training in accessing the eCRF and entering data. Only designated and trained staff will receive personal access to the eCRF.
The data reported in the eCRF must be consistent with the source documents. The eCRF will never be considered as a source document for the study.

15.3 Document storage

The Investigator will have to keep the documentation relating to this clinical investigation for at least 10 years from the conclusion or for a longer period, if required by the applicable legislation.

The documentation of the clinical investigation must be kept in a safe place which, if necessary, allows for timely recovery.

If the Investigator wishes to transfer the clinical investigation documents to another location, he/she must inform the Sponsor in advance.

16. Insurance

The insurance coverage of the risks relating to the study is guaranteed by an insurance policy stipulated ad hoc by the Promoter pursuant to the Ministerial Decree of 14 July 2009. The insurance coverage will be covered by the Promoter.

17. Steering Committee

This study will have a data monitoring steering committee which will include representatives of the Promoter and the Principal Investigator. All study endpoints, objectives and safety data will be reviewed regularly by the steering committee which will meet periodically in order to carry out a timely analysis of the tests progressively carried out. The steering committee will have the possibility to decide to suspend the investigation in case of security problems and may

recommend changes to the investigation, including discontinuation, if there is a change in the
risk/benefit ratio for participating subjects.

18.Bibliography

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