CLINICAL STUDY PROTOCOL

Arrhythmia Burden in Patients with Impulse Dynamics Optimizer Smart Device Implantation: Retrospective and Prospective Evaluation

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Abbreviations

Abbreviation	Explanation

AF=Atrial fibrillation
CCM= Cardiac Contractility Modulation
CHF=congestive heart failure
CIED= cardiovascular implantable electronic device
FDA=Food and Drug Administration
HFrEF=heart failure with reduced ejection fraction
ICD=Internal Cardioverter Defibrillator
ILR=implantable loop recorder
PPM=Permanent pacemaker
LVEF=left ventricular ejection fraction
NYHA=New York Heart Association
VA=Ventricular arrhythmia
VF=Ventricular fibrillation
VT=Ventricular tachycardia

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Summary

The Impulse Dynamics Optimizer Device is a Food and Drug Administration (FDA) approved, commercially available device indicated for patients with heart failure with reduced ejection fraction (HFrEF), currently being implanted per FDA recommendation. Many candidates of this device have a previously implanted cardiovascular implantable electronic device (CIED)- internal cardioverter defibrillator (ICD) or permanent pacemaker (PM). Patients with heart failure are at high risk for both atrial and ventricular cardiac arrhythmias.

The aim of this study is to evaluate up to 200 patients for Atrial fibrillation (AF) burden episode data obtained from interrogation of their CIED 8 months or greater after Optimizer implant, and compare arrhythmia burden 6 months before Optimizer Cardiac Contractility Modulation (CCM) device insertion to 6 months or greater after Optimizer insertion, after an immediate implantation blanking period of 2 months.

1 – Introduction

The Impulse Dynamics Optimizer is indicated for patients with New York Heart Association (NYHA) class III congestive heart failure (CHF) with left ventricular ejection fraction (LVEF) between 25 and 45% who are not candidates for cardiac resynchronization therapy. The Optimizer device requires a minimally invasive implant by a cardiac electrophysiologist with two transvenous pacemaker wires implanted into the right ventricular septum and attached to a generator in an infraclavicular region, much like a pacemaker. The Optimizer device provides CCM through improved calcium handling and has been shown to reverse the negative remodeling of the left ventricle seen in HFrEF and improve left ventricular contractile strength.

We plan to enroll a maximum of 200 patients with existing or newly implanted Impulse Dynamics Optimizer with concurrent previously implanted CIED.

2 – Background

AF demonstrates an average prevalence of 25% in HFrEF, and is the most common sustained arrhythmia encountered in the HFrEF population (1). AF burden in HFrEF is estimated at 35%. AF increases risks of CHF hospitalizations and mortality in HFrEF (2). Episodes of AF longer than 24 hours in a non HFrEF population substantially increased risk of stroke (3). Sudden cardiac death, most often a result of ventricular arrhythmia (VA), accounts for 30-50% of the deaths in heart failure patients (4-5). CCM is a novel therapy for patients with heart failure with a variety of short and long-term benefits. While CCM has been shown to improve health status and reduce hospitalization rates in those with AF (6), there is a paucity of data examining the impact of CCM therapy on arrhythmia burden.

3 – Rationale, Objectives and Hypothesis

3.1 Study Rationale

There are no studies that assess the impact of the Optimizer device on atrial and ventricular arrhythmias, and any investigation is unique and may add value. The study will be performed in two arms. The first arm will be retrospective and the second arm will be prospective. We will perform a retrospective review of atrial and ventricular arrhythmias that occur 6 months before and 8 months after the Optimizer device is implanted in patients with a CIED with the ability to interpret atrial signals. The 8 months post implant period will include a 2 month blanking period which will allow for the therapeutic effects of CCM. Patients who have undergone Optimizer implantation, but do not have at least 8 months of follow up, can be enrolled in the retrospective arm and signed informed consent will be required. The prospective arm will include patients who have had a CIED with the ability to interpret atrial signals for at least 6 months and have a clinical indication for CCM therapy as per standard of care. These patients will be followed for 8 months post Optimizer implant, including an initial 2 month post Optimizer implant blanking period.

3.2 Hypothesis

We hypothesize that treatment with Optimizer will result in a 20% reduction of AF burden.

3.3 Primary Objective

The primary objective for both the retrospective and prospective arms of the study is to compare the AF burden noted 6 months pre Optimizer implant to 6 post Optimizer months (post Optimizer months 3-8), after 2 month blanking period

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3.4 Exploratory Objectives

All exploratory objectives will be performed for both retrospective and prospective arms separately and together with comparisons to be made between the following groups:

1. 6 months pre Optimizer to 6 post Optimizer months (post Optimizer months 3-8), after 2 month blanking period
2. 6 months pre Optimizer to 6 post Optimizer months (post Optimizer months 1-6)
3. 3 months pre Optimizer to 3 post Optimizer months (post Optimizer months 3-5), after 2 month blanking period
4. 3 months pre Optimizer to 3 post Optimizer months (post Optimizer months 6-8), after 2 month blanking period
5. 3 months pre Optimizer to 3 post Optimizer months (post Optimizer months 1-3)
6. 3 months pre Optimizer to 3 post Optimizer months (post Optimizer months 4-6)

3.4.1 Exploratory Objective One

Exploratory objective one is to compare the AF burden between groups 2-6 noted above.

3.4.2 Exploratory Objective Two

Exploratory objective two is to compare the number of VA episodes between all groups noted above.

3.4.3 Exploratory Objective Three

Exploratory objective three is to compare the AF burden after censoring subjects who underwent cardioversion or catheter ablation of AF during entire study period between all groups noted above.

3.4.4 Exploratory Objective Four

Exploratory objective four is to compare the AF burden after censoring subjects who had addition of antiarrhythmic drug, underwent cardioversion, or underwent catheter ablation during entire study period between all groups noted above.

3.4.5 Exploratory Objective Five

Exploratory objective five is to compare the number of hospitalizations between all groups noted above.

3.4.6 Exploratory Objective Six

Exploratory objective six is to compare the number of stroke events between all groups noted above.

3.4.7 Exploratory Objective Seven

Exploratory objective seven is to compare the number of catheter ablations between all groups noted above.

3.4.8 Exploratory Objective Eight

Exploratory objective eight is to compare the number of cardioversions between all groups noted above.

3.4.9 Exploratory Objective Nine

Exploratory objective nine is to compare the number of AF events ≥ 24 hours between all groups noted above.

4 - Study Design

4.1 General Design

The study will be conducted in two arms. The retrospective arm will be an observational evaluation of subjects with a CIED with the ability to interpret atrial signals implanted at least 6 months prior to Optimizer implantation. Additionally, these subjects will be at least 8 months post Optimizer implant at the time of study approval. Subjects with an appropriate CIED and who have undergone Optimizer implantation, but do not have at least 8 months of post Optimizer implantation follow up, can be enrolled in the retrospective arm, but signed informed consent will be required.

The prospective arm will be an observational evaluation of subjects with an appropriate CIED implanted at least 6 months prior and scheduled to undergo Optimizer implantation as per standard of care. Informed consent will be obtained from all subjects in the prospective arm at a recommended time of 2-4 weeks before scheduled Optimizer implant date. A CIED interrogation (remote or in-person) is to be performed 2-4 weeks prior to Optimizer implant date as per standard of care. If AF burden is noted to be between 1% and 99% (reported for any time equal to or less than the prior 6 month period), the patient can be enrolled into the prospective arm of the study. Arrhythmia burden data from the CIED manufacturer will also be requested; if this data does not corroborate AF burden between 1% and 99% then the patient will be considered a screen failure. AF burden and VA episodes will be assessed remotely through the CIED manufacturer and compared from the pre implantation period to the post implantation period, as defined above. The prospective arm will allow attainment of information prospectively during 8 months of follow up after Optimizer implantation, including an initial 2 month post Optimizer implant blanking period.

Evaluation for both arms will include:

1. Pre-6 months to Optimizer implant (will be subcategorized into pre-6 to pre-3 months, and pre-3 months to Optimizer implant)
2. Optimizer implant date to post-8 months [will be subcategorized into Optimizer implant to post 2 months (blanking period), post-2 months to post-5 months, and post-5 months to post-8 months], and if applicable every 3 months thereafter.

In terms of arrhythmia reporting, AF burden will be reported as (1) hours of AF/day (2) percent AF per day and (3) number of AF episodes ≥24 hours/1 month period, including in the 2 month blanking period.

VA episodes will be categorized into types and number of events as reported by the CIED as (1) treated VT and treated VF together and (2) untreated non-sustained VT, treated VT, and treated VF together.

4.1.1 Study Duration

The study will last approximately 2 years to allow for enrollment.

4.1.2 Number of Study Sites

The study will be performed at the primary site, Hackensack University Medical Center, and up to 50 additional subsites in the USA currently implanting Impulse Dynamics Optimizer devices per standard of care.

4.2 Study Population

The population will include adult patients, at least 18 years of age.

1. Retrospective study
    a. CIED with the ability to interpret atrial signals implanted at least 6 months prior to Optimizer implantation AND Optimizer implantation at least 6 months post CIED implantation and with at least 8 months of post Optimizer implantation follow up.
    b. OR if the patient has an appropriate CIED with at least 6 months of follow up prior to Optimizer implantation, but less than 8 months of follow up after Optimizer implantation (will require a signed informed consent form).

2. Prospective study

    CIED with the ability to interpret atrial signals implanted at least 6 months prior to CCM implantation AND scheduled CCM implant which was prescribed for standard clinical indications.

4.2.1 Number of Participants

We would like to evaluate up to 200 subjects from up to 50 subsites.

4.2.2 Eligibility Criteria

The population will include subjects with the following for the:

1. Retrospective arm
    a. Optimizer implantation at least 6 months post CIED implantation and with at least 8 months of post Optimizer implantation follow up
    b. Patient has an appropriate CIED with at least 6 months of follow up prior to Optimizer implantation, but less than 8 months of follow up after Optimizer implantation (will require a signed informed consent form).

2. Prospective arm
    a. CIED with the ability to interpret atrial signals implanted at least 6 months prior to Optimizer implantation;
    b. Scheduled Optimizer implant which was prescribed for standard clinical indications.

4.2.3 Inclusion Criteria

1. 1%≤AF burden≤99% in the 6 month period prior to Optimizer implant as documented the patient's CIED
2. 18 years of age or older on day of signing consent
3. Any gender
4. Functional dual chamber pacemaker or ICD and using remote follow up for their CIED
5. Not scheduled for planned catheter ablation or cardioversion
6. Ability to sign consent in English or Spanish

4.2.4 Exclusion criteria

1. Permanent atrial fibrillation
2. Pregnancy (in prospective arm only)
3. Expected survival <1 year

4.3 Study procedures

AF burden and VT episodes will be remotely accessed from the CIED manufacturer.
The prospective arm will allow prospective data collection for 8 months after Optimizer implantation, including a 2 month blanking period immediately after Optimizer implantation.

For the retrospective and the prospective arms, the data will be evaluated in the same manner, except as noted below, and will be performed as follows:

1. Pre-6 months to Optimizer implant (will be subcategorized into pre-6 to pre-3 months, and pre-3 months to Optimizer implant), to ensure 1%≤AF burden≤99% (otherwise subjects will be excluded).

2. Optimizer implant date will be followed by a 60 day blanking period. The patients will be followed for 8 months [will be subcategorized into Optimizer implant to post-2 months (blanking period), post-2 month blanking period to post-5 months, and post-5 months to post-8 months, and every 3 months thereafter until the study is completed).

AF burden will be reported as (1) hours of AF/day (2) percent AF per day and (3) number of AF episodes ≥24 hours/1 month period, including the blanking period.

Demographics, development of medical events (hospitalization, stroke) and arrhythmia related history (presence/absence of medications) and interventions, such as cardioversion, antiarrhythmic drug administration, or catheter ablation will be recorded.

VA episodes will be categorized into types and number of events as reported by the CIED as (1) treated VT and treated VF together and (2) untreated non-sustained VT, treated VT, and treated VF together.

4.4 Risks and Benefits

The subjects will not obtain any direct benefit from participation. Conducting this study may help identify new benefits of the Optimizer implant on arrhythmia burden and as a result help patients with AF in the future.

There are no physical risks related given the nature of this study and the fact that all procedures took place as per standard of care. The only foreseeable risk is related to breach of confidentiality since data is accessed for research purposes. All measures will be taken to minimize this risk and data will be stored in a coded manner and only de-identified data will be shared across institutions (see details in section 6).

5 – Methods

5.1 Sample Size Justification

The sample size is based on a statistical test of whether AF burden is reduced after Optimizer implant compared to the pre-implant period. We assume median pre-Optimizer implant AF burden of approximately 25%, which may be a conservative estimate given similar or higher reported device-monitored AF burden over 24 weeks in a genetically-defined group of heart failure patients (6). We hypothesize a 20% change in post-Optimizer AF burden (5% absolute reduction). The sample size calculation is based on a non-parametric Wilcoxon signed-rank test of the paired change in pre-Optimizer to post-Optimizer AF burden. Assuming a mean reduction of 5% and a standard deviation of 15% for the paired change in AF burden, alpha of 0.05 and power of 0.8, the required sample size is 77 patients. This sample size provides power >0.8 for a paired t-test. Based on a missing data rate of up to approximately 20% (e.g. due to dropout or unavailable device AF burden data), we plan to include up to 15 more subjects for a total of up to 92 subjects per arm.

The sample was calculated using PASS (Kaysville, UT) 2022 software.

5.2 Analysis Population

All patients identified and enrolled will be included in the analyses.

5.3 Statistical Methods

Descriptive statistics will be calculated for patient characteristics [age, gender (female/male), race/ethnicity (American Indian or Alaska Native, Asian, Black or African American, Hispanic, Native Hawaiian or Other Pacific Islander, White), body-mass index, presence of comorbid conditions (asthma, cancer, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, renal insufficiency, stroke), prior rhythm controlling strategies for AF or VT (antiarrhythmics, cardioversion, catheter ablation). For continuous variables, visual inspection of q-q plots for skewness and outliers along with the Shapiro-Wilk test ($p>0.05$ indicates no deviation from normality and $p<0.05$ indicates deviation from normality) will be used to evaluate normality or normal continuous variables, the mean, standard deviation, and range will be calculated. For non-normal continuous variables, the median, interquartile range, and range will be calculated. For categorical variables, counts and percentages will be reported.

All statistical analyses will be performed using SAS 9.4 (SAS Institute Inc., Cary, NC). All hypothesis tests will be two-sided with significance level $\alpha=0.05$. Any p-value below 0.05 will be deemed statistically significant.

5.3.1 Statistical Methods for Primary Objective

Primary Objective: The primary objective for both the retrospective and prospective arms of the study is to compare the AF burden noted 6 months pre Optimizer implant to 6 post Optimizer months (post Optimizer months 3-8), after 2 month blanking period

A patient's AF burden is measured as the cumulative time spent in AF over the assessment period divided by the cumulative follow-up time of the assessment period. The difference in AF burden between the post-Optimizer and pre-Optimizer AF assessment periods will be analyzed as a continuous variable. Visual inspection of q-q plots for skewness and outliers along with the Shapiro-Wilk test ($p>0.05$ indicates no deviation from normality and $p<0.05$ indicates deviation from normality) will be used to evaluate normality. If the distribution of changes in AF burden is approximately normally distributed, a paired t-test will be used for analysis and the mean, standard deviation, and range will be reported. Otherwise, if the distribution is non-normal, a Wilcoxon signed-rank test will be performed and the median, interquartile range, and range will be reported.

5.3.2 Statistical Methods for Exploratory Objectives

All exploratory objectives will be performed for both retrospective and prospective arms separately and together with comparisons to be made between the following groups:

1. 6 months pre Optimizer to 6 post Optimizer months (post Optimizer months 3-8), after 2 month blanking period
2. 6 months pre Optimizer to 6 post Optimizer months (post Optimizer months 1-6)
3. 3 months pre Optimizer to 3 post Optimizer months (post Optimizer months 3-5), after 2 month blanking period
4. 3 months pre Optimizer to 3 post Optimizer months (post Optimizer months 6-8), after 2 month blanking period
5. 3 months pre Optimizer to 3 post Optimizer months (post Optimizer months 1-3)
6. 3 months pre Optimizer to 3 post Optimizer months (post Optimizer months 4-6)

Exploratory objective one is to compare the AF burden between groups 2-6 noted above.

Exploratory objective two is to compare the number of VA episodes between all groups noted above.

Exploratory objective three is to compare the AF burden after censoring subjects who underwent cardioversion or catheter ablation of AF during entire study period between all groups noted above.

Exploratory objective four is to compare the AF burden after censoring subjects who had addition of antiarrhythmic drug, underwent cardioversion, or underwent catheter ablation during entire study period between all groups noted above.

Exploratory objective five is to compare the number of hospitalizations between all groups noted above.

Exploratory objective six is to compare the number of stroke events between all groups noted above.

Exploratory objective seven is to compare the number of catheter ablations between all groups noted above.

Exploratory objective eight is to compare the number of cardioversions between all groups noted above.

Exploratory objective nine is to compare the number of AF events ≥ 24 hours between all groups noted above.

A patient's AF burden is measured as the cumulative time spent in AF over the assessment period divided by the cumulative follow-up time of the assessment period. The difference in AF burden between the post-Optimizer and pre-Optimizer AF assessment periods will be analyzed as a continuous variable. Visual inspection of q-q plots for skewness and outliers along with the Shapiro-Wilk test ($p>0.05$ indicates no deviation from normality and $p<0.05$ indicates deviation from normality) will be used to evaluate normality. If the distribution of changes in AF burden is approximately normally distributed, a paired t-test will be used for analysis and the mean, standard deviation, and range will be reported. Otherwise, if the distribution is non-normal, a Wilcoxon signed-rank test will be performed and the median, interquartile range, and range will be reported.

VA episode counts will be tabulated for the pre-Optimizer and post-Optimizer assessment periods. A Poisson generalized estimating equation (GEE) analysis accounting for clustering of paired counts within subject may be performed to compare the rate of VA episodes between the pre-Optimizer and post-Optimizer assessment periods.

5.4. Interim Analyses

Descriptive interim analyses will be performed after the complete data for increments of 25 patients are available. Interim analyses will be conducted according to the primary and exploratory objective statistical methods. Stopping the study early on the basis of interim data analysis is not planned.

5.5 Data Management

All data will be entered into the HMH REDCap and imported into SAS 9.4 where all data queries will be generated for out of range values/invalid data until all data issues are resolved. Each site's team will be provided with temporary and restricted access to the HMH REDCap instance. Team members will enter data directly into the REDCap and will only have access to their own site data apart from HMH, the lead site, which will have overall access to all the deidentified datasets for analysis purposes (see section 6 for details).
The HMH team will be responsible to build and maintain the REDCap database and provide access as per IRB approvals.
Each site will be responsible for the quality of the data entered. At the end of the data collection, data will be reviewed for "outliers" and any inconsistencies will be reviewed with the local sites.

6 - Trial Administration

6.1 Ethical Considerations - Institutional Review Board (IRB) Review

The study will be conducted according to the International Conference on Harmonization (ICH), Good Clinical Practice (GCP), the Declaration of Helsinki, Institutional Review Boards (IRB) and in accordance with the U.S. Code of Federal Regulations on Protection of Human Rights (21 CFR 50).

6.2 Institutional Review Board (IRB) Review (list the IRB of record)

The final study protocol and data collection tools will be approved by the WIRB. Approval will be received in writing before study initiation.
Any changes to the study design will be formally documented in amendments and be approved by the IRB prior to implementation.

6.3 Data management (collection, storage etc.)

Data will be entered into REDCap, hosted at HMH, in a de-identified fashion with discrete variables (noted above). Subjects will be given a unique study ID number. The key linking the subject ID number to the medical record number and phone number will be kept separate from coded study data and will only be accessible by authorized study team members. The key will either be stored in a locked drawer or password protected spreadsheet.
The REDCap project will be built using REDCap DataAccess groups (DAG), a REDCap feature in which only users within a given Data Access Group can access records created by users within that group. This feature may be useful in the case like this, of a multi-site or multi-group project that requires that groups not be able to access another group's data. Each group will only have access to its own data and only de-identified data can be shared with all necessary legal agreements in place. Identifying information will remain at each site.
Non-HMH collaborators will be given temporary access to the HMH REDCap project and will be assigned to each DAG according to their site and needs.

6.4 Informed consent

A consent waiver for subjects enrolled in the Retrospective Arm. Subjects enrolled in the Prospective Arm will be required to provide informed consent. Patients who underwent Optimizer implant and have < 8 months of follow up, will be included in the retrospective arm and will require informed consent. Each site will be responsible to obtain consent for the prospective patients, document consent appropriately and monitor for compliance regarding the consenting process. Sites should perform an independent review of the Informed Consent Form and Process and document said review to provide to the Coordinating Site as requested.

6.5 Study Records (retention etc.)

Records will be retained in accordance with regulatory and organizational requirements, but for no less than six (6) years following the completion of the study. Disposal of records will be performed according to regulations.

6.6 Publication Plan

This study is meant for publication. The PI holds the main responsibility for publication. Interim analysis may also be published. If results of this study are to be reported or published, no information that could potentially identify patients will be included.

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