SignalHF

Instructions for use
Exclusively for clinical investigation

Document Reference	Date
IFU2-IM008-INSTRUCTIONS FOR USE-EXCLUSIVELY FOR CLINICAL INVESTIGATION	20250601

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Document revisions

Version	Modification
20230324	First version
20230402	Review for MDR regulation
20230705	Indication for use changed to add (over 18 yo)
20230831	Clinical study results summary reported in Section 6, Add the warnings following usability study. Change of version.
20230927	Add of information about artificial intelligence used and the physiological and demographic variables being used by the AI/ML model underlying the device.
20231021	Add of the warning “In patient populations unlikely to have acute decompensation of HF, the use of the algorithm may have less and possibly poor PPV and NPV.” And “The actual numeric “score” does not correlate to a higher percent chance of hospitalization outside of the thresholds specified. The score always needs further investigation.” Add of the performance analysis per manufacturer, device model type and number of leads Changes on intended use and indication for use.
20231117	Update of indication for use + minor modification
20240222	Add of the list of different degrees of contribution in section 3.4.2 Degrees of contribution
20240328	Review for V1.0.2
20240603	Update of intended use
20250505	Update to SignalHF V2: Changed risk prediction from 30-day HF hospitalization risk to long-term HF risk status (Low, Medium, High over 12 months) for monitoring personalization. Updated device description, intended use, indications, clinical benefits, output descriptions, performances accordingly. Addition of part “Intended patient population”.
20250523	Add of performances validation part

1. Introduction

This document describes the intended use and operation of the device SignalHF when it is used with a compatible Remote Monitoring Platform.

Device name	**SignalHF** version 2.0.0
Manufacturer	**IMPLICITY** **USA** 185 Alewife Brook Parkway Suite 210, Cambridge, MA 02138 (USA) **Europe** 29 RUE DU LOUVRE 75002 Paris (FRANCE)
Contact information and technical support	support@implicity.com phone USA: (+1) 929 350 7056 (9a.m to 6p.m EST) Europe: +33 (0) 9 61 67 41 14 (9a.m to 6p.m CET)
Basic UDI DI	3770025266IM008RM
First CE mark	NA

Carefully read all instructions prior to use.
Observe all warnings and precautions noted throughout these instructions.
Failure to do so may result in complications in use of this product.

NOT YET CE MARK ONLY FOR CLINICAL INVESTIGATION

2. SignalHF device information

2.1 Device description

SignalHF is a software as medical device (SaMD) including artificial intelligence (AI) using a proprietary and validated algorithm to determine and differentiate a patient's long-term risk of decompensation. SignalHF classifies patients into "**Low**", "**Medium**", or "**High**" risk categories for future HF-related worsening conditions or hospitalizations over an anticipated 12-month period.

The algorithm determines the HF risk status using data obtained from:

- CIED data including a diverse set of physiologic measures remotely accessible (e.g. activity, atrial burden, heart rate variability, heart rate, heart rate at rest, thoracic impedance, premature ventricular contractions per hour, left and right ventricular pacing, lead measurements and episodes information and details)
- Personal Health Records available in the platform
    - Demographics: age and sex
    - Comorbidities:
        - Heart failure
        - Chronic respiratory disease
        - Coronary disease

The HF risk status is intended to support healthcare professionals in personalizing patient monitoring and follow-up strategies, in order to better assess when patient therapy should be modified based on their clinical judgement and expertise. The status provided through SignalHF can be displayed on any compatible HF monitoring platform, including the Implicity platform.
SignalHF does not provide real-time alerts for acute events. Rather, it is designed to evaluate factors that may indicate chronic worsening of HF status and to determine long-term risk. HCP's decisions should not be based solely on the device data which serves as adjunct information, but rather on the full clinical and medical picture and record of the patient. Future clinical evaluation of the SignalHF SaMD will determine how this risk stratification can better assess the patient status regarding HF over time and support risk management.

2.2 Intended use

SignalHF is intended to be used by qualified healthcare professionals (HCPs) as adjunctive information when remotely managing heart failure patients by providing a long-term heart failure risk status (e.g., "Low", "Medium", "High" risk of worsening condition or risk of HF hospitalization over the next 12 months) based on cardiac parameters and patient data. This status aims to help in the personalization of patient monitoring and management strategies. The device is designed to be used with physiological data from compatible and patient pre-existing sensors such as cardiac implanted electronic devices (e.g. heart rate, patient activity, thoracic impedance, etc.) along with available clinical parameters (e.g. demographics, and comorbidities).

SignalHF provides adjunct information for qualified HCPs to use in conjunction with clinical evaluation that is part of standard clinical practice and should not replace standard of care treatment.

2.3 Indication for use

SignalHF is intended for use by qualified healthcare professionals (HCP) managing patients over 18 years old who are receiving physiological monitoring for Heart Failure surveillance and implanted with a compatible Cardiac Implantable Electronic Devices (CIED) (i.e., compatible pacemakers, ICDs, and CRTs).

The SignalHF System provides additive information to use in conjunction with standard clinical evaluation.

SignalHF is intended to determine and provide the patient's long-term risk status for HF (e.g., Low, Medium, or High risk over the next 12 months) to aid in patient management and monitoring personalization. SignalHF is intended for adjunctive use with other physiological vital signs and patient symptoms and information and is not intended to independently direct therapy.

2.4 Intended users

SignalHF is intended to be used by qualified healthcare professionals (HCPs) such as heart failure physicians and nurse practitioners, in charge of the remote monitoring program of patients at risk of heart failure decompensation.

2.5 Intended patient population

IM008 is designed to be used on patients over 18 years old considered by physicians or HF specialists to be at risk of HF, implanted with a CIED (ICD, CRT-D, pacemaker or CRT-P) which includes a remote monitoring system capable of monitoring physiologic data.

This target population is at risk for worsening HF, for which the IM008 algorithm by providing a long-term risk status, may support clinically beneficial patient management.

2.6 Intended clinical benefit

SignalHF enables better identification and classification of patients at risk of heart failure events in the next 12 months, leading to personalized care and management adapted to their health status, and a potential reduction in the number of hospitalizations.

Table 1: Clinical benefit parameters of SignalHF with measurable clinical outcomes

Clinical Benefit category	Relevant and meaningful clinical benefit parameters	Measurable clinical outcome(s)
Type of clinical benefit for ICD/CRT-D patient population	Reduction of the number of HF-related hospitalizations	Rate of HF hospitalizations (%)
Clinical performance of the algorithm - magnitude	SignalHF enables to classify patient into the right HF events risk status.	Sensitivity (% of patients classified in each of the three groups)

2.7 Residual risks

There is no residual risk using SignalHF.

2.8 Contraindications and/or limitation

This version of SignalHF is compatible with ICD, CRT-D, PM and CRT-P devices from Medtronic, Boston Scientific and Biotronik.

The INTEGRATOR must make sure not to send to IM008 any data generated by a non-compatible CIED.

Use of the IM008 with devices not specified above as compatible will not yield reliable results. Integrators must display to end users a warning about non-reliability of IM008 HF status for these devices.

SignalHF is not intended for pediatric use.

At least 20 days is needed for input of classification.

2.9 Device output labels

The output of SignalHF is a long-term HF risk status (Low, Medium, or High) displayed on any compatible HF monitoring platform, including the Implicity platform. The algorithm determines this HF risk status using data obtained from (i) a diverse set of physiologic or ECG measures generated in the patient's cardiac implant remotely accessible (activity, atrial burden, heart rate variability, heart rate, heart rate at rest, thoracic impedance (for fluid retention), and premature ventricular contractions per hour), and (ii) his/her available Personal Health Records (demographics, comorbidities).

2.10 PHI storage

SignalHF does not store any patient health information (PHI) data permanently. SignalHF is intended to be interfaced with a Remote Monitoring Platform which manages user authentication and PHI permanent data storage.

3. Instructions for use

3.1 Warnings and precautions

- SignalHF should be used within the scope of its intended use and indication for use described in section 2.2 and 2.3.

- SignalHF should be used in accordance with the conditions of these instructions for use and the instructions for use of the remote monitoring platform.

- **Cybersecurity:** SignalHF must be hosted in a secure environment isolated from direct access from the Internet. Requirements are defined in the installation instructions (IFU1-IM008-INSTALLATION INSTRUCTIONS).

- This manual contains screenshot examples. These screenshots are provided for reference only and are not intended to convey actual operating techniques.

- **THIS VERSION IS EXCLUSIVELY FOR CLINICAL INVESTIGATION**

Any concerning incident related to the device should be reported to Implicity and to the competent authority of the Member State in which the user and/or patient is located, and/or other regulatory authorities as appropriate.

3.2 Device installation

Prior to use, SignalHF must be installed on a remote monitoring platform according to the IM008 Installation Instructions. Please refer to this document for information on requirements for Platform compatibility.

3.3 Activation/deactivation of SignalHF

Once authenticated on the Platform, the user (the clinician) should have access to their medical center's settings page, where the user can access SignalHF's documentation and activate or deactivate SignalHF.
The user should find SignalHF's version and short description and shall be able to download the instructions for use.

The user can also decide at any time to activate or deactivate SignalHF for all the compatible devices associated to his or her medical center in the Platform (by selecting the check box "use the algorithm"), or for some select patients only:

- Once "use" is checked, SignalHF is activated and every new data received from the cardiac implantable electronic device will be processed by SignalHF upon reception by the Platform.
- When "use" is unchecked, SignalHF is deactivated and new data received from the cardiac implantable electronic device will not be processed by SignalHF.

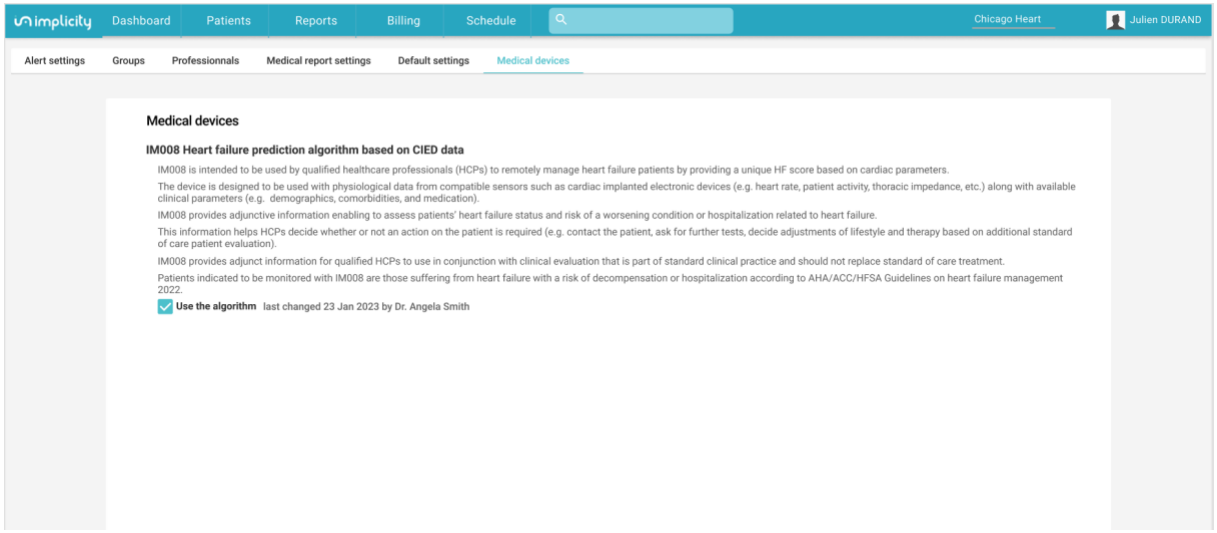


Figure 1: The settings page of the IMPLICITY Remote Monitoring Platform used to activate/deactivate SignalHF.

3.4 SignalHF output

SignalHF output is displayed in a Heart Failure-dedicated section of a Remote Monitoring Platform.
The following screenshot is an example of how SignalHF results can be displayed in the Remote Monitoring Platform.
The monitoring platform using SignalHF should display at least:

- The manufacturer and model type of the cardiac implant of the patient
- The current SignalHF status label
- CE marked medical device label

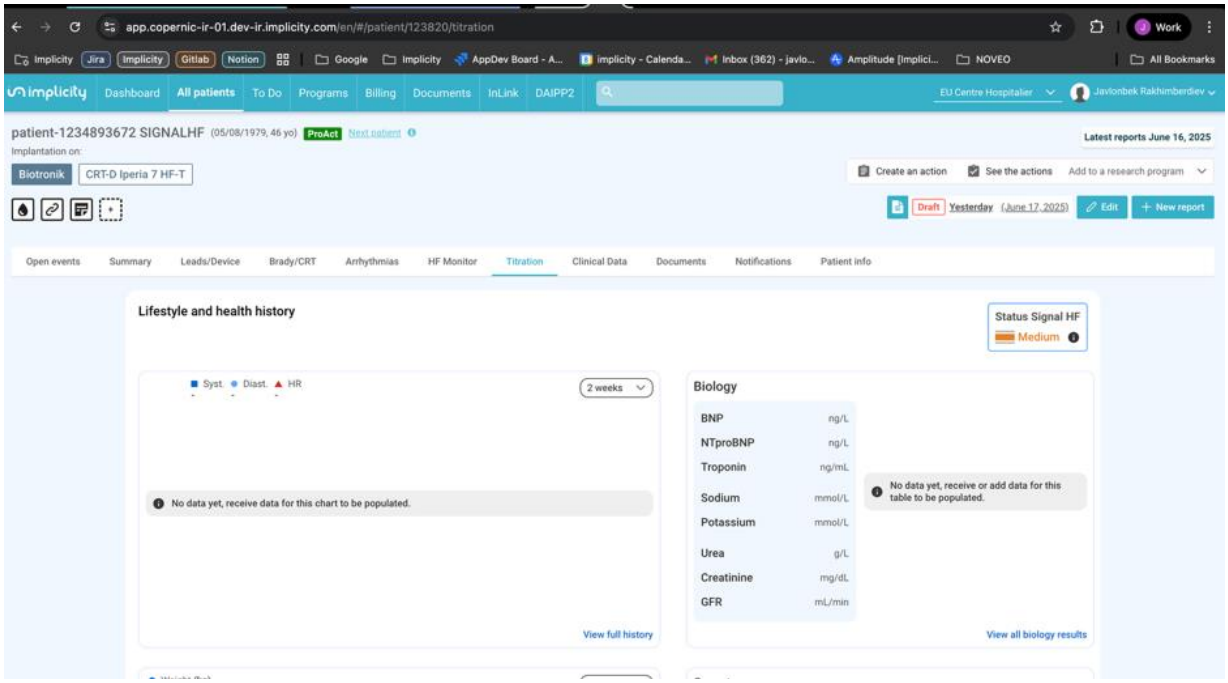


Figure 2: Example of SignalHF output

3.4.1 HF Risk Status

The SignalHF system determines a patient's long-term risk status for Heart Failure based on an analysis of CIED data and patient demographics. This status is categorized to help personalize patient monitoring and management. The patient's long-term risk status for Heart Failure is categorized as follows:

- **Low risk of HF:**
  - **Definition:** The patient has a low predicted risk of HF-related hospitalization within the next 12 months (e.g., an expectation of 0 hospitalizations).
  - **Implication for management:** These patients may be considered stable from an HF perspective based on CIED data. Management may involve standard monitoring with potentially less frequent alerts for certain conditions (e.g., less symptom form alerts for important weight gain if other indicators are stable) and consideration for more assertive medication titration if clinically appropriate. A risk of HF can still be present based on other factors like comorbidities and other non-CIED physiological data.
- **Medium risk of HF:**
  - **Definition:** The patient has a medium predicted risk of HF-related hospitalization within the next 12 months (e.g., an expectation of 1-2 hospitalizations).

- **Implication for management:** These patients typically require standard follow-up and continued guideline-directed medical therapy (GDMT). A risk of HF can still be present based on other factors like comorbidities and other non-CIED physiological data.

- **High risk of HF:**
  - **Definition:** The patient has a high predicted risk of HF-related hospitalization within the next 12 months (e.g., an expectation of 3+ hospitalizations).
  - **Implication for management:** These patients may be considered unstable or at higher risk. Management may involve closer attention, potentially more frequent alerts (e.g., alerts sooner or for progressive weight gain), more frequent symptom assessments, and careful medication titration.

Warning: The displayed risk status (Low, Medium, High) is based on the algorithm's analysis of available data. It always requires further investigation and interpretation by a qualified HCP in conjunction with other clinical information and the patient's overall condition. The status should not be the sole basis for therapeutic decisions.

3.4.2 Data integrity

On any given day, if the data from the patient's CIED could not be processed, or if there has not been enough data to determine a status, the status will not be determined or displayed. If the data could not be processed for several days, or if there have not been enough data to determine a status, the status will not be determined or displayed for the corresponding days. If no status has been determined for a given period, the status display will remain blank.

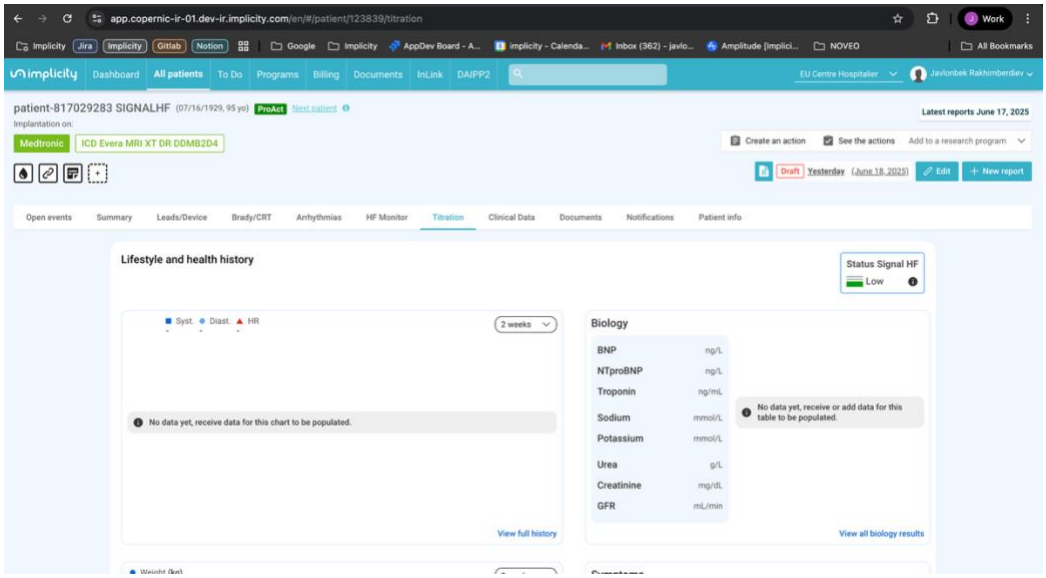
Warning: No value or empty charts do NOT mean that there is no risk for HF.

4. Examples of output results from SignalHF

The following examples show output results from SignalHF.

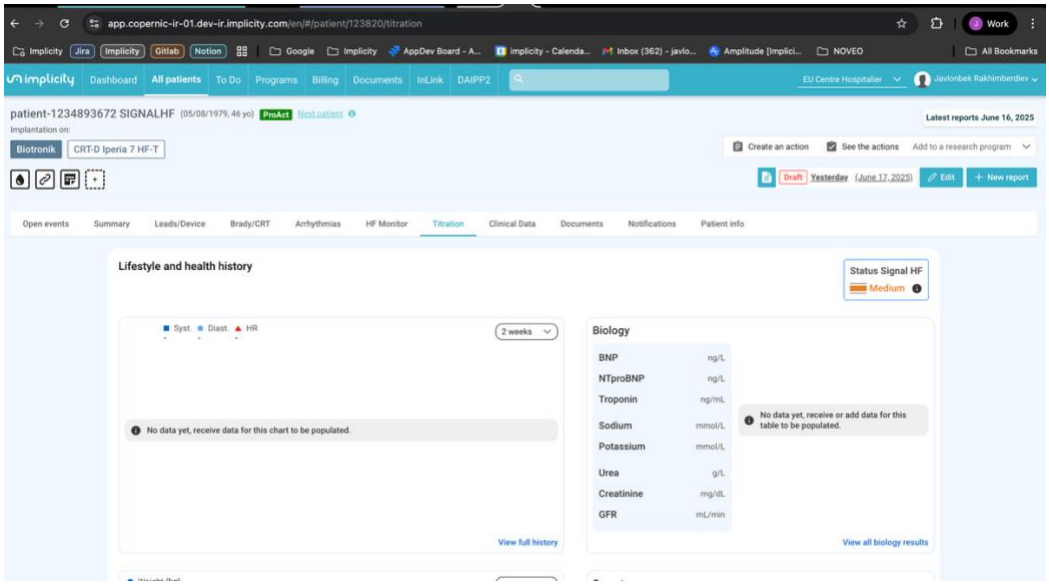
Example 1

In this example, the patient has a "**Low**" risk of hospitalization for HF within 12 months.



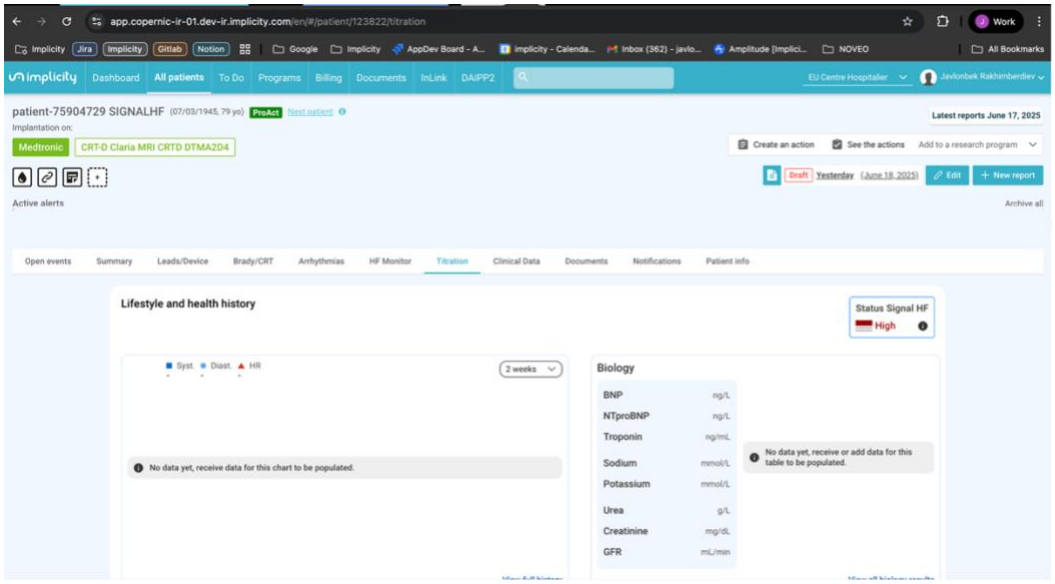
Example 2

In this example, the patient has a “**Medium”** risk of hospitalization for HF within 12 months.



Example 3

In this example, the patient has a “**High**” risk of hospitalization for HF within 12 months.



5. Performances validation

5.1 Constraints and targets thresholds

The performance of SignalHF (V2.0.0) is evaluated based on its ability to accurately determine a patient's long-term HF risk status (Low, Medium, or High) for future HF-related worsening conditions or hospitalizations over an anticipated 12-month period. Unlike previous versions or other market solutions that rely on score-based alerts, SignalHF V2.0.0 provides a clear risk category to facilitate personalized patient management.

Implicity trained a model using a “clinical validation dataset” corresponding to all patients implanted with a CIED (PM, CRT-P, ICD, CRT-D) and included in the SNDS between 2010 and each year-end during follow-up period until 2023.

We define a HF event as a hospitalization with HF as primary diagnosis, and a HF-related event as an hospitalization with HF as secondary diagnosis. Patients with no HF event (patients with no HF or HF-related event) are the ones for which no hospitalization with HF as primary diagnosis (with HF as primary or secondary diagnosis) was observed between 2010 and the end of the considered year.

Safety constraints for SignalHF V2.0.0:

- ***Safety High Sensitivity***: This metric, calculated as [number of (predicted high AND real high) + number of (predicted medium AND real high)] / [total number of real high] ≥ 90%, is pertinent to ensure that nearly all patients who are truly at high risk for HF events are accurately identified as either "High" or at least "Medium" risk by the system. This is crucial for patient safety, as it minimizes the chance of missing critical cases that require intensive clinical attention.
- ***Low NPV (Negative Predictive Value):*** This metric, calculated as [number of (real low AND predicted low)] / [total number of predicted low] ≥ 90%, is pertinent to ensure the reliability of a "Low" risk prediction. A high NPV for the "Low" category is vital to prevent false reassurance for the clinician, supporting appropriate and potentially more proactive management strategies for those truly at minimal risk, as suggested by the model.

Performance targets for SignalHF V2.0.0:

- ***Low Specificity:*** This metric, calculated as [number of (predicted low AND real low)] / [total number of real low] ≥ 25%, is pertinent to reflect a deliberate design choice that prioritizes caution. A lower specificity for the "Low" category implies that the system is more inclined to classify a truly low-risk patient into a "Medium" or "High" category if there is any uncertainty. This reduces the risk of underestimating a patient's condition, ensuring that clinical attention is not unduly reduced for patients who might benefit from closer monitoring.
- ***High Sensitivity:*** This metric, calculated as [number of (predicted high AND real high)] / [total number of real high] ≥ 75%, is pertinent to ensure that a high proportion of patients who are genuinely at "High" risk for HF events are correctly identified as such. This target is essential for efficient resource allocation and for prompting timely and intensive interventions for the patients who need them most.

5.2 Results and conclusion

The clinical validation dataset was composed of 6042 patients, averaging 70.6 years of age and primarily male (72.1%). The most frequently used devices among these patients are pacemakers (37.4%) and ICDs (35.9%), with Biotronik and Medtronic being the dominant manufacturers. The patient population exhibits a high burden of comorbidities, notably hypertension (85.9%) and heart arrhythmias (81.5%). Other significant conditions include coronary disease (54.4%), chronic respiratory disease (30.1%), diabetes (26.6%), and obesity/high BMI (26.9%), while renal failure is present in a small minority (1.3%). Here below is reported a comprehensive table of the population.

Epidemiology of the clinical validation dataset

Demographic Variable	**Clinical cohort**
Nb of patients	6042
Age (years)	70.6 ± 13.6
Sex	
Female (%)	27.9
Male (%)	72.1
Device model	
ICD (%)	35.9
CRT-D (%)	23.2
Pacemaker (%)	37.4
CRT-P (%)	3.4
Manufacturer device model	
Biotronik (%)	42.9
Boston Scientific (%)	17.1
Medtronic (%)	39.9
Comorbidities	
Renal failure(%)	1.3
Chronic respiratory disease (%)	30.1
Coronary disease (%)	54.4
Heart Arrythmias (%)	81.5
Hypertension (%)	85.9
Diabetes (%)	26.6
Obesity/High BMI(%)	26.9

The high sensitivity of SignalHF, measured at 81% for the general population (with and without HF, 95% CI: 75% - 87%) and at 77% for the HF population (95% CI: 69% - 84%), surpasses the specified performance target of ≥ 75%. This indicates the system's proficiency in accurately identifying a substantial proportion of patients who are genuinely at high risk for HF events, thereby supporting efficient resource allocation and timely intervention strategies.

Of particular importance for patient safety, the safety high sensitivity achieved 94% for the general population (95% CI: 89% - 97%) and 91% for the HF population (95% CI: 85% - 95%), exceeding its safety constraint of ≥ 90%. This outcome signifies SignalHF's strong capability to ensure that nearly all true high-risk patients are correctly classified as either "High" or "Medium" risk, thereby minimizing the probability of critical case oversight.

The Negative Predictive Value (NPV) for low risk was calculated at 98% for the general population (95% CI: 97% - 98%) and at 95% for the HF population (95% CI: 93% - 96%), successfully meeting the safety constraint of ≥ 90%. This high NPV confirms the reliability of a "Low" risk prediction, which is crucial for preventing false reassurance for both clinicians and patients and facilitating appropriate, potentially more proactive, management strategies for individuals truly at minimal risk.

Lastly, the low specificity for low-risk predictions registered at 34% for the general population (95% CI: 33% - 35%) and at 26% for the HF population (95% CI: 24% - 28%), which aligns with the performance target of ≥ 25%. This metric reflects a deliberate design choice that prioritizes caution. The system exhibits a propensity to classify a genuinely low-risk patient into a "Medium" or "High" category when uncertainty exists. While this approach may result in a higher rate of false positives for elevated risk categories, it effectively mitigates the risk of underestimating a patient's condition, ensuring that clinical attention is not inadvertently diminished for patients who may benefit from closer monitoring.

Patient population with and without HF:

Table 2: Safety and performance results for the general population

	Threshold	Value
High sensitivity	≥ 75%	81 % (75 % - 87 %)
Safety high sensitivity	≥ 90%	94 % (89 % - 97 %)
Low NPV	≥ 90%	98 % (97 % - 98 %)
Low specificity	of ≥ 25%	34 % (33 % - 35 %)

Focus on **HF population**:

Table 3: Safety and performance results for the HF population

	Threshold	Results
High sensitivity	≥ 75%	77 % (69 % - 84 %)
Safety high sensitivity	≥ 90%	91 % (85 % - 95 %)
Low NPV	≥ 90%	95 % (93 % - 96 %)
Low specificity	of ≥ 25%	26 % (24 % - 28 %)

In conclusion, the clinical validation set analysis confirms that **SignalHF consistently meets its critical safety and performance benchmarks.** The system demonstrates a high capacity for identifying high-risk individuals and providing dependable low-risk predictions, while maintaining a conservative approach to minimize the potential for under-recognition of patient risk.

6. Material Requirements

The material requirements are available in the installation instruction: IFU1-IM008-Installation Instruction

7. Explanation of Symbols used

Symbol	Name	Description
	Date of manufacture	Symbol indicating the "date of manufacture." The symbol shall be adjacent to the date that the product was manufactured, expressed as four digits for the year and two digits for the month and where appropriate, two digits for the day.
	Manufacturer	This symbol displayed on the label is accompanied by the name, address of the manufacturer (Implicity) and product version release date (date of manufacture).
	Medical Device	This symbol is displayed on the label to indicate that the product is a medical device.
	Catalogue Number	This symbol displayed on the label is accompanied by the manufacturer's catalogue number.
	Caution	This symbol displayed on the label is a safety symbol, indicating that there are specific warnings or precautions associated with the device which are not found on the label. These precautions/warnings are described in the Instructions for Use.
	Consult Instruction for Use	This symbol displayed on the label indicates that the Instruction for Use for the device should be consulted. The Instruction for use is Available online.
	CE mark	This symbol displayed on the label indicates that this medical device has been awarded the CE mark.
	Rx Only	This symbol displayed on the label is applicable in the United States and means: "CAUTION: Federal law restricts this device to sale by or on the order of a physician."
	UDI	This symbol displayed before the unique device identifier.