SUPPLEMENTAL MATERIAL

Detection of Atrial Fibrillation in a Large Population using Wearable Devices: the Fitbit Heart Study

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Supplemental Methods

Sensitivity was defined as the fraction of participants with atrial fibrillation (AF) on the electrocardiogram (ECG) during the one-week ECG patch monitor who had an irregular heart rhythm detection (IHRD). Specificity was defined as the fraction of participants without AF on the ECG patch monitor who did not have an IHRD. Analyses of sensitivity and specificity utilized the clinical ECG report to ascertain presence of AF and did not include manual cardiologist adjudication of the entire one-week full-disclosure ECG waveform tracing.

Fitbit software routinely estimates time spent in different heart rate zones each day and time asleep, which were used to calculate device wear time and sleep wear time, respectively. Wear time was calculated as median hours per day of wear and as the proportion of days of wear with one or more hours of wear time. Wear time was calculated for the enrolled sample during the study duration and for the ECG patch subset during the one-week monitoring period.
Figure S1. Schematic of software algorithm for detecting irregular heart rhythms.

Each box represents a five-minute pulse tachogram, with a 50% (2.5 minute) overlap of each pulse tachogram window. The algorithm analyzes the pulse tachogram while the participant is stationary and requires 11 consecutive analyzable tachograms to be irregular to generate an irregular heart rhythm detection (IHRD). At least 30 minutes of a sensed irregular rhythm is therefore required for the algorithm to generate an IHRD. Unanalyzable periods do not interrupt the algorithm, whereas a negative tachogram does. The 11 irregular tachograms must be within a 24-hour period. Examples are shown for a) 11 irregular pulse tachograms without any unanalyzable tachograms, generating an IHRD after 30 min, b) 11 irregular tachograms with four unanalyzable tachograms interspersed, generating an IHRD after 40 minutes, and c) an intervening negative pulse tachogram, which interrupts the algorithm, resets the counter, and therefore does not generate an IHRD. The count of analyzable tachograms in a sequence is displayed. The IHRD window is the time from the start of the first irregular tachogram to the end of the 11th irregular tachogram. For the 241 participants with an IHRD during ECG patch monitoring, the median IHRD window of the first IHRD was 35 (interquartile range, 30 to 72) minutes.
Proportions were calculated per user, and the median value across users is shown. The figures correspond to a median of 44.4 (interquartile range 34.9 – 51.0) hours per person of analyzable data during sleep, and 7.9 (interquartile range 4.3 – 12.5) hours during awake periods. Data correspond to 1040 participants; from the 1,057 in the electrocardiogram patch subgroup, 17 did not have complete tachogram and sleep data for this analysis.
Table S1. Missing self-reported data frequencies.

| Characteristic                  | Total Enrolled (n=455,699) | IHRD Notification Subgroup (n=4,728) | ECG Patch Subgroup (n=1,057) | ECG Confirmed AF Subgroup (n=340) | Did not attend a telehealth visit (n=3,057) | Attended a telehealth visit (n=1,671) |
|--------------------------------|-----------------------------|--------------------------------------|------------------------------|----------------------------------|-----------------------------------------|----------------------------------------|
| Age distribution               | 165 (0.04%)                 | 0 (0%)                               | 0 (0%)                       | 0 (0%)                           | 0 (0%)                                   | 0 (0%)                                  |
| Sex                            | 8 (0%)                      | 0 (0%)                               | 0 (0%)                       | 0 (0%)                           | 0 (0%)                                   | 0 (0%)                                  |
| Race and Ethnicity             | 23,410 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| Congestive heart failure       | 23,414 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| Diabetes                       | 23,414 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| Family history of AF           | 23,414 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| Hypertension                   | 23,414 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| Obesity (body mass index ≥ 30 kg/m²) | 4,075 (0.89%)              | 33 (0.7%)                            | 6 (0.57%)                    | 3 (0.88%)                        | 11 (0.66%)                               | 22 (0.72%)                              |
| Vascular disease               | 23,414 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| Sleep apnea                    | 23,414 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| Stroke                         | 23,414 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| Current smoking*               | 23,414 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| Current alcohol use*           | 23,414 (5.14%)              | 295 (6.24%)                          | 60 (5.68%)                   | 20 (5.88%)                       | 87 (5.21%)                               | 208 (6.8%)                              |
| CHA2DS2-VASc score             | 24,574 (5.39%)              | 303 (6.41%)                          | 61 (5.77%)                   | 20 (5.88%)                       | 91 (5.45%)                               | 212 (6.93%)                             |

Data are n (%).
*Current smoking and alcohol use were defined as daily or less than daily.
CHA2DS2-VASc is a stroke prediction score for patients with AF in which one point is allocated for each of congestive heart failure, hypertension, age ≥ 65 years, diabetes, vascular disease, and female sex, an additional point is allocated for age ≥ 75 years, and two points are allocated for prior stroke or TIA; higher scores denote greater risk.
AF = atrial fibrillation or flutter; ECG = electrocardiography; IHRD = Irregular Heart Rhythm Detection, TIA = transient ischemic attack.
Table S2. Fitbit device wear time.

|                                | Enrolled (n=455,699) | IHRD notification group (n=4,728) | During ECG patch monitoring (n=1,057) |
|--------------------------------|----------------------|----------------------------------|--------------------------------------|
| Median hours of wear time per day per person | 23 (22–24) | 23 (23–24) | 23 (23–24) |
| Days with at least one or more hours of wear time / Days at risk for an IHRD notification |                      |                                  |                                      |
| ≥ 1 hour                       | 99% (85–100)         | 100% (95–100)                    | 100% (98–100)                       |
| ≥ 6 hours                      | 98% (82–100)         | 100% (93–100)                    | 100% (98–100)                       |
| ≥ 12 hours                     | 95% (73–100)         | 98% (89–100)                     | 99% (95–100)                        |
| ≥ 18 hours                     | 85% (54–96)          | 92% (75–98)                      | 96% (87–99)                         |
| ≥ 23 hours                     | 56% (29–73)          | 62% (40–76)                      | 68% (51–78)                         |

Data are median (interquartile range). AF = atrial fibrillation or flutter; ECG = electrocardiogram; IHRD = Irregular Heart Rhythm Detection; IQR = interquartile range.
Table S3. Characteristics of 4,728 participants who received IHRD notifications stratified by attendance at a telehealth visit.

| Characteristic                              | Did not attend a telehealth visit (n=3,057) | Attended a telehealth visit (n=1,671) | P value |
|---------------------------------------------|--------------------------------------------|---------------------------------------|---------|
| Age distribution                            |                                            |                                       |         |
| ≥ 75 years                                  | 340 (11.1%)                                | 120 (7.2%)                            | <0.001  |
| 65-74 years                                 | 1,030 (33.7%)                              | 580 (34.7%)                           |         |
| 55-64 years                                 | 1,018 (33.3%)                              | 605 (36.2%)                           |         |
| 40-54 years                                 | 510 (16.7%)                                | 266 (15.9%)                           |         |
| 22-39 years                                 | 159 (5.2%)                                 | 100 (6.0%)                            |         |
| Not reported                                | 0 (0.0%)                                   | 0 (0.0%)                              |         |
| Sex                                         |                                            |                                       | 0.03    |
| Male                                       | 1,796 (58.8%)                              | 917 (54.9%)                           |         |
| Female                                      | 1,256 (41.1%)                              | 749 (44.8%)                           |         |
| Not reported                                | 0 (0.0%)                                   | 0 (0.0%)                              |         |
| Race and Ethnicity                          |                                            |                                       | <0.001  |
| White Non-Hispanic                         | 2,394 (78.3%)                              | 1,418 (84.9%)                         |         |
| Black Non-Hispanic                         | 140 (4.6%)                                 | 40 (2.4%)                             |         |
| Hispanic                                    | 113 (3.7%)                                 | 53 (3.2%)                             |         |
| Asian                                       | 55 (1.8%)                                  | 14 (0.8%)                             |         |
| Native American or Alaskan Native          | 16 (0.5%)                                  | 5 (0.3%)                              |         |
| Native Hawaiian or other Pacific Islander   | 5 (0.2%)                                   | 4 (0.2%)                              |         |
| Multiracial                                 | 55 (1.8%)                                  | 26 (1.6%)                             |         |
| Not reported                                | 71 (2.3%)                                  | 24 (1.4%)                             |         |
| Medical History                             |                                            |                                       |         |
| Congestive heart failure                    | 124 (4.4%)                                 | 20 (1.3%)                             | <0.001  |
| Diabetes                                    | 327 (11.5%)                                | 131 (8.3%)                            | 0.001   |
| Family history of AF                        | 892 (22.6%)                                | 349 (20.9%)                           | 0.18    |
| Hypertension                                | 1,346 (47.2%)                              | 679 (42.9%)                           | 0.01    |
| Obesity (body mass index ≥ 30 kg/m²)        | 1,368 (45.1%)                              | 662 (39.9%)                           | 0.001   |
| Vascular disease                            | 133 (4.7%)                                 | 49 (3.1%)                             | <0.001  |
| Sleep apnea                                 | 704 (24.7%)                                | 352 (22.2%)                           | 0.07    |
| Stroke                                      | 81 (2.8%)                                  | 13 (0.8%)                             | <0.001  |
| Current smoking*                            | 180 (5.9%)                                 | 72 (4.3%)                             | 0.03    |
| Current alcohol use*                        | 1,945 (63.6%)                              | 1,164 (69.7%)                         | <0.001  |
| CHA₂DS₂VASc score ≥ 2 for men or ≥ 3 for women | 1,073 (37.7%)                              | 494 (31.3%)                           | <0.001  |

Data are n (%). Percentages include individuals with missing self-reported data; missing data frequencies are summarized in Table S1. P values were derived from chi-square tests.

*Current smoking and alcohol use were defined as daily or less than daily.

CHA₂DS₂VASc is a stroke prediction score for patients with AF in which one point is allocated for each of congestive heart failure, hypertension, age ≥ 65 years, diabetes, vascular disease, and female sex, an additional point is allocated for age ≥ 75 years, and two points are allocated for prior stroke or TIA; higher scores denote greater risk.

IHRD = Irregular Heart Rhythm Detection; AF = atrial fibrillation or flutter; TIA = transient ischemic attack.
Table S4. Adjudicated cardiac rhythms during the first IHRD concurrent with ECG patch monitoring among individuals without ECG patch-confirmed AF.

| Individual | Predominant rhythm(s)                                      | Other rhythm(s)                                                                                                                                 |
|------------|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 1          | Normal Sinus Rhythm, Supraventricular Tachyarrhythm        | Premature Atrial Contractions, Normal Sinus Rhythm, Tachycardia, Supraventricular Tachycardia, Multifocal Atrial Tachycardia                   |
| 2          | Normal Sinus Rhythm                                        | Normal Sinus Rhythm, Premature Atrial Contractions                                                                                         |
| 3          | Supraventricular Tachyarrhythm                             | Normal Sinus Rhythm, Tachycardia, Supraventricular Tachycardia, Multifocal Atrial Tachycardia                                               |
| 4          | Normal Sinus Rhythm                                        | Premature Atrial Contractions, Normal Sinus Rhythm, Supraventricular Tachycardia, Premature Ventricular Contractions, Artifact Present      |

AF = atrial fibrillation or flutter; ECG = electrocardiogram; IHRD = irregular heart rhythm detection
**Table S5.** Sensitivity analysis of the IHRD positive predictive value for concurrent AF during ECG patch monitoring stratified by CHA₂DS₂-VASc score.

| Stratum                              | n with concurrent AF / N with IHRDs | PPV, (95% CI)       |
|--------------------------------------|-------------------------------------|---------------------|
| CHA₂DS₂-VASc ≥2 in men or ≥3 in women| 62 / 64                             | 96.9% (89.2–99.6)   |
| CHA₂DS₂-VASc >0 and <2 in men or >1 and <3 in women | 79 / 79                             | 100.0% (95.4–100.0) |
| CHA₂DS₂-VASc 0 in men or 1 in women  | 74 / 75                             | 98.7% (92.8–100.0)  |

CHA₂DS₂-VASc is a stroke prediction score for patients with AF in which one point is allocated for each of congestive heart failure, hypertension, age ≥65 years, diabetes, vascular disease, and female sex, an additional point is allocated for age ≥75 years, and two points are allocated for prior stroke or TIA; higher scores denote greater risk. CHA₂DS₂-VASc score data were missing for 17 of the 225 participants in whom an IHRD occurred during ECG patch monitoring.

AF = atrial fibrillation or flutter; CI = confidence interval; ECG = electrocardiogram; IHRD = irregular heart rhythm detection; PPV = positive predictive value
**Table S6.** Potential reasons for absence of an IHRD during ECG patch monitoring among individuals with AF on the ECG patch.

| Potential reason                                                   | n   |
|-------------------------------------------------------------------|-----|
| AF occurred during the daytime when fewer periods of inactivity were available for the algorithm | 56  |
| Fewer than 11 consecutive irregular tachograms present            | 49  |
| No analyzable PPG data                                           | 5   |
| **Total**                                                        | 110 |

AF = atrial fibrillation or flutter; ECG = electrocardiogram; IHRD = irregular heart rhythm detection; PPG = photoplethysmography
Table S7. Distribution of longest AF episode duration among participants with AF on ECG patch.

| Duration     | AF on ECG Patch (n=340) |
|--------------|-------------------------|
| 30 sec – 6 min | 21 (6.2%)               |
| 6 min – 1 hr  | 37 (10.9%)              |
| 1 hr – 6 hrs  | 103 (30.3%)             |
| 6 hrs – 24 hrs| 97 (28.5%)              |
| > 24 hrs     | 82 (24.1%)              |

AF = atrial fibrillation or flutter; ECG = electrocardiogram
Table S8. Adverse event summary among the 1,275 participants who reported an adverse event.

| Adverse event                                         | n events |
|-------------------------------------------------------|----------|
| Skin Irritation from Fitbit Device                    | 977      |
| Skin Irritation from ECG Patch                        | 615      |
| Anxiety from study                                    | 1,124    |
| Arrhythmia on ECG patch requiring notification        | 11       |
| Symptoms reported to telehealth provider requiring follow-up care | 1        |
| Other                                                 | 4        |
| Total                                                 | 2,732    |

ECG = electrocardiogram
Table S9. Comparison of wearable photoplethysmography algorithms for irregular heart rhythm detection.

|                                | Fitbit Heart Study                  | Apple Heart Study*                           | Huawei Heart Study†                           |
|--------------------------------|-------------------------------------|----------------------------------------------|----------------------------------------------|
| Pulse tachogram duration       | 5 minutes                           | 1 minute                                     | 1 minute (45 seconds if subject-initiated)    |
| Interval between pulse         | Continuous, overlapping by 50% (i.e.,| Every 2 hours at baseline                     | Every 10 minutes                             |
| tachograms                     | new tachogram acquired every 2.5    | Every 15 minutes once an irregular pulse      |                                               |
|                                | minutes)                            | tachogram is sampled                         |                                               |
| Inactivity required            | Yes                                 | Yes                                          | Unknown                                      |
| Criterion for irregular heart  | 11 / 11 consecutive overlapping pulse| 5 / 6 consecutive pulse tachograms are        | 10 / 10 consecutive pulse tachograms are      |
| rhythm detection               | tachograms are irregular             | tachograms are irregular                      | irregular for initial No.=10 OR               |
|                                |                                     |                                               | T% of pulse tachograms are irregular for No.>10*|
| Minimum time window required   | 30 minutes                          | 61 minutes                                   | 91 minutes                                   |
| for irregular heart rhythm     |                                     |                                              |                                              |
| detection†                     |                                     |                                              |                                              |
| Maximum time window allowed    | 24 hours                            | 48 hours                                     | Not specified                                |
| for irregular heart rhythm     |                                     |                                              |                                              |
| detection                       |                                     |                                              |                                              |

*The threshold T was not reported
†Minimum time from the start of the first irregular tachogram to the end of the last irregular tachogram
Clinical Protocol Plan:
Validation of Software for Assessment of Atrial Fibrillation From PPG Data Acquired by a Wearable Smartwatch

Protocol Version: C
Protocol Date: October 9, 2020

| National Clinical Trial (NCT) Identified Number: | NCT04380415 |
|-----------------------------------------------|-------------|
| Sponsor                                       | Fitbit, Inc.
|                                               | 199 Fremont Street,
|                                               | 14th Floor San Francisco, CA 94105
|                                               | United States |
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PROTOCOL APPROVAL PAGE

Study Title:  Validation of Software for Assessment of Atrial Fibrillation From PPG Data Acquired by a Wearable Smartwatch

Protocol Version:  C

Protocol Date:  October 9, 2020

This minimal risk study will be conducted in the United States in accordance with applicable parts of 21 CFR Parts 50, 54, 56 and 812.

I have read and approved this protocol and agree on its contents.

Anthony Z. Faranesh  
Signature  
October 18, 2020

[ ] [ ]
[Sponsor Contact]  Signature  Date
Fitbit Inc.

[ ] [ ]
[Sponsor Regulatory Approval]  Signature  Date
Fitbit Inc.
INVESTIGATOR’S SIGNATURE PAGE

Study Title: Validation of Software for Assessment of Atrial Fibrillation From PPG Data Acquired by a Wearable Smartwatch

Protocol Version: C

Protocol Date: October 9, 2020

I have read this Study Protocol and agree to adhere to the requirements of this current version of the protocol.

I have not been restricted from participating in clinical research, nor is any action pending that could result in such restriction. If this occurs, I shall provide immediate notification to the Sponsor.

I have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with applicable parts of 21 CFR Parts 50, 54, 56 and 812, and all governing IRB requirements.

Steven A. Lubitz    October 15, 2020

_____________________    _____________________    __________
Investigator Name   Signature    Date
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## List of Abbreviations

| Abbreviation | Description                                      |
|--------------|--------------------------------------------------|
| AE           | Adverse Event                                   |
| CFR          | Code of Federal Regulations                     |
| CIP          | Clinical Investigational Plan                   |
| CMP          | Clinical Monitoring Plan                        |
| CRF          | Case Report Form                                |
| DMP          | Data Management Plan                            |
| EC           | Ethics Committee                                |
| eCRF         | Electronic Case Report Forms                    |
| ECS          | ECG Data Set                                    |
| ENS          | Enrolled Data Set                               |
| FDA          | Food and Drug Administration                    |
| GCP          | Good Clinical Practice                          |
| HIPAA        | Health Insurance Portability and Accountability Act |
| IB           | Investigator’s Brochure                         |
| ICH          | International Conference on Harmonisation       |
| IHRA         | Irregular Heart Rhythm Alert                    |
| IHRD         | Irregular Heart Rhythm Detection                |
| IRB          | Institutional Review Board                      |
| ISO          | International Organization for Standardization  |
| NTS          | Notification Data Set                           |
| PI           | Principal Investigator                          |
Statement of Compliance

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

- ICH E6(R2) Good Clinical Practice and ANSI/AAMI/ISO 14155:2011, Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.
1 Protocol Summary

1.1 Synopsis

| Title | Validation of Software for Assessment of Atrial Fibrillation From PPG Data Acquired by a Wearable Smartwatch |
|-------|----------------------------------------------------------------------------------------------------------|
| Version | C |
| Date | October 9, 2020 |
| Design | Prospective, single arm, observational, minimal risk study. |

**Objectives:**

- **Objective 1:** To evaluate the effectiveness of the Fitbit Rhythm Detect Algorithm in identifying subjects with undiagnosed atrial fibrillation or atrial flutter (AF), during simultaneous ECG monitoring.

- **Objective 2:** To assess the concordance of pulse tachograms positive for AF by the Fitbit Rhythm Detect Algorithm with ECG detected episodes of AF during simultaneous ECG monitoring.

**Endpoints:**

- **Primary:** Simultaneous measurement of AF ≥ 30 seconds on ECG patch monitor during any of the pulse tachograms that generate the first Irregular Heart Rhythm Detection (IHRD) during ECG monitoring.

- **Secondary:** Simultaneous measurement of AF ≥ 30 seconds on the ECG patch monitor during each of the pulse tachograms that contributed to the first IHRD, among those IHRDs confirmed by ECG.

**Inclusion Criteria**

1. Smartphone with latest Fitbit app installed.
2. Fitbit account, with one of the following devices paired: Ionic, Versa, Versa Lite, Versa 2, Versa 3, Charge 3, Charge 4, Inspire HR, Inspire 2, or Sense updated to the latest available firmware.
3. Age ≥ 22 years at time of eligibility screening, ascertained from self-report.

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4. United States resident at time of eligibility screening, defined by self-report  
5. Proficient in written and spoken English, defined by self-report of being able to provide consent in English.  
6. Valid email address

| **Exclusion Criteria** | 1. Self-reported diagnosis or history of Atrial Fibrillation at the time of screening.  
2. Self-reported diagnosis or history of Atrial Flutter at the time of screening.  
3. Currently on anticoagulation therapy, as self-reported at the time of screening.  
4. Cardiac pacemaker or implantable cardioverter-defibrillator, as self-reported at the time of screening. |

| **Test Device** | Fitbit Rhythm Detect algorithm |

| **Duration of Study Participation** | Participants will be able to enroll from approximately Q2, 2020 to Q4, 2020. Participants may contribute up to 30 days of retrospective data upon enrollment and will contribute prospective data thereafter. Participants who receive a notification will receive a 90-day Patient Reported Outcomes survey 90 days after the notification. All participants will receive an End of Study Patient Reported Outcomes survey, which they will have until Q1, 2021 to complete. |

| **Number of Participants** | The enrollment will be capped at 1,000,000 participants. It is anticipated that approximately 200,000 participants will enroll, with less than 1% receiving notifications during the monitoring period. Enrollment targets are set to achieve approximately two-thirds of the ECG patches to be from those 65 and older and one-third of the patches from those younger than 65. |
1.2 Study Schema

Figure 1: Study design
### 1.3 Schedule of Events

Table 1: Schedule of events.

| Study Procedure       | Screening, Consent and Enrollment | Study Visit 1         | ECG Monitor Wear | Study Visit 2           | 90 Day PRO  | End of Study PRO |
|-----------------------|-----------------------------------|-----------------------|------------------|------------------------|-------------|------------------|
| Study Day             | Day 0                             | within 30 days of notification | 7 days; worn within 45 days of Visit 1 | within 60 days of Visit 1 | 90 days after notification |                |

**All Enrolled Participants**

- Inclusion / Exclusion Criteria
- Informed Consent
- Demographics
- Medical History
- Survey

**Notification Subgroup**

- Review Eligibility Criteria and Medical History
- ECG Monitor Ordered

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2 Introduction

2.1 Study Rationale

Based upon the FDA’s final guidance of Software as a Medical Device (SaMD): Clinical Evaluation issued on December 8, 2017, the Company has used factors identified in the SaMD definition statement (from SaMD N12) to determine that the PPG Rhythm Detect is a software-only medical application that falls within the category of a SaMD.

The goal of this study is to validate the Fitbit PPG Rhythm Detect software algorithm for the presence of atrial fibrillation or atrial flutter (AF) using data derived from a Fitbit wrist-worn consumer device that features a photoplethysmography (PPG) sensor. The intended user population is adults 22 years and older without a previous diagnosis of AF. The performance of the software application will be measured against an FDA approved ambulatory ECG device as reference standards. The Fitbit software is intended as a pre-screening technology. It should identify candidates for whom further testing is recommended. The software is not intended to be a diagnostic system nor is it for use in real-time or continuous monitoring.

2.2 Background

Cardiac arrhythmias are a spectrum of disorders involving an abnormal sequence of electrical impulses in the heart. One of the most important cardiac arrhythmias, from a public health perspective, is AF. Affecting between 3 to 6 million people in the United States, AF is the primary diagnosis for more than 450,000 admissions annually and leads to treatment costs that exceed $25 billion.¹ Risk factors for AF include advanced age, high blood pressure, underlying heart disease, and family history.²
AF is associated with a several-fold higher risk of stroke, and this propensity is further magnified by increasing age. Stroke risk with AF is modified by concomitant conditions such as diabetes, hypertension, and reduced left ventricular systolic function. Since patients are often asymptomatic in AF, it may be recognized only after a stroke or other clinical event. For the estimated 200,000 U.S. patients each year who suffer a cryptogenic stroke, in which other identifiable causes are excluded, more than 10% may have occult AF as a predisposing factor that is missed using existing monitoring technology.

Currently, the diagnosis of AF is made by 12-lead ECG or telemetry. This is straightforward when present at the clinical encounter, but identification may be elusive if episodes are paroxysmal, as occurs in up to one-fourth of cases.

Being that AF is often clinically silent, it has been estimated that 1.3% of AF is undiagnosed in individuals 65 or older (the estimate for age 18-64 is 0.09%), leading to an increased risk of stroke and disease burden. Pulse palpation to assess pulse irregularity is a common method for screening of AF in primary care and is shown to be effective as a screening strategy in the SAFE study (Screening for Atrial Fibrillation in the Elderly). The European Society of Cardiology (ESC) recommends opportunistic pulse palpation in all patients ≥65 years of age or in high-risk subgroups followed by an ECG if irregular, to allow for timely AF detection. The Company proposes using the PPG Rhythm Detect feature for real-time analysis of heart rhythm related data. This data is recorded from compatible Fitbit devices and evaluated by the Software System to detect the possible presence of atrial fibrillation. Consumer grade wrist-worn devices have become very popular in recent years, with millions of Americans voluntarily wearing tracking devices almost continuously. This emerging market represents a significant opportunity to utilize existing sensors on these devices which are noninvasive. Such a system will be able to cue users to the possible presence of atrial fibrillation symptoms and recommend that they follow up with their healthcare provider to determine if they are at risk for atrial fibrillation.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Wearing an ambulatory ECG device may be physically uncomfortable for the subjects due to the application and removal of the adhesive patch. The adhesive may cause minor skin irritation, which should resolve once it is removed. For some subjects, it may be necessary to shave body hair to ensure good contact with the patch. The patch is water resistant, but it should not
be submerged in water. Subjects may shower, but they will be asked to refrain from bathing, swimming, or going in a hot tub or jacuzzi.

The risk of using the Fitbit device is minor skin irritation if the subject has an unanticipated reaction to the device or band.

A new diagnosis of cardiac arrhythmia may be determined based on the ECG data obtained during this study. This new diagnosis may require additional clinical follow-up and care. Recommended treatments such as anticoagulation, ablation, or cardioversion carry with them inherent risks that should be discussed with a healthcare provider.

2.3.2 Known Potential Benefits

A new diagnosis of cardiac arrhythmia may be determined based on the ECG data obtained during this study. This new diagnosis may result in treatment or intervention that could be of clinical benefit to the participant.

2.3.3 Assessment of Potential Risks and Benefits

The risks associated with participation in the protocol are minimal. The risk of using the Fitbit device is minor skin irritation if the subject has an unanticipated reaction to the device or band. The risk of the ambulatory ECG device is discomfort or skin irritation associated with the adhesive patch. The ambulatory ECG is necessary to provide a reference standard for comparison. Any new diagnosis or clinical information will be based on the ambulatory ECG results confirmed by a cardiologist. The benefits of the development of a software algorithm to screen for AF are significant. The feature could help facilitate revealing new cases of AF in otherwise undiagnosed subjects, resulting in early treatment and prevention of stroke.
## 3 Objectives and Endpoints

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|------------|-----------|-----------------------------|
| **Primary** |           |                             |
| To evaluate the effectiveness of the Fitbit Rhythm Detect Algorithm in identifying subjects with undiagnosed atrial fibrillation or atrial flutter (AF), during simultaneous ECG monitoring. | Primary Endpoint: Simultaneous measurement of AF ≥ 30 seconds on ECG patch monitor during any of the pulse tachograms that generate the first IHRD during ECG monitoring. | This proportion represents the PPV of the first IHRD during simultaneous ECG monitoring. The first IHRD represents the first user facing alert during this period. It is an easily interpretable metric of the value of the test. Because of the low prevalence of the disease condition and the deliberate high specificity of the test, PPV is more appropriate than sensitivity and specificity. |
| **Secondary** |           |                             |
| To assess the concordance of pulse tachograms positive for AF by the Fitbit Rhythm Detect Algorithm with ECG detected episodes of AF during simultaneous ECG monitoring. | Simultaneous measurement of AF ≥ 30 seconds on the ECG patch monitor during each of the pulse tachograms that contributed to the first IHRD, | This proportion represents the PPV of the individual tachograms which lead to the first IHRD during ECG monitoring. The aggregate of the individual tachograms is indicative of the frequency and duration of irregular rhythm |
among those IHRDs confirmed by ECG. episodes, which can inform follow-up testing.
4 Study Design

4.1 Overall Design

This study, sponsored by Fitbit, is a digital study recruiting from the general population of Fitbit users and a clinical population at high-risk for AF. The purpose of the study is to evaluate the accuracy of the Fitbit PPG RhythmDetect Software System algorithm in providing notifications for identifying rhythms suggestive of AF (atrial fibrillation or atrial flutter).

The study cohort will consist of subjects without a known history of AF recruited from existing US Fitbit users, age 22 and older. The eligible U.S. Fitbit population (age 22 and older with compatible devices who are active users) is estimated to be 3.8 million, of which approximately 600K (16%) are age 65 and older. The prevalence of undiagnosed AF is estimated to be ~1% for those age 65 and older and ~0.1% for those age 18-64. This equates to 6,000 age 65+ and 3,200 age 22-64 potential users with undiagnosed AF.

For the trial, we will analyze up to 30 days of retrospective data when it is available, as episodes farther back in time are less likely to be confirmed on subsequent ECG monitoring (although the time course of AF episodes in undiagnosed people has not been well studied). In addition to the retrospective data analysis, data will also be collected and analyzed prospectively from users once they enroll.

Subjects who receive a software notification will be asked to contact a telehealth provider, PlushCare. A telehealth provider provides services such as booking an appointment with a physician and physician visits through virtual tools (e.g. phone, computers etc.). A telehealth provider also provides services such as filling out prescriptions or sending out prescription medical devices. The subjects contacting PlushCare will be provided services to book an appointment with a healthcare provider. If the healthcare provider determines the subject is eligible (by confirming criteria for initial enrollment and that the user is not experiencing emergent symptoms), a mobile cardiac ECG monitor will be ordered from BioTel. Eligibility will be determined after wearing the Fitbit device and cardiac monitor simultaneously for up to one week, the ECG monitor will be sent back for analysis. The results of the ECG monitor will be reviewed with the participant during a second telehealth visit.

Telehealth Visits

Participants who receive irregular heart rhythm alerts (IHRAs) will be prompted to contact PlushCare for a virtual consultation. If criteria for initial enrollment are confirmed at Visit 1, they will be sent an ambulatory ECG monitor (ePatch, BioTel).
After the ECG monitor is returned and analyzed, participants will be notified that their results are available and will be prompted to contact PlushCare for a second consultation to discuss the results. At Visit 2, if a positive finding occurs, follow-up with their personal healthcare providers will be recommended. If requested by the participant, the telehealth provider can provide a referral.

In the event that data from the ECG monitor is corrupted or too noisy to generate a clinical report, the participant may be contacted to see if they would be willing to wear a second monitor. In the case when a clinical report is not available or is inconclusive, the participant will still be encouraged to book Visit 2. The PlushCare physician will inform the participant that the diagnostic test was inconclusive and recommend follow-up with their primary care provider.

Ambulatory ECG

Eligible participants who receive an IHRA will be shipped a single-lead ECG patch to wear for up to one week. PlushCare physicians will order the ECG monitor directly from BioTelemetry, who will ship an ECG monitor to the subjects. They will be provided with instructions for use and the contact information of BioTelemetry customer support if any assistance is needed. A prepaid mailer will also be provided to return the monitor sensor to BioTelemetry for analysis.

Fitbit Device

Enrolled participants will use their personal Fitbit wristband device for the study. They will be directed to wear their devices as much as possible during the test. Participants may contact Fitbit customer support if they have any questions.

Exit Surveys

Participants who receive an IHRA will be asked to complete a follow-up survey 90 days after the notification. The survey will inquire about follow-up with their healthcare provider and medications or treatment they may have received related to their diagnosis.

All participants, including those who did not receive an IHRA, will be asked to complete an exit survey to collect information regarding their experience participating in the study by March 31, 2021 (estimated).
4.2 Scientific Rationale for Study Design

This general population study design is modeled after the study design of the predicate device (Apple Watch Irregular Rhythm Notification Feature). It is designed to evaluate both the overall notification rates and the PPV of the notifications and individual tachograms in the intended use population. The clinical ambulatory ECG monitor (with physician interpretation) is an FDA-cleared device for diagnosing AF and is the most appropriate choice for a reference for the purpose of reporting PPV of the Fitbit RhythmDetect Software System.

4.3 End of Study Definition

The study is designed to collect data according to the sample size calculations below (See Section 9.7 Sample Size Determination). It is estimated that enrollment and monitoring will run through December 31, 2020, and participants will be given until March 31, 2021 to complete the PRO surveys. An individual’s participation ends after they complete the End of Study survey.
5  Study Population

The study population will be recruited from Fitbit’s existing U.S. population. Recruitment efforts will focus on those 65 years and older, since this population is at significantly higher risk for AF.

The initial assessment of the criteria below will be by self-report. If a subject has a telehealth consultation, all criteria will be confirmed by the telehealth physician.

5.1  Inclusion Criteria

Subjects will be recruited if they meet all of the inclusion criteria:

- Adults 22 years of age or older
- Capable of giving informed consent
- U.S. resident
- No prior history of atrial fibrillation or atrial flutter
- Compatible Fitbit device (Ionic, Charge 3, Charge 4, Versa, Versa Lite, Versa 2, Versa 3, Inspire HR, Inspire 2, Sense) paired to a Fitbit account
- Smartphone with the Fitbit app installed
- Valid mobile phone number
- Valid email address

5.2  Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria at time of screening:

- Diagnosis or history of atrial fibrillation
- Diagnosis or history of atrial flutter
- Use of anticoagulation medication
- Cardiac pacemaker or implantable cardioverter-defibrillator

5.3  Recruitment and Retention

Subjects will be recruited from the existing general population of U.S.-based Fitbit users who are 22 and older, with compatible Fitbit devices. This pool includes approximately 3.8 million individuals. Recruitment will take place through email, Fitbit app notifications, social media, and other marketing channels.

Special attention will be focused on recruiting users 65 years and older (estimated to comprise 600K (16%) of the 3.8 million users). This may entail deploying recruitment materials

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specifically to this population publicizing the study via channels targeted to this demographic. The enrollment period may also be extended for those 65 years and older.

To enhance participant retention after enrollment, the following reminders may be sent to participants via email and/or Fitbit app notifications:

- Those who receive notifications may be reminded daily to follow-up with the PlushCare team for a telehealth visit.
- Once an ECG patch is sent to participants and anticipated wear time has elapsed (approximately 10 days after shipment), daily reminders may be sent to remind them to return the device using the prepaid shipping label.
- After the ECG monitor has been returned and analyzed, participants will be notified that their results are ready and may be reminded to schedule an appointment with PlushCare to discuss their results.

In the predicate study\textsuperscript{11} there was approximately 50% drop off between the notification and the first physician visit, and 30% of participants did not return the ECG monitor. In order to encourage participants who receive a notification to complete the protocol, they may receive an Amazon gift card between $25 and $150. An incentive will not be provided unless certain monthly targets are not met. The incentive will be adjusted based on response, starting at the lower end and incrementally increased if monthly targets are not met, and will be apportioned to completing different steps of the protocol after the initial notification. For example, at the end of Month 2, if fewer than 250 participants who have received an IHRD have completed Visit 1, we will offer $25 for completing Visit 1, and $25 for completing the following steps of the study through Visit 2. The planned incentive schedule is outlined below:

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
 & End of Month 2 & End of Month 3 \\
\hline
Target (n) & 250 (Received IHRD and completed Visit 1) & 500 (Received IHRD and completed Visit 1) \\
\hline
Visit 1 & $25 & $50 \\
\hline
Visit 2 & $25 & $50 \\
\hline
Total & $50 & $100 \\
\hline
\end{tabular}
\end{center}
Participants who complete both Visit 1 and Visit 2 will receive the gift card via email within one week of completing Visit 2. If a participant does not complete Visit 2 within 60 days of Visit 1, they will be compensated for Visit 1 within a week of that 60-day mark.

6 Study Device

The Fitbit Rhythm Detect algorithm is a software algorithm that analyzes heart rate data derived from optical PPG sensors at the wrist. The algorithm identifies irregular heart rhythms (arrhythmias) consistent with atrial fibrillation.

The Fitbit Rhythm Detect algorithm analyzes pulse rate data captured by Fitbit wrist-worn trackers and smartwatches which are equipped with a PPG sensor. The optical PPG sensor detects small changes in blood flow in the microvasculature which correspond to the pulse rate. These data are stored on the Fitbit device and transferred to Fitbit servers via a smartphone. The algorithm is triggered to run on the data when a user syncs (transfers) their data to Fitbit servers. The Analysis of a user’s retrospective data is triggered upon enrollment.

Intervals of pulse rate data are referred to as tachograms. Simultaneous data from device accelerometers are used to determine when the user is sufficiently still to consider the data for analysis, as motion can corrupt the PPG signal. Tachograms are analyzed in five-minute 50% overlapping intervals. If eleven consecutive tachograms are classified as irregular, then an Irregular Heart Rhythm Detection (IHRD) is produced. While the PPG sensors measure the pulse rate continuously, motion will effectively cause blanking periods in the data, and it is possible that the successive tachograms which generate an IHRD will not be continuous in time. There is a requirement that the eleven positive consecutive tachograms occur within a 24 hour period.

For the trial, only the first IHRD triggers an Irregular Heart Rhythm Alert (IHRA), which is a user facing notification surfaced in the form of an email and in-app notifications. For the commercial product, Notifications will be surfaced to the user on a regular (e.g. daily or weekly) basis.

The algorithm is intended to identify heart rhythms consistent with atrial fibrillation, which may benefit from clinical follow-up. The algorithm is not intended to diagnose atrial fibrillation or other arrhythmias. Irregular rhythm notifications should always be confirmed with ECG testing by a clinician.
7 Study Procedures

Figure 2: Study timeline

7.1 Study Timeline

The study will launch Q2, 2020. Fitbit users will receive notifications about the study within their Fitbit app. At the beginning of the trial, the enrollment will be controlled to be limited and gradual, and then incrementally increased. If needed, a virtual waiting room will be used to meter the enrollment. This will be implemented by allowing potential participants to register their interest in the trial, and then they will be subsequently notified to enroll. Subjects will be given the opportunity to review study details and inclusion/exclusion criteria prior to providing informed consent and enrolling in the study. Recruitment will be targeted to those 65 years and older through different communication channels.

Once a participant consents and enrolls, up to 30 days of their retrospective data will be analyzed by the software algorithm. If no retrospective data are available for analysis, then prospective data analysis will commence upon the first data sync from the user.

Enrollment rates will be checked on a regular basis (i.e. weekly or biweekly) to ensure that a sufficient number of 65+ participants are enrolling, with the goal of obtaining ECG patch data from a 2:1 ratio of individuals 65+ and <65 years of age. The demographics of those returning ECG patches for analysis will also be reviewed on a regular basis in order to achieve this goal. Adjustments may be made in recruitment and promotional messaging to achieve these enrollment goals.

It is anticipated to take approximately 8 months to meet the enrollment targets and provide sufficient data to meet our sample size targets, with the study enrollment closing by 12/31/2020 (see Fig 2). The 90 Day PRO surveys will be sent to those who received notifications, and all participants will be sent the EOS survey. The study will then be closed.

Enrollment criteria will be confirmed by PlushCare telehealth physicians during the initial visit. The subject will be sent an ambulatory ECG device to wear along with their personal Fitbit device for up to one week, after which they will return the ECG patch to BioTelemetry for analysis. PlushCare will contact participants to inform them of their results and will provide recommendations for contacting their primary care physicians with the results if appropriate.
Participants who receive a notification will be asked to complete the 90-day follow up survey. All participants will be asked to complete an End of Study Survey.

### 7.2 Participant Timeline

#### 7.2.1 Enrollment

The study participant timeline is shown in Fig. 3. The second event, “Notification,” refers to when the IHRA is sent to the participant. In the case of retrospective analysis, the irregular rhythm may occur up to 30 days before the IHRA is sent to the participant. A subject enrolls into the study at the time when they confirm they meet the study inclusion criteria and sign the informed consent, within the app. People may enroll within their Fitbit app or on a personal computer through a web browser. Participants will be presented with an overview of the study and what to expect as a participant. A dedicated Fitbit customer support team will answer any questions participants might have about the study. Participants may contact the support team by phone or through a contact form on the study’s help page, which will receive a response within 24 hours via email. The user will be asked to provide contact email and phone number, and to confirm they meet the eligibility criteria for the trial. They will then be presented with the consent form and HIPAA authorization form. After signing the consent form, the participant will be asked basic demographic information as well as a brief medical history related to risk factors for AF. During the trial, users will always have access to their signed documents within their app and will be shown the number of days they have been enrolled in the trial.

Participants will be reminded that they should wear their Fitbit device as much as possible, especially while they sleep, so that sufficient data can be acquired during the study. If a user
never receives a notification, monitoring will end in Q4, 2020, and they will be sent the EOS PRO survey in Q1, 2021.

7.2.2 Notification

If an irregular rhythm is identified by the algorithm, an IHRA will be sent to the user notifying them that an irregular heart rhythm suggestive of AF was detected. This notification will be sent via an email and an in-app notification. The analysis to generate a notification is triggered upon synchronization of their Fitbit with their smart phone or comparable device (“device sync). It is expected that participants typically will receive a notification after they wake up and sync their device. In the case of retrospective data analysis, this IHRA could be sent soon after enrollment.

In the notification email there will be a link to the PlushCare platform to book an appointment for Visit 1. In the app, there will be a button the user can push which will link to the PlushCare platform.

Only the initial IHRA will be sent to a participant during the study. After the IHRA is sent, there will be reminders to encourage the participant to book a physician visit to proceed through the protocol. If the user does not schedule a visit within 30 days of receiving the IHRA, they will be placed in the drop-out subgroup.

7.2.3 Telehealth Visits and Cardiac Monitoring

PlushCare ([http://www.plushcare.com](http://www.plushcare.com)) is a healthcare technology company based in San Francisco, CA. They provide a HIPAA compliant technology platform which enables users to have virtual visits with a primary care physician in real time over video. The platform supports visits over a web browser or through their mobile app. The PlushCare physician network is composed of board eligible/certified physicians who are licensed to practice medicine in all 50 states and D.C. When a user books an appointment, they are connected to a physician licensed to practice medicine in the state from where the patient is located at the time of the visit.

When a participant links to the PlushCare platform, user information will be automatically transferred to set up a PlushCare account, and the user will be asked to set up a new PlushCare account password. The participant’s anonymous study ID will also be transferred, which will link the account to the study ID.

During each visit, the PlushCare physician will make notes in the patient record as part of providing clinical care. This information will be retained in PlushCare’s proprietary EMR system, and this information will not be transferred to the Sponsor or other study personnel. During each visit the physician will also record study specific information into a form identified by the anonymous Study ID. This information will be conveyed to the Sponsor and study personnel for analysis. This data will also become part of the participant’s medical record.
Visit 1

The participant will be asked about any cardiovascular symptoms they may be experiencing. In the case of a medical emergency, the physician will follow their emergency protocol and either instruct the participant or a family member to call emergency medical services or will call on the participant’s behalf. Those with emergent symptoms will be moved to the drop-out subgroup and will not receive an ECG patch monitor. They will still receive a 90-day PRO survey and EOS survey.

After confirming the participant is not experiencing any emergent symptoms, the physician will proceed with confirming the study eligibility criteria and reviewing a brief medical history related to risk factors for AF. See below for the specific data fields which will be collected.

The physician will provide information about what the IHRA means, explain that follow up testing is recommended to confirm a diagnosis, and provide information about the ambulatory cardiac monitor that will be ordered.

If the participant does not meet the study eligibility criteria, then the physician will provide a referral upon request. This subject will be moved to the drop-out subgroup.

Visit 1 Data Fields

1. Type of visit (video or telephone)
2. Demographics and contact information
3. Symptoms
4. Medical history
5. Medications
6. Adverse events

Ambulatory Cardiac Monitor

The ambulatory cardiac monitor for the study is the ePatch manufactured by BioTelemetry (https://www.gobio.com/). The ePatch is an adhesive patch worn on the chest which can record a single-lead ECG for up to 14 days. The adhesive typically lasts 7 days, and a participant must then replace the adhesive patch. Because of concerns around participant compliance, participants will be asked to wear the patch for only up to 7 days.
The ECG monitor will be ordered to be sent directly to the participant in a kit which contains instructions and accessories to aid in the application (e.g. disposable razor and skin prep materials). The participant is requested to wear the monitor simultaneously with their Fitbit device for up to 7 days. At the end of the monitoring period, they are asked to mail back the sensor to BioTelemetry in a prepaid envelope included with the kit. Participants may continue wearing their Fitbit device after they return the ECG monitor, but these data will not be used for primary analysis. They will not receive any subsequent IHRAs.

When the sensor is received by BioTelemetry, they will analyze the data and prepare a clinical report. If an emergent rhythm is found, BioTelemetry will contact PlushCare and send them the report, and PlushCare will contact the participant. It should be noted that the cardiac monitor data is evaluated only after the ECG monitor is returned to BioTelemetry, and discovery of these rhythms will take place several days after they occur. The rhythms which will trigger such a clinical alert are:

1. Ventricular fibrillation
2. Torsade de Pointes
3. Ventricular tachycardia, >170 bpm, > 6 secs
4. Tachycardia, ≥ 200bpm, > 30 secs
5. 3rd degree A-V block
6. Pause, > 6 secs

**Visit 2**

When the ECG monitor clinical report is ready it will be sent to PlushCare, who will notify the participant that they should schedule a second visit to discuss the results. During this visit the results of the ECG monitor and clinical options will be discussed. The PlushCare physician can
provide a cardiology referral and/or forward the report directly to the participant’s personal physician if requested. Data similar to those collected during Visit 1 will also be collected, including any new tests or diagnoses since Visit 1.

7.2.4 PRO Surveys

**90-Day Survey**
Approximately 90 days after an IHRA is sent to a participant, an email notification will be sent to the participant with a link to a 90-day PRO survey. The survey will be administered through Qualtrics online survey platform (https://www.qualtrics.com/). Email and in-app reminders may be sent to remind participants to complete the survey. The survey will ask questions about the experience of receiving the IHRA, the experience with the ECG monitor, if the participant discussed the clinical report with other healthcare providers, and additional diagnostics tests or treatments.

**End of Study Survey**
All participants will be sent an End of Study survey, which will also be administered through Qualtrics. Email and in-app reminders may be sent to remind participants to complete the survey. Questions will cover the participant’s experience in the study, knowledge about AF, and any new relevant diagnoses or treatments received during the study.

7.2.5 Drop-out Subgroup

Participants will be moved to the drop-out subgroup and be excluded from the primary and secondary endpoint analysis if they:

1. Receive a notification but fail to book Visit 1 within 30 days.
2. Are found not to meet study eligibility criteria at Visit 1.
3. Require emergency medical services during Visit 1.
4. Fail to wear an ECG monitor within 45 days after Visit 1. Time is measured from Visit 1 date to the first day of ECG patch wear.

7.3 Measures to Minimize Bias

All ECG interpretation will be managed by BioTelemetry Research. All ECG data and reports will be adjudicated by a single U.S. board certified cardiologist. The ECG readers will be blinded to the Rhythm Detect Software System algorithm output. Sampling of the tachograms which determine which ECG traces will be over-read will be managed by ICON, a CRO employed for the study. ICON will be blinded to all ECG data.
To minimize potential sampling bias, we are opening enrollment to all Fitbit users who are 22 and older with no previous history of AF, which is the intended user population for this feature. We intend to target recruitment to those 65 and older because of their increased risk of AF. In order to achieve a greater proportion of those 65 and older, the enrollment period for this age group may be extended beyond that for those less than 65 years of age.

7.4 Study Compliance

Study onboarding material will provide instructions regarding wearing and charging the Fitbit device. Throughout the study, users may receive reminders to proceed with the next steps of the protocol as appropriate (e.g. book a telehealth appointment if an IHRD is received, wear and return the ECG patch monitor, book a follow-up telehealth appointment, fill-out study surveys). Users may contact PlushCare telehealth or Fitbit Customer Service for questions.

Protocol deviations are listed in the Protocol Deviation Criteria Form:

1. Incorrect version of informed consent form signed by participant
2. Subject eligible for ePatch, but ePatch was not ordered and shipped to participant
3. Subject ineligible for ePatch, but received one
4. Unreported SAE
5. Late SAE reporting
6. Visit 1 performed 30 days from IHRA
7. First day of ECG ePatch monitor wear outside 45 days from Visit 1
8. Visit 2 performed outside 60 days from Visit 1
9. Incomplete CRF from either of telehealth Visit 1 or Visit 2
10. ECG monitor vendor (BioTel) does not notify telehealth vendor (PlushCare) of an emergent rhythm discovered on monitor.
11. The ePatch clinical report is not made available to participant who returns an ECG patch.
12. PRO 90-day survey not sent to participant
13. PRO EOS survey not sent to participant within 2 weeks of 90 days from IHRA

Protocol deviations will be reported to the Sponsor on at least a monthly basis and will be logged.
7.5 Concomitant Therapy

For this protocol, current use of an anticoagulant prior to Visit 1 is an exclusion for participation. This will be communicated to participants prior to enrollment, and those who receive an IHRA will confirm this information with a PlushCare telehealth physician. Use of an anticoagulant after enrollment is permitted and this will be evaluated in a tertiary endpoint.
7.6 Discontinuation of Study

If the subject experiences extreme discomfort during the study as a result of the ECG monitor, then they will be instructed to remove the device and they may discontinue use. They will still be asked to mail the patch back to BioTelemetry for analysis. Both PlushCare and BioTelemetry will have protocols for subjects who require immediate medical attention (e.g. they are experiencing severe symptoms, or their ECG monitor reveals a dangerous arrhythmia such as ventricular tachycardia), and in some cases this may result in the subject no longer being able to participate in the study.

7.7 Participant Discontinuation/Withdrawal from the Study

Participants will be informed at the time of consent that they are free to withdraw from the study at any time and for any reason. They will be assured that their medical care will not be affected should they elect to discontinue participation in the study. The date the patient has withdrawn from the study will be recorded. If a subject withdraws from the study, their data will not be used in the primary analysis.

Participants may be discontinued or withdrawn from the study if they are diagnosed with AFib or begin use of anticoagulants after enrollment at any point prior to the first PlushCare visit. This information may be reported by the participant prior to this visit, or it may be discovered at the time of the visit. The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form.

8 Study Assessments and Procedures

8.1 Efficacy Assessments

The primary efficacy assessment is the concordance of the first IHRD during the ECG monitoring period and AF ≥ 30 seconds confirmed by physician interpreted ECG.

The secondary efficacy assessment is the concordance of the individual 5-minute pulse tachograms with AF ≥ 30 seconds confirmed by physician interpreted ECG. Pulse tachograms will be sampled from time windows which generate the first IHRD during the ECG monitoring period.
Additional analyses will be performed as described in the Statistical Analysis Plan. These are:

1. The incidence rate of IHRAs in number per person-years
2. Confirmed AF ≥ 30 seconds on ECG patch monitor subsequent to an IHRA.
3. Self-reported contact with a healthcare provider within 3 months following an IHRA.
4. Proportion of IHRDs which overlap with AF ≥ 30 seconds, based on the clinical report.
5. Simultaneous measurement of confirmed AF ≥ 30 seconds on the ECG patch monitor during each of a randomly selected set of non-overlapping pulse tachograms that contributed to any IHRD.
6. Simultaneous measurement of confirmed AF ≥ 30 seconds on the ECG patch monitor during each of a randomly selected set of non-overlapping positive pulse tachograms that did not contribute to any IHRD.
7. Concordance of IHRDs with arrhythmias other than AF.
8. Maximum duration of confirmed AF (detected on the ECG monitor) of greater than 6 minutes, 1 hour, 6 hours, and 24 hours subsequent to IHRA.
9. During participation in study, self-report of:
   a. new diagnosis of AF
   b. initiation of medical therapies for AF, including anticoagulant, rate-controlling and antiarrhythmic therapy
   c. electrical or chemical cardioversion
   d. Ablation
10. Comparison of time and proportion of time in an irregular rhythm by IHRDs and AF reported by the ECG patch monitor among users with ≥ 30 minutes of continuous AF on the ECG patch monitor. A threshold of 30 minutes is chosen as this corresponds to the minimum time of continuous AF detectable by an IHRD (assuming contiguous overlapping eleven 5 minute tachograms).
11. Correlation of IHRD and AF on ECG patch monitor for different durations of AF episodes
8.2 Safety and Other Assessments

The PI and the study team will meet at least monthly to review the study safety, study procedures, enrollment, protocol deviations, data collection, and adverse events. The PlushCare Telehealth and BioTelemetry teams will generate monthly reports for the study team.

During telehealth visits, if the PlushCare physician determines there is an emergency, they will take appropriate action to ensure the safety of the subject, including arranging for emergency medical services. It will be up to the physician's medical judgement when this is necessary. An example emergency scenario is if a participant is experiencing symptoms such as palpitations or breathlessness consistent with a cardiovascular event such as a stroke or myocardial infarction.

If BioTelemetry detects a dangerous arrhythmia upon analyzing the ECG monitor data, they will notify PlushClare who will contact the participant directly and recommend they seek immediate follow-up care.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). In this study, adverse events would be considered to be the following:

1. Skin irritation from Fitbit device
2. Skin irritation or blister from ECG monitor
3. Anxiety due to study participation

8.3.2 Definition of Serious Adverse Events (SAE)

The general definition of a serious adverse event is as follows (https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event). An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in
death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In this study, Serious Adverse Events would be if a participant requires EMS services to be called during either telehealth Visit 1 or Visit 2, or an arrhythmia is observed on the ECG monitor which requires immediate follow-up. They rhythms are defined to be the following:

| Arrhythmia               | HR          | Duration  |
|--------------------------|-------------|-----------|
| Ventricular Fibrillation  | All Events  | All Events|
| Torsade de Pointes       | All Events  | All Events|
| Ventricular Tachycardia   | > 170 bpm   | > 6 seconds|
| Tachycardia              | ≥ 200 bpm   | > 30 seconds|
| 3rd Degree A-V Block     | All Events  | All Events|
| Pause                    | All Events  | > 6 seconds|

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of Event

The following guidelines will be used to describe the severity of AEs.

- **Mild** – A mild adverse event is one that the symptoms are barely noticeable to the subject. It does not influence performance, require drug treatment or prevent the subject from carrying on with normal life activities.
- **Moderate** – A moderate adverse event is one that the symptoms make the subject uncomfortable and causes some impairment to normal life activities. Treatment for symptom(s) may be required.
● **Severe** – A severe event is one that the symptoms cause severe discomfort to the subject and the severity limits the subject’s normal life activities. Treatment of symptom(s) may be required. Of note, the term “severe” does not necessarily equate to “serious”.

All adverse events will be recorded by PlushCare physicians on CRFs and reported to the study Sponsor.

8.3.3.2 Relationship to Study Intervention

All adverse events (AEs) will have their relationship to study intervention assessed by the clinician who examines the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 Expectedness

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedure.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during telehealth consultation/virtual visit.

All AEs (as defined above) will be captured on the appropriate case report form (CRF) and AE/SAE form.
8.3.5 Adverse Event Reporting

The PlushCare physicians shall complete the Adverse Event Reporting Form and submit to the study Sponsor as soon as possible, but in no event later than 10 working days after the investigator learns of the effect.

8.3.6 Serious Adverse Event Reporting

No Serious Adverse Events (SAE) are expected as a result of participation in this study. However, PlushCare physicians will be instructed to report all AE and SAE to the study Sponsor (Fitbit). The physicians will document the AE and SAE on the case report forms, which will be conveyed to the Sponsor. Fitbit will ensure proper reporting of AE and SAE to the applicable IRB, the U.S. FDA and any other regulatory bodies according to applicable regulations.

8.3.7 Reporting Events to Participants

If a previously undiagnosed cardiac arrhythmia or other abnormality is discovered incidentally during ECG patch wear as result of participating in the study, the subject will be notified, and the ECG data will be sent to the subject upon request, which they can then take the report to their primary care physician.

8.3.8 Reporting Unanticipated Problems to Participants

If an unanticipated problem requires clinical follow up or care, the problem will be reported to the participant with the appropriate guidance.
9  Statistical Considerations

9.1  Data Sets

The following data subsets will be considered for analysis:

| Acronym | Name      | Included                                                                                                                                 |
|---------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------|
| ENS     | Enrolled Set | All enrolled participants.                                                                                                           |
| IHS     | IHRA Set   | Participants who receive an IHRA                                                                                                    |
| ECS     | ECG Set    | Participants who receive and wear an ambulatory ECG patch monitor and provide at least one hour of usable ECG data, which overlaps with analyzable time for the Fitbit algorithm. |
| NTS     | Notification Set | Participants who receive an IHRD during the ECG patch wear time.                                                                   |

All pulse tachograms will be analyzed by the Rhythm Detect software algorithm and classified as AF, not AF, or not analyzable. All ECG data will be adjudicated by BioTelemetry.

9.2  Endpoints

Primary
The primary endpoint is the simultaneous measurement of AF $\geq$ 30 seconds on ECG patch monitor during any of the pulse tachograms that generate the first IHRD.

Secondary
The secondary endpoint of the study is the simultaneous measurement of AF $\geq$ 30 seconds on the ECG patch monitor during each of the pulse tachograms that contributed to the first IHRD, among those IHRDs confirmed by ECG.
9.3 Statistical Approaches

Data will be treated as independent at the participant level and clustered within each participant. For example, multiple detections for a participant will be assumed to be correlated, and multiple tachograms for a participant will be assumed to be correlated.

**Primary Endpoint: IHRD PPV**

For the primary endpoint the IHRD PPV will be calculated as the proportion of detections which are simultaneous with AF ≥ 30 seconds confirmed by ECG. The first IHRD during the ECG monitoring period will be sampled from each subject for this analysis. During ECG monitoring, the first IHRD represents the first user-facing alert a participant would receive. We estimate the true PPV to 80%, and we have designed the study to demonstrate that the one-sided 97.5% confidence interval is > 70%.

**Secondary Endpoint: Tachogram PPV**

For the secondary endpoint the tachogram PPV will be calculated as the proportion of 5 minute tachograms which generate the first IHRD during ECG monitoring which are simultaneous with AF ≥ 30 seconds confirmed by ECG. We estimate the true PPV to be 80%, and we have designed the study to demonstrate that the one-sided 97.5% confidence interval is > 70%.

9.4 Sensitivity and Sub-analyses

Sensitivity analysis will be performed to examine how the endpoint estimates vary by age, gender, and AF risk factors. The endpoint calculations will be repeated for the following subgroups:

1. Age subgroups: <55, 55-64, 65-74, ≥75.
2. Sex
3. AF burden (determined by ECG)
4. CHA2DS2-VASc score (by self report)

9.5 Missing Data

Every effort will be made to collect missing data points where applicable, including:

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1. PlushCare physicians will consult with the subject to complete CRFs and collect information as required to confirm eligibility at Visit 1 and collect AE/SAE data.

2. Missing ECG will be requested from participants if the ECG monitor is not received within 14 days of shipment. Subjects will be contacted up to 3 times to collect ECG monitor and data.

3. In the event the Fitbit is not worn during the 7 day ECG period and/or the use of the Fitbit does not overlap with the use of the ECG patch, the subject may be shipped a second ECG monitor and will be contacted to align the wearable devices and make every effort to collect 7 days with simultaneous use.

4. In the event that data from the ECG monitor is corrupted or too noisy to generate a clinical report, the participant may be contacted to see if they would be willing to wear a second monitor.

9.6 Enrollment and Data Quality Monitoring

Checks will be performed to monitor enrollment, data quality, and returned ECG monitors. Data quality checks are described in the Data Management Plan. Recruitment and enrollment strategies may be adjusted to focus on the 65 years and older demographic, since this is the group most at risk for AF, and is therefore the most interesting group from a clinical perspective.

Enrollment will be controlled by targeted recruitment messaging, with the goal of having at least two-thirds of the enrolled population be 65+ and nearly equal proportions of people with and without retrospective data. Enrollment may be extended for the 65 years and older group in order to achieve this goal.

Checks will be made to assess if participants are able to follow the ECG monitor instructions and provide usable ECG data. These checks will be performed by BioTelemetry, and they will report on patches that do not provide at least one hour of usable data. In these cases, additional patches may be shipped to the participants.

9.7 Sample Size Determination

The sample size for the first endpoint is based on the hypothesis test for the IHRD PPV. Each participant will contribute the first IHRD during ECG monitor wear for analysis. PPV is defined as the proportion of true positive detections over all detections, where a true positive is defined by having AF ≥ 30 seconds confirmed by ECG in the time window of tachograms which
generated the detection. The estimated true detection PPV is 80%, and we will test the hypothesis that the actual PPV is greater than 70% with a one-sided test at a significance level of 2.5% and power of 80%. This results in a minimum sample of 155, with a critical value of 120 to reject the null hypothesis.

The second objective examines the concordance between the 5 minute tachograms which generate the first IHRD during ECG monitoring and AF ≥ 30 seconds detected by the ECG monitor. A true positive tachogram is defined as having at least AF ≥ 30 seconds confirmed by the ECG monitor during the 5 minute tachogram time window. We will test the hypothesis that the actual PPV is greater than 70% with a one-sided test at a significance level of 2.5%. If a single tachogram is sampled from each participant, then from the above analysis we will have 80% power, assuming a minimum sample size of 155.

9.8 Safety Analyses

Safety analysis will be conducted by tracking AEs and SAEs encountered during the study. The following will be summarized:

1. Total number of AEs
2. Total number of SAEs
3. Number of users who experienced an AE or SAE
4. Number of users who experience each type of AE or SAE:
   a. Rash from Fitbit
   b. Rash from ECG monitor
   c. Skin irritation from ECG monitor
   d. Anxiety
   e. Required EMS services during Visit 1 or Visit 2
   f. Detected emergent rhythm on ECG monitor
5. Number of users who had to withdraw from the protocol due to an AE or SAE
10 Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/assent and Other Informational Documents Provided to participants

Consent forms describing in detail the study intent, study procedures, inclusion and exclusion criteria, and risks are given to the participant in the General Population cohort and electronic documentation of informed consent is required prior to continuing on in study procedures. The following consent materials are submitted with this protocol:

1. Informed consent form
2. Onboarding material, including intake surveys
3. Promotional and educational material
4. Scripts to be used by telehealth providers
5. Post-study surveys

10.1.1.2 Consent Procedures and Documentation

Participants will be able to view the IRB-approved informed consent form on a dedicated Fitbit.com study web page. An email address to contact Fitbit’s Tier 3 Customer Support will be provided to participants in case of any questions that arise as they review the informed consent. Tier 3 Customer Support Specialists will be trained on how to properly administer informed consent, in the case of any questions. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without objection. If participants decide to provide consent, they will be asked to type their Fitbit.com login credentials as an electronic signature and they will have access to a copy of the form within the Fitbit.com study web portal, which they will gain access to once they consent to participate. Within this study portal, they will also be provided with additional information on the next steps in the study, and what they can expect in the coming weeks regarding potential notifications and resultant interactions with PlushCare.

10.1.2 Study Discontinuation and Closure

The enrollment shall be closed when it is projected that we have enough participants to achieve the target number of 155 subjects who receive an IHRD during ECG monitoring. After enrollment is closed, IHRAs will be processed for up to an additional 30 days. All participants who receive an alert will be allowed to complete protocol, within the time period limits stated above (e.g. complete Visit 1 within 90 days of the IHRA, wear the ECG patch within 45 days of Visit 1). The study shall be closed upon the completion of the study survey. Upon study closure...
completion all study materials shall be collected or otherwise accounted for and returned to Fitbit.

### 10.1.3 Confidentiality and Privacy

All information gathered from patients, including informed consent, medical records, or any data from the clinical study shall be maintained in a secure manner according to HIPAA rules and guidelines.

### 10.1.4 Future Use of Stored Data

All stored data will have PII removed. All future use of data for development or additional analysis will utilize de-identified data.

### 10.1.5 Key Roles and Study Governance

#### Principal Investigator

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The PI and advisory committee (see below) will review AE/SAEs at monthly meetings. ICON (contract research organization) will aid in data quality monitoring and data reconciliation.

#### 10.1.6 Advisory Committee

An advisory committee made up of subject matter experts in the fields of electrophysiology, primary care, digital health, and behavior economics will be assembled to monitor the trial progression, provide intellectual input, and translate the results to clinical impact. The members are listed below:
| Name                  | Institution                        | Specialty                        |
|-----------------------|------------------------------------|-----------------------------------|
| Steven Lubitz, MD, MPH (PI) | Massachusetts General Hospital       | Electrophysiology                 |
| Andrea Foulkes, PhD    | Massachusetts General Hospital      | Biostatistics                     |
| Steven Atlas, MD, MPH   | Massachusetts General Hospital      | Primary care                      |
| David McManus, MD       | University of Massachusetts         | Electrophysiology                 |
| Daniel Singer, MD       | Massachusetts General Hospital      | Primary care; Epidemiology         |
| Sherry Pagoto, PhD      | University of Connecticut           | Digital health; Behavioral Medicine|

10.1.7 Clinical Monitoring

Clinical monitoring shall be performed by ICON, a CRO partner working with the Sponsor. A sample set of the subjects that complete Visit 1 will undergo validation of subject ID, birth year, sex, medical history and concomitant medication use. A sample set of subjects that complete Visit 2 will undergo validation of subject ID and ECG monitor wear time.

10.1.8 Quality Assurance and Quality Control

Fitbit Quality Assurance shall audit each study vendor at least once. Fitbit Quality Assurance will perform quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe each vendor’s quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the Sponsor and vendor partners (PlushCare and BioTel) for clarification/resolution.

Following written CRO Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP)).
10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data handling and record keeping shall be in accordance with HIPAA rules and guidance. Details for the data management process are included in the Data Management Plan. All electronic records shall be 21 CFR Part 11 compliant, and be held by ICÖN until the completion of the study, at which time they will be conveyed to the Sponsor. An electronic clinical binder will be kept which will contain documentation of IRB approvals, consent approval, and any AE/SAE reported over the course of the study amongst all subjects.

10.1.9.2 Study Records Retention

Study records shall be maintained by the sponsor (Fitbit) for a minimum of two (2) years from the conclusion of the study. Records to be retained are defined in the Data Management Plan.

10.1.10 Protocol Deviations

All deviations to the accepted protocol (this document) shall be documented in writing and approved by all parties and the relevant IRB prior to implementation. Documentation of the deviation and approvals shall be maintained in the site clinical regulatory binder.

10.1.12 Conflict of Interest Policy

Investigators and other entities that may have a conflict of interest, either through financial gain or other considerations, shall agree to and submit a conflict of interest statement disclosing such interests or attesting to a lack thereof. This statement shall be included as part of the Human Subject Research Application, and a signed copy shall be maintained in the site clinical regulatory binder.

11 Protocol Amendment History

| Version | Date    | Description of Change                          | Brief Rationale |
|---------|---------|-----------------------------------------------|-----------------|
| A       | 3/31/2020 | Initial version for submission                |                 |
B 3/31/2020 IRB suggested minor revisions to the protocol, which did not constitute substantive changes. The IRB-approved protocol was assigned rev. B, for document tracking purposes. The changes to the protocol did not warrant any changes to the training materials. The new revision of the protocol was made available to those involved in the execution of the study, but additional training was not considered necessary.

C 10/09/2020 Eliminate third tier incentive. Include planned tertiary analyses. Minor changes to language around primary endpoints. Change requirement to 45 days between Visit 1 and first day of ECG patch wear. Third tier incentive deemed unnecessary to meet recruitment goals. Clarify planned analysis. Harmonize language in description of primary endpoints between Protocol, Statistical Analysis Plan, and ClinicalTrials.gov entry. Added Versa 3, Inspire 2, and Sense to list of allowed, compatible devices. Change in 45 day requirement to allow for delays in shipping.
12 References

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# Fitbit Heart Study

Validation of Software for Assessment of Atrial Fibrillation From PPG Data Acquired by a Wearable Smartwatch: Statistical Analysis Plan

**SAP Version:** B

**SAP Date:** September 27, 2020

| National Clinical Trial (NCT) Identified Number | NCT04380415 |
|-----------------------------------------------|--------------|
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Study Title: Validation of Software for Assessment of Atrial Fibrillation From PPG Data Acquired by a Wearable Smartwatch

SAP Version: B

SAP Date: September 27, 2020

I have read this Statistical Analysis Plan and agree on its content.

Steven A. Lubitz
October 15, 2020

Andrea S. Foulkes
October 18, 2020

Anthony Z. Faranesh
October 18, 2020

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# LIST OF ABBREVIATIONS

| Abbreviation | Explanation                        |
|--------------|------------------------------------|
| AE           | Adverse Event                      |
| AF           | Atrial Fibrillation and Atrial Flutter |
| CI           | Confidence Interval                |
| ECG          | Electrocardiography                |
| ECS          | ECG Monitor Set                    |
| ENS          | Enrolled User Set                  |
| IHRA         | Irregular Heart Rhythm Alert       |
| IHRD         | Irregular Heart Rhythm Detection   |
| NPV          | Negative Predictive Value          |
| NTS          | Notification Set                   |
| PAC          | Premature Atrial Contraction       |
| PPG          | Photoplethysmography               |
| PPV          | Positive Predictive Value          |
| PVC          | Premature Ventricular Contraction  |
| SAE          | Serious Adverse Eve                |

1.1
1 Introduction

This statistical analysis plan (SAP) describes the statistical techniques which will be used to evaluate the ability of the Fitbit Rhythm Detect algorithm to identify atrial fibrillation or atrial flutter (AF) and guide further clinical evaluation.

2 Algorithm Overview

The input to the Fitbit Rhythm Detect algorithm are pulse tachograms, which contain the timing between the peaks in a pulse rate signal, for example, as detected by photoplethysmography at the wrist. Each pulse tachogram spans 5 minutes, and consecutive tachograms overlap by 2.5 minutes. The algorithm classifies each tachogram as either positive for an irregular rhythm, negative for an irregular rhythm, or unanalyzable. A tachogram is classified as unanalyzable if there is substantial motion detected or if there is not sufficient signal. An irregular heart rhythm detection (IHRD) is generated after 11 consecutive positive tachograms. These 11 tachograms do not need to be contiguous, and there may be unanalyzable windows between positive tachograms. The IHRD may not contain any negative tachograms. The IHRDs are generated on a sliding window basis. A schematic illustrating tachograms and IHRDs is shown in Figure 1.

In Figure 1, negative tachograms are indicated in blue (“N”) and positive tachograms are indicated in red (“P”). An IHRD is generated after 11 positive tachograms in succession, with no negative tachograms in between. Tachograms that are classified as unanalyzable are denoted in grey. An IHRD is still generated if unanalyzable windows occur during the series of 11 positive tachograms. Detections – denoted by the circles (“D”) – may contain overlapping windows of tachograms. For example, D1 contains tachograms A1-A11, and D2 contains tachograms A2-A12. Non-overlapping IHRDs refer to detections which do not contain tachograms in common, as with D1 (Alert Window A) and D13 (Alert Window B). Note that the detection window is from the start of the first tachogram to the end of the 11th tachogram.
Figure 1: Schematic for tachograms and IHRD windows. The tachograms are 5 min. and overlap by 2.5 min. The IHRDs are generated on a sliding window basis and also may overlap in time. IHRD windows A (D1) and B (D13) are non-overlapping in time.

3 Study Details

3.1 Study Objectives

Objective 1: To evaluate the effectiveness of the Fitbit Rhythm Detect Algorithm in identifying subjects with undiagnosed atrial fibrillation or atrial flutter (AF), during simultaneous ECG monitoring.

Objective 2: To assess the concordance of pulse tachograms positive for AF by the Fitbit Rhythm Detect Algorithm with ECG detected episodes of AF during simultaneous ECG monitoring.

3.2 Study Endpoints

Primary Endpoint: Simultaneous measurement of AF \( \geq 30 \) seconds on ECG patch monitor during any of the pulse tachograms that generate the first IHRD during ECG monitoring.

Secondary Endpoint: Simultaneous measurement of AF \( \geq 30 \) seconds on the ECG patch monitor during each of the pulse tachograms that contributed to the first IHRD, among those IHRDs confirmed by ECG.

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**Tertiary Endpoints**: Tertiary endpoints will be assessed as described in Section 4.5.

### 3.3 Study Design

This is an interventional trial to evaluate the Fitbit PPG RhythmDetect Software System algorithm for identifying rhythms suggestive of AF. Compatible Fitbit devices with optical sensors can measure the pulse rate using photoplethysmography (PPG), a technique to measure variations in blood volume. While it is normal to have a small amount of heart rate variability, highly irregular rates may be suggestive of arrhythmias such as AF. The Fitbit PPG RhythmDetect Software System algorithm evaluates the beat to beat pulse rate from PPG data in overlapping 5-minute windows (tachograms) and classifies each tachogram as irregular or normal. If there is a large amount of motion (detected by accelerometers on the Fitbit device) or poor signal quality, the tachogram is classified as unanalyzable.

The study population will be recruited from the U.S. Fitbit user base. Participants must meet the following inclusion criteria:

- Adults 22 years of age or older
- Capable of giving informed consent
- U.S. resident
- No prior history of atrial fibrillation or atrial flutter
- Compatible Fitbit device (Ionic, Charge 3, Versa, Versa Lite, Versa 2, Inspire HR)

Individuals will be excluded if any of the following apply:

- Diagnosis or history of Atrial Fibrillation at time of consent
- Diagnosis or history of Atrial Flutter at time of consent
- Current use of anticoagulation medication
- Cardiac pacemaker or implantable cardioverter-defibrillator

A schematic of the study design is shown in Figure 1. After enrollment, the first IHRD is transmitted to a participant as an irregular heart rhythm alert (IHRA). Subjects who receive an
IHRA will be asked to contact a PlushCare telehealth physician. If the physician determines the subject is eligible, a mobile cardiac ECG monitor will be ordered from BioTelemetry, which will be shipped directly to the participant. After wearing the Fitbit device and ECG monitor simultaneously for up to one week, the ECG monitor will be sent to BioTelemetry for analysis. The results of the ECG monitor will be reviewed with the participant during a second telehealth visit. BioTelemetry will perform adjudication of the ECG monitor report as well as adjudication of ECG data paired with individual PPG analysis windows (tachograms). The reviewers will be blinded to the Fitbit algorithm results.

Participants who receive an IHRA will be asked to complete a follow-up survey 90 days after they receive the notification. The survey will ask about follow-up with their healthcare provider and medications or treatments they may have received since enrollment. All participants, including those who did not receive a notification, will be asked to complete an end of study survey to collect information regarding their experience in the study.

Fitbit users may have up to 30 days of retrospective data available for analysis upon enrollment. If a positive result is calculated during the retrospective analysis, then this will be surfaced to the participant as a notification. If no positive notification is calculated from the retrospective analysis, then data will continue to be analyzed prospectively.
3.4 Sample Size Determination

The primary endpoint analysis is based on the positive predictive value (PPV) defined as the proportion of first IHRDs that are true positives, i.e. overlap with ≥ 30 seconds of simultaneous ECG monitor confirmed AF. Overlapping ECG monitor confirmed AF is defined based on the time window of tachograms that generates the IHRD. A sample size of 155 individuals yields 80% power to test the null hypothesis that the true PPV is less than or equal to 70% against the alternative that it is greater than 70% assuming the expected PPV is 80% and a one-sided type-1 error rate of 2.5%.
Using published numbers for studies of the predicate’s device trial, we estimate we need to enroll enough subjects for 1,809 to receive an initial notification and 775 to complete the protocol and provide usable data, as shown in Table 1. To achieve this number, we aim to enroll a sufficient number of subjects to achieve our target sample size of 155. An example projection of the enrollment funnel is shown below in Table 1.

**Table 1: Estimated enrollment funnel for study.**

|               | Enrolled | IHRA | 1st visit | ECG shipped | ECG Usable data | IHRD during ECG |
|---------------|----------|------|-----------|-------------|-----------------|-----------------|
| **Predicate (published)** |          |      |           |             |                 |                 |
|               | 419,297  | 2,161| 945       | 658         | 450             | 86              |
|               | x 0.5%   | x 43.7% | x 70%    | x 68%       | x 19%           |                 |
| **Predicate (de novo)** |          |      |           |             |                 |                 |
|               |          |      |           |             | 226             | 57              |
|               |          |      |           |             | x 25%           |                 |
| **Proposed**  | 258,429  | 1,809| 1,266     | 886         | 620             | 155             |
|               | x 0.7%   | x 70% | x 70%    | x 70%       | x 70%           |                 |

The second endpoint examines the concordance between the eleven 5-minute tachograms contributing to the first IHRD and episodes of AF detected by ECG monitoring, among those IHRDs confirmed by ECG. If we assume at least 70% of the subjects from the primary endpoint analysis are true positives, then the sample size will be 155 x 70% = 108. The estimated proportion of tachograms that are true positives within the first IHRD, among those confirmed by ECG, is 90%. A sample size of 108 achieves 80% power to detect a difference of 0.1 between the actual mean of 0.9 and the null-hypothesized mean of 0.8 with an estimated standard deviation of 0.4 and with a significance level (alpha) of 0.025 using a one-sided one-sample t-test.

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1 Perez, M. V., Mahaffey, K. W., Hedlin, H., Rumsfeld, J. S., Garcia, A., Ferris, T., ... Turakhia, M. P. (2019). Large-scale assessment of a smartwatch to identify atrial fibrillation. *New England Journal of Medicine, 381*(20), 1909–1917

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4 Statistical Analysis

4.1 Analysis datasets

The data sets used in analysis are given as follows:

| Acronym | Name       | Included                                                                 |
|---------|------------|---------------------------------------------------------------------------|
| ENS     | Enrolled Set | All enrolled participants.                                                |
| IHS     | IHRA Set   | Participants who receive an IHRA                                          |
| ECS     | ECG Set    | Participants who receive and wear an ambulatory ECG patch monitor and provide at least one hour of usable ECG data, which overlaps with analyzable time for the Fitbit algorithm. |
| NTS     | Notification Set | Participants who receive an IHRD during the ECG patch wear time.          |

4.2 General analysis considerations

4.2.1 Descriptive statistics

Numeric variables will be summarized using standard summary statistics including mean, standard deviation, median, interquartile range (25th and 75th percentiles) and range. Categorical data will be summarized as proportions.

4.2.2 Multiple patches per participant

In some cases multiple ambulatory ECG patch monitors may be associated with a single user ID. This may happen, for example, if a participant has technical issues with an ECG patch and an a replacement monitor is sent. In such cases, only data from the final patch for a given user will be used for analysis. This is expected to be a rare event.
4.2.3 Time alignment between Fitbit device and ECG monitor

The Fitbit device time is derived from a mobile device during a data sync. If several days occur between syncs, the time on the device may drift. The BioTel ECG monitor has a battery which maintains time on the device. The device clocks on the Fitbit device and ECG monitor are independent, and may independently drift. In order to account for this potential clock misalignment, for each 5-minute tachogram, ECG traces from a minute before and minute after the tachogram window will be evaluated, in addition to the time spanning the tachogram window.

4.2.4 Blinding

The cardiologists performing the tachogram level ECG interpretation will be blinded to the Fitbit algorithm output. To mitigate potential bias in the case where physicians assume that they will only be asked to interpret traces which correspond to positive tachograms, up to two traces per subject in the ECS set corresponding to negative tachograms will be selected and randomly included in the set of ECG traces to be reviewed.

4.2.5 Data quality checks

Data quality will be checked according to the Data Management Plan.

4.2.6 Drop-outs and missing data

Participants will be considered to be in the Drop-out subgroup if they received a notification and if any of the following apply:

1. Fails to complete a telehealth physician appointment within 30 days after the notification
2. Requires immediate medical care during study visit #1 due to urgent symptoms
3. Fails to return the ECG monitor within 45 days after visit #1

We will summarize the number of participants who fall into each of the above categories as well as self-reported reasons for failing to contact study telehealth physician for visit #1 or failure to return the ECG monitor within 45 days after visit #1.

For subjects who drop-out, their data up to that time will be included for analysis.

Every effort will be made to collect missing data points where applicable, including:

1. PlushCare physicians will consult with the subject to complete CRFs and collect information as required to confirm eligibility at Visit 1 and collect AE/SAE data.
2. Reminders will be sent to participants to wear and return their ECG patch monitor. Efforts will be made to contact participants if the ECG monitor is not received within 14 days of shipment.

3. In the event that data from the ECG monitor is corrupted or too noisy to generate a clinical report, the participant may be sent a replacement ECG patch monitor.

4.3 Descriptive characteristics of study sample

4.3.1 Enrollment and follow-up

The numbers and percentages of participants who completed the study, discontinued from the study, as well as the reasons for discontinuation will be summarized by age category and overall for the ENS, ECS, and NTS datasets.

| Age Range | ENS | ECS | NTS |
|-----------|-----|-----|-----|
| age 22-39 N |
| - Completed the study, # (%) |
| - Discontinued, # (%) |
| - Reasons for discontinuation |
| age 40-54 N |
| - Completed the study, # (%) |
| - Discontinued, # (%) |
| - Reasons for discontinuation |
| age 55-64 N |
| - Completed the study, # (%) |
| - Discontinued, # (%) |
| - Reasons for discontinuation |
| age 65-74 N |
| - Completed the study, # (%) |
| - Discontinued, # (%) |
| - Reasons for discontinuation |
| age 75+ N |
| - Completed the study, # (%) |
| - Discontinued, # (%) |
| - Reasons for discontinuation |
The number and percent of participants who withdraw from the study will be summarized by age group and overall for the ENS, ECS, and NTS datasets.

| Age Range | Withdrawals, N (%) |
|-----------|--------------------|
|           | ENS                | ECS    | NTS    |
| 22-39     |                    |        |        |
| 40-54     |                    |        |        |
| 55-64     |                    |        |        |
| 65-74     |                    |        |        |
| 75+       |                    |        |        |
| Overall   |                    |        |        |

Protocol deviations (PD) will be summarized using the ENS population

| Age Range | ENS (N) | PD (N) | PDs / ENS (%) |
|-----------|---------|--------|---------------|
| 22-39     |         |        |               |
| 40-54     |         |        |               |
| 55-64     |         |        |               |
| 65-74     |         |        |               |
| 75+       |         |        |               |
| Overall   |         |        |               |
4.3.2 Baseline Characteristics

Baseline characteristics including demographics and comorbidities will be summarized by age and overall for both the ENS, ECS, and NTS sets. No statistical tests will be performed to compare baseline characteristics.

If onboarding survey data is missing for participants, they will not be included in the summary data. The numbers of participants included in each category will be reported.

| Characteristic               | Type                  | Categories                                                                 |
|------------------------------|-----------------------|-----------------------------------------------------------------------------|
| Age                          | Categorical           | 22-39, 40-54, 55-64, 65-74, ≥75 years                                       |
| Sex                          | Categorical           | Female, Male, Other or prefer not to say                                    |
| Ethnicity: Hispanic or Latino| Categorical           | Yes, No, Prefer not to say                                                 |
| Race                         | Categorical           | American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other or prefer not to say |
| BMI (from height and weight) | Categorical / Continuous | <30 kg/m² and ≥ 30 kg/m² (optional)                                        |
| Medical History              | Categorical           | Hypertension, Diabetes mellitus, Myocardial infarction, Heart failure, Stroke or TIA, Peripheral arterial disease, Prefer not to say |
| Current Smoking              | Categorical           | Daily, Less than Daily, Not at all, Prefer not to say                      |
| Alcohol                      | Categorical           | Daily, Less than Daily, Not at all, Prefer not to say                      |
4.3.3 Medications

During study visit 1 the physician will record the medications used by a participant. The medications for the those who complete visit 1 will be summarized by age group.

| Drug Category         | N (%) Responding | N (%) on Medication |
|-----------------------|------------------|---------------------|
| Beta blockers         |                  |                     |
| Calcium channel blockers |                |                     |
| Aspirin               |                  |                     |

4.4 Primary and secondary endpoint analysis

4.4.1 Primary Endpoint Analysis

The primary endpoint is the simultaneous measurement of confirmed AF (≥ 30 seconds on the ECG patch monitor) during any of the pulse tachograms that generate the first IHRD during the ECG monitoring period. In the planned commercial use case, the first IHRD would be user facing as an IHRA.

The ECG data corresponding to each of the 11 tachograms which lead to the IHRD will be evaluated, and if there is ≥ 30 seconds of AF during one or more of the tachograms, the IHRD will be considered a true positive. The positive predictive value (PPV) of the alert is given by:

\[
\text{PPV} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}}
\]

The Loading… is expected to be 80%. A point estimate of the Loading… and the corresponding lower bound of a one-sided 97.5% confidence interval will be reported. A one-sided 2.5% level test of the null hypothesis that the true PPV is less than or equal to 70% (Loading…) versus the alternative that the true PPV is greater than 70% (Loading… will be calculated.

4.4.2 Secondary Endpoint Analysis

The secondary study endpoint is simultaneous measurement of confirmed AF (≥ 30 seconds on the ECG patch monitor) during each of the pulse tachograms that contributed to the first IHRD, among those IHRDs confirmed by ECG. The within-person PPV of the tachograms will be estimated as the proportion of positive pulse tachograms which correspond in time with ≥ 30 seconds of AF on the ECG patch monitor.

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The average of the within-person PPV will be estimated and a corresponding 97.5% lower bound will be reported. A one-sided 2.5% level test of the null hypothesis that the true PPV is less than or equal to 80% (Loading…) versus the alternative that the true PPV is greater than 80% (Loading… will be calculated.

### 4.5 Tertiary endpoint analysis

The following additional endpoints will be evaluated. In each case, a point estimate and two-sided 95% confidence interval (unless otherwise indicated) will be reported. As these are exploratory endpoints, intervals will not be adjusted for multiple testing.

1) **The incidence rate of IHRAs in number per person-years**
   - **Data set:** ENS and IHRA
   - **Calculation:** The annualized incidence rate, given by:

   Loading…

   The time in the study for each subject is the minimum of:
   a. Time between enrollment and an IHRA
   b. Time between enrollment and the end of study
   c. Time between enrollment and withdrawal or drop-out from study.

   The time for all enrolled subjects will be summed to provide the denominator above. The numerator is the number of subjects who receive an IHRA (the number in the IHS dataset). For subjects who have up to 30 days of retrospective data, this retrospective analysis time will also be included in the time in study.

2) **Confirmed AF ≥ 30 seconds on ECG patch monitor subsequent to an IHRA.**
   - **Data set:** ECS
   - **Calculation:** This will be estimated as the proportion of the total number of individuals who receive an IHRA who subsequently have confirmed AF ≥ 30 seconds on the ECG patch monitor.

   Loading…

3) **Self-reported contact with a healthcare provider within 3 months following an IHRA.**

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Data set: Subjects who receive an IHRA and complete the 90-day follow-up survey

Calculation: The proportion of individuals who report contact with a healthcare provider in the 90-day follow-up survey.

4) Proportion of IHRDs which overlap with AF ≥ 30 seconds, based on the clinical report.

Data set: ECS with confirmed AF ≥ 30 seconds on the ECG patch monitor.

Calculation: The clinical report contains start and stop times for episodes of AF. For each subject, the number of non-overlapping IHRDs which overlap with episodes of AF ≥ 30 seconds will be assessed. This will be evaluated as:

- Per-subject: Mean of: the per-person number of IHRDs with simultaneous ECG documented AF ≥ 30 seconds / per-person number of IHRDs
- Aggregate PPV across subjects: Number of IHRDs with simultaneous ECG documented AF ≥ 30 seconds / number of IHRDs across all subjects
- Per-subject PPV: Presence of AF concurrent with any IHRD / Number of subjects with an IHRD

5) Simultaneous measurement of confirmed AF ≥ 30 seconds on the ECG patch monitor during each of a randomly selected set of non-overlapping pulse tachograms that contributed to any IHRD.

Data set: NTS

Calculation: For this endpoint, one tachogram will be randomly selected from each of up to the first 20 positive and non-overlapping IHRDs. A true positive tachogram is defined as having ≥ 30 seconds of AF confirmed by ECG during the tachogram time window. If less than 20 IHRDs are available for a participant, then the maximum number will be used. This will be evaluated as:

- Per-subject: Mean of: the per-person number of positive pulse tachograms with simultaneous ECG documented AF ≥ 30 seconds / per-person number of positive pulse tachograms
- Aggregate PPV across subjects: Number of positive pulse tachograms with simultaneous ECG documented AF ≥ 30 seconds / number of positive pulse tachograms across all subjects
- Per-subject PPV: Presence of AF concurrent with any positive pulse tachogram / Number of subjects with a positive pulse tachogram
6) Simultaneous measurement of confirmed AF ≥ 30 seconds on the ECG patch monitor during each of a randomly selected set of non-overlapping positive pulse tachograms that did not contribute to any IHRD.

**Data set:** ECS with ≥ one positive tachogram that did not contribute to any IHRD

**Calculation:** For each user, up to 10 non-overlapping tachograms will be sampled randomly from those positive tachograms which are outside the window of an IHRD. This will be evaluated as:

- **Per-subject:** Mean of: the per-person number of positive pulse tachograms with AF ≥ 30 seconds / per-person number of positive pulse tachograms
- **Aggregate across subjects:** Number of positive pulse tachograms with AF ≥ 30 seconds / number of positive pulse tachograms across all subjects
- **Per-subject PPV:** Presence of AF concurrent with any positive pulse tachogram / Number of subjects with a positive pulse tachogram

7) **Concordance of IHRDs with arrhythmias other than AF.**

**Data set:** The first IHRD for each subject (as selected for the primary endpoint) which does not correspond to ECG confirmed AF.

**Calculation:** For IHRDs from the primary endpoint which do not overlap with AF ≥ 30 seconds, other arrhythmias will be tabulated.

8) **Maximum duration of confirmed AF (detected on the ECG monitor) of greater than 6 minutes, 1 hour, 6 hours, and 24 hours subsequent to IHRA.**

**Data set:** ECS with AF confirmed by ECG

**Calculation:** For each subject with confirmed AF on ECG monitoring, the longest duration episode during the monitoring period will be determined. The proportions of these maximum durations that are greater than 6 minutes, 1 hour, 6 hours and 24 hours will be reported.

9) **During participation in study, self-report of:**

- new diagnosis of AF
- initiation of medical therapies for AF, including anticoagulant, rate-controlling and antiarrhythmic therapy
- electrical or chemical cardioversion
- ablation

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Data set: ENS who complete the end of study survey

Calculation: The numbers of individuals who complete the end of study survey and who report any of the above will be reported as a proportion. The proportion will be tabulated for the ENS group and for just the IHS group separately.

10) Comparison of time and proportion of time in an irregular rhythm by IHRDs and AF reported by the ECG patch monitor among users with ≥ 30 minutes of continuous AF on the ECG patch monitor. A threshold of 30 minutes is chosen as this corresponds to the minimum time of continuous AF detectable by an IHRD (assuming contiguous overlapping eleven 5 minute tachograms).

Data set: Subset of ECS who have ≥ 30 minutes of continuous AF confirmed by ECG

Calculation: For the ECG monitor wear time, total time and proportion of analyzable time will be computed as follows:

Total time in AF

a. Total time in an irregular rhythm (Fitbit algorithm): Total time covered by IHRDs, as defined by the aggregate time of the 11 tachograms that comprise the IHRD. There may be runs of unanalyzable windows, which can constitute a time gap either within or between IHRDs. These time gaps are measured as the time duration of consecutive overlapping unanalyzable windows (with no positive or negative tachograms) and they will not contribute to the overall time. By definition (a) will be restricted to analyzable time periods by the Fitbit.

b. Total time in AF (ECG): Total time in AF as reported by the ECG monitor clinical report.

c. Total time in AF (ECG) during Fitbit analyzable time. Total time in AF as reported by the ECG monitor clinical report, restricted to analyzable time periods by the Fitbit.

Proportion of time in AF

d. Proportion of time in an irregular rhythm (Fitbit algorithm): Total time covered by IHRDs, as calculated in (a), divided by the total analyzable time by the Fitbit algorithm.

e. Proportion of time in AF (ECG): Time in AF, as calculated in (b), divided by the ECG patch wear time. This is labeled as % AF burden.

f. Proportion of time in AF (ECG) during Fitbit analyzable time. Time in AF, as calculated in (c), divided by Fitbit analyzable time. This is labeled as % AF burden, restricted to analyzable time periods by the Fitbit.

Each subject with ≥ 30 minutes of continuous AF confirmed by ECG will contribute one datapoint for each of the above calculations.
We will calculate the following:

**Descriptive statistics**: Mean and standard deviation; median and interquartile range for (a) – (f) above.

**Pairwise correlations**: Correlation coefficient for the following pairs of data:
- i) Total Time in AF: (a) will be plotted separately against (b) and (c)
- ii) Proportion of Time in AF: (d) will be plotted separately against (e) and (f)

11) Correlation of IHRD and AF on ECG patch monitor for different durations of AF episodes

**Data set**: NTS

**Calculation**: Correlation of IHRD length during the ECG patch monitor will be calculated for different length episodes of AF as determined by ECG. The episode lengths, T, defined by the ECG clinical report, will be grouped by a) 1hr ≤ T < 6hrs; b) 6hrs ≤ T < 24hrs ; and c) 24 hrs ≤ T. Each subject can contribute multiple episodes to the analysis. IHRD length will be computed as the sum of time of positive tachograms which comprise the IHRDs which overlap with the ECG AF episode.

**4.6 Subgroup Analyses**

Analysis will be done for the overall dataset as well as by sex and age subgroups (age 22-39, 50-54, 65-74, 75+).

| Age   | N ENS | N IHRD | AF on ECG within detection window | AF on ECG within detection window / N IHRD | 95% CI |
|-------|-------|--------|-----------------------------------|--------------------------------------------|-------|
| 22-39 |       |        |                                   |                                            |       |
| 40-54 |       |        |                                   |                                            |       |
| 55-64 |       |        |                                   |                                            |       |
| 65-74 |       |        |                                   |                                            |       |
| 75+   |       |        |                                   |                                            |       |

| Age   | N tachogram+ | N AF on ECG | N AF on ECG | 95% CI |
|-------|--------------|--------------|--------------|-------|
| 22-39 |              |              |              |       |
| 40-54 |              |              |              |       |
| 55-64 |              |              |              |       |
| 65-74 |              |              |              |       |
| 75+   |              |              |              |       |
Proportions along with 95% confidence intervals for the primary endpoint will be presented separately by age (<40, 40-54, 55-64, 65-74, 75+), sex, race, medical history, type of AF, and non-AF irregular rhythms. Frequency of notification (notifications per person per year) will also be estimated separately by age, sex, race, and medical history in the ENR set. Results will also be presented aggregated over all ages.

The performance of the irregular rhythm notification will also be evaluated according to AF burden. The participants in the ECG group who received confirmation of AF (≥ 30 sec) by ECG monitor will be split into tertiles based on their AF burden. For each tertile, we will calculate (with corresponding 95% confidence intervals):

- Notification PPV (Initial notification vs subsequent AF confirmation on ECG monitor)
- Simultaneous alert PPV (detection and corresponding AF, Endpoint 1)
- Tachogram PPV (Endpoint 2)

### 4.7 Sensitivity Analyses

Sensitivity analyses based on application of generalized linear mixed models to account for within person correlations will be performed to evaluate the impact of the independence assumption for the secondary endpoint analysis.

Additional analyses will be performed to evaluate sensitivity of the irregular rhythm notification performance to different demographics, medical history, and AF burden. Per-protocol analysis will be performed excluding participants with protocol deviations (e.g. were found to meet exclusion criteria based on self-reported data such as existing AF or anti-coagulant use).
We will summarize the self-reported contact with a health care provider, use of subsequent therapies for AF, and reason for not following up with a health care provider within 3 months after notification among participants who receive a notification but do not receive an ePatch.

The impact of the independence assumption for multiple samples take from a given participant will be examined. The correlation between clustered samples within a participant will be evaluated to calculate the variation inflation factor and effective samples size.\(^2,3\) The corresponding confidence interval adjustments will be calculated.

5 Adverse Events

Adverse events will be summarized for the ENS and IHS data sets. For each group, the proportion of users who experience either anxiety or rash (due to the Fitbit device or ECG monitor) will be presented. Users who experience multiple occurrences of a particular adverse event will only be counted once for that event type.

|                      | N ENS | % ENS | N IHS | % IHS |
|----------------------|-------|-------|-------|-------|
| #AEs Anxiety         |       |       |       |       |
| #AEs Rash ePatch     |       |       |       |       |
| #AEs Rash Fitbit device |     |     |       |       |

The incidence of all serious adverse events will be presented for the ENS and NTS sets.

|       | N SAEs | N unique participants with SAEs | SAEs / participants with SAEs |
|-------|--------|---------------------------------|-------------------------------|
| ENS   |        |                                 |                               |
| NTS   |        |                                 |                               |

\(^2\) Rao, J. N. K., & Scott, A. J. (1992). A Simple Method for the Analysis of Clustered Binary Data. *Biometrics, 48*(2), 577–585.

\(^3\) Genders, T. S. S., Sprok, S., Stijnen, T., Steyerberg, E. W., Lesaffre, E., & Hunink, M. G. M. (2012). Methods for calculating sensitivity and specificity of clustered Data: A Tutorial. *Radiology, 265*(3), 910–916.
## 6 SAP Amendment History

| Version | Date      | Description of Change                                                                 | Brief Rationale                                                                                                                                 |
|---------|-----------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| A       | 3/31/2020 | Initial version                                                                       |                                                                                                                                               |
| B       | 9/27/2020 | Clarified and harmonized language for primary and secondary endpoints. Added details of analysis for tertiary endpoints. Added signature page. | Language for primary and secondary endpoints was made consistent across protocol, SAP, and entry in Clinicaltrials.gov. Details of analysis for tertiary endpoints were added for clarity. |