Observational study employing a Medical Device

Clinical Study Protocol

Defining the role of a fertility bracelet for early recognition and monitoring of COVID-19 in Liechtenstein: an observational study (COVI-GAPP)

SHORT TITLE: A fertility tracker for recognition of COVID-19

Study Type:	Clinical trial with Medical Device (MD)
Study Categorisation:	Risk category according to HRA (A)
Study Registration:	Intended registry: International Standard Randomised Controlled Trial Number (ISRCTN) registry The study is conducted in Liechtenstein
Study Identifier:	N/A
Sponsor-Investigator	Prof.Dr.med. Lorenz Risch, PhD MPH MHA, labormedizinisches zentrum Dr. Risch, Wuhrstrasse 14, 9490 Vaduz, Liechtenstein, email lorenz.risch@risch.ch; Phone +41 58 523 3000; Mobile Phone +41 79 642 71 70
Investigational Product:	AVA bracelet
Protocol Version and Date:	**(SPIRIT #3)** Version 1.1 from 6.4.2020 replaces version 1.0 from 5.4.2020

PROTOCOL SIGNATURE FORM

Study Title	Defining the role of a fertility bracelet for early recognition and monitoring of COVID-19 in Liechtenstein (COVI-GAPP)
Study ID	NA

The Sponsor-Investigator has approved the protocol version 1.2 (dated 09/04/2020) and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements in Liechtenstein.

Sponsor-Investigator:

Name: Prof. Dr.med. Lorenz Risch, PhD MPH MHA

Date: Vaduz, 09/04/2020 Signature:

TABLE OF CONTENTS

GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR/DSUR	*Annual Safety Repot / Development Safety Report*
BASEC	*Business Administration System for Ethical Committees*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
SAE	*Serious Adverse Event*

1 STUDY SYNOPSIS

Provide a structured synopsis containing all important information, preferably in tabular view:

Sponsor-Investigator	Prof.Dr.med. Lorenz Risch, PhD MPH MHA, labormedizinisches zentrum Dr. Risch, Wuhrstrasse 14, 9490 Vaduz, Liechtenstein, email lorenz.risch@risch.ch; Phone +41 58 523 3000; Mobile Phone +41 79 642 71 70
Study Title:	Defining the role of a fertility bracelet for early recognition and monitoring of COVID-19 in Liechtenstein (COVI-GAPP)
Short Title / Study ID:	A fertility tracker for recognition of COVID-19
Protocol Version and Date:	Version 1.1 (dated 06/04/2020)
Trial registration:	Intended registry: International Standard Randomised Controlled Trial Number (ISRCTN) registry
Study category and Rationale	Category A according to ClinO Art 20. The fertility tracker has a CE-mark, in the intended use, it is stated by means of the fertility tracker, "parameters are collected to improve the quality of the prediction and to provide general information on health and wellness". The fertility tracker employs non-invasive nightly monitoring of temperature, breath rate, pulse rate, and movements during sleep.
Clinical Phase:	Phase of development an algorithm for early recognition and monitoring of COVID-19
Background and Rationale:	Nightly monitoring of temperature, breath rate, pulse rate, movement by means of the AVA bracelet originally intended for cycle tracking in women. Whereas temperature is a sign of inflammation, breath rate can be regarded in function of affected airways, heart rate variability can be regarded as a marker of stress. All these parameters are expected to be altered in COVID-19 infection. From the measurements, algorithms for early prediction of COVID-19 will be developed. Risk for participants is low (non-invasive monitoring and blood sampling) the expected benefit is large, as algorithms trained on the obtained data recordings are expected to recognize COVID-19 earlier than clinical symptoms. The latter would allow for earlier isolation and stratification as well as monitoring of COVID-19 affected patients preventing further spread and allowing for appropriate healthcare.
Objective(s):	Primary objective A.) To see whether the AVA bracelet is capable to reliably identify persons with COVID19 infection early, before they get clinically. This would allow for early isolation and testing of contact persons, thereby preventing extensive spreading of the Virus. When reversing the process of lockdown of social and economic systems or during a so called second wave of the COVID-19 pandemic, the AVA bracelet could serve as a sensitive tool to observe relapsing infection rates. Secondary objective a.) To see whether the AVA bracelet would serve to recognize severe cases early allowing for risk stratification, early treatment and allocation of adequate care to patients with COVID19. b.) To obtain a seroprevalence of COVID19 affected cases in the population of Liechtenstein.
Outcome(s):	Occurrence of COVID-19 infection, Severity of COVID-19 infection.
Study design:	Observational population-based cohort study employing a CE-marked medical device.
Inclusion / Exclusion criteria:	Inclusion criteria: participant of the GAPP study. Exclusion criteria: Inability to provide informed consent.

Measurements and procedures:	Serological status for SARS-CoV2-antibodies will be determined at the beginning and the end of the study. The participants will be asked to answer a questionnaire about recent infections at study entry, undergo baseline serological testing. Study participants will be monitored overnight with the employed fertility tracker. We will collect information about clinically documented infections in all participants during follow-up, and provide serology at the end of the study. The study and participant recruitment will be performed within the study organization of the GAPP study, an ongoing prospective follow-up study. Baseline characteristics and other clinical information will be used from the GAPP study database.
Study Product / Intervention:	The fertility tracker automatically saves physiological information every 10 seconds throughout the night, requiring at least 4 hours of relatively uninterrupted sleep each night to stabilize parameter measurements. The wrist-worn bracelet acts as a data logger, recording and storing user's physiological sensors signals as raw datasets throughout the night. Currently, the user synchronizes the bracelet to the mobile phone application the following morning. It is planned that participants wear the fertility tracker overnight during the study period.
Control Intervention (if applicable):	Not applicable
Number of Participants with Rationale:	Participants of the ongoing population based GAPP cohort study conducted in Liechtenstein will be included (n=2170; study approved by KEK ZH Stv.-Nr. 66/09). These will receive the AVA bracelet for free. We eventually might attain a sample size of 5000 participant by onboarding additional participants. For this second phase, we will seek separate ethical approval.
Study Duration:	The course of the pandemic can currently not be predicted and is critical for the duration of the study. WE anticipate a duration of nearly 3 years.
Study Schedule:	Participants should be included as fast as possible, in order to catch as many endpoints during the COVID-19 pandemic. Planned 12/04/2020 of First-Participant-In Planned 31/12/2021 of Last-Participant-Out Depending on the course of the pandemic, the study can be terminated earlier.
Investigator(s):	Prof. Dr.med. David Conen, McMaster University, Hamilton (conend@mcmaster.ca), Dr.med. Martin Risch, Private University Liechtenstein, Triesen (martin.risch@risch.ch), Dr. Stefanie Aeschbacher, Universität Basel (stefanie.aeschbacher@usb.ch) , Kirsten Grossmann MSc, Private University Liechtenstein (kirsten.grossmann@risch.ch) , Dr.Maureen Cronin, MD PhD, Chief medical Officer AVA for women (maureen.cronin@avawomen.com)
Study Centre(s):	Single-centre study. GAPP-Studie c/o labormedizinisches zentrum Dr. Risch, Wuhrstrasse 14, 9490 Vaduz
Statistical Considerations:	Prediction of the development of COVID-19 infection will be modeled on the base of nightly monitoring of temperature, breath rate, pulse rate and movements by means of machine learning methods. Algorithms will be trained by comparing monitoring data of COVID-19 diseased and non-diseased individuals by a big data approach employing machine learning. The project partner AVA for women has already used such an approach to predict fertile days in women with a higher than 90% accuracy. The seroprevalence of COVID-19 will be presented as count (percentage) and we will standardize these numbers to the general population of the Principality of Liechtenstein. The sample size is given by the sample size included in the GAPP study.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ISO EN 14155 as well as all national legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

The WHO has declared the current coronavirus (COVID-19) outbreak to be a pandemic and therefore a Public Health Emergency of International Concern. It is crucial to rapidly gain a better understanding of the newly identified virus, especially in relation to potential clinical and public health measures that can be immediately used to improve patients' health and/or contain the spread of COVID-19. In particular, development of early and reliable detection of COVID-19 carriers and symptomatic individuals suspected of COVID-19 infection is needed. We are proposing to test the utility of a CE marked, marketed medical device that can continually track changes in physiological parameters in detecting early signs of a COVID-19 infection. In particular, the device's ability to register increases in physiological parameters associated with fever (e.g., resting pulse rate, breathing rate, and skin temperature) could render it an ideal candidate during screening point of care (POC), both for potential COVID-19 infections in asymptomatic, exposed users and asymptomatic users unsure of their exposure status.

This proposal aims to optimize efficient patient management, public health preparedness, and response to current and future outbreaks of COVID-19 infection; leveraging an existing medical-grade technology may allow clinicians and researchers to more rapidly evaluate patients' wellbeing, thereby enabling faster case detection. Additionally, healthcare professionals and researchers may benefit from using this device to monitor patients with confirmed cases of COVID-19. Synced to a central app via Bluetooth, the device measures physiological parameters continuously while the user sleeps; its design inherently alleviates the need for healthcare professionals to take the patient's temperature, breathing rate and pulse rate. We believe that, by reducing the in-person contact between patients and their care team, the AVA bracelet could also lower potential transmission rates among nurses, doctors, and/or researchers studying COVID-19's development [1]. This medical device is able to measure skin temperature, pulse rate, and breathing rate simultaneously, and thus may prove helpful in combatting a public health crisis through its potential to rapidly detect novel COVID-19 cases and enable remote surveillance of .

Studies on COVID-19, including one conducted by the World Health Organization's Joint Mission with China, reported that fever (87.9% of cases), dry cough (67.7% of cases), and shortness of breath (18.6% of cases) are the most frequent presenting symptoms [2-4]. Close to half (44%) of infected Chinese patients reported to treatment centers with fever as their first presenting symptom [2]. Our proposal is to test the utility of a CE-marked, marketed, wrist-worn medical device (AVA bracelet) that tracks breathing rate, pulse rate, skin temperature, heart rate variability and skin perfusion to generate data on potential early signs of COVID-19 in users at home [1]. While not specific to COVID-19, during a fever, body temperature and pulse rate increase [5-7] and shortness of breath can be measured by increased breathing rate. In a person with a known COVID-19 exposure, these signs could be indicative of an infection and helping with triaging for medical care [5]. A recent paper examining the validity of wrist temperatures compared to forehead and tympanic temperatures among Chinese COVID-19 patients found less overall variability in wrist temperatures [5].

The authors assessed individuals' temperatures upon their arrival to the medical clinic, demonstrating the importance of reliable knowledge about patients' vital signs at time of triage. Our research vision takes this finding a step further; what if, for example, healthcare professionals and doctors had patient-provided access to a record of their pulse rate, temperature, and breathing rate over the past week or month, measured by a regulatory-approved medical device? Could this help expedite triaging and lead to more data-informed decisions around identifying potential cases for reference to a medical setting where they could receive official diagnosis and treatment? Alternatively, a study could also probe the utility of the AVA bracelet as a remote continuous measurement device, worn during sleep to monitor for potential infection in exposed or high-risk populations in self-isolation at home. These are just some of the initial research questions we have identified as potential applications for the AVA bracelet; collaborative scientific inquiry and further proposals are welcome, as we consider how to best enlist our medical device in the management of COVID-19.

The AVA bracelet automatically saves physiological information every 10 seconds throughout the

night, requiring at least 4 hours of relatively uninterrupted sleep each night to stabilize parameter measurements [1]. The wrist-worn bracelet acts as a data logger, recording and storing user's physiological sensors signals as raw datasets throughout the night. Currently, the user synchronizes the bracelet to the mobile application the following morning. The mobile app reads the raw datasets via Bluetooth Low Energy (BLE) and transfers them to the backend. After computation and preprocessing of the physiological parameters based on the bracelet's recordings, an algorithm obtains pre-processed physiological parameters changes that are transferred back to the mobile app and displayed to the user.

Rapid action is required current the ongoing pandemic. The GAPP study is ideally suited to function as a platform to test the AVA device in a population with a high exposure to COVID-19 viruses and a high prevalence of testing [8]. GAPP is ongoing and therefore this project can be launched in a very short time period.

The intervention of observing study participants with the AVA bracelet, a medical device, together with planned blood drawings entails only minimal risks and burdens and, according to ClinO Art 20. can be categorized as category A.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

We hypothesize that by monitoring temperature, breath rate, pulse rate, and movements, it is possible to predict the occurrence of COVID-19 infection. We hypothesize, that temperature will increase due to inflammation/infection, breath rate will increase due to subclinical affection of lungs by COVID-19, heart rate variability as an indicator of stress will be diminished both as a consequence of infection also reflecting severity of infection. Further, we anticipate that registration of characteristic movements also allows to recognize cough. Fever, breathing problems, and cough are all clinical cornerstones in the diagnosis of COVID-19 infection. WE further hypothesize that the alterations in measured parameters antecede the occurrence of clinical symptoms.

Primary objective

A.) To see whether the AVA bracelet is capable to reliably identify persons with COVID19 infection early, before they get clinically. This would allow for early isolation and testing of contact persons, thereby preventing extensive spreading of the Virus. When reversing the process of lockdown of social and economic systems or during a so called second wave of the COVID-19 pandemic, the AVA bracelet could serve as a sensitive tool to observe relapsing infection rates.

Secondary objective

a.) To see whether the AVA bracelet would serve to recognize severe cases early allowing for risk stratification, early treatment and allocation of adequate care to patients with COVID19.

b.) To obtain a seroprevalence of COVID19 affected cases in the population of Liechtenstein.

3.2 Primary and secondary endpoints

Primary endpoint is the occurrence of COVID-19 infection, as assessed by clinical signs, serology and/or RT-PCR testing Date of occurrence, clinical symptoms and laboratory results, how infection was diagnosed is collected to describe the primary endpoint.The endpoints will be collected by periodic reports obtained on questioning the study participants. Participants and the

treating healthcare institutions will be contacted to obtain respective information.

As a secondary endpoint severity of COVID-19 infection will be assessed. Participants and the treating healthcare institutions will be contacted to obtain respective information. The following parameters will be collected: Hospitalization needed within 30 days of COVID-19 diagnosis (including timing)? ICU admission within 30 days of COVID-19 diagnosis (including timing)? Use of mechanical ventilation within 30 days of COVID-19 diagnosis (including timing)? Participant reported health status after COVID-19 diagnosis (including timing)? COVID-19 related mortality? Quantiative RT-PCR results (viral loads) and quantitative Immunoassay results of COVID-19 specific laboratory markers? Results of other respiratory pathogens in COVID-19 negative participants available? Further healthcare contact of patients tested negative for COVID-19?

3.3 Study design

This is a prospective cohort study employing a medical device (the AVA bracelet) as a monitoring tool. The GAPP study is already running since June 2010 and, after the baseline exam has been conducting follow-up visits every 3-5 years. Currently, the second follow-up period is being conducted. Due to the COVID-19 pandemic, the regular follow-up has been suspended. The study collective is very well described.

3.4. Study intervention

As soon as possible after ethical approval (within 1 week), study participants are offered an AVA bracelet. They will be asked to wear the AVA bracelet during the night until the study will be terminated. Temperature, breath rate, pulse rate and movings are recorded. Information on COVID-19 specific health status is collected at study start and symptomatic patients will be diagnosed for COVID-19, as recommended by national guidelines. At the end of the study blood will be drawn for serological analysis of anti-SARS-CoV2 antibodies.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

The GAPP study is a population based national cohort including 2170 study participants aged 25 to 41 at baseline. This number relates to about 32% of the whole population. Since the study was started to enrol participants from 2010, the study participants are now 35 to 51 years old [8].

The GAPP study (study homepage www.blutdruck.li) is an ongoing national cohort study done in the principality of Liechtenstein with a cooperation from the University Basel, Private University Liechtenstein, McMaster University Hamilton, and the labormedizinische zentrum Dr. Risch in Liechtenstein. Between 2010 and 2014 all inhabitants of Liechtenstein aged 25-41 years old were asked to participate in the study, and 2170 could be enrolled. The aim of the study is to identify the determinants for the development of hypertension and other cardiovascular risk factors. A large number of baseline characteristics and health information was collected in all participants. Several blood, urinary and genetic markers were collected. By ongoing follow-up we collect information on changes in health information and other characteristics are collected. Currently the second follow-up cycle is ongoing.

GAPP is very well established scientifically. More than 30 scientific manuscripts have been published so far, some of them in major international journals [8-41]. Therefore, the quality of the data collection is well recognized. In summary, the GAPP study provides a unique platform that would allow rapid evaluation of a promising medical device that has the potential to alleviate the suffering through the current COVID-19 pandemic.

The choice of the study population is ideal, as the organization is already in place, the study participants are already enrolled. With such a setting, the important and urgent study question can be addressed immediately.

Inclusion criteria:

- Participant of the GAPP study
- Providing consent to the present study

Exclusion criteria:

- Inability to provide informed consent

It is not planned to include vulnerable participants into the study.

After a first phase of including participants from the GAPP-study, we eventually might attain a sample size of 5000 participant by onboarding additional participants. For this second phase, we will seek separate ethical approval.

4.2 Recruitment, screening and informed consent procedure

The GAPP study department harbors 6 collaborators performing the study visits of the study participants onsite at the GAPP study facility (Wuhrstrasse 14) in Vaduz, Liechtenstein. The department has 4 consultation rooms and 3 office rooms. The proximity to the consultation rooms of the labormedizinische zentrum Dr. Risch allows for rapid scale-up of activities. Since the study is up and running and has a very good reputation within the study cohort and the whole country, starting the evaluation of the AVA watch in the COVID-19 pandemic is readily available. According to the world rankings, Liechtenstein is one of the countries with the highest incidences of COVID-19 (1582 cases per million persons, first case 2. March 2020), but on the other hand also has one of the highest testing frequencies for SARS-CoV-2 (2.75 percent of the whole population tested by March 29th 2020). Proximity of laboratory and study center, nationwide coverage of laboratory analysis, running national cohort, international cooperation, government support are all success factors for the envisaged project.
Participants already provided informed consent for participation in the GAPP study. As the study organization has an up-to-date address database, study participants are contacted by letter, email or telephonically. They will receive the participant information and called in into the study center upon stating their will to participate, where the AVA bracelet will be distributed. They will be offered opportunity to ask questions before providing informed consent by telephone, email, or at the occasion of device distribution, namely before the AVA bracelet will be distributed.
The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. The time between obtaining the study information and starting the distribution of AVA bracelets is at least 1 day.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure. The consent form will be signed and dated by the investigator or his designee at the same time as the participant sign. A copy of the signed informed consent will be given to the study participant, if requested. The consent form will be retained as

part of the study records. The informed consent process is documented in the participant database and any discrepancy to the process described in the protocol must be explained. No compensation is offered to study participants. They can keep the AVA bracelet after terminating the study.

4.3 Study procedures

The study starts as soon as ethical approval is obtained, preferably in calender week 15 2020. The rapid study start is intended in order to capture as many COVID-19 cases as possible. The study will be ongoing until the COVID-19 pandemic is eradicated, a vaccine or curative therapy has become available, or if the Investigators come to the decision to terminate the study. Due to the unclear course of the pandemic, it is not possible to provide an exact date of study duration. We anticipate that the study should be terminated on 31st December 2021 the latest.

First, study participants will be contacted by mail with the study information and the informed onsent sheet. After providing informed consent (in case of questions, the study staff can be contacted for questions at the contact information already known to the study participants) the study participants, baseline clinical information is provided in a study questionnaire. The study participants will then obtain an AVA bracelet, either by post or in the study center. Informed consent will be discussed personally on the occasion of a personal contact due to provision of the AVA bracelet or presentation for blood sampling.

While the AVA Bracelet was designed to measure physiological changes across the menstrual cycle. its sensors work across genders and age groups. We foresee that the device is capable of providing relevant insights for men and women alike during this pandemic, including among those populations most at risk of developing serious complications from COVID-19, including: people over the age of 60 and people with underlying conditions like hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer. The AVA bracelet automatically saves physiological information every 10 seconds throughout the night, requiring at least 4 hours of relatively uninterrupted sleep each night to stabilize parameter measurements. The wrist-worn bracelet acts as a data logger, recording and storing user's physiological sensors signals as raw datasets throughout the night. Currently, the user synchronizes the bracelet to the mobile phone application the following morning. The mobile app reads the raw datasets via Bluetooth Low Energy (BLE) and transfers them to the backend. After computation and preprocessing of the physiological parameters based on the bracelet's recordings, an algorithm obtains pre-processed physiological parameters changes that are transferred back to the mobile app and displayed to the user.

Designed to combine multiparameter measurement into one device, the AVA bracelet could leverage its real-time monitoring system to fight a novel health threat. We believe the simple but continuous monitoring of temperature, breathing and pulse rates could provide guidance around if and when people should seek medical care. Furthermore, the recorded physiological data could improve our knowledge of COVID-19's early signs and overall trajectory.

Figure 1: Illustration of the AVA bracelet

The AVA bracelet is intended to monitor a woman's fertility by measuring and recording physiological parameters (body temperature, resting pulse, heart rate variability, and breathing rate) as an aid in ovulation prediction to aid in conception (not to be used for contraception). Its intended use is to measure and display physiological parameters to aid women in ovulation prediction to facilitate conception. Additionally, parameters are collected to improve the quality of the prediction and to provide general information on health and wellness. The device is CE-marked (certificate see Appendix 2).

We will obtain COVID-19 specific information at baseline and study participants will asked to provide COVID-19 specific symptoms during the study duration. In case of the occurrence of COVID-19 specific symptoms, participants will be asked to undergo RT-PCR and serological testing according to national guidelines by utilizing routine healthcare. We will conduct periodic surveys (e.g. every 14 days) requesting the study participants to provide information regarding their health status. Study participants will be asked to provide a blood sample at the end of the study for serological studies of COVID-19 (investigation of SARS-CoV2-antibodies). The flowchart of the participant journey within the present investigation is summarized in Figure 2. A summary of the study visits is provided in Appendix 1.

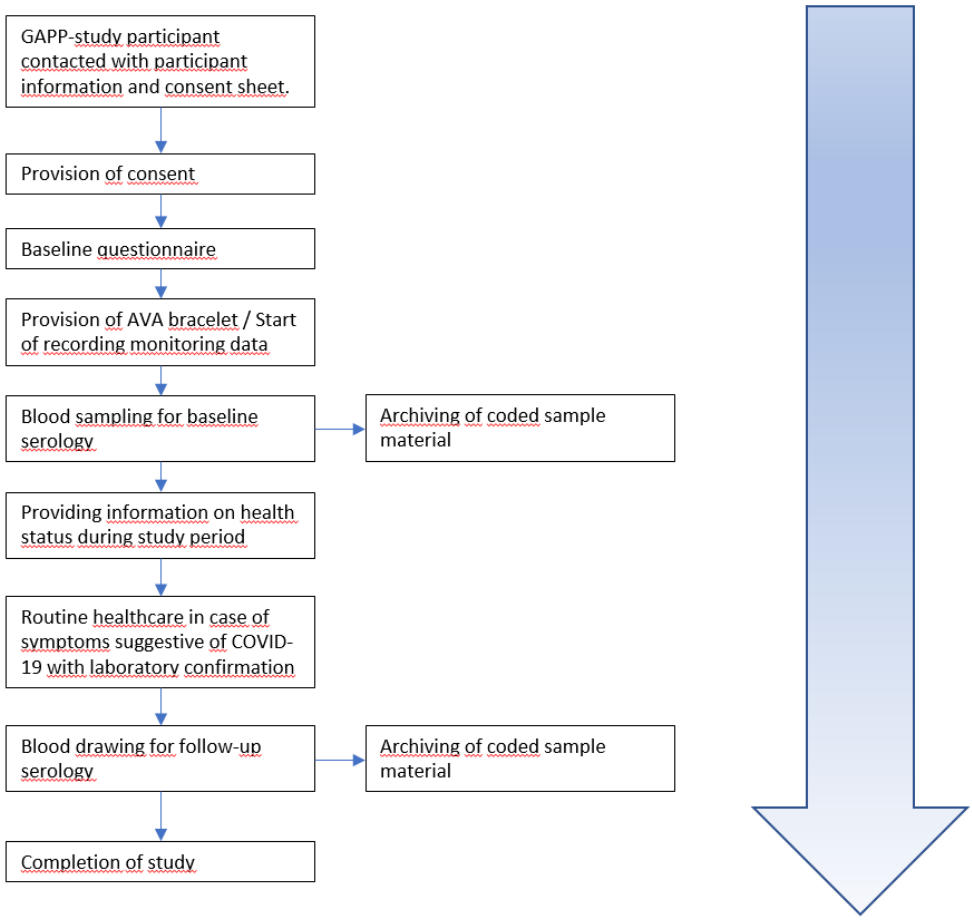

Figure 2: Journey of study participants.

4.4 Withdrawal and discontinuation

If a study participants withdraw from the study, recording of AVA bracelet data will be stopped. Data is stored in a coded manner and the decoding information for concerned individuals will be

irreversibly destroyed.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

Together with Dr. Maureen Cronin and her team, data will be analysed by machine learning procedures. By training models, we aim to identify characteristic patterns of the recorded physiological parameters in order to predict the occurrence of COVID-19 infection. We intend to employ software packages such as R or SAS for modeling.

The present study is an (non-funded) associated partner to the COVID-RED consortium, which applied for a Horizon 2020 grant (see grant application as a document accompanying the present study protocol. Depending on the realization of that project, we will contribute data to that joint project.

The sample size of 2170 is given by the already existing study population. At a later stage, we may think of enlarging the sample size to 5000 by offering non-GAPP participants a participation in the study. However, this would be subject of a protocol amendment.

5.2. Handling of missing data and drop-outs

Should participants not regularly record data with the AVA bracelet, cases will be excluded from further analysis.

6 REGULATORY ASPECTS AND SAFETY

Device deficiencies and all adverse events (AE) including all serious adverse events (SAE) are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire study period, i.e. from patient's informed consent until the last protocol-specific procedure. As only non-invasive monitoring is performed during the study period, no safety follow-up period is needed. Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or study procedure [ISO 14155, 6.4.1.].

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ISO 14155, the HRA as well as other locally relevant legal and regulatory requirements.

6.1.1 Foreseeable adverse events and anticipated adverse device effects

Due to the non-invasive nature of the monitoring, the likelihood for foreseeable adverse events and the occurrence of anticipated adverse device effects is low. The most likely reason for an anticipated adverse device effect is a dysfunctional device making registration of monitoring data impossible.

6.1.2 Definition and Assessment of safety related events

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2].

This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons this is restricted to events related to the investigational medical device.

Adverse Device Effect (ADE)
Adverse event related to the use of an investigational medical device [ISO 14155: 3.1].
This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Event (SAE) [European regulation on medical devices 2017/745, art. 58].
Any adverse event that led to any of the following:
(a) death,
(b) serious deterioration in the health of the subject that resulted in any of the following:
(i) life-threatening illness or injury,
(ii) permanent impairment of a body structure or a body function,
(iii) hospitalisation or prolongation of patient hospitalisation,
(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
(v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are submitted to the EC via BASEC within 7 days. A planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

Device deficiency
Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling [ISO 14155: 3.15].

Health hazards that require measures
Findings in the trial that may affect the safety of study participants and, which require preventive or corrective measures intended to protect the health and safety of study participants SAE [ClinO Art. 37].

Causal Relationship of SAE [MEDDEV 2.7/3 revision 3, May 2015].
A causal relationship towards the medical device or study procedure should be rated as follows:
- Not related: The relationship to the device or procedures can be excluded.
- Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause.
- Causal relationship: The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

Device deficiencies that might have led to an SAE are always related to the medical device.

6.1.3 Reporting of Safety related events

Reporting to Sponsor-Investigator:

All SAEs, device deficiencies and health hazards that require measures are reported to the Sponsor-Investigator within 24 hours upon becoming aware of the event. Device deficiencies are assessed regarding their potential to lead to an SAE.

Pregnancies

Depending of the study, reporting of pregnancies is not necessary.

Reporting to Authorities:

In Category A studies, the sponsor is subject to the notification requirements specified in Art. 15 of the MedDO of 17 October 2011 (SR 812.213).

It is the Investigator's responsibility to report to the Ethics Committee via BASEC device deficiencies that could have led to serious adverse events if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate within 7 days [ClinO Art. 42].

Health hazards that require measures are reported to the Ethics Committee via BASEC within 2 days [ClinO Art. 37].

Periodic safety reporting:

A yearly safety update-report is submitted by the Investigator to the Ethics Committee via BASEC.

A report is submitted to the Amt für Gesundheit of the Principality of Liechtenstein by the Sponsor-Investigator, as defined in Art. 15a,b of the MedDO of 17 October 2011 (SR 812.213).

6.3 (Periodic) safety reporting

An annual safety report (ASR/DSUR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs).

6.4 Radiation

Use of the device is not subject to radiation.

6.5 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).

A list of substantial changes is also available on www.swissethics.ch.

A list of all non-substantial amendements will be submitted once a year to the competent EC together with the ASR.

6.7 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely before 31st December 2021,

- When the COVID-19 pandemic is eradicated,
- A vaccine or curative therapy has become available

- Insufficient compliance of the study participants to the study protocol
- Due to ethical concerns,
- Due to insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice occure that make the continuation of the study unwise
- Early evidence of harm or benefit of the observations with the AVA bracelet

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

The www.swissethics.ch template concerning the notification of completion, discontinuation or interruption of the clinical trial is used for this purpose.

Health-related data at the end of the study are introduced into the GAPP study database.

6.8 Insurance

In the event of study-related damage or injuries, the liability of the institution labormedizinisches zentrum Dr. Risch in Vaduz provides compensation, except for claims that arise from misconduct or gross negligence.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

The expected scientific value is expected to be large considering the threat of the pandemic and the need for earliest possible identification of COVID-19 affected cases. The methodology chosen is ideal: it is based on a study already in operation, with funding already obtained, a bracelet already approved and in use for fertility tracking, ready to start immediately. No vulnerable individuals will be included.

7.2 Risk-benefit assessment

Risk for participants is low (non-invasive monitoring and blood sampling). The expected benefit is large, as algorithms trained on the obtained data recordings are expected to recognize COVID-19 earlier than clinical symptoms. The latter would allow for earlier isolation and stratification as well as monitoring of COVID-19 affected patients preventing further spread and allowing for appropriate healthcare.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

Study personnel trained on all important study related aspects is employed for conducting the study. Once yearly, an independent audit is done by Prof. Dr. Christoph Saely from the Vorarlberg Institute of Vascular Investigation and Treatment.

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

The GAPP study employs secuTrial and MOLIS to record data. Both systems have audit trails. For each participant a CRF is maintained. CRFs are identified by coded information used in the GAPP study. Further, the source data of the AVA bracelets is recorded within the computer systems of AVA. These data are kept strictly confidential and cannot be changed.

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number. Access to computer systems is highly restricted by two-level passwords. Access on data is recorded in a traceable manner. Data is backed up at the data center of the labormedizinisches zentrum Dr. Risch in Vaduz.

Biological material in this study is not identified by participant name but by a unique participant number. Biological material is appropriately stored at -80°C in a restricted area only accessible to the authorised study personnel at the GAPP-study and the labormedinisches zentrum Dr. Risch.

8.4 Retention and destruction of study data and biological material

All study data and biological material are archived at the labormedizinisches zentrum Dr. Risch in Vaduz for 10 years after study termination or premature termination of the study. After the study sera will be destroyed according to the normal process within the ISO-17025 accredited labormedizinisches zentrum Dr. Risch.

9 MONITORING AND REGISTRATION

The external auditor Prof. Dr.Christoph Saely will be conducting a monitoring visit before starting the present study and once yearly.

It is intended that the study will be registered in the Intended registry: International Standard Randomised Controlled Trial Number (ISRCTN) registry.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

The study is funded by the government of the principality of Liechtenstein (75000 CHF), the prince of Liechtenstein (350’000 CHF) and the Hanela Stiftung Aarau (100’000 CHF). Further funding will be sought. The funding sources did not have any role in conceiving the study idea, planning of the study, and will not have any role in the decision to publish. It is planned to publish the study data in peer reviewed scientific journals. Decision to publish will be done by a majority of

investigators. Authorship will be clarified according to the ICMJE-criteria. Aggregate data will be provided upon request to qualified external research proposals. Dr. Maureen Cronin is employee of AVA. All other investigators are independent of AVA.

10 REFERENCES

1. Goodale BM, Shilaih M, Falco L, Dammeier F, Hamvas G, Leeners B. Wearable Sensors Reveal Menses-Driven Changes in Physiology and Enable Prediction of the Fertile Window: Observational Study. J Med Internet Res 2019;21:e13404.
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.
3. Sahu KK, Mishra AK, Lal A. Novel coronavirus (2019-nCoV): Update on 3rd Coronavirus Outbreak of 21st Century. QJM 2020.
4. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020.
5. Chen G, Xie J, Dai G, et al. Validity of Wrist and Forehead Temperature in Temperature Screening in the General Population During the Outbreak of 2019 Novel Coronavirus: a prospective real-world study. medRxiv 2020:2020.03.02.20030148.
6. Karjalainen J, Viitasalo M. Fever and cardiac rhythm. Arch Intern Med 1986;146:1169-71.
7. Lyon DM. The Relation of Pulse-rate to Temperature in Febrile Conditions. QJM: An International Journal of Medicine 1927;os-20:205-18.
8. Conen D, Schon T, Aeschbacher S, et al. Genetic and phenotypic determinants of blood pressure and other cardiovascular risk factors (GAPP). Swiss Med Wkly 2013;143:w13728.
9. Aeschbacher S, Bossard M, Ruperti Repilado FJ, et al. Healthy lifestyle and heart rate variability in young adults. Eur J Prev Cardiol 2016;23:1037-44.
10. Aeschbacher S, Bossard M, Schoen T, et al. Heart Rate Variability and Sleep-Related Breathing Disorders in the General Population. Am J Cardiol 2016;118:912-7.
11. Aeschbacher S, Metin F, Bossard M, et al. Relationships of electrocardiographic parameters with ambulatory hypertension in young and healthy adults. Int J Cardiol 2016;202:300-4.
12. Aeschbacher S, Mongiat M, Bernasconi R, et al. Aldosterone-to-renin ratio and blood pressure in young adults from the general population. Am Heart J 2020;222:199-207.
13. Aeschbacher S, Schoen T, Bossard M, et al. Relationship between high-sensitivity cardiac troponin I and blood pressure among young and healthy adults. Am J Hypertens 2015;28:789-96.
14. Aeschbacher S, Schoen T, Clair C, et al. Association of smoking and nicotine dependence with pre-diabetes in young and healthy adults. Swiss Med Wkly 2014;144:w14019.
15. Aeschbacher S, Schoen T, Dorig L, et al. Heart rate, heart rate variability and inflammatory biomarkers among young and healthy adults. Ann Med 2017;49:32-41.
16. Bernasconi R, Aeschbacher S, Blum S, et al. Fibroblast growth factor 23 and renal function among young and healthy individuals. Clin Chem Lab Med 2018;56:1483-9.
17. Blum J, Aeschbacher S, Schoen T, et al. Prevalence of prediabetes according to hemoglobin A1c versus fasting plasma glucose criteria in healthy adults. Acta Diabetol 2015;52:631-2.
18. Bossard M, Aeschbacher S, Schoen T, et al. Serum bilirubin levels and risk of prediabetes in young and healthy adults. Int J Cardiol 2014;171:e24-5.

19. Bossard M, Pumpol K, van der Lely S, et al. Plasma endothelin-1 and cardiovascular risk among young and healthy adults. Atherosclerosis 2015;239:186-91.
20. Bossard M, Theriault S, Aeschbacher S, et al. Factors independently associated with cardiac troponin I levels in young and healthy adults from the general population. Clin Res Cardiol 2017;106:96-104.
21. Conen D, Aeschbacher S, Thijs L, et al. Age-specific differences between conventional and ambulatory daytime blood pressure values. Hypertension 2014;64:1073-9.
22. Egli P, Aeschbacher S, Bossard M, et al. Relationships of kidney injury molecule-1 with renal function and cardiovascular risk factors in the general population. Clin Chim Acta 2018;478:13-7.
23. Evangelou E, Gao H, Chu C, et al. New alcohol-related genes suggest shared genetic mechanisms with neuropsychiatric disorders. Nat Hum Behav 2019;3:950-61.
24. Evangelou E, Warren HR, Mosen-Ansorena D, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nat Genet 2018;50:1412-25.
25. Filipovic MG, Aeschbacher S, Reiner MF, et al. Whole blood omega-3 fatty acid concentrations are inversely associated with blood pressure in young, healthy adults. J Hypertens 2018;36:1548-54.
26. Fischer A, Bossard M, Aeschbacher S, et al. Plasma levels of endothelin-1 and renal function among young and healthy adults. Clin Chem Lab Med 2017;55:1202-8.
27. Kofler T, Bossard M, Aeschbacher S, et al. The interrelationships of birthweight, inflammation and body composition in healthy adults. Eur J Clin Invest 2016;46:342-8.
28. Kofler T, Theriault S, Bossard M, et al. Relationships of Measured and Genetically Determined Height With the Cardiac Conduction System in Healthy Adults. Circ Arrhythm Electrophysiol 2017;10.
29. Krisai P, Aeschbacher S, Ruperti Repilado FJ, et al. Healthy lifestyle and glucagon-like peptide-1 in young and healthy adults: A population-based study. Prev Med 2017;101:72-6.
30. Krisai P, Aeschbacher S, Schoen T, et al. Glucagon-like peptide-1 and blood pressure in young and healthy adults from the general population. Hypertension 2015;65:306-12.
31. Krisai P, Leib S, Aeschbacher S, et al. Relationships of iron metabolism with insulin resistance and glucose levels in young and healthy adults. Eur J Intern Med 2016;32:31-7.
32. Marti-Soler H, Gubelmann C, Aeschbacher S, et al. Seasonality of cardiovascular risk factors: an analysis including over 230 000 participants in 15 countries. Heart 2014;100:1517-23.
33. Maseli A, Aeschbacher S, Schoen T, et al. Healthy Lifestyle and Blood Pressure Variability in Young Adults. Am J Hypertens 2017;30:690-9.
34. Roselli C, Chaffin MD, Weng LC, et al. Multi-ethnic genome-wide association study for atrial fibrillation. Nat Genet 2018;50:1225-33.
35. Ruperti Repilado FJ, Aeschbacher S, Bossard M, et al. Relationship of N-Terminal fragment of Pro-B-Type Natriuretic Peptide and copeptin with erythrocytes-related parameters: A population-based study. Clin Biochem 2016;49:651-6.
36. Schoen T, Aeschbacher S, Leuppi JD, et al. Subclinical sleep apnoea and plasma levels of endothelin-1 among young and healthy adults. Open Heart 2017;4:e000523.
37. Schoen T, Aeschbacher S, Leuppi JD, et al. Subclinical sleep apnoea and plasma levels of endothelin-1 among young and healthy adults. Open Heart 2017;4:e000523.
38. Schoen T, Hohmann EM, Van Der Lely S, et al. Plasma copeptin levels and ambulatory blood pressure characteristics in healthy adults. J Hypertens 2015;33:1571-9.

39. van der Stouwe JG, Aeschbacher S, Krisai P, et al. Plasma levels of glucagon-like peptide 1 and markers of obesity among young and healthy adults. Clin Endocrinol (Oxf) 2015;83:636-42.
40. van der Stouwe JG, Carmeli C, Aeschbacher S, et al. Association of 24-Hour Blood Pressure With Urinary Sodium Excretion in Healthy Adults. Am J Hypertens 2018;31:784-91.
41. von Rotz M, Aeschbacher S, Bossard M, et al. Risk factors for premature ventricular contractions in young and healthy adults. Heart 2017;103:702-7.
42. Common Terminology Criteria for Adverse Events (CTCAE)
https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
43. Declaration of Helsinki
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
44. Federal Act on Data Protection (FADP)
https://www.admin.ch/opc/en/classified-compilation/19920153/index.html
45. Human Research Act (HRA)
https://www.admin.ch/opc/de/classified-compilation/20061313/index.html
46. International Conference on Harmonization (ICH) E6(R2) Guideline for Good Clinical Practice
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf
47. International Conference on Harmonization (ICH) E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf
48. Ordinance on Clinical Trials in Human Research (ClinO)
https://www.admin.ch/opc/de/classified-compilation/20121176/index.html

Appendix 1: Schedule of assessments

Time (hour, day, week)	>-1 day	0	Occurrence of symptoms	Periodic reporting (e.g. 14 days)	Final study visit
Visit	Information	Distribution of bracelet / provision of COVID-19 related information	Visit at occurrence of COVID-19 specific symptoms		Final study visit
Oral and written patient information	+				
Written consent		+			
Inclusion-/ exclusion criteria		+			
Medical history		+			
Participant characteristics		+			
Procedures			+		
Intervention		+	+		
Questionnaire		+	+	+	+
Sampling		+	+		+

Appendix 2: Declaration of conformity of the AVA bracelet.

KONFORMITÄTSERKLÄRUNG
DECLARATION DE CONFORMITE
DECLARATION OF CONFORMITY
DICHIARAZIONE DI CONFORMITA

Name und Adresse der Firma Nom et adresse de l'entreprise Nome e indirizzo della ditta Name and address of the firm	Ava AG Gutstrasse 73 CH-8055 Zürich
Name und Adresse der Zertifizierungsstelle Nom et adresse de l'autorité de certification Nome e indirizzo della ditta organismo di certificazione Name and address of the certification body	TÜV SÜD Product Service GmbH Zertifizierstelle Ridlerstrasse 65 80339 München Germany

Wir erklären in alleiniger Verantwortung, dass das Medizinprodukt
Nous déclarons sous notre propre responsabilité que le dispositif médical
Dichiariamo sotto nostra responsabilità che il dispositivo medico
We declare under our sole responsibility that the medical device

Ava

Artikel Nr. Article nr. / Article nr. / Nummero articolo / Article no.	PNA00003, PNA00004, PNA00013, PNA0044
der Klasse de la classe / of class / della classe / class	I
Seriennummer: numéro de lot / Numero di lotto / serial number	---

allen Anforderungen der folgenden Richtlinien entsprechen, die anwendbar sind /
remplit toutes les exigences de la directive sur les dispositifs médicaux 93/42/CEE qui le concernent /
soddisfa tutte le disposizioni della direttiva 93/42/CEE che lo riguardano /
meets all the provisions of the directive 93/42/EEC which apply to it.

Angewandte harmonisierte Normen, nationale Normen oder andere normative Dokumente / Normes harmonisées, normes nationales et autres documents normatifs appliqués / Norme armonizzate o nazionali applicate, altri documenti normativi applicati / Applied harmonised standards, national standards or other normative documents	EN ISO 13485:2016 MDD 93/42/EG:2007 ISO 14971:2012 IEC 62304:2015 IEC 62366:2016 RED 53/EU 2014 IEC 60601-1-6 : 2015 ISO 10993-1, 5, 12, 18
Konformitätsbewertungsverfahren Procédure d'évaluation de la conformité Procedimentodi valutazione della conformità Conformity assessment procedure	93/42/EG, Annex II
Konformitätsbewertung gültig bis : Declaraction de conformite est valide jusqu'à : Declaration of conformity is valid until: Dichiarazione di conformita in vigore a:	May 26th, 2020

Ort, Datum / Lieu, date /
Luogo, data / Place, date

Zurich OCT 4 2019

Name und Funktion / Nom et fonction /
Nome e funzione / Name and function

Pascal Koenig CEO