Photoplethysmography to detect circulatory arrest: A study in patients with induced cardiac arrests

- DETECT-1 -

(October 2023)

Protocol amendments:

Amendment 1 - June 2022: the maximum number of patients in whom no circulatory arrest was induced (no need for rapid ventricular pacing with aortic balloon dilatation during TAVR) that could be included was increased and it was better explained that the collected data is used as non-circulatory arrest data.

Amendment 2 - November 2022: the number of TAVR-patients to be included was increased, and number of s-ICD and VT ablation patients was decreased.

Amendment 3 – October 2023: removing extended data collection from the protocol, detailing the statistical analysis including addition of a subgroup for external validation.

PROTOCOL TITLE 'Photoplethysmography to detect circulatory arrest'

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Project leader/coordinating investigator	Project leader: prof. dr. N. van Royen Coordinating investigator: dr. J.L. Bonnes
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Subsidising party	Dutch Heart Foundation
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Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CCU	**Coronary Care Unit**
CPR	**Cardiopulmonary resuscitation**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
ECG	**Electrocardiogram**
ED	**Emergency department**
EDC	**Electronic data capture**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
HIPAA	**Health Insurance Portability and Accountability Act**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICD	**Implantable cardioverter defibrillator**
ICU	**Intensive care unit**
IMDD	**Investigational Medical Device Dossier**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
ISO	**International organization for standardization**
LED	**Light Emitting Diode**

METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
OHCA	**Out-of-hospital cardiac arrest**
PPG	**Photoplythesmography**
ROSC	**Return of spontaneous circulation**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TAVR	**Transcatheter Aortic Valve Replacement**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
VT	**Ventricular tachycardia**
VF	**Ventricular fibrillation**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Out-of-hospital cardiac arrest (OHCA) is a leading cause of global mortality. Delays to initiation of cardiopulmonary resuscitation (CPR) should be as short as possible to achieve the highest survival chance. To reduce treatment delays automated cardiac arrest detection and call for help would be ideal. Photoplethysmography (PPG) is an optical technique often used in sport/smartwatches to monitor heart rhythm at the skin and based on previous studies it seems to have potential to detect circulatory arrest.

Objective: To study photoplethysmography signals during 1) induced circulatory arrest; 2) cardiac rhythms without circulatory arrest, and to construct a PPG-based algorithm for circulatory arrest detection.

Study design: Prospective multicenter observational study.

Study population: 1) Patients scheduled for defibrillation testing after (subcutaneous) implantable cardioverter defibrillator (ICD) implantation; 2) Patients undergoing transcatheter aortic valve replacement (TAVR) with intended rapid ventricular pacing; 3) Patients undergoing ventricular tachycardia ablation.

Intervention: Patients will be equipped with a wristband with a PPG-sensor to record PPG signals during hospital stay including during induced circulatory arrests. The circulatory arrest inductions are part of routine practice during above-described procedures and are not a study-related intervention. In case this is not routine practice, an arterial line will be inserted as reference standard for circulatory arrest.

Main study parameters/endpoints: Primary endpoints: Sensitivity for circulatory arrest and false positive circulatory arrest alarms.. Secondary endpoints: Positive predictive value for circulatory arrest, Specificity for detection of pulsatile PPG signal, PPG-signal characteristics.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Given the observational nature of this study and the non-invasive comfortable wristband used for PPG signal recording, the medical risk associated with study participation is negligible. Insertion of an arterial line may carry small risks as outlined in this protocol.

1. INTRODUCTION AND RATIONALE

Out-of-hospital cardiac arrest (OHCA) is a leading cause of global mortality, with 300 cases in the Netherlands each week (1). Survival to hospital discharge is about 25% and depends on fast recognition of cardiac arrest and immediate initiation of cardiopulmonary resuscitation (CPR) (1-3). Survival chance decreases with 5-10% per minute delay to defibrillation emphasizing the need to keep treatment delays as short as possible (2). The establishment of a nationwide network of lay rescuers initiating CPR prior to ambulance arrival has contributed to shortening of treatment delays and improved survival (3). Automated cardiac arrest detection and call for help would be a next important step, also enabling timely help for victims of unwitnessed cardiac arrest, constituting 25-50% of all cardiac arrest victims (1,4).

Contemporary wearable technologies may play an important role to fulfil this goal (5). The risk of sudden cardiac death increases already from the fourth decade in life, and in about half of cases cardiac arrest is the first manifestation of disease (1,6). Therefore, a tool for automated cardiac arrest detection should be widely applicable and comfortable to wear.

Photoplethysmography (PPG) is a low-cost, non-invasive optical technique using measurements at the skin to detect blood volume changes in the microvascular bed of tissue (7). It is used in pulse oximeters to provide measurements of oxygen saturation and in sport/smartwatches to monitor heart rate (5,7). Additionally, it is increasingly used in commercially available medically oriented devices to detect cardiac arrhythmias, most often focusing on detection of atrial fibrillation (5). Given its reflection of hemodynamic information, this technique may also be suitable to detect circulatory arrest (8).

A previous study in animals has shown feasibility of detection of hemodynamically unstable cardiac arrhythmias using a single derived parameter of the PPG signal (8). Additionally, high correlation was shown between changes in blood pressure and PPG output. In cardiac arrest patients, PPG is under active investigation to detect return of spontaneous circulation (ROSC) during resuscitation and seems to perform even better dan manual pulse palpation (9-11). In contrast to the electrocardiogram (ECG) reflecting electrical activity of the heart, PPG provides assessment of hemodynamic status, and therefore functions more as a derivative of the mechanical activity of the heart. This is important as it enables not only detection of ventricular fibrillation and asystole, but also pulseless electrical activity, which is the initial cardiac rhythm in about 20% of cardiac arrests (12).

In the DETECT-project, we aim to further develop an existing medically oriented wristband to fulfil the goal of automated cardiac arrest detection and activation the emergency

medical chain. In the present DETECT-1 study, we will study PPG signals in relation to induced circulatory arrests and develop a PPG-based algorithm for detection of circulatory arrest.

2. OBJECTIVES

Primary Objectives:
1) To study PPG signal characteristics in relation to circulatory arrest in patients with induced circulatory arrest.
2) To construct a PPG-based algorithm for detection of circulatory arrest based on induced circulatory arrest data in patients.
3) To study the performance (sensitivity and false positive alarms) of the developed PPG-based algorithm for detection of circulatory arrest in patients with induced circulatory arrests.

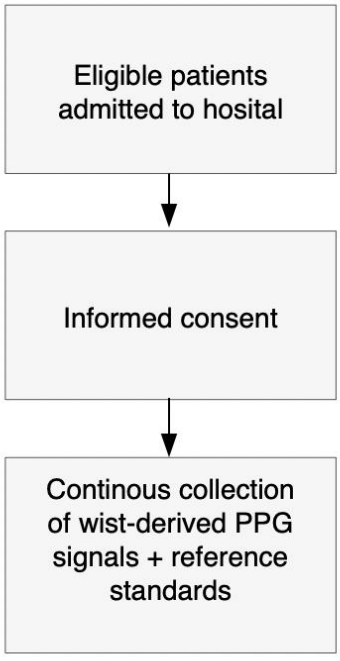
Secondary Objective(s):
- To study the positive predictive value of the developed algorithm for circulatory arrest detection.
- To study the specificity of the developed circulatory arrest detection algorithm.

- To identify potential sources of false positive alarms for circulatory arrests.
- To study PPG signal characteristics in relation to hemodynamically stable cardiac arrhythmias.
- To study PPG signal characteristics in relation to hemodynamically unstable cardiac arrhythmias.
- To study PPG signal characteristics prior to and after TAVR procedure to assess the impact of aortic stenosis and/or regurgitation on the PPG signal.
- To study PPG signal characteristics in patients with and without systemic hypertension.
- To study PPG signal characteristics in relation to left ventricular ejection fraction in patients without relevant valvular lesions.

3. STUDY DESIGN

The DETECT-1 is a Dutch prospective multicenter observational cohort study performed in a hospital setting. Included patients are hospitalized for ICD implantation, VT ablation or TAVR procedure.
Expected study duration is 2 years.
Data of induced circulatory arrests will be collected in the following settings/patients:
- Patients who undergo ventricular fibrillation induction during defibrillation testing after (subcutaneous) ICD implantation. This is performed as routine practice to test the ability of the implanted device to sense, detect and terminate ventricular fibrillation cardiac arrest appropriately.
- As part of TAVR procedure, rapid ventricular pacing is performed during valve deployment resulting in short-lasting circulatory arrest.
- During ventricular tachycardia (VT) ablation procedure, hemodynamically unstable VT/VF is induced in about 1/3.

Flowchart:



4. STUDY POPULATION

4.1 Population (base)

The study population will consist of hospitalized patients who undergo short-lasting circulatory arrest induction as part of routine practice during some invasive procedures.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet one of the following criteria:

- Planned to undergo ventricular fibrillation induction during defibrillation testing after ICD implantation
- Undergoing TAVR procedure with intended rapid ventricular pacing
- Undergoing ventricular tachycardia ablation

Additionally, a subject must meet all of the following criteria:

- Age => 18 years
- Fitting the wristband

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Unwilling or unable to provide informed consent
- Known hemodynamically relevant subclavian artery stenosis
- Medical issues that interfere with wearing of the wristband (e.g. skin disorders)
- Unavailability of wristband used for PPG recording

4.4 Sample size calculation

Targeting a desired sensitivity of 95%, 200 true events allow estimation of sensitivity with precision (expressed as expected width of the 95% confidence interval) of +/- 3%, which is considered adequate. As for specificity, a substantially larger number of “non-events” can be sampled, precision for estimating specificity will be larger.

In this study, we will primarily collect data of induced circulatory arrest, obtained during controlled settings with appropriate reference standards (ECG and (invasive) blood pressure measurements). To collect a sufficient amount of PPG data with true events, the

sample size will be 276 patients consisting of an estimated number of n=200 TAVR-patients (event rate 1/1), n=20 ICD-patients (event rate 1/1) and n=56 VT-ablation patients (event rate 1/3). In case ventricular fibrillation induction or rapid ventricular pacing is not performed or does not result in complete circulatory arrest (as determined on (invasive) blood pressure measurements), the number of patients included will be increased to guarantee the anticipated number of true events, with a maximum of 80 additional patients. Data of the patients without induced circulatory arrest will be used as non-cardiac arrest data.

5. TREATMENT OF SUBJECTS

Not applicable.

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

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

PPG data will be collected during hospital stay using the CardioWatch 287-2 (Corsano Health B.V.). The CardioWatch 287 is a medically certified wireless remote monitoring system intended for continuous collection of physiological data in home and healthcare settings. This includes heart rate, heart rate variability (R-R interval), respiration rate, activity and sleep. CardioWatch 287-1 is a CE medical device certified under EU-MDR standards. Additional documentation including certificates and the investigational medical device dossier (IMDD) is available as Attachments. The CardioWatch 287-2 incorporates additional light emitting diodes ((LED); red and infared light) to improve PPG registration. Data is transmitted wirelessly from the device via the application to a health cloud where it is stored and made available for further analysis. The software complies with the General Data Protection Regulation (GDPR) and Health Insurance Portability and Accountability Act (HIPAA) privacy and security rules.

7.2 Summary of findings from non-clinical studies

Summary of information regarding the quality, manufacture and control of the non-investigational medical product can be found in the Investigational Medical Device Dossier (IMDD).

7.3 Summary of findings from clinical studies

Summary of information regarding the results of clinical studies of the non-investigational medical product can be found in the Investigational Medical Device Dossier (IMDD).

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

- Sensitivity of the developed algorithm for circulatory arrest detection and false positive circulatory arrest alarms.

8.1.2 Secondary study parameters/endpoints

- Specificity of the developed circulatory arrest detection algorithm.
- Positive predictive value of the developed algorithm for circulatory arrest detection
- PPG-derived signal characteristics during circulatory and non-circulatory arrest
- Sources of noise
- Sources of false positive alarms

8.1.3 Other study parameters

- Demographic data
- Medical history including cardiac history and peripheral artery disease
- Cardiovascular risk factors
- Medication use
- Haemoglobin, thyroid function if available
- Echocardiographic parameters of left and right ventricular and valvular functions
- Invasive cardiac pressure and blood pressure recordings
- Non-invasive blood pressure recordings
- Procedural characteristics

8.2 Randomisation, blinding and treatment allocation

Not applicable.

8.3 Study procedures

Study procedures for the above-described groups of study patients are described below.

8.3.1 ICD-patients

As part of routine practice, after subcutaneous implantable cardioverter defibrillator (ICD) implantation or replacement defibrillation testing is performed to test the ability of the implanted device to sense, detect and terminate ventricular fibrillation appropriately. This involves induction of ventricular fibrillation resulting in short-lasting circulatory arrest. During the entire procedure patients will wear the wristband. This enables collection of PPG data in settings with and without circulatory arrest. The presence of circulatory arrest is confirmed by simultaneously recorded invasive blood pressure measurements and ECG recordings. Therefore, in patients in whom this is not standard of care, consent will be asked to insert an arterial line into the radial artery to measure blood pressure during ventricular fibrillation to confirm complete circulatory arrest. ECG and invasive blood pressure measurements will be digitally stored and collected. Available echocardiographic data will be collected. The wristband is removed after the procedure. Activities are described in Table 1.

8.3.2 TAVR-patients

During transcatheter aortic valve replacement (TAVR), rapid ventricular pacing is routinely performed during valve deployment resulting in short-lasting cardiac standstill and circulatory compromise. The wristband is applied prior to the procedure. This enables collection of PPG data during the entire procedure, thus including settings with and without circulatory arrest. Presence of circulatory arrest will be ensured based on simultaneous ECG recordings and invasive pressure data. For the latter, routinely recorded invasive pressure recordings will be used. This data will be digitally stored and collected. During a TAVR, an arterial line is routinely inserted to monitor blood pressure (no study-related intervention). Echocardiographic data pre and post TAVR will also be collected. The wristband is removed after the procedure. Activities are described in Table 1.

8.3.2 VT ablation

During VT ablation, hemodynamically unstable VT/VF is induced in about 1/3 of patients. Patients will wear the wristband during the entire procedure. This enables collection of PPG data in settings with and without circulatory arrest. In case an arterial line is not inserted for clinical purposes, patients will be asked consent to do so. The presence of circulatory arrest is confirmed by simultaneously recorded invasive blood pressure measurements and ECG recordings. Therefore, in patients in whom this is not standard of care, consent will be asked to insert an arterial line into the radial artery to measure blood pressure during ventricular fibrillation to confirm complete circulatory arrest. ECG and invasive blood pressure measurements will be digitally stored and collected. Available echocardiographic data will be collected. The wristband is removed after the procedure. Activities are described in Table 1.

Table 1: Study activities

TAVR-patients			
Outpatient clinic/hospital admission	**Admission/Day of TAVR**	**TAVR**	**Day(s) after TAVR**
Screening: Check in- and exclusion criteria	Apply wristband for continuous PPG recording	Continue PPG recording using the wristband.	Collect echocardiographic data
Informed consent if eligible		Save invasive (blood) pressure measurements	
Collect baseline data including available echocardiographic data		Annotate rapid ventricular pacing and save ECG monitoring	
		Remove wristband after the procedure	

ICD-patients/VT ablation patients		
Outpatient clinic/hospital admission	**Admission**	**ICD implantation with defibrillation testing**
Screening: Check in- and exclusion criteria	Apply wristband for continuous PPG recording	Continue PPG recording using the wristband

Informed consent if eligible	12-lead ECG	Insert an arterial line in the radial artery (opposite arm to the wristband)
Collect baseline data including available echocardiographic data		Initiate and save (non-)invasive blood pressure measurements
		Annotate defibrillation testing and save ECG monitoring
		Remove arterial line and wristband after the procedure

8.4 Withdrawal of individual subjects

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

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

8.5 Replacement of individual subjects after withdrawal

In case of withdrawal, subjects will be replaced to facilitate achievement of the needed number of true events to guarantee useful study results.

8.6 Follow-up of subjects withdrawn from treatment

No follow-up will be performed.

8.7 Premature termination of the study

Not applicable**.**

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

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

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

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

Given the observational design of this study, with only additional diagnostic data collection using a PPG sensor in a wristband, the study will follow the recommendations of observational studies with additional diagnostic investigations. Only adverse events related to the use of the wristband or study-related insertion of an arterial line will be documented.

9.2.2 Serious adverse events (SAEs)

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

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

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

Given the observational design of this study, with only additional diagnostic data collection, the study will follow the recommendations of observational studies with additional diagnostic investigations. Only serious adverse events suspected to be related to study participation will be reported individually to the accredited METC within 7 -15 days of first knowledge.

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

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

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

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

In view of the observational design of the study, a data safety monitoring board or safety committee is not established.

10. STATISTICAL ANALYSIS

Categorical data will be presented as numbers (percentages) and compared using Chi- square test or Fisher's exact test. Continuous data will be assessed for normal distribution and presented as means ± standard deviations or medians (interquartile ranges) whichever appropriate. Comparisons will be performed using the Student's t-test or Mann-Whitney U test, whichever appropriate.

For each patient studied, circulatory arrest data (case data) and non-circulatory arrest data (control data) will be collected. The data obtained will be analysed and used for algorithm development at regular intervals: after inclusion of the first 50 patients with at least one circulatory arrest and afterwards after inclusions of another 50 patients. This enables improvement and refinement of the initial algorithm to gain optimal performance. The first iteration provides a first version of the diagnostic algorithm. The second and third iteration will be used to optimize the algorithm. The fourth iteration will be used as final evaluation of the performance of the algorithm (internal validation). All non-circulatory arrest data will be analyzed for false positive circulatory arrest alarms.

As the algorithm will primarily be developed and validated on non-physiologic circulatory arrest induction using rapid ventricular pacing with aortic balloon inflation during transcatheter aortic valve implantation, a second (external) validation will be performed on data of patients with induced shockable cardiac arrest (i.e. induction of ventricular fibrillation or tachycardias). This most closely resembles clinical sudden cardiac arrest. The final cohort of 50 inclusions with at least one induced event, consisting only of patients who underwent VT ablation or VF induction after s-ICD implantation, will be used for this analysis.

The performance of the PPG-based algorithm will be assessed by calculating the sensitivity, specificity, and positive predictive value with 95% confidence intervals. The specificity is reported based on 1-minute intervals of pulsatile PPG signal correctly identified as non-circulatory arrest Reporting will follow the recommendations of the STARD guidelines for studies on diagnostic accuracy. Statistical analyses will be performed using SPSS (IBM, Armonk, USA).

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki version 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Patients planned for defibrillation testing after ICD implantation, TAVR or VT ablation will be screened. In case of eligibility, patients will be informed in detail regarding the additional data collection related to study participation and wearing of the wristband. This will be performed by one of the investigators or study nurse trained and supervised by the investigator. Written information is provided as well. Patients will get as much time as they need to reflect on whether they will participate or not. Application of the wristband and data collection will follow only after the patient signs the informed consent form.

11.3 Objection by minors or incapacitated subjects

See paragraph 11.2

11.4 Benefits and risks assessment, group relatedness

There are no relevant benefits or risks associated with wearing of the wristband to record PPG data.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The cloud-based electronic data capture (EDC) platform CASTOR EDC will be used to capture pseudonymised patient data. This enables high quality storage and reusability of data. Data entry from the electronic patient record into the EDC system will be performed at the participating study site. The data generated in the studies, including (raw) ECG, PPG and hemodynamic data will be encoded, not based on patient initials and date of birth. The subject identification log will be filed at the participating centre. Processing of personal data will comply to the rules of the General Data Protection Regulation (GDPR). PPG and the other sensor data recorded with the CardioWatch will be collected and stored in a certified cloud-system. Details can be found in the Attachment (Cloud Data Management Description CardioWatch 287). In short, the CardioWatch 287 Cloud system is composed of Web servers running on the cloud (hosted by AWS servers located in Frankfurt, Germany) that collect, store and exchange data with authorized medical partners. The collected raw PPG data will be used for algorithm development and is accessible for the investigators. AWS partner is certified ISO 270001 for IT Security Systems. The Corsano cloud is fully GDPR compliant. Technical details and certificates can be found in the Attachment (Cloud Data Management Description CardioWatch 287).

12.2 Monitoring and Quality Assurance

Independent monitoring will take place for quality assurance. It will be arranged by the Radboudumc and performed at least once a year. Further details can be found in the monitoring plan.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the

first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

Study results will be published open access according to the arrangements made and described in the clinical trial agreement.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

The study concerns additional diagnostic investigation in the form of collection of PPG data recorded on the skin with a wristband. This does not convey additional risk for the patient. The short-lasting circulatory arrest inductions are part of routine practice during the described procedures and not part of the study protocol. Also for the collection of additional parameters including but not limited to invasive blood pressure measurements, routinely recorded data is used. Monitoring with PPG does not replace any other monitoring tool during the study.

Only for ICD/VT ablation patients, we will ask additional consent to insert an arterial line in the radial artery to measure blood pressure invasively during the procedure as this is not routine practice. In case consent is not given, patients can participate without arterial line insertion. Complications following radial artery cannulation include permanent ischemic damage (0.09%), temporary occlusion (20%), sepsis (0.13%), local infection (0.72%), pseudoaneurysm (0.09%), hematoma (14.4%), bleeding 0.53%. Generally temporary occlusion of the radial artery has no serious sequelae. Permanent occlusion appears to be rare (0.09%) (14). In the majority of studies on which these incidences are based, the arterial line was inserted for longer term invasive monitoring (e.g. during intensive care unit stay). It is expected that complication rates will be lower with planned insertion of an arterial line under optimal circumstances and only for monitoring during the procedure.

The product used for PPG recording is a comfortable wristband (CardioWatch 287 - Corsano Health B.V.) intended for continuous collection of physiological data in home and healthcare settings. Recorded data is saved in a certified cloud-based data management system as described in Section 12.1.

13.2 Synthesis

Automated cardiac arrest detection may be an important next step in outcome improvement of OHCA-patients given the extreme importance of short treatment delays. Based on animal studies, circulatory arrest detection seems possible using PPG recordings. In this DETECT-1 study in patients, we will collect PPG data of induced circulatory arrests to develop an PPG-based algorithm for circulatory arrest detection, with the overall goal of

the DETECT project to develop a wristband with the functionality to automatically detect cardiac arrest and activate the emergency medical chain.

14. REFERENCES

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Attachments

Investigational Medical Device Dossier CardioWatch 287-2

Medical Device File CardioWatch 287-2

Certificate of Compliance CardioWatch 287-2

Quality Management System Certificate Corsano Health B.V.

Instruction Manual CardioWatch 287 (only for investigators)

Cloud Data Management Description