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Rationale and design of the SafeHeart study: Development and testing of a mHealth tool for the prediction of arrhythmic events and implantable cardioverter-defibrillator therapy

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BACKGROUND Patients with an implantable cardioverter-defibrillator (ICD) are at a high risk of malignant ventricular arrhythmias. The use of remote ICD monitoring, wearable devices, and patient-reported outcomes generate large volumes of potential valuable data. Artificial intelligence–based methods can be used to develop personalized prediction models and improve early-warning systems.

OBJECTIVE The purpose of this study was to develop an integrated web-based personalized prediction engine for ICD therapy.

METHODS This international, multicenter, prospective, observational study consists of 2 phases: (1) a development study and (2) a feasibility study. We plan to enroll 400 participants with an ICD (with or without cardiac resynchronization therapy) on remote monitoring: 300 participants in the development study and 100 in the feasibility study. During 12-month follow-up, electronic health record data, remote monitoring data, accelerometry-assessed physical behavior data, and patient-reported data are collected. By using machine- and deep-learning approaches, a prediction engine is developed to assess the risk probability of ICD therapy (shock and antitachycardia pacing). The feasibility of the prediction engine as a clinical tool, the SafeHeart Platform, is assessed during the feasibility study.

RESULTS Development study recruitment commenced in 2021. The feasibility study starts in 2022.

CONCLUSION SafeHeart is the first study to prospectively collect a multimodal data set to construct a personalized prediction engine for ICD therapy. Moreover, SafeHeart explores the integration and added value of detailed objective accelerometer data in the prediction of clinical events. The translation of the SafeHeart Platform to clinical practice is examined during the feasibility study.

KEYWORDS Accelerometry; Artificial intelligence; Implantable cardioverter-defibrillator; Prediction model; Wearable

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Introduction
Implantable cardioverter-defibrillator (ICD) implantation is the cornerstone of the prevention of sudden cardiac death through the termination of ventricular arrhythmias for either primary prevention or secondary prevention.1 Despite improvements in pharmacological and nonpharmacological treatments,2,3 a meta-analysis of 5 clinical trials with 5516 participants showed that 18% received appropriate ICD therapy and 10% received inappropriate ICD therapy during an average follow-up time period of 2.4 years.4 Aside from the potential harm related to ICD shock on the myocardium itself, ICD therapy has an adverse psychological impact.

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and may reduce quality of life (QoL). Also, ICD therapy—both appropriate and inappropriate—poses a burden on clinical staff and affects health care expenditure. Several risk prediction and stratification models have been developed to assess the risk of ICD therapy (Online Supplemental Appendix Table A1). External validation of 3 previously developed risk stratification models for benefit of ICD implantation (ie, risk of death before first ICD intervention) rendered C statistics between 0.66 and 0.75. The recently published Multicentre Autonomic Defibrillator Implantation Trial-ICD and The Dutch outcome in ICD therapy prediction scores have demonstrated similar discriminative performance; the external validation of both scores yielded C statistics of 0.75 and 0.60, respectively. Although these models could aid in the risk stratification for ICD implantation, there are considerable differences in these models in terms of the included variables and predictive performance. Also, these aforementioned scores are merely based on clinical variables marked by significant collinearity and lack the ability for real-time prediction of arrhythmic events.

In addition to conventional patient data (eg, electrocardiography, imaging, laboratory biomarkers, and medical history), the digital health landscape is increasingly shaped by the continuous collection of health data through wearable devices and telehealth and mHealth apps. The increasing availability of and expertise in analytical techniques based on artificial intelligence (AI), such as machine learning and deep learning, enable the analysis of multiple time series data. By leveraging these AI-based techniques and exploiting various novel data sources (eg, wearable devices, remote device monitoring, and patient-reported outcomes), we aim to develop a prediction algorithm for ICD therapy integrated into a web-based clinician’s dashboard. Together with data from a patient app, wearable accelerometry, and remote ICD monitoring, this constitutes the SafeHeart Platform: an early warning system for the prediction of ICD therapy, alarming 30 days in advance; and a clinical decision support system that informs the clinician of the most important parameters affecting the likelihood of an event.

Methods
Study design
The SafeHeart study is an international, multicenter, prospective, observational study consisting of 2 phases: (1) a development study and (2) a feasibility study. A total of 400 participants with an ICD or cardiac resynchronization therapy with defibrillator (CRT-D) will be enrolled: 300 in the development study and 100 in the feasibility study. During the 12-month development study, data are collected from 4 sources: (1) electronic health records (EHRs), (2) remote ICD monitoring data, (3) wearable accelerometry, and (4) patient-reported outcome measures. The study flow chart can be seen in Figure 1. A prediction algorithm will be developed that provides the probability of impending ICD therapy (shock or antitachycardia pacing [ATP]) and displays the feature importance for each individual prediction trigger. Subsequently, during the 6-month feasibility study, the clinical utility, acceptability, safety, and feasibility of the SafeHeart Platform is assessed by exploiting both quantitative and qualitative methods from the perspectives of clinicians and participants. The feasibility study is not designed to specifically evaluate the outcome of interest—the prediction accuracy of the primary end point—but investigates the potential for the translation of the SafeHeart Platform to clinical practice (Figure 2).

Study setting
The study is conducted at 2 cardiology departments at university hospitals in the Netherlands (Amsterdam University Medical Center location Academic Medical Center, University of Amsterdam) and Denmark (Copenhagen University Hospital—Rigshospitalet). Ethics approval was obtained at the 2 participating institutions, and the study is conducted in accordance with the Declaration of Helsinki as revised in 2013. The study is registered at the National Trial Registration in the Netherlands (Trial NL9218; [https://www.trialregister.nl]). Informed consent will be obtained for all participants.

Participant selection
In order to have sufficient events in our patient cohort, we aim to target the ICD carriers that are at a high risk of therapy, that is, patients who have already experienced an arrhythmia event or received (in)appropriate therapy. Therefore, the following eligibility criteria are applied:

**Inclusion criteria**
- ICD or CRT-D implantation for either primary or secondary prevention less than 5 years before enrollment
- Having received appropriate or inappropriate ICD therapy or proof of ventricular arrhythmias in the last 8 years before enrollment
- Participation in the remote monitoring program
- Participant 18 years or older

**Exclusion criteria**
- Life expectancy of less than 1 year
- Participants with circumstances that prevent follow-up (emigration, change of hospital for follow-up, and dropping out of the remote monitoring program)
- Participants who are unable to wear the accelerometer wristband (eg, allergic to the material)
- Clinically unstable participants
- End stage of heart failure (New York Heart Association [NYHA] class IV)
- Participants unable to complete a questionnaire
- Participants who do not understand the local language (Dutch or Danish)
- Serious physical disability (eg, wheelchair bound)
- Planned ablation for ventricular tachycardia (VT)
- Significant movement disorder (ie, hemiplegia or Parkinson disease or similar)
- Unwillingness to participate

The study population for the development study and feasibility study is similar applying the same inclusion and exclusion criteria, but participants are allowed to take part in 1 of the 2 studies only.

**Study end points**

The primary study end point during the development study is a composite of both appropriate and inappropriate ICD therapies (defibrillator shock or ATP). Secondary end points include appropriate ICD therapy alone, heart failure–related hospitalization, supraventricular arrhythmia onset, and
mortality. During the feasibility study, the feasibility is assessed on the basis of clinical utility, acceptability, safety, and implementation of the SafeHeart Platform.

**Data collection**
Data are collected from 4 data sources during both the development study and the feasibility study: (1) electronic health records, (2) remote ICD monitoring, (3) wearable accelerometry, and (4) patient-reported data as summarized in Table 1.

**Clinical data from EHRs**
Clinical data are collected prospectively from EHRs. Clinical data include demographic characteristics, comorbidities, cardiac history, cardiac imaging examinations, laboratory evaluations, and medications. These data are collected at the time of device implantation, study baseline, and end of follow-up.

**Remote ICD monitoring data**
The second type of data are prospectively collected remote ICD monitoring data, where information is communicated from the ICD or CRT-D device to the health care team in real time by using wireless technology and a Bluetooth-enabled device. Devices from all vendors are used. The metrics include, but are not limited to, the time of transmission, onset of an arrhythmic episode, heart rate, heart rhythm (ie, ventricular arrhythmia [VT], ventricular fibrillation [VF]) and supraventricular arrhythmia), arrhythmia duration, therapy (shock, ATP, and aborted shocks), device function (lead impedance and battery), and other device-measured metrics (physical activity measured by the device and percentage of pacing). Transmissions sent from the device include scheduled routine device controls and participant-activated or device-activated transmissions.

**Wearable accelerometry data**
Body-worn accelerometers are activity trackers that enable continuous measurement of long-term physical behavior in a free-living environment. Physical behavior encompasses an individual’s behavior and activities throughout the day and night, including physical activity (intensity, frequency, volume, and type), gait, posture, sleep behavior, and rest-activity patterns. Raw data are collected from the accelerometers, after which open and proprietary algorithms are applied for the conversion of raw data into specific metrics such as sleep time, sleep efficiency, sleep duration, time spent in moderate-to-vigorous physical activity, and sedentary time (Table 2). In this study, accelerometry data are collected through research-grade, wrist-worn, triaxial accelerometers: GENEActiv and Activinsights Band (Activinsights Ltd., Kimbolton, UK; specifications of both wearables are displayed in Table 3). Unlike GENEActiv, the Activinsights Band accelerometer is compatible with a mobile application that will facilitate real-time data collection, making it suitable for integration within the SafeHeart Platform.

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**Table 1** Data sources and variables in the SafeHeart study

<table>
<thead>
<tr>
<th>Modality</th>
<th>Source</th>
<th>Baseline/time-varying data</th>
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<tbody>
<tr>
<td></td>
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<td>Baseline (static)</td>
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<td></td>
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<td>Dynamic (temporally varying)</td>
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<tr>
<td>Clinical data</td>
<td>Electronic health records</td>
<td>• Demographic variables</td>
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<td></td>
<td></td>
<td>• Left ventricular functionality</td>
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<tr>
<td></td>
<td></td>
<td>• (Cardiac) history</td>
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<td></td>
<td>• Comorbidities</td>
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<td>• Medication usage</td>
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<td>• Genetic predisposition</td>
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<td></td>
<td>• Diagnostic imaging, ECG</td>
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<td></td>
<td></td>
<td>• Laboratory examination</td>
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<tr>
<td>Remote monitoring</td>
<td>Research database</td>
<td>• Worsening of LV functionality</td>
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<tr>
<td></td>
<td>(all vendors included)</td>
<td>• Change in medication</td>
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<td></td>
<td></td>
<td>• Heart failure hospitalization</td>
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<tr>
<td>Physical behavior</td>
<td>Wearable accelerometry</td>
<td>• MACE</td>
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<tr>
<td></td>
<td></td>
<td>• Change in laboratory examinations</td>
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<tr>
<td>Patient-reported outcomes</td>
<td>Participant diary</td>
<td>• (Transient) ventricular arrhythmia onset/burden</td>
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<tr>
<td></td>
<td>Questionnaires (E05D-5L, KCCQ)</td>
<td>• Supraventricular arrhythmia onset/burden</td>
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<td>• Pacing percentages</td>
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<td>• Device diagnostics</td>
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<td>• Device-measured activity</td>
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<td>• Fluid index</td>
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<td>• Heart rate variability*</td>
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<td>• Worsening of functional capacity</td>
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<td>• Lifestyle changes</td>
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<td>• Change in rest-activity patterns</td>
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<td>• Sleep behavior changes</td>
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<td></td>
<td></td>
<td>• Symptomatic heart failure</td>
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<td></td>
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<td>• Quality of life over time</td>
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</table>

ECG = electrocardiography; E05D-5L = European Quality of Life Scale-5 Dimensions-5 Levels; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; MACE = major adverse cardiac events; N/A = not available; NYHA = New York Heart Association.

*Availability of these parameters differs per vendor.
Patient-reported outcomes
The fourth data type is patient-reported outcomes consisting of 2 questionnaires and participants’ diaries. The questionnaires are the generic health-related European Quality of Life Scale-5 dimensions-5 levels and the disease-specific Kansas City Cardiomyopathy Questionnaire filled out at baseline and at 6-month intervals.14,15 The European Quality of Life Scale-5 dimensions-5 levels questionnaire assesses the patient-reported health status and consists of 5 domains—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—along with a visual analog scale where participants rate their health on a scale of 0 (worst score) to 100 (best score). The Kansas City Cardiomyopathy Questionnaire is a questionnaire specifically developed to assess the health-related QoL in participants diagnosed with cardiomyopathy. It consists of 23 items and domains (symptoms, physical limitations, self-efficacy, QoL, symptom stability, and social limitation). Participants’ diaries concerning self-reported cardiac symptoms (eg, vertigo, palpitations, and chest pain), weight, and blood pressure (if available through private possession of a measuring device) will be collected together with the wearables biweekly during the development study and electronically retrieved during the feasibility study. A 2-week sleep diary is also completed by the participant at 3 time points during the development study.

Follow-up
Follow-up is done periodically in the outpatient department or by telephone interview every 6 months. During these follow-ups, changes in medication use and NYHA class will be evaluated and participants will be asked to fill out QoL questionnaires. The primary and secondary end points are evaluated by the investigator through monitoring of EHRs (Table 4).

Prediction algorithm development
The SafeHeart prediction algorithm is an extension of a predecessor model developed from a larger data set that

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<table>
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<tr>
<th>Measure class and description</th>
<th>Digital clinical measures</th>
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<tbody>
<tr>
<td><strong>Seconds/minutes</strong>&lt;br&gt;Data characterization measures&lt;br&gt;Statistical measures calculated from raw sensor data over short periods of time (events)</td>
<td>• Acceleration magnitude&lt;br&gt;• Principal frequency&lt;br&gt;• Arm elevation and wrist rotation (mean, variance, and MAD)&lt;br&gt;• Step interval&lt;br&gt;• Mean environment light&lt;br&gt;• Near body temperature</td>
</tr>
<tr>
<td><strong>Behavioral and physiological classification measures</strong>&lt;br&gt;Behavior measures inferred from characterized data events using models, heuristics, and meta-data&lt;br&gt;&lt;i&gt;&lt; 1 d (including nocturnal and diurnal separation)&lt;/i&gt;&lt;br&gt;Short-term summary measures&lt;br&gt;SUMMARIES of&lt;br&gt;• data characteristics or&lt;br&gt;• behavioral and physiological classifications</td>
<td>• Sleep, inactive, and sitting/lying&lt;br&gt;• Standing, active, walking, and exercising bouts&lt;br&gt;• Sit-to-stand transitions&lt;br&gt;• Mean activity intensity&lt;br&gt;• Sedentary/light/moderate/vigorous time&lt;br&gt;• Six-minute maximum intensity&lt;br&gt;• Daytime sleep&lt;br&gt;• Total steps per day&lt;br&gt;• High cadence steps&lt;br&gt;• Entropy&lt;br&gt;• Sleep onset and rise times&lt;br&gt;• Mid-sleep time&lt;br&gt;• Sleep duration and efficiency&lt;br&gt;• Sleep interruption and fragmentation&lt;br&gt;• Wear time&lt;br&gt;• Rest-activity rhythm (acrophase, mesor, amplitude, and robustness)&lt;br&gt;• Sleep and activity level trends&lt;br&gt;• Sleep duration variability&lt;br&gt;• Activity intensities&lt;br&gt;• Step cadence and sleep parameters by age, sex, clinical history, and self-reported quality of life</td>
</tr>
<tr>
<td><strong>Multiple days</strong>&lt;br&gt;Long-term summary measures&lt;br&gt;Summaries of&lt;br&gt;• data characteristics or&lt;br&gt;• behavioral and physiological classifications</td>
<td>&lt;i&gt;Short-term summary measures&lt;/i&gt;</td>
</tr>
<tr>
<td><strong>Months</strong>&lt;br&gt;Population measures&lt;br&gt;Statistics describing&lt;br&gt;• distribution of data characteristics&lt;br&gt;• behavioral and physiological classifications&lt;br&gt;• summary measures for a population</td>
<td>&lt;i&gt;Daily summary measures&lt;/i&gt;</td>
</tr>
<tr>
<td><strong>Population measures</strong>&lt;br&gt;Statistics describing&lt;br&gt;• distribution of data characteristics&lt;br&gt;• behavioral and physiological classifications&lt;br&gt;• summary measures for a population</td>
<td>&lt;i&gt;Sleep and activity level trends&lt;/i&gt;</td>
</tr>
<tr>
<td><strong>Acrophase</strong> = time of peak activity; <strong>amplitude</strong> = range of activity; <strong>MAD</strong> = mean amplitude deviation; <strong>mesor</strong> = mean activity.</td>
<td>&lt;i&gt;Rest-activity rhythm (acrophase, mesor, amplitude, and robustness)&lt;/i&gt;</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Use during the SafeHeart study</th>
<th>Sensor output</th>
<th>Size and weight</th>
<th>Data analytics</th>
<th>Data extraction</th>
<th>Battery life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENEActiv Development study</strong> (0–6 mo)</td>
<td>Acceleration between 10 and 100 Hz, near body temperature, and light exposure</td>
<td>40 mm wide × 13 mm deep, 27 g</td>
<td>Raw data measurement. Features and measures can be created with standard time-domain statistics, frequency domain approaches, pattern/structure detection, or dedicated algorithms</td>
<td>Via a USB connection</td>
<td>Can record data continuously for 1 wk and 1 mo depending on the sample frequency</td>
</tr>
<tr>
<td><strong>Activinsights Band Development</strong> (6–12 mo) and feasibility study</td>
<td>Behavioral event output (eg, sit, stand, walk, and sleep)</td>
<td>23 mm wide × 13 mm deep, 25 g</td>
<td>Infer time spent in a range of behavioral states using algorithms</td>
<td>Wirelessly to a computer or phone</td>
<td>Can record and communicate data continuously for up to 1 y</td>
</tr>
</tbody>
</table>
consisted of 11,921 transmissions from 1251 participants with an ICD, followed over a 4-year period from 2015 to 2019 at Copenhagen University Hospital-Rigshospitalet. This model was trained on transmission data from remote device monitoring to predict the risk of VT and VF. The data set contained 74,149 arrhythmia episodes, each characterized by 7 variables such as the type of arrhythmia (eg, VT, VF, supraventricular tachycardia, and atrial fibrillation), ICD treatment of the arrhythmia, duration of the episode, and maximum heart rate reached during the episode. The random forest machine learning prediction method provided optimal results compared with other classifier methods (supervised, unsupervised, and deep learning methods) when considering the trade-offs between model performance and explainability. Other models tested included KNeighborsClassifier, GradientBoostingClassifier, AdaBoostClassifier, SVC (Support Vector Classifier), and LSTM (Long Short-Term Memory) neural network. The algorithm was subsequently tested on 2342 of the transmissions, achieving an accuracy of 0.96 with a positive predictive value of 0.67 and a negative predictive value of 0.97 for the prediction of VT and VF 30 days in advance. In the SafeHeart study, this previously developed model is expanded with prospectively collected data during the development study to assess and improve the predictive performance. The aim is to fix the prediction model for the feasibility testing. In the present study, multiple models, including those previously examined, will be evaluated on the basis of several aspects: accuracy, explainability, and generalizability, and the best performing model will be used for the further development of the SafeHeart Platform. For the development of the SafeHeart prediction model, we will use data previously gathered from transmissions and enhance this with prospectively enriched data sources: accelerometry, the electronic health records, and patient-reported outcomes derived from questionnaires. This will allow the evaluation of the previous model using the new data as well as testing the new model on the original data containing only transmission data. The end product of the development study is a new prediction model. In case of a new testing and validation of the new data set during the development study, we will use repeated random splits of the data into training and test data sets.

After the development study, we will use the best performing model and validate it in a fixed feasibility study with 100 patients in total.

### Sample size

As proposed by Figueroa et al, the sample size calculation for prediction algorithms can be estimated using weighted fitting of learning curves on a smaller annotated training set. However, in this early exploratory study where novel data are added to an existing model of which the predictive value is uncertain, it is unrealistic to accurately define the required sample size. With regard to the primary end point (ICD therapy), the number of days of accelerometer data collection is critical for sample size estimation. A prior study by Almehmadi et al demonstrated a cumulative incidence of appropriate ICD therapy (ATP and shock) of 28.5% at 1 year after de novo ICD implantation for secondary prevention. With respect to inappropriate ICD therapy, in a combined primary and secondary prevention ICD patient cohort, a cumulative incidence of 7% was seen for
inappropriate ICD shock in the first year after implantation.\textsuperscript{18} Therefore, we assume an incidence of the primary end point of total ICD therapy—both appropriate and inappropriate ICD therapies—of 25\% (equivalent to a daily incidence of 0.0685\%). With a targeted sensitivity of 95\%, a total of 106,580 days of accelerometer data is required, met by following 292 patients for a year. Considering the 300 patients included in the development study alone, we exceed the minimum required sample size. In addition to accelerometer data, we expect to collect up to 3000 transmissions from remote device monitoring, 900 patient-reported outcome data points, and a minimum of 40 clinical variables from the EHR (eg, sociodemographic, medication usage, and comorbidities).

**Statistical analysis and covariates**

The model performance is evaluated on the basis of the accuracy, sensitivity (recall), specificity, positive predictive value (precision), negative predictive value, and the area under the curve. The accuracy of the models is compared using a 2-sided McNemar test, and a 1-sided binomial test is used to curve. The accuracy of the models is compared using a 2-
technology development is used. An important limitation to the study could be suboptimal compliance with the wearable; however, prior studies have indicated high compliance with accelerometers when used for shorter time periods than in our study. It is yet uncertain what noncompliance rate generally applies specifically to a population with an ICD. Furthermore, SafeHeart examines a high-risk population, potentially limiting the generalizability to primary prevention patients or lower risk patients. Related to this, the power to predict arrhythmia is dependent on the occurrence and distribution of clinical end points between participants in this specific patient population. A sample size calculation was made on the basis of expected event rates, but the risk remains of receiving few end points aggregated in the same few participants affecting the generalizability of the results. Last, although AI-based prediction tools have clear advantages over more classical statistical models in terms of accuracy, these “black-box algorithms” are limited in their interpretability, which hinders clinical application. Through the display of feature relevance, presenting reasons for an alarm being triggered and use of the local interpretable model-agnostic explanation procedure, more insight into the algorithm is given.

Conclusion
The SafeHeart study is the first to prospectively develop a platform consisting of a patient app, remote monitoring, wearable accelerometer, and a clinician’s dashboard. The prediction algorithm for ICD therapy is based on a multi-modal data set integrating clinical data, remote monitoring, high-resolution accelerometer data, and patient-reported outcomes. Clinical implementation of the results will be facilitated by combining a development and a feasibility study in 1 prospective study design. With the SafeHeart study we aim to provide clinicians with a clinical decision support system that assists in follow-up care for ICD carriers. The SafeHeart study will inform the design of a future randomized controlled trial that compares standard of care to the SafeHeart platform. The prediction algorithm for ICD therapy is based on a multi-modal data set integrating clinical data, remote monitoring, high-resolution accelerometer data, and patient-reported outcomes. Clinical implementation of the results will be facilitated by combining a development and a feasibility study in 1 prospective study design. With the SafeHeart study we aim to provide clinicians with a clinical decision support system that assists in follow-up care for ICD carriers. The SafeHeart study will inform the design of a future randomized controlled trial that compares standard of care to the SafeHeart platform.

Acknowledgments
We thank Merijn Hofland, Bsc, clinical automation specialist at Amsterdam UMC, for his help in building the research data infrastructure. We thank the participants of the study. Furthermore, we thank the European Union funding program for research and innovation for the Horizon 2020 (grant number: Eurostars project E!113994- SafeHeart).

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Disclosures
Dr Andersen is cofounder of Vital Beats and has stock ownership. He is coauthor of a pending patent application that is within the field of this study. Mr Langford is an employee and shareholder of Activinsights Ltd, the manufacturers of the behavioral assessment wearable used in the study. The rest of the authors report no conflicts of interest.

Authorship
All authors attest they meet the current International Committee of Medical Journal Editors criteria for authorship.

Patient Consent
All patients provide written informed consent before inclusion.

Ethics Statement
The authors designed the study and gathered and analyzed the data according to the Helsinki Declaration guidelines on human research. The research protocol used in this study was reviewed and approved by the institutional review board.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.cvdhj.2021.10.002.

References


