Detection of Atrial Fibrillation Recurrence Post-Ablation Using Photoplethysmography-Based Smartphone App (FibriCheck)

Principal Investigator: Prof Prashanthan Sanders, MBBS, PhD

Centre for Heart Rhythm Disorders

University of Adelaide, AUSTRALIA

Email: prash.sanders@adelaide.edu.au

Associate Investigator: Dr Suraya Hani Kamsani, MBBS, MPhil Candidate

Centre for Heart Rhythm Disorders

University of Adelaide, AUSTRALIA

Email: surayahani.kamsani@adelaide.edu.au

Associate Investigator: Dr Melissa E. Middeldorp, PhD

Centre for Heart Rhythm Disorders

University of Adelaide, AUSTRALIA

Email: melissa.middeldorp@adelaide.edu.au

Investigators and affiliations linked to this project

Investigators' names	Affiliation linked to the project
Prof Prashanthan Sanders	Central Adelaide Local Health Network
Dr Suraya Hani Kamsani	University of Adelaide
Dr Melissa E. Middeldorp	University of Adelaide

I. BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia globally. Its prevalence from 1990 to 2019 has almost doubled with the Global Burden of Disease (GBD) 2019 estimated at 59.7 million (95% UI: 45.7 to 75.3 million) cases of AF [1]. This trend is mostly attributable to population ageing and growth, increasing comorbidities such as hypertension and obesity, and further amplified by greater awareness and detection among the general population [2, 3]. AF is known to be responsible for up to 30% of all ischemic strokes and is associated with an increased risk of heart failure and mortality [2, 4, 5]. Thus, AF poses a substantial challenge in public health, and improved prevention with multidisciplinary team management is crucial in handling this epidemic.

The contemporary approach to AF management is patient-centred and encompasses optimization of stroke prevention, improvement of symptoms with rate or rhythm control and reduction in cardiovascular risk factors and comorbidities [6]. Catheter ablation has been established as a rhythm control strategy for symptomatic AF patients after antiarrhythmic drug failure [6-9]. Recent studies including STOP AF First, EARLY AF 4, and Cryo-FIRST trials have shown significant advantages of catheter ablation as first-line therapy in maintaining sinus rhythm for patients with paroxysmal episodes [10-12].

Maintenance of sinus rhythm after AF ablation can be achieved in 50-70% of patients at 1-year post-procedure [12-17]. However, recurrence after AF ablation is still relatively common; especially within the first 3 months [18]. Continuous monitoring with implantable cardiac monitor is currently considered the gold standard in detection of recurrence and assessment of ablation outcome [19]. However, this strategy is invasive and costly. Other rhythm monitoring strategies include intermittent, symptom-guided ECG recording, Holter monitor and transtelephonic monitors. Although these methods are non-invasive, they are poorly tolerated over long period of time and lacks sensitivity for detecting AF recurrences [19, 20].

A possible alternative that can provide both long-term but non-invasive approach to rhythm monitoring is the utilisation of smartphone applications. Recently, several smartphone applications for the detection of AF are accessible to the general public [21-27]. Majority of these applications utilize the smartphone's built-in camera with photoplethysmography (PPG) technology to detect changes in blood volume in the microvascular bed of tissue [28, 29]. This simple, non-invasive optical measurement technique only requires a light-emitting diode to illuminate the skin and a photodetector to measure the minute variation in light intensity transmitted by the tissues. This is then registered by the app to determine a particular individual's heart rate and rhythm. Sinus rhythm will present as regular pulse-to-pulse intervals with similar morphologies whereas AF typically manifests with variation in intervals between pulses and pulse morphologies in a PPG signal [28].

FibriCheck (Qompium NV, Hasselt, Belgium) is one of the smartphone apps that has been clinically validated for the detection of AF [30]. It is the first medical smartphone app that received both CE mark and US Food & Drug Administration (FDA). This app has also been proven to be a useful tool for AF screening both in mass population screening and in high-risk groups in general practice settings [31, 32]. Recently, FibriCheck has been utilised as part of a remote app-based teleconsultation and integrated AF management project involving multiple centres in Europe (TeleCheck-AF) [33-35]. This mobile health (mHealth) supported infrastructure was shown to be easy to set up and used by both patients and centres and could present an attractive complement to the current standard of face-to-face consultation for an integrated AF management [33]. To date, only a small study has been conducted on the use of FibriCheck post-AF ablation [36] and thus, further evidence is needed to assess its capability in detection of AF recurrence post-ablation.

II. HYPOTHESES

a. FibriCheck is a feasible rhythm monitoring strategy to detect recurrence in patients after AF ablation

b. FibriCheck can detect AF with good accuracy in patients following AF ablation

III. OBJECTIVES

a. To assess the ease of use of FibriCheck as a rhythm monitoring strategy in patients post AF ablation

b. To evaluate patients' compliance to FibriCheck monitoring schedule in patients post AF ablation

c. To determine the AF detection yield of FibriCheck in patients post AF ablation

d. To compare the accuracy of FibriCheck for AF detection to other rhythm monitoring strategies

IV. METHODS

1. Study design

This will be a prospective cohort study.

2. Recruitment sites

Participants will be recruited in the wards and clinics of the Cardiology Department of the following centres:

- Cardiovascular Centre
- Royal Adelaide Hospital
- Ashford Hospital

3. Study population

a. Inclusion criteria:

- Patients with symptomatic AF undergoing AF ablation procedure

- Aged 18 years or older
- Owner of a smartphone

b. Exclusion criteria:

- Patients with pacemakers
- Inability to use a smartphone app due to physical, visual or cognitive impairment
- Unwilling or unable to comply fully with study procedures and follow-up

There will be only one participant group. All participants will have to fulfil the above selection criteria.

4. Sample size

To our knowledge, only one small study has utilised FibriCheck following AF ablation [36]. For the estimation of our sample size, we used an estimated prevalence of AF recurrence following ablation detected by Holter monitor at 30% as previously reported [19, 37]. Based on a previous study, sensitivity for Holter detection of AF recurrence is estimated at 40% and FibriCheck at 70%[19]. The minimum sample size for this study to provide 80% power at 0.05 significance level is 98, based on Equivalence Tests for Pairwise Proportion Differences in a Williams Cross-Over Design, with a drop-out rate of 20% [38].

5. FibriCheck characteristics

a. Approval by regulatory bodies

The FibriCheck app has been approved as a Class IIa medical device by the EU in 2016 (certificate number BE16/819942412) and received clearance from the United States Food and Drug Administration (reference number: K173872) in 2018. It has also obtained the Australian

Register of Therapeutic Goods Certificate (ARTG Identifier: 336797) by the Therapeutic Goods Administration (TGA), Department of Health, Australian Government in 2020.

- **Conditions of approval by the United States Food and Drug Administration:** FibriCheck is indicated for self-testing by adult patients who have been diagnosed with, or are susceptible to developing, atrial fibrillation and who would like to monitor and record their heart rhythms on an intermittent basis.
- **Conditions of approval by the Australian Register of Therapeutic Goods:** the software is intended to be used by adults with known or suspected heart conditions, such as atrial fibrillation, to record pulse waveform and to monitor heart rhythm. The FibriCheck mobile application is only intended to record, display, store and transmit PPG data.

b. Permissions required from the user

Before its use, the FibriCheck application needs the following permissions from the user:

- Access to smartphone camera (to scan QR code and record PPG)
- Access to internet
- Access to send notifications

6. Study procedure

a. Recruitment of participants

Potential participants will be identified in the outpatient clinic at the time of AF ablation procedure referral or during first follow up after the procedure. They will first be approached by a member of the study team with an invitation to participate in the study. Potential participants will be given ample time (at least a week in many cases or longer as there is usually a wait time between being referred for ablation and date of procedure being undertaken) to consider their decision to participate in the study. All participants will be screened for eligibility and once deemed eligible

will be asked to sign an informed consent form by the associate investigator. After informed consent is obtained, the FibriCheck app will be installed in the participant's smartphone for free with detailed instructions regarding its use (Appendix 1a: Setting up an account with FibriCheck app).

b. Remote heart rate and rhythm assessment with FibriCheck

- **Measurement of heart rate and rhythm**

  The heart rate and rhythm measurement will be done using the FibriCheck app, which utilizes the smartphone's built-in camera. To start measuring, participants will be instructed to be in the seated position with the arm resting on a table, placing their (index) finger on the camera of the smartphone for 60 seconds. They will be reminded to keep still during the measurement process to minimize motion artifacts during the recording (Appendix 1b: Making a measurement with FibriCheck).

- **Recording of symptoms**

  Participants will be asked to complete a short questionnaire in the context screen after each measurement (Appendix 1c: Recording context of measurement with FibriCheck). This will include details on activities the participants were doing before the measurement (i.e. exercising, resting) and whether they were experiencing any symptoms.

- **Frequency of measurement**

  Participants will be asked to take measurements twice daily and additionally when experiencing symptoms for a period of 28-days at an interval of every 3-months post-ablation for the duration of the study. They will be encouraged to allow pop-up notifications and alarm reminders to ensure compliance during this period. The monitoring duration will also be scheduled to coincide with standard post-ablation clinic follow up with concurrent Holter monitoring at 3-monthly intervals.

- **Data processing**

  PPG signals collected by the app will initially be analysed based on quality metrics. Each measurement will be then evaluated using the FibriCheck AF algorithm, which is based on R-R interval variability analysis and automatically classifies the recording into 4 categories: 1. Normal sinus rhythm, 2. Inadequate signal, 3. Possible AF, and 4. Possible irregular heart rhythm (ectopic beats or other arrhythmias) (Appendix 1d: FibriCheck automatic interpretation; Appendix 1e: FibriCheck report). The study investigators will be emailed an alert should there be any abnormal tracing and will adjudicate any abnormal measurements by checking the online platform regularly. The participants will be instructed to seek emergent medical care if they feel unwell, to follow their action plan provided as part of the post-procedural care and to not rely on the app to guide them.

- **App usability**

  Participants will be asked to complete two sets of questionnaires on their perception and experience of using the FibriCheck app at enrolment and at the end of the study. Answers will be graded on a 5-step scale, ranging from "completely disagree" to "fully agree". These questionnaires were developed as part of a pilot usability study on FibriCheck and have not been validated previously [32] (Supplementary Material 1: Smartphone technology perception questionnaire; Supplementary Material 2: FibriCheck app usage questionnaire).

- **Access to the FibriCheck app after completion of the study**

  The FibriCheck app will not be removed from the participant's smartphone after the completion of the study by the investigators. However, as the app free subscription is only valid for the duration of the study, patients who wish to continue using the app

will be able to do so at their own cost. Further measurements after the study completion will not be accessible to the investigators.

- **Cost to participants**

  The FibriCheck app will be provided to the participants free of charge for the duration of the study.

c. Standard of care for post-AF ablation

No change will be made to the participants pre or post AF Ablation care. Participants will be followed up as per the usual standard of care provided by the treating electrophysiologist in the outpatient clinic. Standard protocolized follow up schedule at the enrolling institutions is: 1-week with 2D echocardiogram and clinician review, 3-month with 4-days Holter monitor and review and at 6-month with echo, Holter monitor and review, 9-month with Holter monitor and 12-month with echo, Holter and stress test.

7. Outcomes

a. Primary Outcome

- Detection of post-ablation AF recurrence by the FibriCheck app.
    - AF Duration = (Time between the last sinus rhythm and first detected AF/2) + Time between first detection to last detection of AF + (Time between last detected AF to first sinus rhythm/2). This estimation is based on a previous report comparing AF burden as measured from PPG-based mHealth with insertable cardiac monitor [39]. (Appendix 2)
    - AF Burden = Proportion of time patient in AF during monitoring period (%)

b. Secondary Outcomes

- FibriCheck app usability and technology perception as reported by the participants.
- Adherence to the scheduled PPG measurements.

- Compliance = Total number of measurements/ Total number of recommended measurements
- Motivation = Number of days of at least 2 measurements/ Total number of recommended monitoring days

- Comparison of AF detection with Holter monitoring.

8. Data Collection

a. Clinical data

- Sociodemographic information: age, sex, level of education, tobacco and alcohol use
- Baseline anthropomorphic measurements: height, weight, blood pressure
- Co-morbidities: hypertension, diabetes, heart failure, chronic kidney disease, coronary artery disease, chronic obstructive pulmonary disease, sleep apnoea, previous stroke/ transient ischemic attack, CHA_2DS_2-VASc score
- AF history: Type - paroxysmal or persistent, duration, frequency/ month
- Medications including anticoagulation and antiarrhythmic drugs
- Baseline 2D echocardiogram parameters – left atrial size and volume, left ventricular ejection fraction, diastolic dysfunction

b. Procedural data

- AF ablation strategy
- Procedure duration
- Left atrial time
- Fluoroscopy time
- Adverse events

c. FibriCheck data

- Number of measurements done per day and throughout the study period
- AF events detection

- Detection of other arrhythmias
- Reported symptoms
- Smartphone technology perception
- FibriCheck usage perception

d. Post-ablation follow-up data

- 2D echocardiogram parameters at 1 week and 6-month intervals
- AF detection from Holter monitor at 3-month and 6-month

9. Statistical Analysis

Statistical analysis will be conducted with Stata version 16 (StataCorp, College Station, Texas, United States). Descriptive statistics will be presented for continuous variables using mean±SD or median (Q1 to Q3) according to the distribution. Categorical variables will be summarized with numbers and percentages. Group comparisons for continuous variables will be analyzed using Mann-Whitney U tests while for categorical variables, $\chi 2$ tests will be performed to assess differences between the groups. Atrial fibrillation detection rates with FibriCheck and Holter monitoring will be evaluated and agreement between the two methods will be determined with Cohen's kappa coefficient. A p-value of ≤ 0.05 will be considered statistically significant.

V. ETHICAL CONSIDERATIONS

1. Recruitment and informed consent

The investigators will obtain ethical approval from appropriate Institutional Review Boards (IRB) and ensure that the study will be conducted in accordance to the protocol approved by the IRB and to the principles outlined in the Declaration of Helsinki. Details of the study and all the procedures involved including potential risks and benefits and the use of the study results

will be explained to the participants. All participants will sign an informed consent form prior to inclusion in the study.

2. Participant withdrawal

Participants will be able to withdraw their consent at any time during the study. Withdrawal of consent will be documented in the participant's source notes and will not affect the participant's usual medical care.

3. Potential benefits to participants

One potential direct benefit to participants will be the detection of AF recurrence by the FibriCheck app after their ablation procedure. Access to the app will also be provided free of charge to the participants during the course of the study.

4. Potential risks to participants

Participants of this study will not be exposed to any direct risk as the FibriCheck app uses non-invasive method for heart rhythm monitoring. Risks of the ablation procedure itself will be recorded but will not be considered as part of the outcome of the study.

5. Confidentiality, storage, retention and destruction of participants' information

All participant information obtained in relation to the study will be kept confidential and will only be used for the purpose of this study. Access to confidential information will be limited to authorised investigators and will only be disclosed with the participant's permission, except as required by law.

Information collected will not be de-identified to allow correct pairing of participant's results to patient profile. This is vital to ensure all data is analysed and reported accurately. Heart rhythm monitoring data from the FibriCheck app will be stored securely in cloud-based servers which are situated inside the European Economic Area (AWS – Frankfurt – Germany). The data will be stored in a study account that will be accessible only by the study team. The Fibricheck app has received both the ISO/IEC 27001:2013 (for security information

management system) and ISO/IEC 27701:2019 (for privacy information management system) certifications.

All printed copies, forms and other project information will be kept in secure swipe-card and password-protected offices at the University of Adelaide. Electronic data collected will be stored in the internationally recognised Research Electronic Data Capture (REDCap) database format on local university secure servers, with internet connection but only accessible through secure approved institutional access for project investigators and the database manager. This database logs all episodes of user access, design and data changes made.

Once the study is completed, participants' information will be de-identified and stored in secure archiving facilities at the University of Adelaide for 15 years, after which it will be securely destroyed in accordance with locally approved procedures. Only authorised research staff will be able to re-identify the data if required prior to data destruction.

In addition to the processes described above, data may otherwise be discoverable through processes of law or for assessing compliance with research procedures. In accordance with relevant Australian and/or South Australian privacy and other relevant laws, participants have the right to access their personal data, and the right to request for rectification or erasure of their personal information collected and stored by researchers.

6. Study ownership

This study is owned by the University of Adelaide.

VI. CONFLICT OF INTERESTS

The researchers involved do not have any conflicts of interest. There is no financial relationship between the university or investigators with FibriCheck.

VII. PUBLICATION

Results will be published as an original article in a relevant journal.

VIII. REFERENCES

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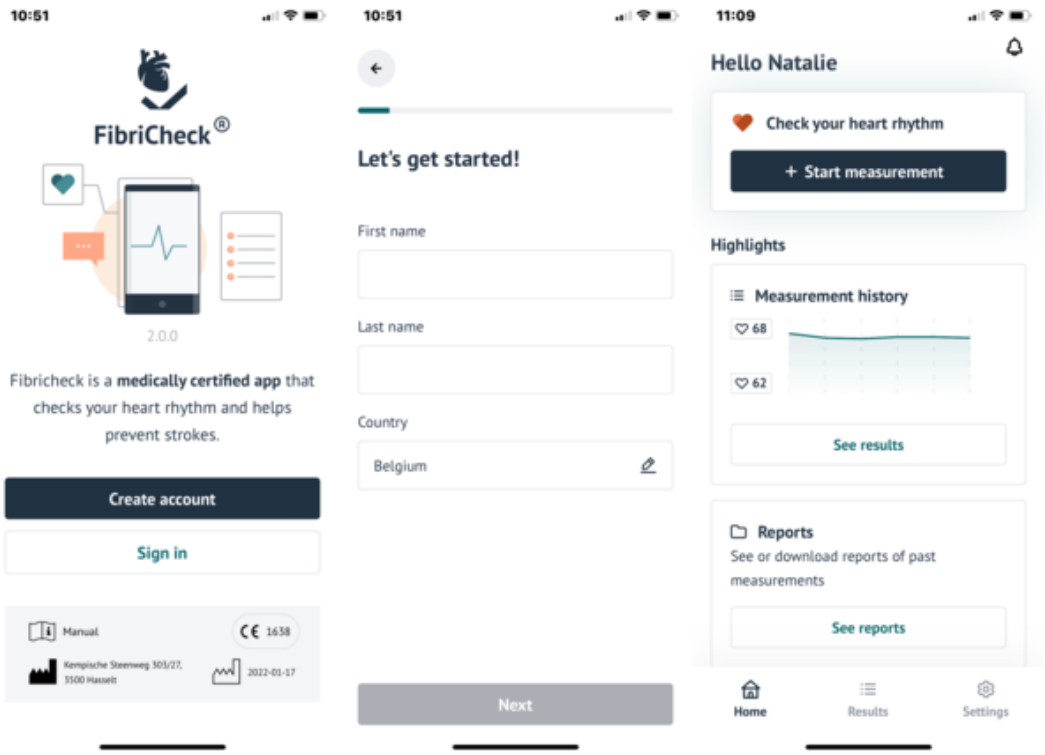
IX. APPENDIX

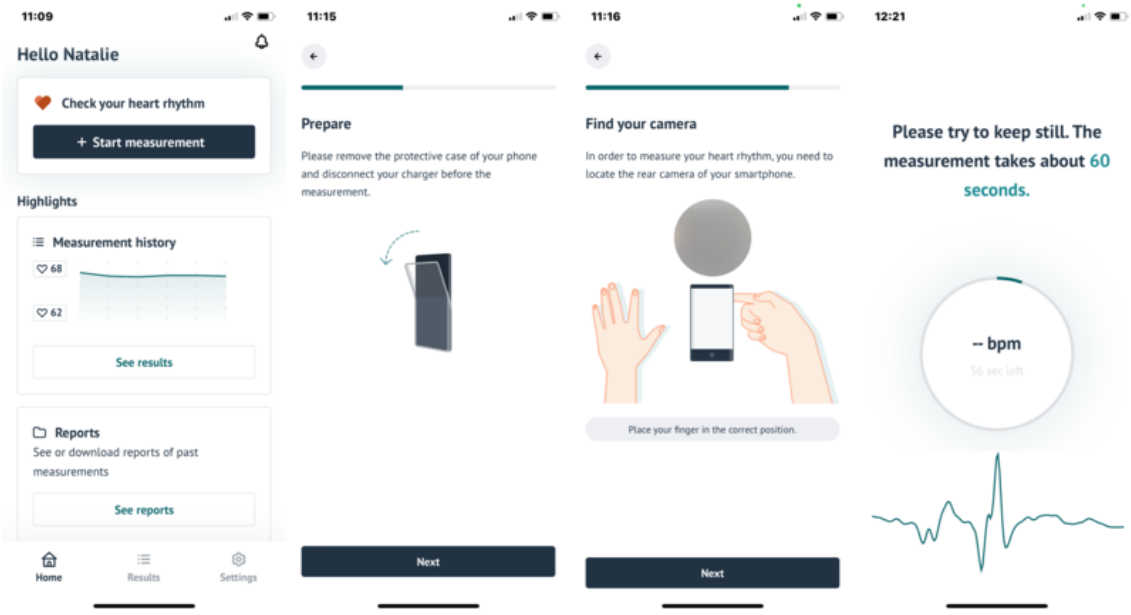
1. FibriCheck App: Instructions of use

From: FibriCheck. Instructions for Use – App. 2.1.3, 2022-03-08. Available at https://pages.fibricheck.com/ifu/app/2.1.3/en/

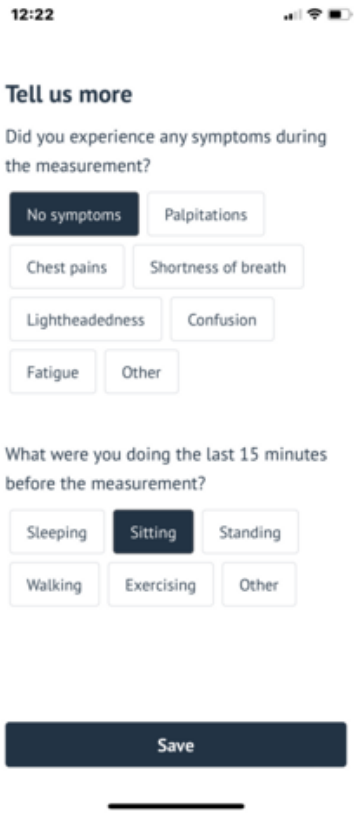
a. Setting up an account with FibriCheck app



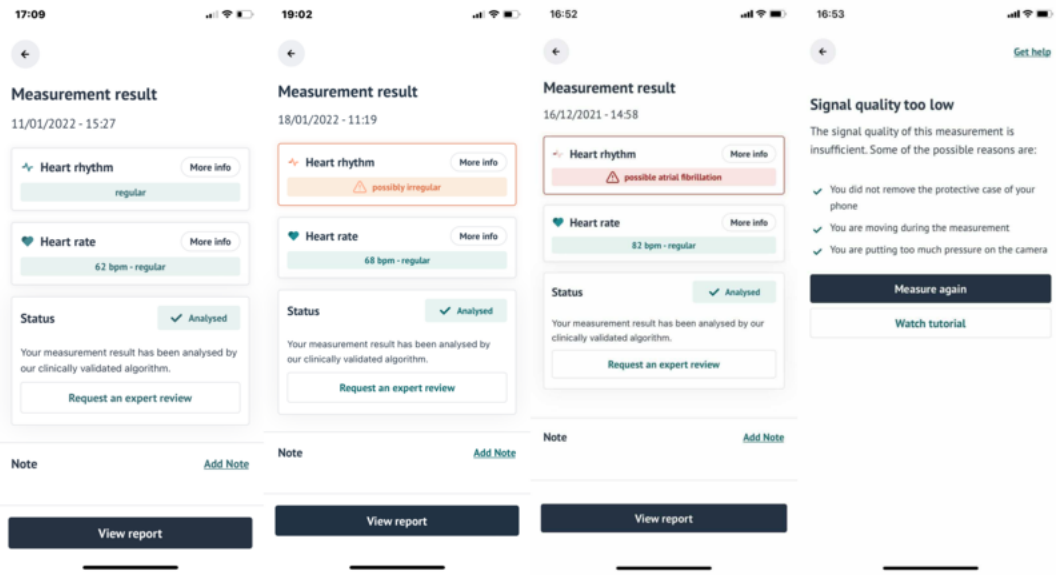
b. Making a measurement with FibriCheck



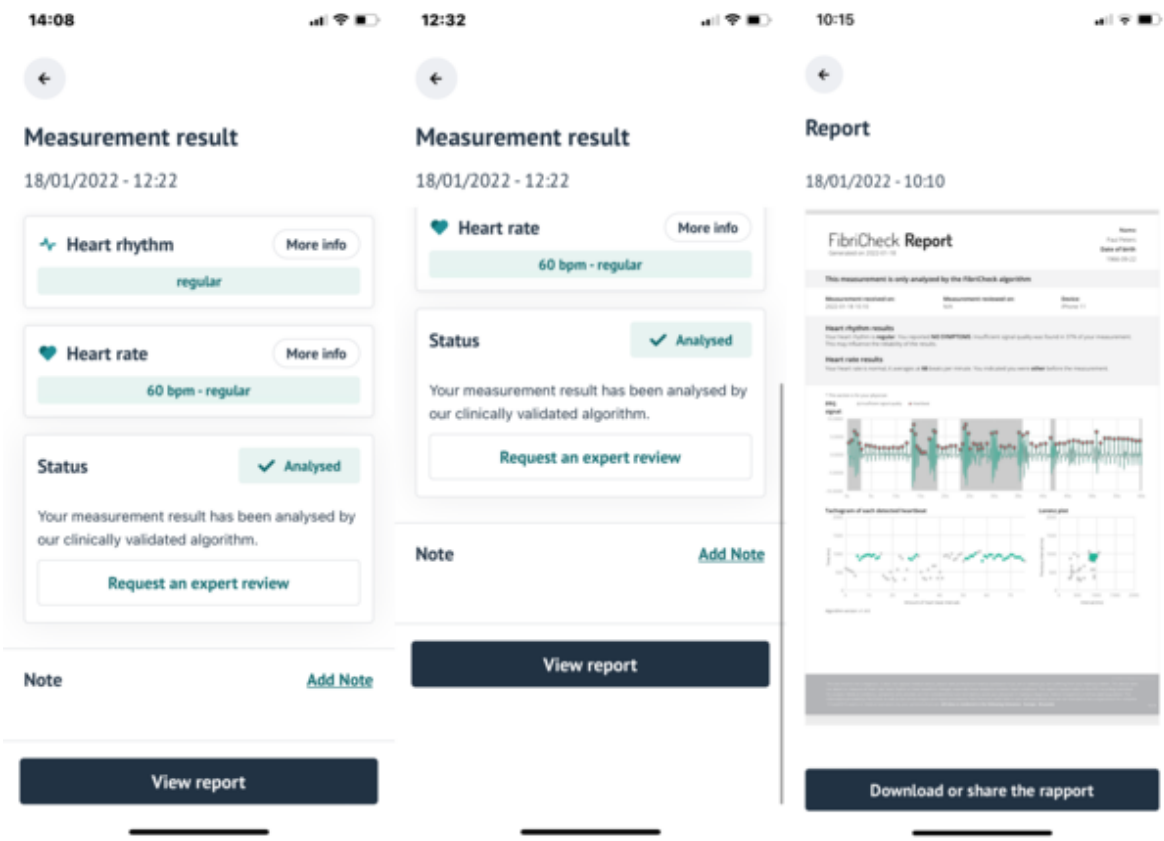
c. Recording context of measurement with FibriCheck



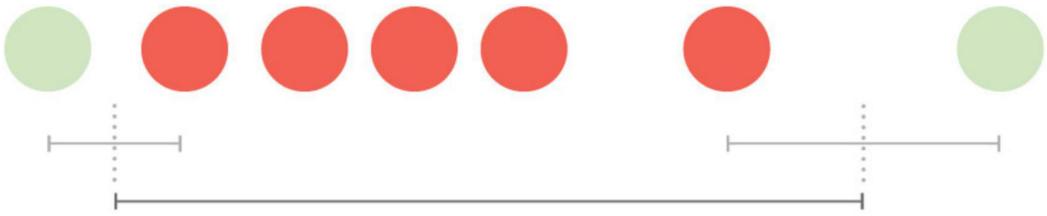
d. FibriCheck automatic interpretation



e. FibriCheck report



2. Estimation of AF duration from FibriCheck app



From Wouters F et al. Frontiers in cardiovascular medicine. 2022. 9: p. 839853.