

**DE NOVO CLASSIFICATION REQUEST FOR
IRREGULAR RHYTHM NOTIFICATION FEATURE**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Photoplethysmograph analysis software for over-the-counter use. A photoplethysmograph analysis software device for over-the-counter use analyzes photoplethysmograph data and provides information for identifying irregular heart rhythms. This device is not intended to provide a diagnosis.

NEW REGULATION NUMBER: 21 CFR 870.2790

CLASSIFICATION: Class II

PRODUCT CODE: QDB

BACKGROUND

DEVICE NAME: Irregular Rhythm Notification Feature

SUBMISSION NUMBER: DEN180042

DATE OF DE NOVO: August 8, 2018

CONTACT: Apple Inc.
One Apple Park Way
Cupertino, CA 95014

INDICATIONS FOR USE

The Irregular Rhythm Notification Feature is a software-only mobile medical application that is intended to be used with the Apple Watch. The feature analyzes pulse rate data to identify episodes of irregular heart rhythms suggestive of atrial fibrillation (AFib) and provides a notification to the user. The feature is intended for over-the-counter (OTC) use. It is not intended to provide a notification on every episode of irregular rhythm suggestive of AFib and the absence of a notification is not intended to indicate no disease process is present; rather the feature is intended to opportunistically surface a notification of possible AFib when sufficient data are available for analysis. These data are only captured when the user is still. Along with the user's risk factors, the feature can be used to supplement the decision for AFib screening. The feature is not intended to replace traditional methods of diagnosis or treatment.

The feature has not been tested for and is not intended for use in people under 22 years of age. It is also not intended for use in individuals previously diagnosed with AFib.

LIMITATIONS

The Irregular Rhythm Notification Feature cannot detect heart attacks. If you ever experience chest pain, pressure, tightness, or what you think is a heart attack, call emergency services.

The Irregular Rhythm Notification Feature is not constantly looking for AFib and should not be relied on as a continuous monitor. This means the feature cannot detect all instances of AFib, and people with AFib may not get a notification.

Apple Watch may be unable to collect data when Apple Watch is in close vicinity to strong electromagnetic fields (e.g. electromagnetic anti-theft systems, metal detectors).

A number of factors can impact the ability of the feature to measure your pulse and detect an irregular rhythm suggestive of AFib. These include factors like motion, hand and finger movements, dark tattoos on the wrist, and the amount of blood flow to your skin (which can be reduced by cold temperatures).

DO NOT wear your Apple Watch during a medical procedure (e.g., magnetic resonance imaging, diathermy, lithotripsy, cautery and external defibrillation procedures).

DO NOT change your medication without talking to your doctor.

Not intended for use by individuals under age 22.

Not intended for use by individuals previously diagnosed with AFib.

Notifications made by this feature are potential findings, not a complete diagnosis of cardiac conditions. All notifications should be reviewed by a medical professional for clinical decision-making.

Apple does not guarantee that you are not experiencing an arrhythmia or other health conditions even in the absence of an irregular rhythm notification. You should notify your physician if you experience any changes to your health.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

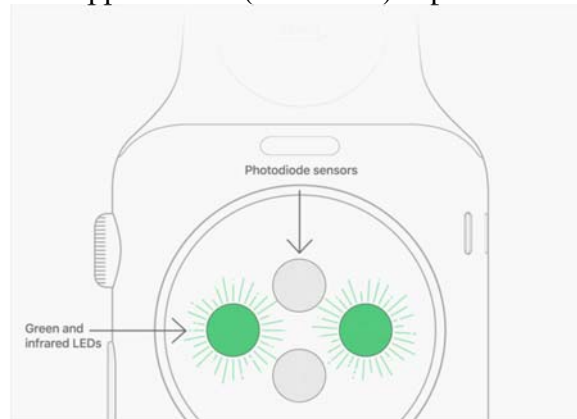
The Irregular Rhythm Notification Feature comprises a pair of mobile medical apps, one on Apple Watch and the other on the iPhone. The Irregular Rhythm Notification Feature analyzes pulse rate data collected by the Apple Watch photoplethysmograph (PPG) sensor to identify episodes of irregular heart rhythms consistent with atrial fibrillation (referred to in this document as AF or AFib) and provides a notification to the user. It is a background screening tool and there is no way for a user to initiate analysis of pulse rate data. The Irregular Rhythm Notification Feature is part of the Health App, which allows users to store, manage, and share health and fitness data, and comes pre-installed on every iPhone. Users must opt-in and go through on-boarding prior to use of the Irregular Rhythm Notification Feature.

The Irregular Rhythm Notification Feature is not intended to diagnose atrial fibrillation, and is not intended to be used to guide clinical treatment or care.

Platform/PPG

The Irregular Rhythm Notification Feature leverages heart rate data collected from the commercially available PPG sensor on Series 1 and later Apple Watch platforms. The Apple Watch uses green LED lights paired with light-sensitive photodiodes to detect relative changes in the amount of blood flowing through a user's wrist at any given moment. When the heart beats it sends a pressure wave down the vasculature, causing a momentary increase in blood volume when it passes by the sensor. By monitoring these changes in blood flow, the Apple Watch can measure the heart rate. Further, under stationary conditions the sensor can detect individual pulses when they reach the periphery and thereby measure the beat-to-beat intervals.

A schematic of the sensors on the Apple Watch (Series 1-3) is provided below.



Currently, Apple Watch attempts to collect and analyze a one-minute beat-to-beat sequence (called a “tachogram”) in the background (i.e., with no user action required) approximately every 4 hours, depending on user activity. A minimum of (b) (4) pulses is required for a measurement to be considered successful and stored in HealthKit; measurements are stored as beat-to-beat time intervals. Measurements that do not meet the specification are discarded and never surfaced to the user in any form.

Irregular Rhythm Notification Feature

The Irregular Rhythm Notification Feature refers to the tachogram classification algorithm, confirmation cycle algorithm, and the AF notification generation. Tachogram analysis is initiated when the Irregular Rhythm Notification Feature retrieves a new tachogram from Watch HealthKit. Tachograms are classified as either irregular or not AF. If a sufficient number of tachograms are retrieved and classified to meet the notification threshold (5 of 6 sequential tachograms classified as irregular within a 48-hour period), a notification indicating that the heart rhythm has shown signs of AF will be displayed to the user. Individual tachogram classification results for sequences that do not meet the notification threshold are not accessible to the user. If an irregular heart rhythm suggestive of AF is identified, the Irregular Rhythm Notification Feature will transfer the AF notification to the iPhone App through HealthKit sync. In addition to indicating the finding of signs of AF, the notification will encourage the user to seek medical care if they have not previously been diagnosed with AF.

iPhone App

Apple considers the iPhone App to be the Irregular Rhythm Notification Feature User Interface (UI) Framework as well as the information included in the Atrial Fibrillation Notification portion of the Health App. The Irregular Rhythm Notification Feature UI Framework contains the onboarding and educational materials that a user must review prior to enabling AF notifications. The iPhone App is designed to work in combination with the Irregular Rhythm Notification Feature Watch App and will display a history of all prior atrial fibrillation notifications. The user is also able to view a list of times when each of the irregular tachograms contributing to the notification was generated.

SUMMARY OF NONCLINICAL/BENCH STUDIES

SOFTWARE

Irregular Rhythm Notification Feature has a Moderate Level of Concern (LOC). Appropriate documentation was provided to support the validation of the software for a Moderate LOC in accordance with FDA's 2005 guidance titled, "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.*"

PERFORMANCE TESTING – BENCH

Irregular Rhythm Notification Feature was subjected to a series of bench tests to assess its functional performance. These tests were performed on a version of the device that was sufficiently representative of the final version of the device. The engineering bench testing summarized in the table below was performed to demonstrate acceptable performance of the device for its intended use. Bench testing results were compared to commercial, FDA-cleared clinical ECG.

Performance/Input Signal Testing (Bench) Summary

Test		Description	
Deep Breathing Testing		Evaluate performance during sinus rhythm variation due to respiratory sinus arrhythmia.	
External Aggressor Condition testing	Riding in a car (vibration)	44 subjects, 1434 measurements	Determine the effect of factors known to lead to systematic false positive spot measurements for any individual or use case.
	Targeted Hand + finger motions	20 subjects, 246 measurements	
	Low perfusion	102 subjects, 2461 measurements	
	Hand Tremors	143 subjects, 936 measurements	
Skin Tone Performance		Validation of algorithm performance on PPG acquired across 1124 subjects, 1.3 million measurements. Algorithm performance showed no clinically relevant difference from the very darkest Fitzpatrick VI subjects to very light-skinned Fitzpatrick I subjects. No algorithm changes or signal processing modifications are necessary to account for differences in skin tone.	
Input Signal Source Qualification		Effects of PPG hardware on Apple Watch Series versions compatible with the Irregular Heart Rhythm Feature on the input signal used to quantify the effect on the algorithm performance and found to have no measured difference. Input signal source validation was repeated on every compatible watch version.	

SUMMARY OF CLINICAL INFORMATION

Clinical Study

The sponsor provided a clinical study protocol and results to support the safety and effectiveness of the device. This study used data collected from a subset of participants enrolled in a large, prospective, single-arm study conducted to investigate if the PPG data collected by the Apple Watch can be used to identify episodes of AF-related irregular heart rhythm in users without known atrial fibrillation. The sub-study enrolled only those participants from the the larger study who received one prior Irregular Rhythm notification.

Once enrolled, the study participants wore their Apple Watch with the Irregular Rhythm feature as per normal usage while being monitored with a 7-day ambulatory patch ECG recorder. For each one-minute irregular rhythm episode (tachogram) identified by the software, the corresponding patch ECG recording was extracted and classified by independent cardiologists as either “Sinus rhythm”, “AF”, “Unreadable”, or “Other Irregular Rhythm.” The primary objective of the study is to determine if the tachogram classification algorithm has acceptable positive predictive value as compared to ambulatory ECG patch monitoring in identifying irregular rhythms consistent with atrial fibrillation.

A total of 269 subjects were included in the Full Analysis Set (FAS). The mean age was 59.2 ± 13.3 years, and 80.2% (210/269) were male. Of the 269 subjects, 27 were removed from the FAS due to data exclusions and 16 subjects were removed due to lack of ambulatory ECG monitor data. Accordingly, 226 subjects provided analyzable ECG monitor data and tachogram data and were included in the efficacy analyses. Among these 226 subjects during the ambulatory ECG

monitoring (on average of 6.3 days), 2634 (out of a total of 10432 tachograms) irregular tachograms were recorded, and 57 subjects (25.2%) received at least one alert. Using the ambulatory ECG monitor data as the reference, the positive predictive value (PPV) of spot irregular tachograms to detect AF was 66.6% (lower 97.5% confidence bound: 63.0%). The results failed to meet the pre-specified (b) (4) % performance goal.

Despite failing to meet the primary study endpoint, the results of secondary and additional analyses are supportive of the device's effectiveness to detect AF. Per the protocol-specified secondary analysis, the notification-level PPV for AF in this enriched population was 78.9% (95% CI: 66.1%, 88.6%). A post hoc analysis was also performed to determine the proportion of subjects who had documented atrial fibrillation during the entire 7-day patch cardiac monitoring. Of the 226 subjects, who already received one or more device notifications before enrolling in the sub-study, the probability of being diagnosed with AF on subsequent 7-day patch cardiac monitoring was 41.6% (95% CI: 35.1%, 48.3%).

Human Factors and Usability Study

The sponsor provided a Human Factors and Usability study which included a total of 37 participants from the two user groups for the Irregular Rhythm Notification Feature:

- Individuals who have concern regarding arrhythmias and have an active interest in monitoring potential arrhythmias ("Active Interest", n=16), and
- Individuals who do not have concern regarding arrhythmias and do not have an active interest in monitoring potential arrhythmias but who might use the app out of casual or passing interest ("Passive Interest", n=21).

Both groups included participants with and without past experiences with iPhones and Apple Watches.

All participants set up the app, which was meant to simulate the actual on-boarding process. The participants then experienced a decay period of approximately 1 hour, and then a testing session that lasted approximately 30 minutes. Sessions took place in a simulated home environment representative of an expected environment of use in real life. Both observational data and subjective evaluations were collected.

Overall, usability testing demonstrated that the Irregular Rhythm Notification Feature is safe and effective for the intended users, uses, and use environments. In particular:

- 36/37 participants successfully responded indicating that a lack of a notification from the App would not affect their medical decisions.
- 35/35 participants successfully received a notification and indicated they would not reduce care if experiencing acute symptoms.

Pediatric Extrapolation

The device is indicated for use only in adults – that is, persons aged 22 and older. The Federal Food, Drug, and Cosmetic Act defines pediatric patients as persons aged 21 or younger. In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The labeling for the device is sufficient and satisfies the requirements of 21 CFR 801.109. The labeling consists of Instructions for Use and an onboarding sequence. The Instructions for Use include the indications for use; a description of the device, precautions; a detailed summary of the clinical data collected in support of the device; a list of potential adverse events; and instructions for the safe use of the device.

Please see the Limitations section above for important contraindications, warnings and precautions presented in the device labeling.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of photoplethysmograph analysis software for over-the-counter use and the measures necessary to mitigate these risks.

Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Poor quality incoming PPG signal resulting in failure to detect irregular heart rhythms	Clinical performance testing Human factors testing Labeling
Misinterpretation and/or over-reliance on device output, leading to: <ul style="list-style-type: none">• Failure to seek treatment despite acute symptoms (e.g., fluttering sensation in the chest, lightheadedness, and irregular pulse)• Discontinuing or modifying treatment for chronic heart condition	Human factors testing Labeling
False negative resulting in failure to detect irregular heart rhythms and delay of further evaluation or treatment	Clinical performance testing Software verification, validation, and hazard analysis Non-clinical performance testing Labeling

False positive resulting in additional unnecessary medical procedures	Clinical performance testing Software verification, validation, and hazard analysis Non-clinical performance testing Labeling
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SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the photoplethysmograph analysis software for over-the-counter use is subject to the following special controls:

1. Clinical performance testing must demonstrate the performance characteristics of the detection algorithm under anticipated conditions of use.
2. Software verification, validation, and hazard analysis must be performed. Documentation must include a characterization of the technical specifications of the software, including the detection algorithm and its inputs and outputs.
3. Non-clinical performance testing must demonstrate the ability of the device to detect adequate PPG signal quality.
4. Human factors and usability testing must demonstrate the following:
 - a. The user can correctly use the device based solely on reading the device labeling; and
 - b. The user can correctly interpret the device output and understand when to seek medical care.
5. Labeling must include:
 - a. Hardware platform and operating system requirements;
 - b. Situations in which the device may not operate at an expected performance level;
 - c. A summary of the clinical performance testing conducted with the device;
 - d. A description of what the device measures and outputs to the user; and
 - e. Guidance on interpretation of any results.

BENEFIT/RISK DETERMINATION

The Irregular Rhythm Notification Feature is an effective device for identifying abnormal pulse rates that may suggest the presence of atrial fibrillation. When a user receives one or more alerts from the device, the probability of diagnosing AF via subsequent 7-day ambulatory cardiac ECG monitoring is 41.6%. The device is not intended to diagnose AF, but it provides an accessible tool to identify individuals who are likely to benefit from further AF screening with ECG-based methods. It can be used to prescreen persons outside of the traditional high-risk population (i.e., age < 65 years) to improve the subsequent diagnostic yield of AF screening.

The risks of the device are mostly associated with false positive and false negative results, which can lead to either delay of further treatment (false negative) or unnecessary medical procedures (false positive). Clinical testing, under the conditions of use, is required to: 1) ensure that the device

is provided with sufficient incoming PPG signal quality, and 2) characterize the likelihood of false results. Labeling is also required to help the user interpret the results they receive. Here, the labeling specifically states that the feature is not intended to replace traditional methods of diagnosis and that diagnosis for AF should still be done by ECG confirmation.

Even when the device provides a true result, there is also a probable risk of users misinterpreting the device output and using it to disregard acute symptoms, e.g. symptoms indicative of a heart attack; alternatively, users may interpret the device output as providing permission to avoid compliance with an existing prescribed treatment for a chronic heart condition. Users may also view the device as providing a definitive diagnosis of AF even though a positive result is intended only to notify the user of an irregular rhythm suggestive of AF and supplement the decision for AF screening. However, this risk of misinterpretation can be mitigated through labeling and requiring a human factors evaluation of whether users understand how the device output should be interpreted and when to seek further care from a physician.

Since AF is associated with serious potential complications, a device that can provide early detection or improve the efficiency of AF screening is clinically valuable. On a large scale, the benefits to health of improved AF detection outweighs the risks of false results and misinterpretation. There is a reasonable assurance of safety and effectiveness for the device when used as intended.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for the software analysis of PPG data for the identification of irregular heart rhythm that may indicate the presence of AF in a general population, the probable benefits outweigh the probable risks for the Irregular Rhythm Notification Feature. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Irregular Rhythm Notification Feature is granted and the device is classified under the following:

Product Code: QDB

Device Type: Photoplethysmograph analysis software for over-the-counter use

Class: II

Regulation: 21 CFR 870.2790