Heart Watch Study: a Pragmatic Randomized Controlled Trial

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Protocol Title: Heart Watch Study: a Pragmatic Randomized Controlled Trial

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(*If applicable*) **Clinicaltrials.gov Registration #:** NCT04468321

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   We plan to conduct a randomized, controlled trial to determine the impact of the Apple Watch Series 6 on both patient-reported outcomes and clinical utilization over 1 year. Our research method will employ a patient-centered health data-sharing platform (called Hugo) for real-world surveillance of outcomes in 150 total patients after they receive direct current cardioversion (DCCV) or catheter ablation for treatment of atrial fibrillation or atrial flutter. We will recruit a total of 150 patients across 3 clinical sites- 60 at Yale-New Haven Hospital, 60 at the Mayo Clinic, and 30 at Duke Health- before they undergo DCCV for atrial fibrillation or atrial flutter or after they undergo catheter ablation for atrial fibrillation or atrial flutter. Half of the patients will be randomized to receive the Apple Watch Series 6, while half will receive a control device (Withings Move). Patients will then be queried about specific symptoms related to atrial fibrillation and medication adherence monthly for a total of 6 times post-procedure (6 months) and also at 12 months. This project will provide novel and needed post-market data about the recently cleared Apple Watch Series 6 ECG and irregular rhythm detection notification features and, on a larger scale, help delineate the impact of an innovative digital health technology on real-world patient outcomes.

   Specific Aim 1: To assess the impact of using the Apple Watch ECG and irregular rhythm notification features on patient-reported outcomes and clinical utilization after patients receive cardioversion or catheter ablation for atrial fibrillation or atrial flutter.

   Specific Aim 2: To determine the accuracy of the Apple Watch ECG compared to physician interpretation of 12-lead ECGs obtained in routine clinical care.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   The project is expected to be completed no later than June 2024 with enrollment beginning August 2021. Monitoring of each patient lasts a total of 12 months post-procedure. As batches of patients complete the 6-month follow-up duration, we will begin to clean and review the data on a rolling basis. We will examine data for 1 year after enrollment.

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   The pace of innovation for digital health technologies is accelerating. Many novel technologies employ software as a medical device and enable consumers to access their own health data in previously unimaginable ways. Simultaneously, the Food and Drug Administration (FDA) is establishing a nimble, least burdensome regulatory framework for such technologies under its Digital Health Innovation Action Plan.[1,2] For software-based medical devices, the agency has initiated a Software Precertification (Pre-Cert) Pilot; a key element is collecting and interpreting post-market, real-world data about software performance.[3] In September 2018, FDA cleared 2 software features for the Apple Watch: 1) to detect irregular heart rhythms likely to be atrial fibrillation[4] and 2) to generate a single-lead ECG.[5] However, several risks were identified, including: misinterpretation and/or over-reliance on the device, false negatives, and false positives; mitigation strategies were also identified.[4,5] Similar consumer digital technologies and software applications are growing in use and increasingly brought to FDA for clearance as medical devices. Therefore, there is a need to assess

the clinical impact of these devices through active surveillance to guide future labeling and risk mitigation strategies. Further, there are discussions to bring the Apple Watch to Medicare beneficiaries.[6]

Therefore, we have planned a multi-center, post-market randomized, controlled trial to understand the safety and effectiveness of the Apple Watch ECG and irregular rhythm notification features on patient-reported outcomes and clinical utilization in real-world patients receiving cardioversion or catheter ablation for atrial fibrillation or atrial flutter. Patients receiving cardioversion or catheter ablation for atrial fibrillation or atrial flutter will be randomized to receive the Apple Watch Series 6 or the Withings Move used as a control device. Using a patient-centered health data-sharing platform for data collection and aggregation, we will monitor patient quality of life for 12 months. We will also examine additional treatment for atrial tachyarrhythmias and how clinical utilization differs between the 2 groups. Finally, we will assess the Apple Watch's ability to serve as a tool for post-market ECG surveillance monitoring by examining its accuracy compared to physician interpretation of 12-lead ECGs obtained in routine clinical care. This study is funded by the National Evaluation System for health Technology Coordinating Center (NESTcc) and advances the use of real-world data generation in peoples' home environments and the use of routinely collected clinical data to support safety and effectiveness evaluations.

Of note, we will be leveraging infrastructure from a recently-completed study for this work. We recently completed a 60-patient study conducted by the Yale-Mayo Clinic FDA Center for Excellence in Regulatory Science and Innovation, of which 30 patients were enrolled at Yale-New Haven Hospital (IRB Protocol #2000021455), YNHH Principal Investigator: Joseph S. Ross, MD, MHS, which pilot tested the feasibility of using the Hugo Health platform for post-market surveillance of patients after either catheter-based atrial fibrillation ablation or bariatric surgery. Thirty additional patients were enrolled at Mayo Clinic.

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

Overall Study Design

This will be a prospective multi-center, randomized, controlled trial of 150 patients conducted to assess the impact of individual use of the Apple Watch on patient-reported and clinical outcomes at 1 year. Sixty of these patients will be recruited at Yale-New Haven Hospital. This sample size was calculated assuming 80% power to detect an effect size of 8.8 on the AFEQT questionnaire (slightly higher than the minimal clinically important difference of 5), with alpha 0.05. Additionally, we will validate Apple Watch Series 6 ECG readings when a simultaneous 12-lead ECG is obtained in clinical practice; the purpose of this validation is to assess the Apple Watch's ability to serve as a heart rate and ECG monitoring tool that may be used for periodic rhythm checks in post-market surveillance of other medical products (such as catheters used for atrial fibrillation ablation or antiarrhythmic medications).

Enrollment Procedure

As part of routine practice, outpatients who are planned to undergo cardioversion for atrial fibrillation or atrial flutter at Yale-New Haven Hospital will be contacted via phone by the department scheduler to confirm their scheduled time for their procedure. At this time the scheduler will tell the patient he/she may be eligible for a study examining the impact of using a wearable digital health device following cardioversion and then

ask about interest in the study (Please see appendix for script). Should they express interest, the scheduler will let them know that a Research Associate (RA) may reach out to them in advance of their procedure to discuss the study in further detail. The scheduler will then provide the RA with the patient's preferred contact information.

Once the patient has expressed interest in the study, the RA will open the patient's chart to ensure that the patient has a history of atrial fibrillation or atrial flutter before calling the patient. If there is not a confirmed diagnosis in the chart, the RA will confirm with a study clinician. The RA will attempt to contact the patient by phone in advance of their procedure. The RA will then use a checklist to confirm the patient meets all of the eligibility criteria (see below), including asking if they receive primary and cardiology care in the Yale-New Haven Health System. If the patient does not receive primary care in the Yale-New Haven Health System, the RA will ask the patient a) where they receive primary care and b) if they have a patient portal account for that provider. If the patient has a portal account for their primary care provider and that provider uses an Epic- or Cerner-based EHR, they are eligible for this study. If they do not, they will be considered ineligible. The RA will then review the process with the patient and inform him/her that participation is optional but if they would like to learn more and possibly enroll, they should arrive 60 minutes before their scheduled arrival time to meet and go through the consent and enrollment process. The RA will also ask the patient to bring his/her smartphone and YNHH MyChart login information (if they have it) and any phone account passwords with them that day, as well as advising them to update their device to the latest iOS if they have not done so already. The RA will be able to provide guidance on updating the device, if necessary.

A member of the clinical team may also introduce the study to eligible patients. If the patient expresses interest in being contacted, a member of the office staff will provide the RA with the patient's preferred contact information.

If a member of the clinical team identifies a patient that has been admitted to the hospital and will undergo DCCV in the next 24-48 hours, that patient would qualify for this study and the study clinician will inform the RA about the patient. The RA will then approach the patient and use a checklist to confirm the patient meets all of the eligibility criteria (see below). The RA will then review the study with the patient and inform him/her that participation is optional but if they would like to learn more and possibly enroll the RA will walk through the consent and enrollment process with them. The RA will be able to provide guidance on updating the device, if necessary.

On the day of the anticipated cardioversion, or the day prior for inpatients, the RA will then review the study consent form and discuss the specifics of the study described below. If, after reviewing, the patient agrees to the study, then he/she will be asked to sign the digital consent and authorization form for YNHH in the Hugo platform.

Separately, patients undergoing catheter ablation for atrial fibrillation or atrial flutter will be informed about study eligibility by their physician. As with cardioversion patients, the RA will attempt to contact the patient by phone in advance of their procedure. The RA will then use a checklist to confirm the patient meets all of the eligibility criteria (see below), including asking if they receive primary and cardiology care in the Yale-New Haven Health System. If the patient does not receive primary care in the Yale-New Haven Health System, the RA will ask the patient a) where they receive primary care and b) if they have a patient portal account for that provider. If the patient has a portal account for their primary care provider and that provider uses an Epic- or Cerner-based EHR, they are eligible for this study. If they do not, they will be considered ineligible. The RA will then review the process with the patient and inform him/her that participation is optional but if they would like to learn more and possibly enroll, they will have the option after their ablation, on the first post-

procedure day. If the patient is interested and eligible, the RA will ask the patient to bring his/her smartphone and YNHH MyChart login information (if they have it) and any phone account passwords with them that day, as well as advising them to update their device to the latest iOS if they have not done so already. On the first post-procedural day, patients will be approached by the RA to assess and ensure patients meet inclusion criteria and are interested in study participation. The RA will use a checklist to confirm the patient meets all of the eligibility criteria (see below). The RA will then review the study with the patient and inform him/her that participation is optional but if they would like to learn more and possibly enroll the RA will walk through the consent and enrollment process with them. The RA will be able to provide guidance on updating the device, if necessary.

We will ensure that the patient has a full and clear understanding that enrollment will not in any way impact his/her care nor alter the standard post-procedure follow-up visits. As a part of the consent process, the RA will also make clear to the patient that this study will not replace their normal medical care and advise him/her that should they begin having new or worrying symptoms to contact their doctor or emergency services directly, exactly as the patient would have done if he/she were not enrolled in our study. During enrollment the patient will also confirm their preferred contact method should the RA need to reach them during or after the follow-up period. Patients can indicate if they prefer text, email, and/or phone calls. In addition to their preferred method, we will ask them if they would be willing to be contacted by each modality. Should they indicate text or phone calls, the RA will offer to enter or suggest that the patient enter, the RA's Yale office number into their contact list so that they are aware when it is the study staff trying to reach them.

The RA will then assist the patient in linking his/her YNHH electronic health records to the Hugo platform. This linkage enables the patient to share all of the data available as part of their electronic health record data via their patient portal, with our researcher team. Because the patient-centered health data-sharing platform (Hugo) obtains patient data through patient portals, all patients who connect will need a YNHH MyChart account. The RA will assist the patients in creating a MyChart account if they do not already have one. Once the patient has completed the MyChart sign-up process, then the RA will assist the patient in creating and activating an account for the mobile health platform, Hugo, on either the study laptop or on the patient's personal smartphone depending on the patient's preference. Some patients may need to reset their MyChart password, and the RA will help them to do so. The RA will also assist the patient in connecting any other health systems found in the Hugo platform where they have received care by showing the study participant how to enter their patient portal credentials; for patients who receive primary care outside of YNHH but within an Epic- or Cerner-based electronic health record, we will ensure that patients connect data from that health system. Patients will receive a digital version of the 20-item Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire via email or text message (per patient preference); this questionnaire assesses symptoms, daily activities, treatment concern, and satisfaction.

At this time, the patient will be randomized 1:1 to the Apple Watch or control (Withings) arm using a central randomization algorithm. Patients randomized to the former will receive an Apple Watch Series 6 (WiFi/GPS) or a Withings Move. For Apple Watch patients, an Apple HealthKit account will be set up and linked to the Hugo platform; they will also need to install the Hugo App for iPhones which will enable receipt of Apple Watch-related data. Patients randomized to a Withings Move will be assisted in setting up a Withings Health Mate account, which will be linked to the Hugo platform. While setting up the Apple Watch application, RAs will assist patients in answering that they have not been previously diagnosed with atrial fibrillation (as enrichment of the study population with people likely to have recurrent atrial fibrillation and/or atrial flutter is necessary to understand how this device functions in people diagnosed with atrial fibrillation and/or atrial flutter).

We will also ask the patients to self-report their sex, race, ethnicity, and their preferred contact method. We will also ask if they have any of the following co-morbidities: arrhythmias other than atrial fibrillation or atrial flutter (and ask them to report which one(s), if any), hypertension, diabetes mellitus, high cholesterol, sleep apnea, coronary artery disease (including myocardial infarction/heart attack), heart failure, stroke, weak or failing kidneys, any liver condition, cancer, asthma, emphysema, depression, PTSD, or generalized anxiety disorder.

For patients undergoing cardioversion, the RA will attempt to complete all of the enrollment steps before the patient's procedure (cardioversion). Review of and signing of the consent will always be required prior to the procedure. In order to not impact the clinical workflow, some enrollment procedures may be completed post-operatively, if necessary, due to time constraints. If any part of enrollment needs to be completed post-procedure, the RA will always wait a minimum of 20 minutes after the patient is brought into recovery to allow any sedatives to wear off and confirm with the post-op nursing staff that the patient is awake, and that it is acceptable to approach them. Before proceeding with any enrollment procedures, the RA will then confirm the patient is alert and oriented by asking the patient to confirm their name, why they are in the hospital, and what city they are currently in. They will be asked to confirm that they recall the study and are amenable to continuing the enrollment process. The RA will aim to only have items such as syncing the devices to the phone and/or connecting any portal to Hugo, to be completed after the procedure. The baseline survey will be prioritized to be completed, after informed consent, pre-procedure.

For patients who had undergone catheter ablation for atrial fibrillation or atrial flutter, all enrollment procedures will occur only on the first post-procedural day, when the patient is generally recovering and awaiting discharge.

Of note, even though the Apple Watch Series 6 device is not intended for use in individuals previously diagnosed with atrial fibrillation, the ECG feature is not recommended for users with arrhythmias *except* for atrial fibrillation and sinus rhythm (since the software can only distinguish these two heart rhythms)[5]. People with atrial fibrillation may be more likely to purchase this device than others to monitor their rhythm and correlate with symptoms. Indeed, in the Apple Heart Study, nearly 20% of first study visit participants reported a diagnosis of atrial fibrillation/flutter before enrollment, even though a history of atrial fibrillation was an exclusion criterion.[7] Few digital health studies have enrolled patients with clinical morbidities to examine outcomes; such studies have instead focused on healthy volunteers.[8] Our study will address this limitation. Additionally, a study examining the impact of the Apple Watch on patient-reported outcomes and clinical utilization requires an enriched population; otherwise, study duration would be many years with a population size multiples larger than our proposal, resulting in significant cost and delays in generating much-needed evidence.

For patients undergoing cardioversion, if there is time before the cardioversion and always after the cardioversion, we will ask the patient to obtain an ECG using the Apple Watch Series 6 (and the RA will assist the patient if needed), with the 10-second interval that has the best resolution and is free from artifact for comparison to the interpretation of a 12-lead ECG obtained for clinical care (as these are 10 seconds long). If possible, we will also ask the patient to take a SpO2 reading while the RA is present and they are connected to a standard, medical grade pulse oximeter in the clinical setting.

A separate survey, both for patients undergoing cardioversion and who received catheter ablation for atrial fibrillation or flutter, will be sent at enrollment asking patients, only with the help of study staff, to enter both their Apple Watch pulse oximeter reading and the reading taken using a medical grade SpO2 monitor.

The RA will record the total time (minutes) for enrollment of each patient, including: device and account setup, in-person consenting, baseline survey (if the RA is present), ECG measurement (if performed) and SpO2 measurement (for Apple Watch patients). The RA will record a total time, and segment the times into discrete enrollment steps, if possible. The RA will not record time that the RA is not with the patient (for example, when the patient is undergoing cardioversion). The RA will also record enrollment type (inpatient or outpatient, with all patients undergoing catheter ablation considered inpatients) within Hugo. After enrollment, patients will also receive a follow-up email that contains their consent form as well as to again provide contact information should they have any questions or concerns about the study.

If a patient refuses to participate, then we will note the number of people who refused. If the patient is agreeable, we will then administer a short questionnaire to understand his/her rationale for not participating in the study, to understand potential reasons for non-participation. Please see Appendix for questionnaire.

If for any reason, portal and/or device connections cannot be completed at the time of enrollment (i.e., there is not enough time to complete, patient does not have their passwords with them, etc.), the RA will follow up with the patient via phone to finish the connections. Up to 3 attempts will be made to contact the patient. If there is no response via phone, the study team will send a letter via postal mail, asking the patient to complete their connections.

Follow-Up

Patients will be asked to wear and sync the device they received, Apple Watch Series 6 or Withings Move, from the time of enrollment forward for 12 months. This includes wearing it at all outpatient visits and opening the Withings Health Mate or Hugo Health iPhone applications every 7 days to ensure data syncs. We will ask patients to obtain an Apple Watch ECG whenever they obtain an ECG in routine clinical care, and to record symptoms that they had at the time of obtaining the ECG. They will be asked not to share the Apple Watch with anyone else for the 12-month duration of the study, nor their iPhone or iCloud accounts. We will suggest people charge their Apple Watch for the minimum necessary time and try to wear it for as much time as possible. We will not provide any anticipatory guidance to people about what they are supposed to do if they receive an irregular rhythm notification or a reading on their ECG app reading showing atrial fibrillation, as the goal of the study is to observe the natural history of patient-reported outcomes and health care utilization in response to device use.

Based on experience from prior studies, we anticipate being able to successfully and seamlessly stream electronic health record as well as patient-generated data from the Apple Watch and Apple HealthKit (including irregular rhythm notifications, high heart rates, low heart rates, and other data, which may include SpO2), as well as from the Health Mate platform for patients randomized to Withings Move, into our researcher database using the Hugo platform. For the AFEQT questionnaire, patients will receive this via secure email or text message link monthly for 6 months and then at 12 months. During the first 6 months, if they do not respond within 24 hours, they will receive a reminder. If they do not respond within 48 hours, they will receive a second reminder. Should there still be no response after an additional 48 hours, the RA will reach out to the patient via phone to follow-up to ask the patient to complete the unanswered survey.

A weekly automated reminder (text or email – based on the patient's preference) will be sent from Hugo, reminding patients to wear and sync their device. If no data are received, the RA will reach out to the patient via phone to follow-up. RAs will record if they successfully reach patients and if reasons for lack of data are identified.

Additionally, patients in the control (Withings Move) arm will receive a small stipend in addition to the Withings Move for completion of PROMs (patients in the Apple Watch arm will have received an Apple Watch, which we will explain comes with the expectation of responses to monthly PROMs, which would not be expected to take more than 5-10 minutes). We will also ask patients to obtain a final Apple Watch ECG at 6 months. Patients will be asked to share all of their Apple Watch-obtained ECGs with the research team by sending them to afibstudy@yale.edu. which has been created specifically for this study. For patients randomized to the Apple Watch, we will also send them a reminder at the end of the 6 months to send us any ECGs that they may have obtained on their device. We will also attempt to obtain ECGs directly through a connection between Hugo and Apple.

If patients choose to share other data, such as by connecting their pharmacies or claims, through the Hugo platform that will be noted in our study and those data will be made available for analyses.

If a patient reaches out to any member of the study team to withdraw from this study, we will ask if he/she would be willing to share why they have decided to withdraw. If they are willing to share, we will document that reason.

Analytic Plan

Baseline characteristics to be collected will be patient age, sex, location of primary care, location of primary cardiac care, and the comorbidities mentioned above. At baseline, patients will also be queried about their likelihood to use personal digital devices for health care purposes outside of this study, including if they have previously used a personal digital device and if they have previously used a personal digital device for cardiovascular monitoring.

Primary Outcome: Difference in the Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire[9] global score at 6 months compared to baseline

Secondary Clinical Outcomes

1. Change within individual domains of AFEQT questionnaire (symptoms, daily activities, treatment concern, and treatment satisfaction) monthly (at 1, 2, 3, 4, 5, and 6 months as well as at 12 months)
2. Additional clinical treatment for atrial fibrillation or flutter at 6 and 12 months: a composite outcome of rhythm control intervention, which is defined as at least one additional cardioversion, initiation of antiarrhythmic medical therapy, dose escalation of antiarrhythmic medication, change to another antiarrhythmic medication, or ablation for atrial fibrillation or flutter. The medication data will be obtained primarily from electronic health record data.
3. Acute care use at 6 and 12 months: emergency department visits, observation stays, all hospitalizations
4. Outpatient care use at 6 and 12 months: outpatient primary care visits, outpatient cardiology or cardiac electrophysiology visits, and scheduled telephone encounters.
5. Rhythm-related diagnostic testing at 6 and 12 months: total ECGs and total outpatient heart rhythm monitors
6. Anticoagulation persistence: through adopting the Brief Medication Questionnaire and asking patients if they have taken their anticoagulant, and for how many days in the past 1 week (monthly at 1, 2, 3, 4, 5, and 6 months as well as at 12 months)

For the primary outcome, we will calculate the difference in the AFEQT global questionnaire score at baseline and 6 months and perform a comparison between the patients randomized to the Apple Watch and patients randomized to Withings Move.

The secondary clinical utilization outcomes will be compared between the two groups. Data obtained through Hugo will be used to obtain most outcomes. Electronic health records will be used to review ECG tracings. We will also trend patients' monthly responses about anticoagulation adherence.

The secondary outcomes for accuracy of Apple Watch Software Features that will be compared are a comparison of the heart rhythm (identical to 12-lead ECG or different), rate (difference in beats per minute), and intervals: PR, QRS, and QT interval (difference in milliseconds) between what is assessed by the Apple Watch ECG feature and 12-lead ECGs during hospitalization or outpatient follow-up. This will be a blinded independent assessment of the Apple Watch ECG, and we will calculate both inter-observer reliability (among two reading cardiologists of Apple Watch ECGs), as well as intra-observer reliability.

As an exploratory outcome, we will aim to assess differences between SpO2 from the Apple Watch and medical grade readings.

The metrics we plan to collect are as follows:

A. Enrollment-related
- Number of people asked for study participation and number enrolled
    - Among patients who decline enrollment, if willing, the reason for declining

B. PROM-related (for all PROMs)
- Proportion of items completed
- Content of PROM responses

C. Personal Digital Device-related
- Number of patients who obtain Apple Watch ECGs over the study period, and the number of ECGs obtained
- Number of patients who receive an irregular rhythm notification during the study period, and the number of irregular rhythm notifications per patient
- Data obtained from Apple HealthKit and Withings Move

As each patient completes 12 months of follow-up, all patient data will be sent to the Mayo Clinic, where an analyst will clean and curate the data made available through the Hugo platform.

Finally, at the official end of the study (i.e. at 12 months post-procedure), study participants will receive a close-out questionnaire (see below) to assess occurrence of atrial fibrillation/atrial flutter, quality of life, anticoagulation medications, and device usage.

4. Genetic Testing N/A ☒

5. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

We will recruit a total of 60 study participants undergoing cardioversion for atrial fibrillation or atrial flutter at Yale-New Haven Hospital. Yale-New Haven Hospital in New Haven, CT sees over 79,000 patients a year with

approximately 65,000 adult patients and there are approximately 1 to 3 cardioversions performed daily as well as more than 700 ablations annually.

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

Pregnant women or females of childbearing potential have the potential of being enrolled in this study but will not be specifically recruited for enrollment preferentially over other patients. We anticipate that this study presents minimal risk to pregnant women.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion criteria:

- Age >22
- English-speaking
- Planned for direct current cardioversion for atrial fibrillation or atrial flutter, as noted by referring clinical staff or on chart review
- Post-procedure day 1 after catheter ablation for atrial fibrillation or atrial flutter
- Participant is willing and able to read and sign consent and participate in study
- Participant lives independently and does not require continuous care
- Participant has an email account (or is willing to create one)
- Participant has a compatible smartphone (iPhone 6s or later)
- Participant is willing to wear only the device they are randomized to receive for the study period for as many hours during the day as they are able, except for time spent charging the device or in environments that may be suboptimal for the device
- Participant is willing to use the Hugo mobile health platform and Apple Watch Series 6 or Withings Move
- Participant has cardiology care at YNHH, Duke Health, or Mayo Clinic and primary care in a health system with a patient portal

8. How will **eligibility** be determined, and by whom?

To be eligible, patients must meet the inclusion criteria listed above. A checklist will be used by the research associate (RA) to determine if the patient is eligible for this study.

For patients planned for cardioversion, once the scheduler or member of the clinical care team has introduced the study and if the patient has expressed interest in the study, the RA will review the patient's chart to confirm they have a history of atrial fibrillation or atrial flutter before contacting the patient. The RA will confirm that the patient meets all the eligibility requirements and discuss the specifics of the study described above. For inpatients, if a member of the clinical team identifies a patient that has been admitted to the hospital and will undergo DCCV in the next 24-48 hours that would qualify for this study, a clinician will inform the RA about the patient. The RA will then approach the patient and use a checklist to confirm the patient meets all of the eligibility criteria

For patients who are planned for catheter ablation for atrial fibrillation or atrial flutter, these patients will be informed by their physicians and screened for eligibility by research coordinators in advance of their procedure. Eligible patients will be identified on their first post-procedure day by research coordinators while the patient is recovering on the hospital ward, and usually planned for discharge, and eligibility will be confirmed prior to enrollment.

9. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The risk to patient privacy is no different with this study than it is with any other study that securely collects and appropriately stores personally identifiable information or protected health information.
The Hugo platform, like many other personal health records, is not a covered entity; therefore, the HIPAA privacy rule does not apply to this platform. The Hugo Health platform does take all necessary precautions, including industry-standard encryption, to minimize privacy and security risks to personally identifiable information stored on behalf of study participants. Hugo Health makes publicly available its Security Statement (https://hugo.health/security), its Privacy Notice (https://hugo.health/privacy-policy), and Terms of Service (http://hugo.health/terms-of-service)

Participants will undergo the possible inconvenience of filling out electronic patient-reported outcome measure surveys, which should take no more than 10 minutes monthly for a total of 8 times, as well as a close-out questionnaire that should take no longer than 5 minutes. Participants will also experience the possible inconvenience of wearing an Apple Watch or Withings Move for extended periods of time and syncing these devices with the Hugo Health platform.

Although the Apple Watch ECG and irregular rhythm notification detection features have been cleared by the FDA as a de novo classification device, the FDA's approval letter noted multiple identified risks to health, which were:
Poor quality ECG signal resulting in failure to detect arrhythmia; misinterpretation and/or over-reliance on the device output, leading to: failure to seek treatment despite acute symptoms and/or discontinuing or modifying treatment for chronic heart conditions; false-negative resulting in failure to identify arrhythmia and delay of further evaluation or treatment; and false-positive resulting in additional unnecessary medical procedures.[4 5] Further, we will clearly state to the patients that this study should in no way impact their regular care plans.

10. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

All patient data will be collected, handled, and stored according to the most rigorous accepted standards. Staff involved in the study will be appropriately trained to maximize data security and technical systems will meet or exceed requirements imposed by HIPAA. Sensitive information will always be encrypted in transit and at rest.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal risk to patients
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? No children will be involved in this study
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

The principal investigators (PI) are responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency regularly. During the review process the PIs will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The PIs or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

PROMs and syncable data received will not be reviewed by researchers, and this fact will be made clear to study participants at enrollment. Patients will be informed that symptoms reported in this study are not being monitored or evaluated in real-time and that any adverse or severe symptoms should be reported directly to their physician(s), or emergency room physicians as they would have in the normal course of their care.

The study coordinators will regularly monitor the status of the portal data (EHR/Apple Watch/Withings) coming into the Hugo platform using the Hugo study dashboard only available to research staff listed on the IRB. Within this dashboard, the research staff will be able to review the connection status of all portals connected to each patient's Hugo account. Should a connectivity issue be noticed by research staff, they will note the connection issue reported by the dashboard and determine if the issue is limited to one participant, or if multiple participants are experiencing the same problem. The research staff will then follow up directly with the Hugo support team.

Once the source of the issue is identified, research staff will follow up with the affected patients as needed to correct the issue in a timely fashion.

Research staff will also keep track of any technical issues reported by patients during their follow-up period. If the technical issues are not able to be resolved by the research staff, or if multiple patients report the same problem, the research staff will forward the issue to the Hugo Health support team to identify and correct the issue and in order to follow-up with those patients affected.

d. For multi-site studies for which the Yale PI serves as the lead investigator:
    i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
    ii. What provisions are in place for management of interim results?
    iii. What will the multi-site process be for protocol modifications?

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

All analyses will be intention-to-treat. For the primary outcome, we will calculate the difference in the AFEQT global questionnaire score at baseline and 6 months for patients randomized to the Apple Watch and patients randomized to the Withings Move arm.

The secondary clinical utilization outcomes will also be compared between the two groups using an intent-to-treat approach. Hugo will be the primary mechanism used to obtain clinical outcomes and clinical utilization, with comparisons between groups. We will also trend patients' monthly responses about anticoagulation adherence. In an additional secondary analysis, we will examine all of the outcomes at 12 months.

For the secondary outcomes for accuracy of Apple Watch Software Features that will be compared are a comparison of the heart rhythm (identical to 12-lead ECG or different), rate (difference in beats per minute), and PR, QRS, and QT intervals (difference in milliseconds) between what is assessed by the Apple Watch ECG feature and 12-lead ECGs during hospitalization or outpatient follow-up care. We will aim to compare the SpO2 readings taken by the Apple Watch at baseline to the measure taken by the standard, medical grade pulse oximeter

This sample size was calculated assuming 80% power to detect an effect size of 8.8 on the AFEQT questionnaire (slightly higher than the minimal clinically important difference of 5), with alpha 0.05.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DEVICES ☐N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No

If Yes, please be aware of the following requirements:

A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request**; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

In September 2018, FDA cleared 2 software features for the Apple Watch: 1) to detect irregular heart rhythms likely to be atrial fibrillation[4] and 2) to generate a single-lead ECG.[5] Both of these features were classified as Class II. Several risks were identified, including: misinterpretation and/or over-reliance on the device, false negatives, and false positives; mitigation strategies were also identified.[4 5] Of note, the Apple Watch Series 6 device is not intended for use in individuals under the age of 22 or those previously diagnosed with atrial fibrillation, and the ECG feature is not recommended for users with arrhythmias *except* for atrial fibrillation and sinus rhythm (since the software can only distinguish these two heart rhythms)[5]. People with atrial fibrillation may be more likely to purchase this device than others to monitor their rhythm and correlate with symptoms. Indeed, in the Apple Heart Study, nearly 20% of first study visit participants reported a diagnosis of atrial fibrillation/flutter before enrollment, even though a history of atrial fibrillation was an exclusion criterion.[7] Combined, tens of millions of Apple Watches and Withings devices have been purchased worldwide by consumers.

As an a general wellness product, the Withings Move has been deemed a 'Low-Risk Device' by the FDA[10] and is therefore not deemed a medical grade device.

3. Source:
   a) Identify the source of the device to be used.
   All Apple Watch Series 6 used in this study will be purchased directly from Apple. Withings Move devices will be purchased directly from Withings.

   b) Is the device provided free of charge to subjects? ☒Yes ☐No

4. Investigational device accountability: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): N/a

   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): N/a

   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: N/a

   d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: N/a

   e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: N/a

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: 60 Participants
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: 150 Participants

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☐ Flyers
☐ Posters
☐ Letter
☐ Medical record review*
☐ Departmental/Center newsletters
☐ YCCI Recruitment database
☒ Other: The scheduler/clinical care team for cardioversions will identify patients scheduled to undergo cardioversion for atrial fibrillation or atrial flutter and tell them about the study when confirming their procedure and ask if they have an iPhone 6s or later. If the patient meets these enrollment criteria and expresses interest in the study, a research associate may reach out to further screen and then discuss meeting to complete enrollment. Clinicians may also identify patients admitted to the hospital and scheduled to undergo DCCV in the next 24-48 hours. The clinician would then alert the study RA who will approach the patient to discuss the study and possible enrollment. Clinicians will have identified patients planned for catheter ablation for atrial fibrillation or atrial flutter, who will be screened by phone to confirm that they meet eligibility criteria prior to their procedure and, if the patient is eligible and still interested, will be enrolled on their first post-procedural day.

☐ Internet/web postings
☐ Mass email solicitation
☐ Departmental/Center website
☐ Departmental/Center research boards
☐ Web-based clinical trial registries
☐ Social Media (Twitter/Facebook):

☐ Radio
☐ Telephone
☐ Television
☐ Newspaper
☐ Clinicaltrails.gov

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. **Recruitment Procedures:**

a. Describe how potential subjects will be identified.

Patients will be identified prior to cardioversion for atrial fibrillation or atrial flutter when being called with a reminder about their scheduled procedure or by a study clinician upon admission to the hospital. Similarly,

patients undergoing catheter ablation for atrial fibrillation or atrial flutter will be identified by a study clinician before or after hospital admission for their procedure.

b. Describe how potential subjects are contacted.

Eligible patients who are planned for cardioversion will be contacted by the department scheduler when confirming their procedure as part of routine practice who will then let them know about the study. If the patient expresses interest in the study, a research associate will open the patient's chart to ensure that the patient has a history of atrial fibrillation or atrial flutter before calling the patient. If there is not a confirmed diagnosis in the chart, the RA will confirm with a study clinician. If a diagnosis is confirmed, the RA will then reach out to the patient to further screen for inclusion criteria, discuss the study in more detail, and to determine a time to meet to complete enrollment before their procedure.

A member of the clinical team may also introduce the study to eligible patients. If the patient expresses interest in being contacted, a member of the office staff will provide the RA with the patient's preferred contact information.

If a member of the clinical team identifies a patient that has been admitted to the hospital and will undergo DCCV in the next 24-48 hours that would qualify for this study, a clinician will inform the RA about the patient. The RA will then approach the patient and use a checklist to confirm the patient meets all of the eligibility criteria (see below). The RA will then review the process with the patient and inform him/her that participation is optional but if they would like to learn more and possibly enroll the RA will walk through the consent and enrollment process with them. The RA will be able to provide guidance on updating the device, if necessary.

For patients undergoing catheter ablation for atrial fibrillation or atrial flutter, a member of the clinical team will introduce the study to eligible patients.

c. Who is recruiting potential subjects?

Postgraduate associates Emanuela Pinci and Mikas Grewal will recruit potential participants at YNHH.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects
☒Yes, some of the subjects
☐No

If yes, describe the nature of this relationship.

It is possible that Drs. Akar, Hummel, or Freeman, co-investigators of this study, may have treated patients at some point prior to their procedure. Neither of these physicians would directly enroll the patient in the study, and care would not be impacted in any way if a patient consents or does not consent to participation in the study.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: For patients planned for cardioversion, we would aim to ensure that outpatients have a history of atrial fibrillation or atrial flutter prior to making them come in early and complete steps that would lead to their likely enrollment in this study. Only those outpatients that express interest in the study to the scheduler would have their record reviewed.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: For patients planned for cardioversion, the aim would be to ensure the patient meets the inclusion criteria prior to asking them to come in early before their procedure. Therefore we would not yet have had the opportunity to ask them to sign an authorization.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

As part of routine practice, patients who are planned to undergo outpatient cardioversion for atrial fibrillation or atrial flutter at Yale-New Haven Hospital will be contacted via phone by the department scheduler to confirm their scheduled time for their procedure. At this time the scheduler will tell the patient he/she may be eligible for a study examining the impact of using a wearable digital health device following cardioversion and then ask about interest in the study (Please see appendix for script). Should they express interest, the scheduler will let them know that if they are eligible a Research Associate (RA) will reach out to them in advance of their procedure to discuss the study in further detail. The scheduler will then provide the RA with the patient's preferred contact information.

Once the patient has expressed interest in the study, the RA will open the patient's chart to ensure that the patient has a history of atrial fibrillation or atrial flutter before calling the patient. If there is not a confirmed diagnosis in the chart, the RA will confirm with a study clinician. If deemed eligible, the RA will then attempt to contact the patient by phone in advance of their procedure. The RA will then use a checklist to confirm the patient meets all of the eligibility criteria, including confirming that they receive primary and cardiology care in the Yale-New Haven Health System. If the patient does not receive primary care in the Yale-New Haven Health System, the RA will ask the patient a) where they receive primary care and b) if they have a patient portal account for that provider. If the patient has a portal account for their primary care provider and that

provider uses an Epic- or Cerner-based EHR, they are eligible for this study. If they do not, they will be considered ineligible.. The RA will then review the process with the patient and inform him/her that participation is optional but if they would like to learn more and possibly enroll, they should arrive 60 minutes before their scheduled arrival time to meet and go through the consent and enrollment process. The RA will also ask the patient to bring his/her smartphone and YNHH MyChart login information (if they have it) and any phone account passwords with them that day, as well as advising them to update their device to the latest iOS, if they have not done so already. The RA will be able to provide guidance on updating the device, if necessary.

A member of the clinical team may also introduce the study to eligible patients. If the patient expresses interest in being contacted, a member of the office staff will provide the RA with the patient's preferred contact information.

If a member of the clinical team identifies a patient that has been admitted to the hospital and will undergo DCCV in the next 24-48 hours that would qualify for this study, a clinician will inform the RA about the patient. The RA will then approach the patient and use a checklist to confirm the patient meets all of the eligibility criteria (see below). The RA will then review the process with the patient and inform him/her that participation is optional but if they would like to learn more and possibly enroll the RA will walk through the consent and enrollment process with them. The RA will be able to provide guidance on updating the device, if necessary.

On the day of the anticipated cardioversion, and including the day prior for inpatients, the RA will then review the study consent form and discuss the specifics of the study described below. If, after reviewing, the patient agrees to the study, then he/she will be asked to sign the digital consent and authorization form in the Hugo platform. We will ensure that the patient has a full and clear understanding that enrollment will not in any way impact his/her care nor alter the standard post-procedure follow-up visits. As a part of the consent process, the RA will also make clear to the patient that this study will not replace their normal medical care and advise him/her that should they begin having new or worrying symptoms to contact their doctor or emergency services directly, exactly as the patient would have done if he/she were not enrolled in our study. During enrollment the patient will also confirm their preferred contact method should the RA need to reach them during or after the follow-up period. Patients can indicate if they prefer text, email, and/or phone calls. In addition to their preferred method, we will ask them if they would be willing to be contacted by each modality. Should they indicate text or phone calls, the RA will offer to enter or suggest that the patient enter, the RA's Yale office number into their contact list so that they are aware when it is the study staff trying to reach them.

Separately, patients undergoing catheter ablation for atrial fibrillation or atrial flutter will be informed about study eligibility by their physician. As with cardioversion patients, the RA will attempt to contact the patient by phone in advance of their procedure. The RA will then use a checklist to confirm the patient meets all of the eligibility criteria (see below), including asking if they receive primary and cardiology care in the Yale-New Haven Health System. If the patient does not receive primary care in the Yale-New Haven Health System, the RA will ask the patient a) where they receive primary care and b) if they have a patient portal account for that provider. If the patient has a portal account for their primary care provider and that provider uses an Epic- or Cerner-based EHR, they are eligible for this study. If they do not, they will be considered ineligible. The RA will then review the process with the patient and inform him/her that participation is optional but if they would like to learn more and possibly enroll, they will have the option after their ablation, on the first post-procedure day. If the patient is interested and eligible, the RA will ask the patient to bring his/her smartphone and YNHH MyChart login information (if they have it) and any phone account passwords with them that day,

as well as advising them to update their device to the latest iOS if they have not done so already. On the first post-procedural day, patients will be approached by the RA to assess and ensure patients meet inclusion criteria and are interested in study participation. The RA will use a checklist to confirm the patient meets all of the eligibility criteria. The RA will then review the study with the patient and inform him/her that participation is optional but if they would like to learn more and possibly enroll the RA will walk through the consent and enrollment process with them. The RA will be able to provide guidance on updating the device, if necessary.

After enrollment, patients will also receive a follow-up email that contains their consent form as well as to again provide contact information should they have any questions or concerns about the study.

If a patient refuses to participate, then we will note the number of people who refused. If the patient is agreeable, we will then administer a short questionnaire to understand his/her rationale for not participating in the study, to understand potential reasons for non-participation. Please see Appendix for questionnaire.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   All consenting participants must be capable of providing informed consent in order to participate in the study. Participants who are cognitively impaired will not be eligible for the study. To participate in this study, subjects must be alert and oriented to person, time and place, and able to consent for themselves. No surrogate consents will be accepted.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

   N/A as non-English speaking people will not be asked to participate in this study

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. *Please review the guidance and presentation on use of the short form available on the HRPP website.*

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☐Requesting a waiver of signed consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☐

☒ Requesting a waiver of consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

   Age, gender, date of birth and several categories of health information (provider encounters, notes – if available, medication lists, problem lists, family history, allergies, laboratory findings, procedures, immunizations, vital signs, and medical record numbers) will be collected via the Hugo platform. Patients will also be asked to self-report race, ethnicity, weight, and co-morbidities/pre-existing conditions as part of the baseline questionnaire, in addition to pre-existing conditions pulled into Hugo from the EHR. We will also be

collecting data provided and synced to the Hugo platform from the Apple HealthKit (including Apple Watch data) and the Withings Health Mate platform.

The PI and clinicians directly involved in this study (Drs. Joseph Ross, Joseph Akar, James Hummel, and James Freeman) will also have access to the patient's medical record, with read-only access, within the YNHH electronic medical record (EMR) system. This data will not leave the EMR system in any way and is only being used to review ECG tracings and readings captured by the Apple Watch in conjunction with those captured during routine clinical care. The YNHH Epic EHR and the ECG archiving system, Epiphany will be used by the study team when reviewing the ECG data. Data access to the YNHH EMR for research purposes will only be granted after all necessary trainings are complete and sign off is received from the Yale IRB and YNHH medical records department using the Yale-New Haven Health System's Research Request for Medical Records Access form.

2. How will the research data be collected, recorded and stored?
   After obtaining consent, patients will be requested to share data from their Hugo personal health records to the study over SSL with a minimum of 128-bit encryption. This data will be transferred to Mayo Clinic to a data analyst associated with this project for cleaning and analysis. Access to this data will only be available to designated study personnel with collaborators at the Mayo Clinic receiving their own IRB approval.

   EKG data will be sent by patients using the Apple HealthKit built-in function. The Apple Health platform allows patients to designate an email to securely share EKG tracing. EKG tracings from Yale patients will be sent to the secure Afibstudy@yale.edu email address, and all tracings will be deidentified and stored on a Secure box drive with access only grant to the Yale study team. For the Apple Watch EKG review only deidentified data will be used. Access to this deidentified data will only by available to study personnel, with collaborators at each site receiving their own IRB approval.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   Data stored at the Mayo Clinic is protected within its firewalls and all access is password protected. EKG tracings for Yale patients will be saved on a password-protected secure Box drive with access granted to members of the Yale study team.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Data will be maintained on secure, encrypted servers at Mayo Clinic after completion of the research study for a minimum of 5 years after publication of our findings in a peer-reviewed journal (in such case as there is a need to return to the original data source to validate a finding or respond to a question).

Study participants will always have access to their health data and the ability to download their personalized health record and take it with them through Hugo. After the completion of the study, we will also make summary level findings available to participants, without any identifiable personal health information.

6. If appropriate, has a Certificate of Confidentiality been obtained*?*
Since the data obtained are from broad health characteristics from personal health records that do not target any particular sensitive research areas, a CoC has not been obtained.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Individuals who participate in this study will have access to their health data along with the choice and ability to share it with researchers through the Hugo platform. Patients will be contributing to an advancement in the understanding of expected outcomes from novel wearable medical technologies, including the Apple Watch – which is already used by hundreds of thousands of individuals. Participants will also have the option of continuing access to their data at the end of the study, if they so wish, and receive updates to the Hugo Health platform. Using the provided Apple Watch, participants may also gain additional awareness and information regarding their heart rate, rhythm, health, and activity; using the provided Withings Move, participants may gain additional awareness and information regarding their activity.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?

   The alternative to participating in the proposed study is to not participate. Participation and non-participation will have no impact on the course of treatment that the patient will receive.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Patients who are not randomized to receive the Apple Watch will receive a small stipend for their time contributed as part of this study. An estimated hourly stipend based on the average minimum wage in Connecticut ($10) will be provided. This will result in a total stipend of up to $80.

   These payments will be made via a Visa pre-paid card through the platform Tremendous which is linked to the Hugo platform. As surveys are completed, the balance will be automatically credited to the patient's account which is linked to the email address they used to set up their Hugo account. Patients will receive payments every 30 days when they respond to the study surveys. When these payments are ready, patients will receive an email with instructions on how to redeem their payment. The Visa card will then be sent to

their email as a digital ecard. Patients may redeem their payments at any time once they have accrued a balance.

Patients in the Apple Watch arm will be given the necessary Apple Watch to keep. The fair market value of this device is $399.00. Patients in the Withings arm will be provided with a Withings Move to keep. The fair market value of this device is $69.95.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   The platform, technology, devices, and apps used in this study will be provided to participants free of cost. Updates to the platform will also be provided free of cost for the duration of the study. Participants will still be responsible for any costs associated with routine follow-ups or doctor's visits, as they would be in the normal processes of care. Participants will still be responsible for any co-pay required by their insurance company for standard treatments. Participants are responsible for data charges that may be incurred for utilizing the online features of Hugo, Withings, or Apple Watch when not connected to Wi-Fi.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs? *Write here*

   b. Where and from whom may treatment be obtained? *Write here*
   c. Are there any limits to the treatment being provided? *Write here*
   d. Who will pay for this treatment? *Write here*
   e. How will the medical treatment be accessed by subjects? *Write here*

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☒ No ☐

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☒ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☒

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☒

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

References

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