Appendix 1: Literature Search report (099-21178) and Protocol (099-21179) of the

Clinical Evaluation Report for the ECG 1.0 App, ECG 2.0 App and Irregular Rhythm Notification Feature (IRNF) 1.0

APN: 099-21180
Revision: D

ECO 0034300226

LITERATURE SEARCH PROTOCOL:

ECG 1.0, ECG 2.0 APP

AND

IRREGULAR RHYTHM NOTIFICATION FEATURE 1.0 (IRNF)

DOCUMENT NUMBER: 099-21177
REVISION: C

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1.0 OVERVIEW

A focused literature search and a summarization of the identified medical literature are to be performed to:

1. Evaluate the current state-of-the-art of the detection of and screening for atrial fibrillation (AFib)/intended use; and

2. Identify clinical literature pertaining to the safety and performance of the ECG 1.0 App, ECG 2.0 App, and Irregular Rhythm Notification 1.0 Feature (IRNF).

This protocol outlines the key components of the subsequent Literature Report and the methods and procedures that will be used to generate the report.

Apple Inc. has established a comprehensive Risk Management process for medical devices compiled in accordance with the requirements of ISO 14971:2012 *Medical devices – Application of risk management to medical devices*. The individual documents all have had cross-functional input and review. The Risk Management documentation is reviewed and updated periodically, as well as whenever a new hazard or risk factor is identified. Apple's Risk Management process also provides for a comprehensive analysis and approval of the residual risks from proposed and completed mitigations. This Literature Protocol and subsequent Report will inform the Clinical Evaluation Report(s) (CERs) of Apple products, which are an ongoing portion of the Risk Management process.

2.0 OBJECTIVE

Two clinical literature search strategies are defined in this protocol. The purpose of the Safety and Performance clinical literature search strategy is to identify, appraise, analyze and summarize favorable and unfavorable data pertaining to the Apple ECG 1.0 App, ECG 2.0 App, and IRNF 1.0. The resulting Literature Search Report will be used to support the Apple Apple ECG 1.0 App, ECG 2.0 App, and IRNF 1.0 CER.

A separate State of the Art (SOTA) search strategy is defined to identify clinical literature pertaining to the current state-of-the-art in the detection of and screening for undiagnosed AFib, which is consistent with the intended use of the ECG 1.0 App, ECG 2.0 App, and IRNF 1.0. The SOTA literature search will be focused on addressing the following questions:

- What is the patient population and medical condition being treated and what are the alternatives (medical options and similar devices) available to the target populations?
- What are the advantages/benefits, or performance outcomes, and disadvantages/limitations, or adverse effects for the alternative options?
- Is the subject device state of the art? What is the current gold standard?

The current literature search to be conducted is in addition to the previous clinical literature searches listed in the Literature Search Protocols below.

- 099-21177 Rev. A. Literature Search Protocol: Detection and Screening of Atrial Fibrillation (AFib): Apple ECG App and IRN Feature (25 November 2019)

- 099-15419, Rev. B/099-15420, Rev. B. Literature Search Protocol: Detection and Screening of Undiagnosed Atrial Fibrillation (AFib) (23 August 2019).
    - (Note: there was no change in the search terms from Rev. A to Rev. B of this protocol. Two document numbers were assigned to the literature search protocol in support of the separate ECG App CEP (099-15415) and IRNF CEP (099-15416). The documents are otherwise identical, and the device evaluations have since been merged into a single clinical evaluation (CEP 099-21179; Literature Search Protocol 099-21177).
- 099-21177 Rev. B. Literature Search Protocol: Detection and Screening of Atrial Fibrillation (AFib): Apple ECG 1.0 App, 2.0 App, and IRNF 1.0, Rev B, 04 September 2020. Apple Inc.

Updated SOP (099-19205 – Clinical Evaluation, Rev. B to Rev. C) guiding the clinical evaluation process defines a 5-year literature search period pertaining to the state of the art as well as safety and performance of the device under evaluation.

3.0 REFERENCES

Council Directive 93/42/EEC of 93/42/EEC of 14 June 1993 concerning Medical Devices as amended by 2007/47/EC (MDD)

MEDDEV 2.7/1 Rev. 4, Clinical Evaluation: A Guide for Manufacturers and Notified Bodies

EU Medical Device Regulation 2017/745 (MDR)

SG5/N2R8: 2007, GHTF SG5 Document on Clinical Evaluation

SOP 099-19205 rev. C: Clinical Evaluation

099-15419/099-15420: Literature Search Protocol: Detection and Screening of Undiagnosed Atrial Fibrillation (AFib), Rev. B, 23 August 2019.

099-21177: Literature Search Protocol: Detection and Screening of Undiagnosed Atrial Fibrillation (AFib): Apple ECG App and IRN Feature, Rev. A, 25 November 2019. Apple, Inc.

099-21178: Literature Search Report: Detection and Screening of Undiagnosed Atrial Fibrillation (AFib): Apple ECG App and IRN Feature, Rev. A, 25 November 2019. Apple, Inc.

099-21177: Literature Search Protocol: Detection and Screening of Undiagnosed Atrial Fibrillation (AFib): Apple ECG 1.0 App, ECG 2.0 App, and IRNF 1.0, Rev B, 04 September 2020. Apple Inc.

4.0 METHODS AND PROCEDURES

The literature review and summary will be performed according to the guidelines stipulated in GHTF guidance on Clinical Evaluation and MEDDEV 2.7.1 Rev. 4 and are to include both negative and positive publications. The PICO method will be used to develop the

search strategy. Patient characteristics and interventions will be used to define the search terms. Controls(s) and outcomes will be used to guide the data analysis.

PICO Search Strategy:

- Patient Characteristics: This search will focus on subjects with potentially undiagnosed atrial fibrillation that could be diagnosed or detected through screening methods.
- Interventions: Methods of screening for and detection of undiagnosed atrial fibrillation or irregular heart rhythms, including electrocardiogram (ECG) and irregular rhythm notification (IRN).
- Controls: This search will focus on the role of wearable technology in screening for and detection of undiagnosed atrial fibrillation.
- Outcomes: Outcomes of this search will focus on identifying methods of screening for and detection of undiagnosed atrial fibrillation, to enable comparison of the safety and performance outcomes.

4.1 DATABASES

The following data sources will be searched to obtain evidence of clinical safety and performance for the devices under evaluation.

- *PubMed* represents a broad review of the literature, which includes well accepted sources and provides adequate information. While not as complete as other databases (e.g., Embase), for the purpose of gathering general information on the current state-of-the-art and "gold standard," PubMed includes sufficient data to support this objective. If PubMed is unable to provide a varied (providing both positive and negative results) and substantial pool of data, other databases may be utilized. (https://www.ncbi.nlm.nih.gov/pubmed/)
- *ClinicalTrials.gov* is a resource provided by the U.S. National Library of Medicine, and contains 362,558 research studies in 219 countries. This source will be searched to identify clinical trials pertaining to the devices under evaluation or similar devices. (https://clinicaltrials.gov/)
- *EU Clinical Trials Register* identifies information on 38,787 clinical trials conducted in the European Union (EU) and the European Economic Area (EEA).

  (https://www.clinicaltrialsregister.eu/ctr-search/search)
- *WHO International Clinical Trials Registry Platform (ICTRP)* identifies information contained in a network of international clinical trial registers. (https://www.who.int/ictrp/en/)

PubMed will be searched to obtain information pertaining to the State of the Art in the field of atrial fibrillation screening and detection.

4.2 SCIENTIFIC LITERATURE DATABASE SEARCH METHODOLOGY – DEVICES UNDER EVALUATION

Table 1–Table 4 identify the search terms and filters that will be used to obtain relevant human clinical data pertaining to the safety and performance of the Apple ECG 1.0 App, ECG 2.0 App, and IRNF.

Table 1. PubMed Search Criteria – Devices Under Evaluation

Search ID	Search Term	Search Period	Filters
1	("Apple Watch" OR iPhone) AND "Atrial Fibrillation"	January 1, 2016 – December 31, 2020	• Full Text • English • Article type: Clinical study, clinical trial, comparative study, journal article, randomized controlled trial, validation study
2	("Apple Watch" OR iPhone) AND (ECG OR Electrocardiogram)		
3	("Apple Watch" OR iPhone) AND (IRN* OR "irregular rhythm" OR arrhythmia)		

Clinical Trials

Table 2. ClinicalTrials.gov – Devices under Evaluation

Search ID	Search Term	Search Period	Filters
4	(Apple OR Watch OR iPhone) AND "Atrial Fibrillation"	Last update posted: January 1, 2016 – December 31, 2020	• Study type: All studies • Studies with Results • Studies that Accept Healthy Volunteers
5	(Apple OR Watch OR iPhone) AND (ECG OR Electrocardiogram)		
6	(Apple OR Watch OR iPhone) AND (IRN* OR "irregular rhythm" OR arrhythmia)		

Table 3. EU Clinical Trials Register – Devices under Evaluation

Search ID	Search Term	Search Period	Filters
7	(Apple OR Watch OR iPhone) AND Atrial Fibrillation	January 1, 2016 – December 31, 2020	• Trials with Results
8	(Apple OR Watch OR iPhone) AND (ECG OR Electrocardiogram)		
9	(Apple OR Watch OR iPhone) AND (IRN* OR irregular rhythm OR arrhythmia)		

Table 4. WHO ICTRP – Devices under Evaluation

Search ID	Search Term	Search Period	Filters
10	**Title:** (Apple OR Watch OR iPhone) AND "Atrial Fibrillation" AND **Condition:** Atrial Fibrillation	January 1, 2016 – December 31, 2020	• Trials with Results

	AND **Intervention:** (Apple OR Watch OR iPhone)		• Recruitment status = ALL
11	**Title:** (Apple OR Watch OR iPhone) AND (ECG OR Electrocardiogram) AND **Condition:** Atrial Fibrillation AND **Intervention:** (Apple OR Watch OR iPhone)		
12	Title: (Apple OR Watch OR iPhone) AND (IRN* OR "irregular rhythm" OR arrhythmia) AND Condition: Atrial Fibrillation AND Intervention: (Apple OR Watch OR iPhone)		

4.3 SCIENTIFIC LITERATURE DATABASE SEARCH METHODOLOGY – STATE OF THE ART

Table 5 lists the search criteria that will be used to identify clinical literature pertaining to the State of the Art.

Table 5. PubMed Search Criteria – State of the Art

Search ID	Search Term	Search Period	Filters
13	"Atrial Fibrillation" AND (Diagnosis OR Screening OR Detection) AND Undiagnosed NOT Cancer	January 1, 2016 – December 31, 2020	• English • Full Text • Article type: Clinical study, clinical trial, comparative study, guideline, journal article, meta-analysis, practice guideline, randomized controlled trial, review, systematic review, validation study
14	(ECG OR Electrocardiogram) AND "Atrial Fibrillation" AND Wear*		
15	(IRN* OR "irregular rhythm" OR arrhythmia) AND "Atrial Fibrillation" AND Wear*		

Google Scholar will be used as a supplemental source when PubMed does not provide a satisfactory number of citations. Bibliographies of each of the accepted references may also be reviewed for additional appropriate references.

Should the search result be large in volume (>200 results per search ID), additional terms and filters may be used to focus the search and keep the references to a manageable level. Any additional terms and filters used will be documented in the final report. Literature including meta-analyses, randomized controlled trials (RCTs), as well as prospective, non-randomized clinical evaluations, and literature review articles will be considered for inclusion in this search as these are considered the most robust data sources and tend to have a level of applicability.

4.4 SEARCH TIMELINE

The Apple ECG 1.0 App and IRNF entered the commercial market in December 2018. A previous literature search for the ECG App and IRNF 1.0 was conducted on 18 August, 2020.

The ECG 2.0 App is a pre-market device; literature not held by Apple pertaining specifically to the ECG 2.0 App is not expected to be identified in this literature search, but all results will be documented in the Literature Search Report.

In order to encompass the full current commercial experience of the devices under evaluation, and in compliance with SOP 099-19205: Clinical Evaluation, the clinical safety and performance literature search period will span 01 January 2016 – 31 December 2020.

In order to comprehensively assess the current state of the art in regard to the detection of and screening for AFib and in compliance with SOP 099-19205: Clinical Evaluation, the current SOTA literature search period will span over 01 January 2016 – 31 December 2020.

4.5 SELECTION CRITERIA

Devices under Evaluation

Inclusion criteria:

Based on the justifications provided, the following criteria will be used as inclusion criteria to screen literature citations for relevance/strength of evidence with respect to the safety and performance of the Apple ECG 1.0 App, ECG 2.0 App, and IRNF 1.0.

1. The clinical data presented specifically pertains to the safety and/or performance of the Apple ECG 1.0 App, ECG 2.0 App, and IRNF 1.0 feature or a similar device used for the detection of or screening for AFib.
2. The clinical data presented other new or emerging clinical information with regard to the use of the Apple ECG 1.0 App, ECG 2.0 App, and IRNF 1.0 feature.
3. English language – translation from other languages is not feasible.
4. Human clinical use – human use is most pertinent to establishment of safety and performance of the subject device with the specified intended use. However, should the search results reveal minimal relevant clinical data, the search may be expanded to include relevant data on animal studies.
5. The author's conclusions must be supported by specific clinical data – while review articles can be valuable sources of information, opinion pieces based on personal experience are not appropriate for inclusion.

Exclusion criteria:

The following criteria will be used as exclusion criteria for the literature search:

1. Lack of detail for adequate evaluation – articles not providing specific detail regarding the study procedures cannot be thoroughly evaluated or compared and therefore will be excluded.

2. Not a peer-reviewed article – scientific integrity and robust data are highest in peer-reviewed works and due to scope of the literature, non-peer reviewed articles will be excluded.
3. Not related to the safety and/or performance of the Apple ECG 1.0 App, ECG 2.0 App, and IRNF 1.0 feature or similar devices.

State of the Art

Inclusion criteria:

Based on the justifications provided, the following criteria will be used as inclusion criteria to screen literature citations for relevance/strength of evidence with respect to the detection of and screening for undiagnosed AFib:

1. English language – translation from other languages is not feasible.
2. Human clinical use – human use is most pertinent to establishment of safety and performance of the subject device with the specified intended use. However, should the search results reveal minimal relevant clinical data, the search may be expanded to include relevant data on animal studies.
3. The author's conclusions must be supported by specific clinical data – while review articles can be valuable sources of information, opinion pieces based on personal experience are not appropriate for inclusion.

Exclusion criteria:

The following criteria will be used as exclusion criteria for the literature search:

1. Lack of detail for adequate evaluation – articles not providing specific detail regarding the study procedures cannot be thoroughly evaluated or compared and therefore will be excluded.
2. Not a peer-reviewed article – scientific integrity and robust data are highest in peer-reviewed works and due to scope of the literature, non-peer reviewed articles will be excluded.
3. Not related to the detection of and screening for undiagnosed AFib in a human subject population. Studies pertaining to design and testing of algorithms or software models that have not been tested in or used by human subjects will be excluded.
4. Publication type – articles that present no data (i.e., clinical study design) or data from a limited subject population (i.e., case reports) will be excluded.

4.6 DATA DUPLICATION

Data will also be evaluated to assess the potential for duplication of clinical data. In the event that the same clinical trial is cited in multiple articles, preference will be given to the presentation with the longest time period. Meta-analyses citing data that are presented elsewhere will be noted as such. References collected per this literature search protocol will be recorded in the Literature Search Record accompanying the

Literature Search Report. Results returned in more than one search will be noted as duplicates and will only be appraised once.

4.7 ADDRESSING DATA HELD BY THE MANUFACTURER

Each subsequently performed literature search on the devices under evaluation and the detection of and screening for AFib will encompass the previous 5 years of data. This may lead to duplication of data presented in previous reports. Data identified in the literature that is held by the manufacturer will be identified as such in the Literature Screening Log. The data will be summarized once within the resulting CER.

4.8 APPRAISAL PLAN – DEVICES UNDER EVALUATION

In order to evaluate the clinical data gathered from the scientific literature, a grading system will be utilized. This system was drawn from Appendix D of the Global Harmonization Task Force Clinical Evaluation Study Group (GHTF Guideline SG5/N2R8:2007 Clinical Evaluation 2007). As a general guide, the more level 1 grades a piece of clinical data receives, the greater the weight of evidence provided by that particular dataset in comparison to other datasets. However, these scores will not be used to determine an overall score. Each of the articles will be individually graded based upon each Appraisal Criterion (Table 6).

Table 6. Device under Evaluation Appraisal Criteria

Criteria	Description	Grading System	
Suitability Criteria			
Appropriate device	Were the data generated from the device in question?	D1	Actual device
		D2	Comparable device
		D3	Other device
Appropriate device application	Was the device used for the same intended use (e.g., methods of deployment, application, etc.)?	A1	Same use
		A2	Minor deviation
		A3	Major deviation
Appropriate patient group	Were the data generated from a patient group that is representative of the intended treatment population (e.g., age sex, etc.) and clinical condition (i.e., disease, including state and severity)?	P1	Applicable
		P2	Limited
		P3	Different population
Acceptable report/data collation	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R1	High quality
		R2	Minor deficiencies
		R3	Insufficient information
Data Contribution Criteria			
Data source type	Was the design of the study appropriate?	T1	Yes
		T2	No

Outcome measures	Do the outcome measures reported reflect the intended performance of the device?	O1	Yes
		O2	No
Follow up	Is the duration of follow-up long enough to assess whether duration of treatment effects and identify complications?	F1	Yes
		F2	No
Statistical significance	Has a statistical analysis of the data been provided and is it appropriate?	S1	Yes
		S2	No
Clinical significance	Was the magnitude of the treatment effect observed clinically significant?	C1	Yes
		C2	No

4.9 APPRAISAL PLAN – STATE OF THE ART

In order to evaluate clinical data pertaining to the State of the Art, a grading system will be utilized. Methodological quality and relevancy to the research questions outlined in Section 2.0 will be assessed as illustrated in Table 7. As a general rule, the greater the overall score, the greater the weight of evidence provided by that particular dataset in comparison to other datasets. Some article types, such as reviews and guidelines, have a higher likelihood of scoring poorly in a methodological assessment, but can provide useful and relevant information for the State of the Art. For this reason, these scores will not be used to determine an overall score and will not be used as an exclusion criterion.

Table 7. State of the Art Appraisal Criteria

Relevancy Assessment			
Question #	**Research Question**	**Grading System**	
Q1	What is the current "gold standard" for the detection of or screening for atrial fibrillation?	1	Information relevant to question
		0	No information relevant to question
Q2	What other options exist for the detection of atrial fibrillation?	1	Information relevant to question
		0	No information relevant to question
Q3	What are the risks, benefits and side-effects related to methods of detection of or screening for atrial fibrillation?	1	Information relevant to question
		0	No information relevant to question
Methodology Assessment			
Data Source Type	Was the reported data obtained from appropriately designed and executed studies?	1	Yes
		0	No
		1	Yes

Outcome measures	Do the outcome measures align with the research questions?	0	No
Follow-up	Are the reported durations of follow-up sufficient to assess efficacy of treatment and identify complications?	1	Yes
		0	No
Report Quality	Does the report contain scientifically valid and clinically significant conclusions, adequate disclosures, and appropriate discussion of deviations?	1	Yes
		0	No
Statistical Significance	Has a statistical analysis of the data been provided and is it appropriate?	1	Yes
		0	No

4.10 ANALYSIS PLAN

All studies will be classified: retrospective, prospective (randomized controlled trial), prospective (nonrandomized controlled trial, etc.). No adjustments will be made to any reported factors in an attempt to normalize the assessment across studies. If provided, the following information will be abstracted from each of the selected articles: study type, patients and medical condition, type of treatments used, outcomes, and complications. These key study characteristics will be summarized as needed for each "included" clinical study. An analysis of both favorable and unfavorable data for the evaluation of compliance to relevant safety and performance requirements, and especially the acceptability of risks and undesirable side-effects when weighted against the intended benefits and performance of the Apple ECG 1.0 App, ECG 2.0 App, and IRNF 1.0 will be performed.

5.0 LITERATURE SELECTION

To select representative literature, the identified selection criteria and screening strategies will be used. An initial review of titles and abstracts will be conducted to assess each result for relevance and inclusion or exclusion based on the criteria described in Section 4.5. If excluded, a brief explanation will be provided in the Literature Search Record.

6.0 DATA EXTRACTION, QUALITY ASSESSMENT, DATA SYNTHESIS

The literature selection inclusion and exclusion criteria were formulated to ensure a high quality of reported clinical outcomes. Following assessment of the literature in accordance with the preset selection criteria, the identified references will be included in the Literature Report. The Literature Report will provide the retrieved literature citations and summaries/abstracts of the most salient articles. The literature summarized in the Literature Report will be used in the evaluation of the safety and performance of the Apple ECG 1.0 App, ECG 2.0 App, and IRNF 1.0 and to inform the state-of-the-art discussion of the detection of and screening for AFib.

7.0 LITERATURE REVIEWED

The literature search will cover data sources that were published during the identified period and that report 1) safety and performance factors related to the devices under evaluation and 2) the state-of-the-art in the detection of and screening for AFib. As part of

the review, the articles will be appraised and weighted based on the grading systems presented in Sections 4.8 and 4.9. The appraisal of each identified data source will be provided as an attachment to the Literature Report.

Revision History

Revision	Affected Section(s)	Description of Change
C	2.0, 3.0, 4.2, 4.3, 4.4, 4.9, 8.0	Minor change in format of the objectives; updated the list of previous literature search protocols; updated the referenced documents; updated the planned literature search periods both the SOTA and device under evaluation sections to include Jan 1, 2016 through Dec 31, 2020; minor modification of listed research questions related to the appraisal plan for the SOTA (relevancy assessment); removal of section 8.0 based on the updated template.
B	1, 2, 3, 4.2-4.5, 4.7-4.10, 5.0, 6.0, 7.0, 8.0	Devices under evaluation updated to include ECG 2.0 App throughout; search periods updated; SOTA exclusion criteria updated; language in section 4.7 updated to allow for overlapping results between report periods; added references to previous lit search protocol/report, and SOP 099-19205; added section 8.0; minor editorial and formatting changes.
A	All	Combined ECG app (099-15419) and IRN feature (099-15420) Literature Search Protocols into a single document (099-21177); updated to include separate search for devices under evaluation; updated appraisal criteria for state of the art; updated planned search period for state of the art to include Oct 1, 2018 through Sept. 30, 2019.