Medical Device Development Tool (MDDT) Summary of Evidence and Basis of Qualification

Apple Atrial Fibrillation History Feature

Background

MDDT NAME   Apple Atrial Fibrillation History Feature

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CONTACT   Sam Surette
Apple, Inc.
One Apple Park Way
Cupertino, CA 95014
Email: ssurette@apple.com

Tool Description and Principle of Operation

The Atrial Fibrillation (AFib) History Feature is an FDA-cleared (K213971), commercially available over-the-counter ("OTC") software-only mobile medical application intended for users 22 years of age and over who have a diagnosis of AFib. The feature opportunistically analyzes pulse rate data collected by the general-purpose Apple Watch photoplethysmography (PPG) sensor to identify episodes of irregular heart rhythms consistent with AFib and provides the user with a retrospective estimate of AFib burden (a measure of the amount of time spent in AFib during past Apple Watch wear).

The Apple Watch PPG sensor uses green light-emitting diodes (LEDs) 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 through the vasculature, causing a momentary increase in blood volume when the wave passes by the sensor. By monitoring the change in blood flow, the sensor detects individual pulses when they reach the periphery and thereby measures beat-to-beat intervals. The AFib History Feature analyzes these intervals to determine an estimate of the amount of time spent in AFib during the previous week of Apple Watch wear.

Qualified Context of Use

The Apple AFib History Feature can be used as a biomarker test to help evaluate estimates of AFib burden as a secondary effectiveness endpoint within clinical studies intended to evaluate the safety and effectiveness of cardiac ablation devices. The weekly estimates of AFib burden generated by the AFib History Feature can be used for comparative analysis across arms of a clinical study. The AFib History Feature may be used throughout the clinical study to monitor a participant's weekly estimate of AFib burden in order to compare weekly burden estimates before and after cardiac ablation treatment. The AFib History Feature's utility as a secondary endpoint is not intended to replace the findings of any primary endpoints (i.e., it cannot by itself be used to evaluate the safety and effectiveness of cardiac ablation devices).

Summary of Evidence to Support Qualification

The performance testing to support qualification of the AFib History Feature as a biomarker test for the qualified context of use is derived from the evidence submitted in support of its FDA clearance as a class II photoplethysmograph analysis software for over-the-counter use (K213971).

Apple conducted a prospective clinical study to evaluate the performance of the AFib History Feature device. The performance of the AFib History Feature was evaluated using data from the following two cohorts which included 280 subjects:

- **Non-permanent AFib:** included subjects with known history of paroxysmal or persistent AFib*.
- **Permanent AFib:** included subjects with permanent AFib.
  History of AFib encompasses the 2 years prior to participation in study screening procedures.

The primary endpoint for the AFib History study was the accuracy of the weekly AFib burden estimate defined as the percentage of time a subject is in AFib during wrist device wear over the prior seven (7) consecutive days. The ground truth was established using a reference device (Cardea SOLO Wireless ECG Patch (K123217)). The analysis demonstrated that the lower and upper bounds of the limits of agreement (LOAs) were -11.4% and 12.8%, respectively.[1] The average difference between the AFib History Feature and the reference device's weekly burden estimate was 0.67% with a 95% confidence interval of (-0.05%, 1.38%). 92.9% (260/280) of subjects had paired weekly AFib burden differences within ±5%; 95.7% (268/280) of subjects' weekly AFib burden estimates were within ±10% of the reference.

The generalizability of the device performance was demonstrated through multiple non-powered, subgroup analyses across different user populations. For example, an exploratory endpoint assessing device performance across a range of AFib burden levels was performed and showed negligible differences between the subject and reference device (Table 1).

Table 1: Exploratory Endpoint Assessment

% Burden	Number of Paired AFib Burden Measurements	Average Paired Difference (%, [95% CI])
0	175	1.51 [0.69, 2.35]
0-33	26	1.17 [0.05, 2.29]
33-95	6	2.06 [-1.28, 5.40]
>95	72	-0.86 [-1.52, -0.20]

Furthermore, of the 280 subjects who contributed to the primary endpoint analysis, 36 subjects had reported prior history of catheter ablation for the treatment of AFib. Results from the post-hoc subgroup analysis is presented below (**Table 2**).

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[1] Lu MJ et al. *Int J Biostat.* 2016

Table 2: Post-hoc Subgroup Analysis Results

Had a prior Ablation?	Parameter	Value	95% Confidence Interval
No	Number of Paired AFib Burden Measurements	243	
No	Average Paired Differences (Algorithm – Reference)	0.76%	**[0.19%, 1.33%]**
No	Standard Deviation of Paired Differences	4.53%	
No	Lower Limit of Agreement	-8.29%	**[-9.09%, -7.13%]**
No	Upper Limit of Agreement	9.81%	**[8.65%, 10.61%]**
Yes	Number of Paired AFib Burden Measurements	36	
Yes	Average Paired Differences (Algorithm – Reference)	1.68%	**[-0.64%, 4.00%]**
Yes	Standard Deviation of Paired Differences	6.86%	
Yes	Lower Limit of Agreement	-12.0%	**[-15.8%, -7.77%]**
Yes	**Upper Limit of Agreement**	**15.41%**	**[11.13%, 19.14%]**

The average paired difference remained low (<2%) in both groups and the upper and lower limits of agreement remained within clinically acceptable ranges. The Upper Limit of Agreement in subjects who underwent prior ablation exceeded the pre-specified acceptance criterion of 15%.

Additional subgroup analyses by sex, race, ethnicity, age group, and Fitzpatrick scale (i.e., skin tone) were performed and demonstrated that the device accuracy was similar across subgroups.

Discussion of the Evidence Strength to Support Qualification

The performance data summarized here demonstrate the effectiveness of the AFib History Feature to provide clinically acceptable retrospective weekly AFib burden estimates, thus meeting the objective qualification criteria for the AFib History feature as a biomarker test. The additional sub-group analyses further evaluate the device across two parameters of interest for the qualified context of use: patients across the spectrum of weekly AFib burden and patients who have undergone ablation treatment. While there was a difference in observed performance among those with a prior ablation, the difference could be attributed to the limitations of the study design (e.g., small sample size for the subgroup of patients with a prior AFib ablation procedure). Qualification of the tool in this patient population as a secondary endpoint may support the acquisition of additional data in order to further characterize its performance in this patient population.

Assessment of Advantages/Disadvantages of Qualification

Assessment of Advantages of Using the MDDT:

The clinical value of assessing AFib burden as part of cardiac ablation device effectiveness is acknowledged by the Agency through its guidance documents and by medical device developers who have already incorporated it as a secondary endpoint within clinical studies (such as the ABLATE trial (P100046)). As discussed in the 2004 FDA guidance document, Guidance for Industry and FDA Staff: Clinical Study Design for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation, a reduction in AFib burden can be challenging as a primary endpoint for reasons such as compliance, potential placebo effects, difficulty in determining a clinically significant reduction in AFib burden, as well as the technical difficulties in measuring AFib burden without an implantable device. The Apple AFib History Feature can help address the challenges of patient compliance, potential placebo

effects, and the technical difficulties without an implantable device by allowing for passive, opportunistic AFib burden estimation in a wearable form that is already familiar to Apple Watch users.

The qualification of the Apple AFib History feature as an MDDT may reduce the burden on medical device developers by eliminating the need to provide a rationale for its collection methods and cadence (e.g., weekly outputs compared to conducting a 24-hour Holter monitoring at 6 months post treatment) with respect to AFib burden estimates, thus reducing the barrier of incorporation into clinical studies. Device developers will also be able to capture this valuable information more easily and consistently within clinical studies, which may aid in better understanding the post-treatment characteristics of AFib burden in patients.

Assessment of Disadvantages of Using the MDDT:
While the Apple AFib History Feature addresses many challenges identified by the FDA's guidance documents, it does not provide guidance to device developers as to what should be considered a clinically significant reduction in AFib Burden. Rather it simply provides a method for developers and investigators to capture estimated AFib burden information on a weekly basis for the purpose of comparison between treatment arms; it will be the responsibility of the investigators to define and justify the specific study design and endpoints.

The clinical study used for qualification of the tool was not powered to demonstrate equivalent performance in patients with and without a prior AFib ablation. Therefore, it is possible that performance may be reduced in patients who have undergone prior ablation. Due to the limited data and a study design not focused on this specific patient population, the performance of the device may differ from the overall performance reported above. Furthermore, studies[2] suggest that heart rate variability may be reduced after AFib ablation, which could adversely impact the accuracy of the device. Therefore, there would be benefit in assessment of the tool side-by-side with other means of determining AFib Burden in this patient population.

Additionally, the Apple AFib History Feature does not provide specific time stamps of when AFib episodes occurred, the length of episodes, or ventricular rate during episodes. AFib episode durations shorter than the time between opportunistic measurements may not contribute to the estimate of AFib burden. The feature requires a minimum of 1 week (7 days) to obtain a retrospective estimate of AFib burden. Finally, the feature only works if the participant is wearing the watch, so there may be times when the participant is not being monitored (e.g., during charging or bathing).

The tool does not identify atrial tachyarrhythmias other than AFib (including atrial flutter and atrial tachycardia). Of note, FDA typically requests that the definition of AFib ablation success in studies used to support approval of new ablation catheters include the occurrence of any atrial tachyarrhythmia post-ablation. This limitation underlies the qualified use of the tool as only a secondary endpoint to compare estimates of AFib burden.

Conclusions

The clinical study conducted in support of FDA clearance of AFib History Feature provides sufficient evidence to demonstrate the MDDT is qualified for the proposed context of use, considering both the advantages and disadvantages listed above. The use of the tool as a secondary endpoint may also allow for additional collection of data in order to more fully characterize the performance of the tool in this patient population. The tool may aid in better understanding AFib burden in patients while providing supplemental data to more clinically well-defined endpoints. Use of the tool should consider applicable FDA guidance on digital health technologies, including, "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations," available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-

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[2] Verma A et al. *JAMA Intern Med.* 2013

remote-data-acquisition-clinical-investigations.

Contact Information for Access to Tool

Apple Atrial Fibrillation History Feature is a commercially available tool on Apple Watch Series 4 or later, including all models of Apple Watch SE and Apple Watch Ultra, running watchOS 9 or later, and iPhone 8 or later running iOS 16 or later. Refer to developer.apple.com for resources on using DeveloperKit and HealthKit.

References

1. Lu MJ, Zhong WH, Liu YX, Miao HZ, Li YC, Ji MH. Sample Size for Assessing Agreement between Two Methods of Measurement by Bland-Altman Method. *Int J Biostat.* 2016;12(2):/j/ijb.2016.12.issue-2/ijb-2015-0039/ijb-2015-0039.xml. doi:10.1515/ijb-2015-0039

2. Verma A, Champagne J, Sapp J, et al. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): a prospective, multicenter study. *JAMA Intern Med.* 2013;173(2):149-156. doi:10.1001/jamainternmed.2013.1561