Boston Scientific

HeartLogic™ Algorithm Development and Validation

MultiSENSE STUDY SUMMARY

CAUTION: Federal law restricts this device to sale by or on the order of a physician trained or experienced in device implant and follow-up procedures.

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STUDY AND ALERT ALGORITHM VALIDATION DESIGN

The Multisensor Chronic Evaluations in Ambulatory Heart Failure Patients (MultiSENSE) study was a multi- center, non-randomized, feasibility study designed to collect chronic ambulatory data from multiple sensors available to implanted cardiac devices in order to develop an algorithm for the early detection of worsening Heart Failure (HF). The MultiSENSE data was divided into a Development Set and a Test Set. The Development Set was used to develop the HeartLogic™ Index and Alert algorithm, while the Test Set was used to independently validate the algorithm performance. Performance evaluation was based upon associations between HeartLogic Alerts and events adjudicated by an independent clinical event committee (CEC).

The study was conducted in 93 centers and designed to enroll up to a total of 990 patients with implanted COGNIS® Cardiac Resynchronization Therapy Defibrillator (CRT-D) devices. Upon enrollment, the patient's CRT-D device was converted into Sensor Research Device (SRD-1) by downloading investigational software to enable the collection of the following sensor data without affecting the device hardware or the delivered therapy: heart sounds, transthoracic impedance, respiration, activity and heart rate.

The sensor data were continuously collected by the device and stored in device memory, and downloaded to patient disks at follow-up visits. If the patient was enrolled in LATITUDE® Patient Management System, the sensor data were also captured with the weekly data download. After 12 months of patient follow-up, the SRD-1 device was reconverted to a COGNIS CRT-D device. The patient exited the study following a device check follow-up visit performed one month after the SRD-1 to COGNIS reconversion visit. CEC adjudicated all-cause hospitalizations, and outpatient visits with any IV therapy or augmented oral HF therapies and reported the primary cause (Cardiac/Non-cardiac/Other) and secondary cause of the event.

In addition to device-based sensor data, clinical data was captured electronically in the study database. The clinical data included clinical assessments and measurements required by the MultiSENSE study that were entered by site personnel, and event adjudication information from the CEC.

METHODS

Subject Selection

The MultiSENSE study enrolled patients implanted with a COGNIS CRT-D system. Only patients that met all of the inclusion criteria and none of the exclusion criteria were enrolled.

Inclusion and Exclusion Criteria

Subjects were included in the study if they met the following inclusion criteria:

- Age 18 or above, or of legal age to give informed consent specific to state and national law
- Willing and capable of returning for all follow-up visits and emergency care at the investigational center as medically appropriate
- Willing to participate in all testing associated with this clinical investigation at an approved clinical investigational center
- Currently implanted with a CRT-D system including a COGNIS device (model N119, N120, P107 or P108) with RA, RV and LV leads
- Classified as NYHA Class II, III or IV within the last six months

Subjects were ineligible to participate in the study if they met the following exclusion criteria:

- Inability or refusal to sign the Patient Informed Consent
- Inability or refusal to comply with the follow-up schedule
- Document as pacemaker dependent
- Unable to rest comfortably in a semi-recumbent position for up to 20 minutes

- Implanted with active Medtronic Fidelis lead models: 6930, 6931, 6948 or 6949
- Currently implanted with unipolar RA, RV, or LV leads
- LV sensitivity programmed to less than 0.7 mV AGC
- Subjects that have a history of appropriate tachycardia therapy (external or implanted) for rates <165 bpm within one week of enrollment
- Device battery status indicates approximate time to explant < 2 years
- Likely to undergo lead or PG revision during the course of the study as determined by the investigator
- Receiving regularly scheduled intravenous (IV) inotropic therapy as part of their drug regimen
- Subjects that have received heart or lung transplant
- Receiving mechanical circulatory support
- Subjects who have been referred or admitted for Hospice care
- A life expectancy of less than 12 months per physician discretion
- Enrolled in any concurrent study without Boston Scientific written approval
- Subjects whose devices have previously been converted to the SRD-1 and withdrawn from this study
- Subjects with sub-pectoral COGNIS implant prior to February 1, 2011 with model numbers N119-xxx where xxx is </= 110
- Women who are known to be pregnant or plan to become pregnant within the course of the study
- LV offset is programmed to a value greater than zero

Event Definition

A CEC-adjudicated event was deemed as a Heart Failure Event (HFE) if the primary cause of event was HF and either of the conditions below was met as per the information entered into the adjudication forms:

- Patient was admitted with a calendar date change
- Patient was not hospitalized and received one or more IV medications including diuretics, inotropes, vasodilators, other parenteral therapy, or aquapheresis

To avoid the potential for having an HFE without sufficient sensor data for operation, usable heart failure events (usable HFEs) were defined as HFEs that occurred at least 45 days after study device conversion and prior to study device reconversion AND met the following data availability criteria[1]: at least 60% of the following sensor data present within a 60-day pre-event window and at least 70% of sensor data present within a 15-day pre-event window:

- Device measured first heart sound[2]
- Thoracic Impedance
- Rapid shallow breathing index (ratio of respiratory rate and relative tidal volume)
- Respiratory rate
- Heart rate
- Time active

[1]Exclusion of events due to not meeting data availability criteria was specific to SRD-1 device and MultiSENSE trial design, since gathering high resolution sensor data limited the temporal span of data that could be stored on the device between successive data downloads. Future devices are anticipated to not experience similar levels of lack of data availability due to onboard processing of raw high resolution data.

[2]Data availability of device measured first heart sound covers data availability of device measured third heart sound, thus device measured third heart sound is not repeated in the data availability criteria.

HF Related Events were defined as events adjudicated with a primary or secondary cause of worsening HF that did not meet the definition of usable HFE. In other words, HF Related Events include:

- HFE that either occur within 45 days of device conversion or do not meet the data availability criteria
- Events adjudicated with a secondary cause of worsening HF
- Events adjudicated with a primary cause of worsening HF, but patient was not hospitalized or did not receive IV medications

Algorithm Development

The HeartLogic Index and Alert algorithm was developed and finalized using the Development Set sensor data and HFE information. During the first phase of algorithm development, features that demonstrated meaningful association with HFEs were extracted from individual sensor data into feature trends. The next phase of development included combining the key feature trends into the HeartLogic Index and an associated alert. In brief, multiple feature changes from the patient's own baseline were aggregated and weighted based on an individual daily risk for worsening HF assessment. The algorithm utilizes first and third heart sounds, thoracic impedance, respiration rate, a ratio of respiration rate to tidal volume, heart rate, and patient activity. The clinical relevance of these metrics to HF is summarized in Table 1.

Table 1. Physiological Variables and Their Clinical Relevance

Physiological Variables	Clinical Relevance
Heart Sounds First heart sound Third heart sound	 Associated with ventricular contraction status Associated with early diastolic filling
Thoracic Impedance	Associated with fluid accumulation and pulmonary edema
Respiration Respiration rate Ratio of respiration rate to tidal volume	Rapid shallow breathing patterns associated with shortness of breath
Heart rate	Indicator of cardiac status
Activity	Global patient status and fatigue

Endpoint Definition and Analysis

HeartLogic alerts that start on or before the date of a usable HFE and end no earlier than 30 days before a usable HFE (date of the usable HFE – alert end date ≤ 30) were considered True Positive (TP) alerts. A usable HFE associated with a TP was considered as detected.

HeartLogic alerts that were not TPs are further classified as follows:

- HF related alerts: defined as those alerts that start on or before the date of an HF Related Event and end no earlier than 30 days before a HF Related Event
- Unexplained alerts: defined as alerts other than TPs or HF related alerts.

Sensitivity: Defined as the ratio of total number of detected usable HFEs to the total number of usable HFEs.

Unexplained alert rate (UAR): Defined as the ratio of total number of unexplained alerts to the total usable follow-up duration (in patient-years).

Total usable follow-up duration was defined as the aggregate count of all days when the HeartLogic Index was valid.

The 1st Primary Effectiveness Endpoint was the sensitivity of the HeartLogic alert algorithm for detecting usable HFEs in the Test Set. The 2nd Primary Effectiveness Endpoint was the unexplained alert rate (UAR) per patient-year in the Test Set. The two co-Primary Endpoints were assessed at the nominal Alert

Threshold of 16. The sensitivity in the Test Set was compared against a performance goal (PG) of 40%. An exact (Clopper-Pearson) 2-sided 95% CI for the sensitivity was calculated, and the PG was met if the lower bound of the CI exceeded 40%. The UAR in the Test Set was compared to a PG of 2.0. An intercept-only generalized linear model with a negative binomial link function, offset by the natural logarithm of the patient-years of follow-up, was fit to the Test Set data. The 2-sided 95% CI for UAR was calculated by taking the natural exponential function of the 95% CI of the intercept parameter. The PG was met if the upper bound of this CI was less than 2.0.

In addition to assessing the primary effectiveness endpoints at the nominal Alert Threshold of 16, the performance of the HeartLogic alert was evaluated across a range of threshold options.

Additional Analysis

The HeartLogic Index aggregates measurements from multiple device-based sensors, including Heart Sounds, Thoracic Impedance, Respiration, Night Heart Rate, and Time Active. The respiratory sensor is the only sensor that can be turned off independently when HeartLogic is turned on. Thus there is another alternative sensor configuration for HeartLogic: Respiratory Sensor Off. The performance of the HeartLogic alert at various alert thresholds and the primary effectiveness endpoints were also assessed on the Respiratory Sensor off configurations.

Positive predictive value (PPV), defined as the proportion of alerts that were positively associated with worsening HF (true positives and HF-related alerts), was calculated. The descriptive statistics for the number of days (alert duration) an alert associated with worsening HF was on and the number of days an unexplained alert was on were also calculated.

RESULTS

Patient Demographics and Consort Diagram

Nine hundred and seventy four patients were enrolled from 93 centers (75 US/ 18 international) between July, 2010 and October, 2013. Patient flow and group allocation is summarized in the CONSORT diagram (Figure 1). A total of 500 patients in the Development Set and 400 patients in the Test Set had a successful device conversion to SRD-1, which enabled collection of device based sensor data in these patients.

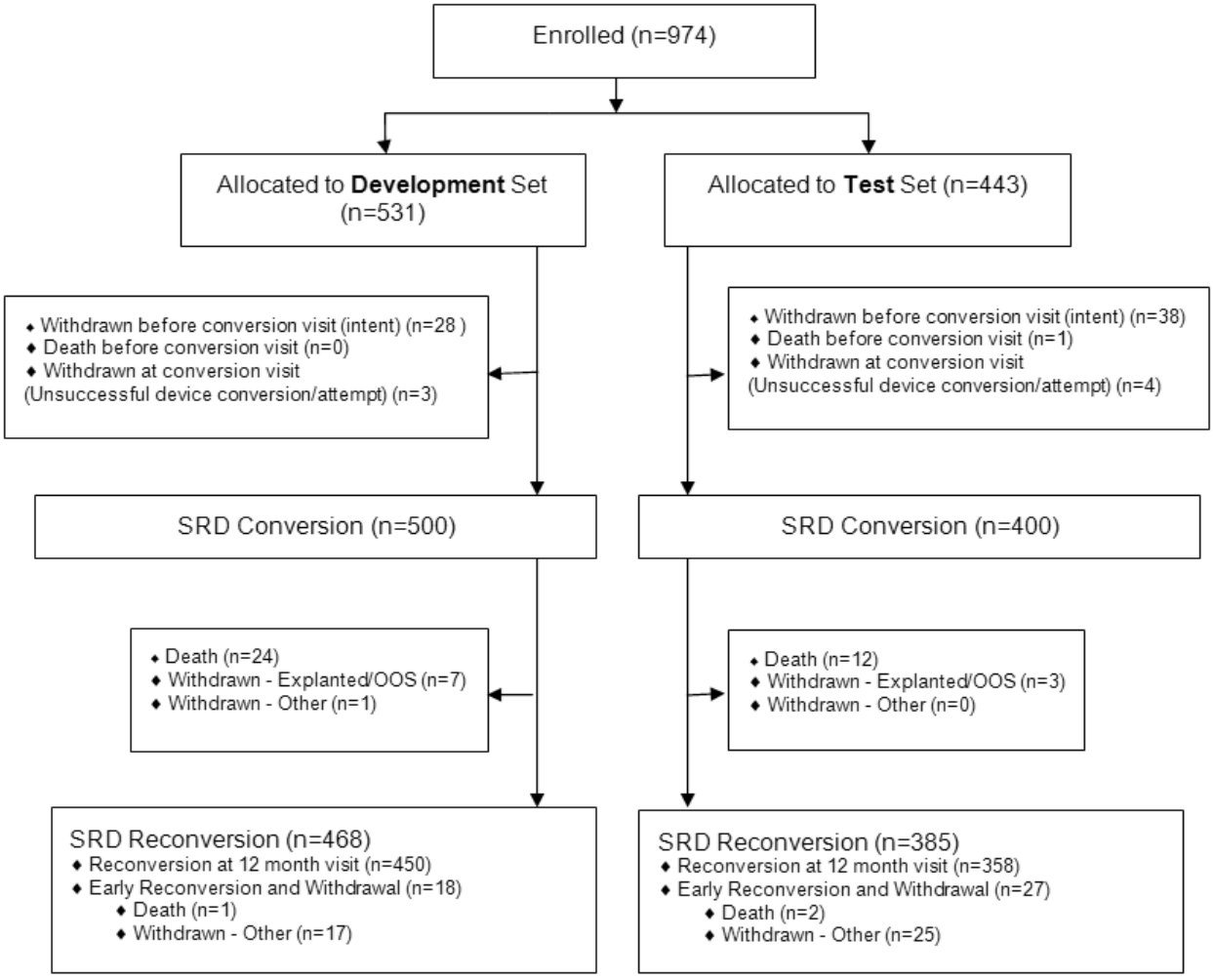

Figure 1. CONSORT diagram illustrating the allocation of patients between Development and Test Set and their flow through the study

The baseline characteristics of each group are summarized in Table 2.

Table 2. Patient Characteristics

Characteristic	Measurement	Development Set (N=500)	Test Set (N=400)	P-value**
Total Patient Count	N	500	400	
Age at Implant (years)	Mean ± SD	66.4 ± 10.7	66.8 ± 10.3	0.52
	Range	33.0 - 88.0	22.0 - 92.0	
Gender	Male	366 (73)	288 (72)	0.69
	Female	134 (27)	112 (28)	
Race	N	462	329	
	White, Not Of Hispanic Origin	344 (74)	258 (78)	0.47
	Black Or African American	75 (16)	52 (16)	

RESULTS

Characteristic	Measurement	Development Set (N=500)	Test Set (N=400)	P-value**
	Hispanic Or Latino	36 (8)	14 (4)	
	Asian	4 (1)	2 (1)	
	Native Hawaiian/ Other Pacific Islander	1 (0)	1 (0)	
	Not Given	1 (0)	1 (0)	
	East Indian	0 (0)	1 (0)	
	Mixed Race	1 (0)	0 (0)	
Body Mass Index (kg/m2)	N	492	400	
	Mean ± SD	30.4 ± 6.6	30.6 ± 7.0	0.61
	Range	16.1 - 54.9	16.6 - 72.3	
NYHA Class	I	25 (5)	18 (5)	0.64
	II	330 (66)	275 (69)	
	III	140 (28)	101 (25)	
	IV	1 (0)	3 (1)	
	Unknown	4 (1)	3 (1)	
LVEF (%)	N	478	381	
	Mean ± SD	29.3 ± 11.4	30.0 ± 11.4	0.35
	Range	9.0 - 70.0	10.0 - 65.0	
History of Cardiac Ischemia	N (%)	263 (53)	194 (49)	0.22
History of Dilated Cardiomyopathy	N (%)	288 (58)	245 (61)	0.27
History of Valvular Disease	N (%)	152 (30)	117 (29)	0.71
History of Valve Surgery	N (%)	43 (9)	35 (9)	0.94
History of Thoracic Surgery	N (%)	67 (13)	57 (14)	0.70
Previous MI	N (%)	201 (40)	153 (38)	0.54
Previous CABG	N (%)	145 (29)	113 (28)	0.80
Asthma	N (%)	47 (9)	41 (10)	0.67
Diabetes	N (%)	218 (44)	162 (41)	0.35
Renal Dysfunction	N (%)	136 (27)	90 (23)	0.11
Hypertension	N (%)	386 (77)	307 (77)	0.87
Depression	N (%)	101 (20)	75 (19)	0.59
Hyperlipidemia	N (%)	390 (78)	302 (76)	0.38
Anemia	N (%)	64 (13)	53 (13)	0.84
Sleep Disordered Breathing (AHI)	N (%)	91 (18)	69 (17)	0.71
Concomitant Medications*	Anticoagulants	446 (89)	326 (82)	0.001
	Beta Blockers	467 (93)	372 (93)	0.81
	Diuretics	383 (77)	311 (78)	0.68
	Ace-Inhibitors	296 (59)	233 (58)	0.77

Characteristic	Measurement	Development Set (N=500)	Test Set (N=400)	P-value**
	Aldosterone Antagonist	185 (37)	175 (44)	0.04
	Vasoactive Drugs	121 (24)	89 (22)	0.49
	Cardiac Glycosides	133 (27)	98 (25)	0.47
	ARBs	128 (26)	101 (25)	0.90
	Antiarrhythmic Medications	108 (22)	85 (21)	0.90
	Calcium Channel Blockers	42 (8)	29 (7)	0.52

* Patients may appear in more than one category so percents may not add to 100.
**P-values are from a Student's T-test for continuous measures and a chi-squared test for categorical measures.

Event Adjudication Summary

Figure 2 shows the classification of events based on CEC adjudication results in the Test Set. The study yielded 50 usable HFE and 92 HF Related events that were used for performance evaluation.

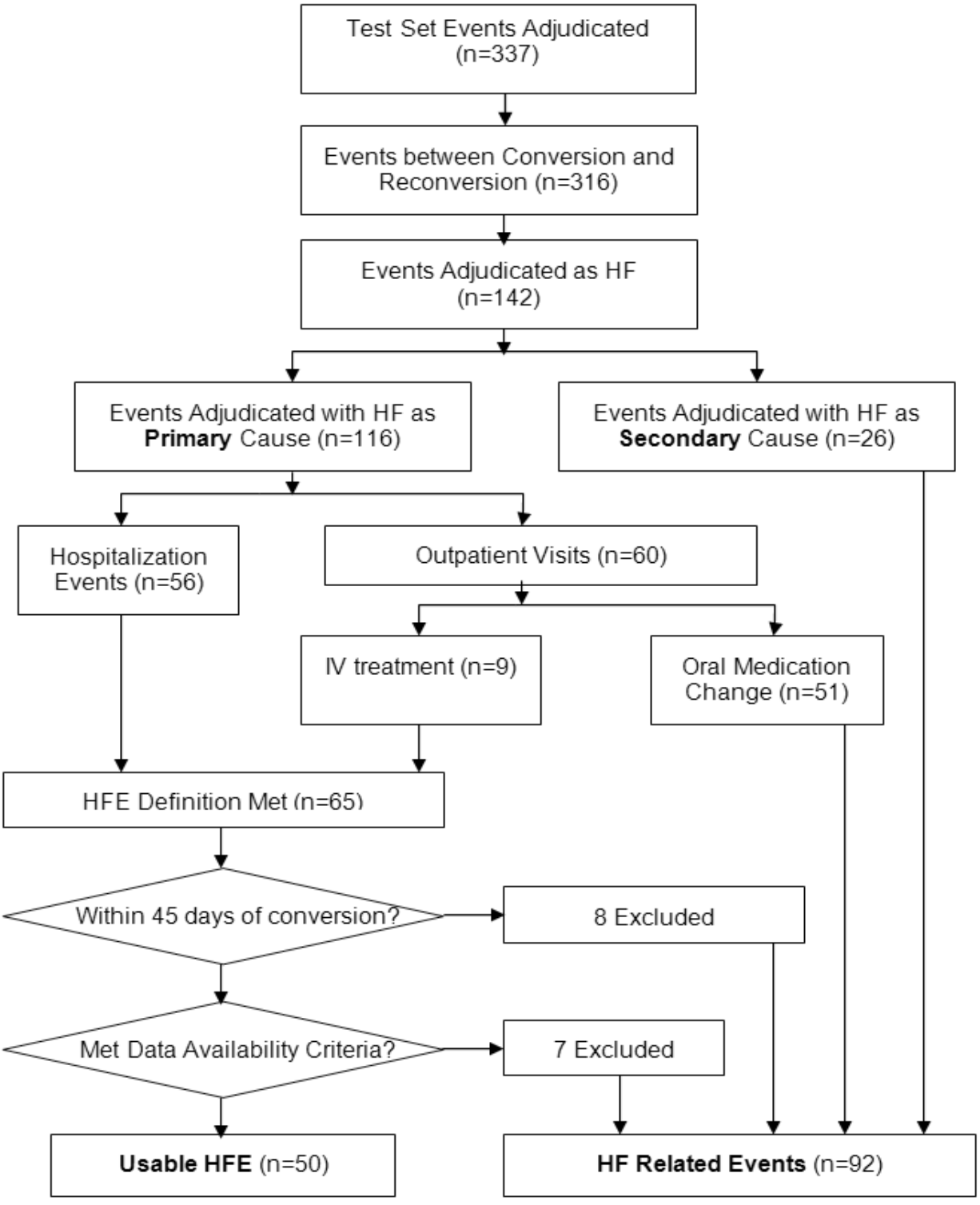

Figure 2. Event Classification in the Test set based on CEC adjudicated results

Development Set Performance

The detection performance in the Development Set is presented in Figure 3. At the nominal Alert Threshold of 16 the observed sensitivity was 82% while the UAR was 1.33 per patient year.

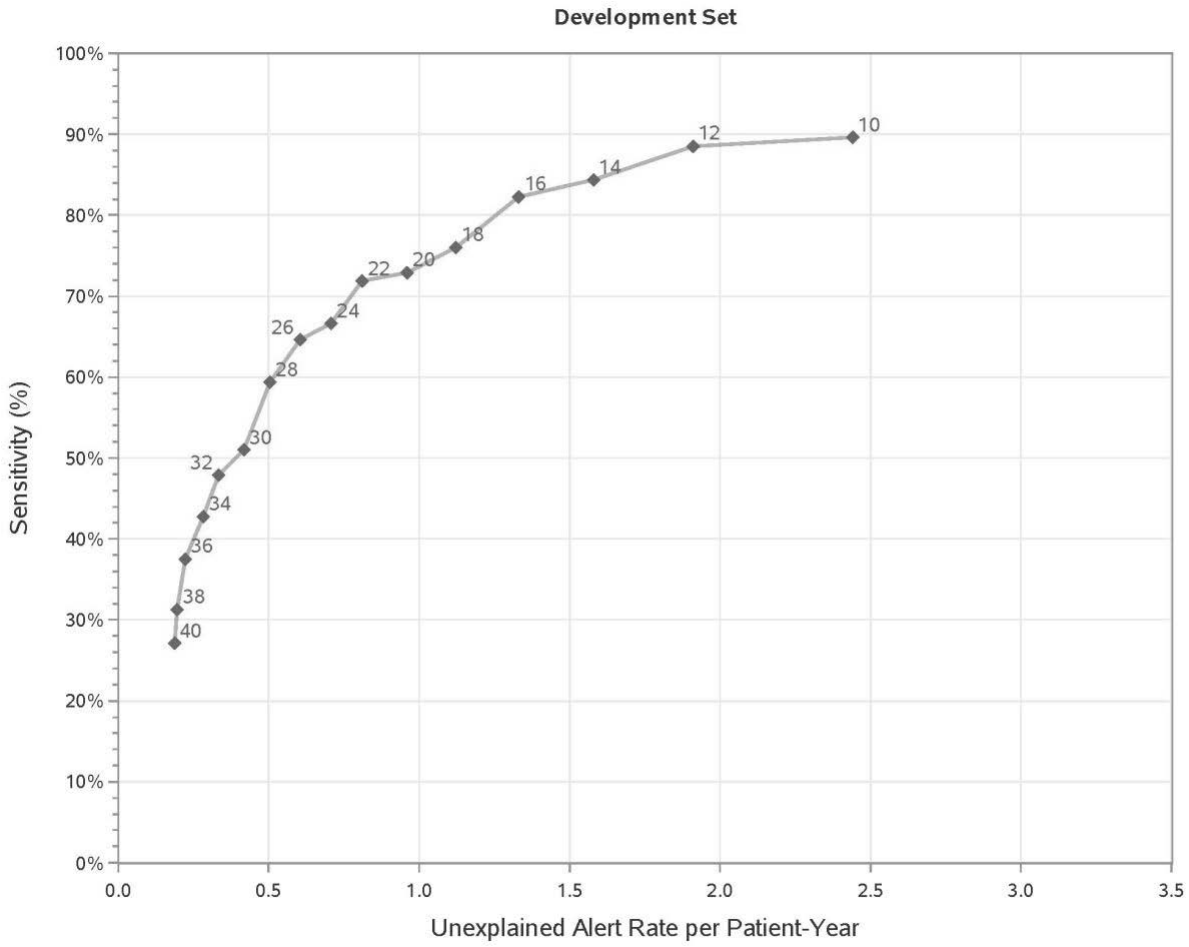

Figure 3. Sensitivity vs UAR of HeartLogic Alert Algorithm at various alert thresholds in the Development Set (Nominal alert threshold = 16)

Test Set Performance

1st Primary Effectiveness Endpoint

As shown in Table 3, at the nominal Alert Threshold of 16, the algorithm yielded a sensitivity of 70%. The lower bound of the 2-sided 95% CI was 55.4%, which exceeded the PG of 40%. **Thus, the 1st Primary effectiveness endpoint was successfully met.**

2nd Primary Effectiveness Endpoint

A total of 469 unexplained alerts over a usable follow-up duration of 320 patient years yielded an observed Unexplained Alert Rate of 1.47. Modelling the UAR based on a negative binomial distribution yielded a mean UAR of 1.48 with a 2-sided 95% CI of 1.32-1.65 which is below the PG of 2.0. **Thus, the 2nd Primary effectiveness endpoint was also successfully met.**

Table 3. Primary Effectiveness Endpoint Assessment

Endpoint	Performance Goal	Result (2-sided 95% CI)	Conclusion
Sensitivity	> 40%	70% (55.4% - 82.1%)	Endpoint Met
UAR	< 2.0	1.48 (1.32-1.65)	Endpoint Met

Since both the co-primary Endpoints were successfully met, HeartLogic alert algorithm was successfully validated.

Performance Evaluation across Thresholds

Sensitivity and UAR at all the configurable alert thresholds are plotted in Figure 4 and shown in Table 4. In addition to the nominal Alert Threshold of 16, 4 additional alert thresholds (14, 18, 20, 22) also met the PG criteria of Sensitivity > 40% and UAR < 2.0 alerts per patient year. In addition, all plotted threshold options met the pre-specified criteria for configurability of observed sensitivity > 20% and observed UAR < 3.5 alerts per patient year.

Table 4. Sensitivity and UAR of HeartLogic Alert Algorithm at various alert thresholds

Alert Threshold	Sensitivity (%)	UAR (per patient year)
10	80	2.69
12	74	2.09
14	74	1.70
16 (nominal)	**70**	**1.48**
18	70	1.22
20	62	1.07
22	60	0.93
24	54	0.82
26	54	0.70
28	54	0.58
30	48	0.49
32	44	0.40
34	42	0.34
36	34	0.28
38	30	0.25
40	22	0.20

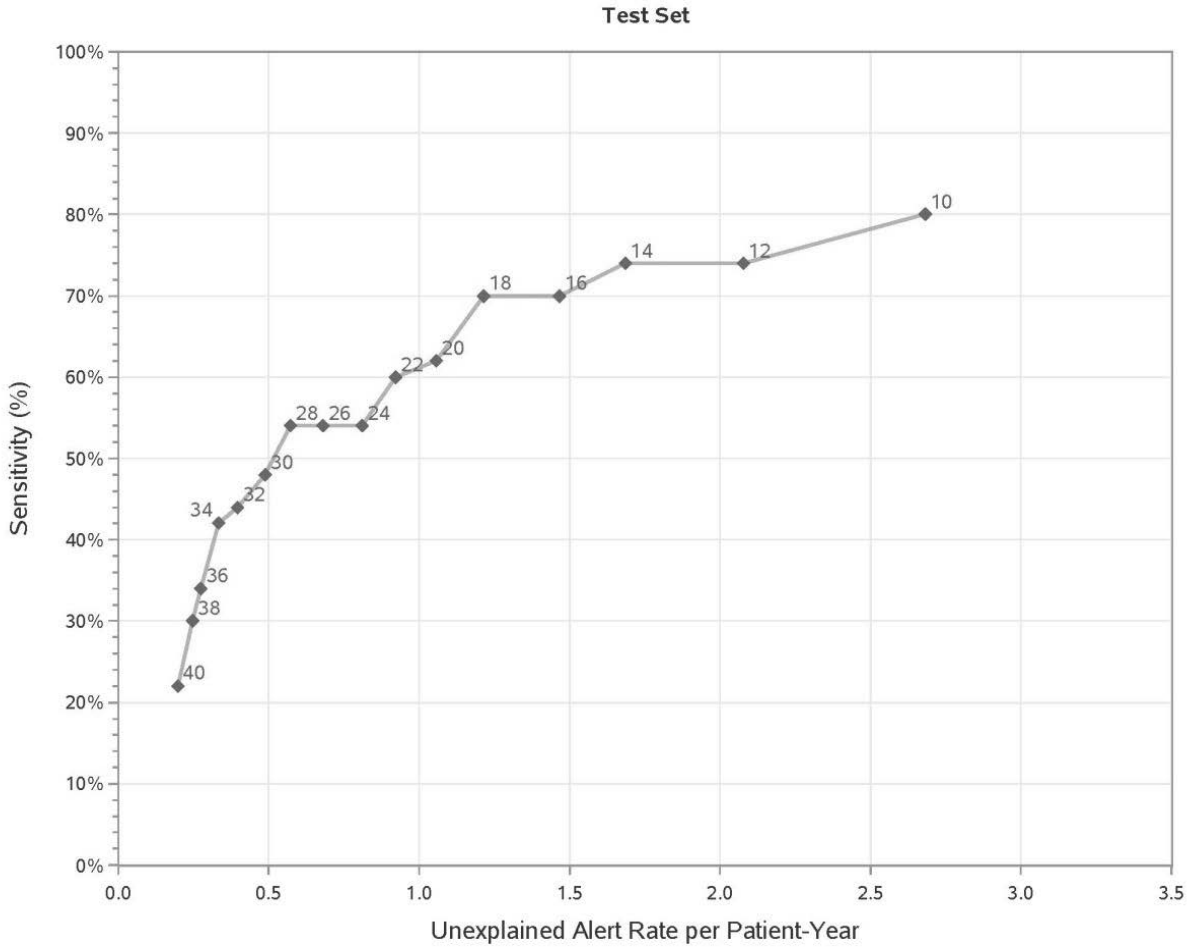

Figure 4. Sensitivity vs UAR of HeartLogic Alert Algorithm at various alert thresholds in the Test Set (Nominal alert threshold = 16)

Additional Results

Figure 5 shows the HeartLogic performance (sensitivity versus UAR) in the Respiratory Sensor On (default, same as Figure 3) and Respiratory Sensor Off (the only other alternative) sensor configurations respectively.

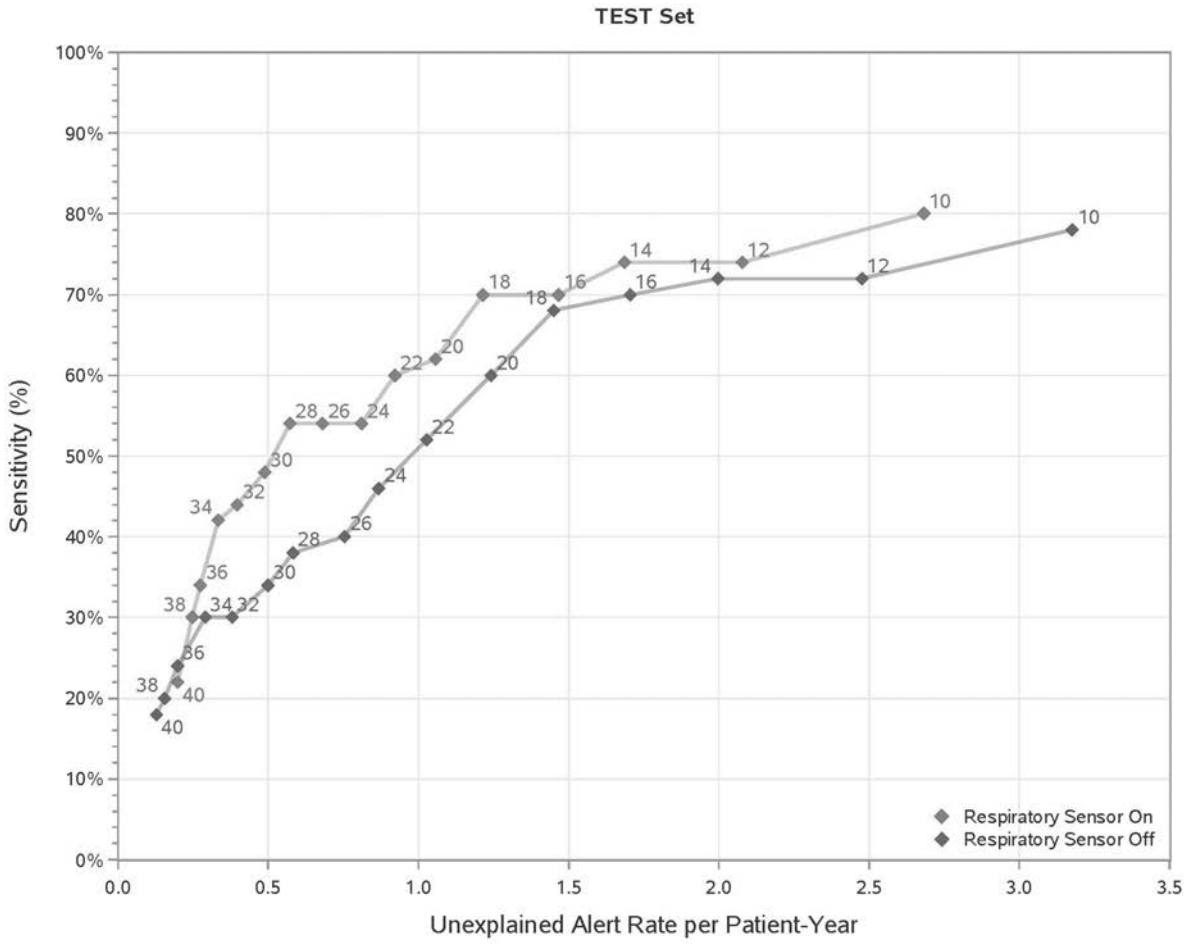

Figure 5. Sensitivity Vs UAR of HeartLogic Alert Algorithm at various alert thresholds in Respiratory Sensor On and Respiratory Sensor Off configurations in the Test Set (Nominal alert threshold = 16)

The primary effectiveness endpoints were also assessed on both the Respiratory Sensor On and the Respiratory Sensor Off configurations, with the results summarized in Table 5. Both configurations met the pre-specified performance goals. Therefore, we conclude that the performance of HeartLogic is validated in the alternative sensor configuration when respiratory sensor is turned off. The performance is the best when all sensors are available.

Table 5. Primary Effectiveness Endpoint Assessment

Endpoint	Performance Goal	Result (2-sided 95% CI): Respiratory Sensor On Configuration	Result (2-sided 95% CI): Respiratory Sensor Off Configuration
Sensitivity	> 40%	70% (55.4% - 82.1%)	70% (55.4% - 82.1%)
UAR	< 2.0	1.48 (1.32-1.65)	1.7 (1.56-1.88)
Conclusion		Both endpoints were met.	Both endpoints were met.

At the nominal Alert Threshold of 16, there were 11.3% of HeartLogic alerts that were positively associated with worsening HF. PPV values for all the configurable alert thresholds are listed in Table 6.

At the nominal Alert Threshold of 16, the mean duration for alerts that were positively associated with worsening HF was 59 days, while the mean duration for unexplained alerts was 35 days. The values for all configurable alert thresholds are also listed in Table 6.

Table 6. Positive predictive value, alert duration for alerts associated with HF, and unexplained alerts at various alert thresholds

Alert Thresholds	PPV, defined as the proportion of alerts that were positively associated with worsening HF	Alert Duration for alerts associated with HF, Days, mean (25%, median, 75%)	Alert Duration for Unexplained Alerts, Days, mean (25%, median, 75%)
10	0.08	61 (23, 46.5, 85)	34 (16, 27, 45)
12	0.09	64 (26, 50, 89)	36 (17, 29, 47)
14	0.10	64 (26, 45, 89)	37 (17, 31, 48)
16 (nominal)	**0.11**	**59 (24, 42.5, 76.5)**	**35 (17, 29, 45)**
18	0.13	56 (23, 41, 72)	34 (16, 29, 45)
20	0.13	51 (23, 39.5, 65.5)	33 (17, 27, 44)
22	0.14	48 (22, 40, 61)	32 (16, 27, 44)
24	0.15	46 (21, 33.5, 58)	32 (17, 27, 43)
26	0.16	46 (21, 34.5, 62)	32 (17, 28, 43)
28	0.18	46 (20, 34, 63.5)	32 (17, 28, 42)
30	0.19	45 (16, 33, 62)	30 (15.5, 26, 42)
32	0.21	47 (16, 36.5, 64)	31 (15, 28, 40)
34	0.22	49 (24, 42, 64)	31 (16, 28, 41)
36	0.22	49 (23, 38, 63)	32 (20.5, 28, 41)
38	0.19	58 (27, 40.5, 92)	31 (19, 27, 40)
40	0.17	70 (37, 61, 101)	31 (19, 27, 39)

CONCLUSIONS

These results, which describe evaluation of the HeartLogic alert algorithm on the Test Set cohort of the MultiSENSE study, indicate that both co-primary endpoints were successfully met; therefore, the HeartLogic Index and alert algorithm has been successfully validated.

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