Heart Failure Indication and Sudden Cardiac Death Prevention Trial Japan

**HINODE**

# CLINICAL INVESTIGATION PLAN

BSC Project Number C2076

**Sponsored By**

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| **Vendors/Labs** | A list of vendors/laboratories involved in the trial is maintained by the sponsor. A complete listing of applicable vendors will be provided to investigational sites. |

**Original Release:** *24 Feb 2017*

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## Revision History

| Revision Number | Release Date | Template number and version | Section | Change | Reason for Change |
|---|---|---|---|---|---|
| **Version AA Doc 92082863** | 24 February 2017 | 90702637, version AH 2016 | | Initial Release | |
| **Version B Doc 92082863** | 27 February 2017 | | 9.2.5. | **Adding: "** or DCM (dilated cardiomyopathy)". As clarification to the non-device inclusion criteria | Inconsistency in wording with ICD inclusion criteria |
| **Version C Doc 92082863** | 13 March 2017 | | 2.<br>4.<br>7.3<br>9.2.<br>9.3.<br>11.1<br>12.3 | **Adjustment of synopsis Wording** issues across the document<br>**Introduction; rational for pacemaker arm**<br>**7.3. Add Endpoint on cause of death**<br>**9.2 Adding and adjusting** inclusion<br>**9.3** and exclusion criteria<br>**11.1 Adjustments**<br>**12.3 Adjustments** | Inconsistency in wording and the need for more specific details for a well-defined subject cohort by inclusion and exclusion criteria |
| **Version D Doc 92082863** | 29 March 2018 | 92120219, version A | Contact Information<br>2.<br>5., 11.4<br>8.1, 8.2, 10.4, 12<br>Figure 8.1-1<br>9.2 | CIP Authors and Affiliation updated to reflect current contact details<br>**Adjustment of synopsis wording** issues across the document<br>Clarification added regarding data collection in case subjects cannot be connected to Latitude<br>**Adjustments** to content for minimum number of subjects required to meet endpoints<br>Close-out window for last subject added for **clarification** purposes<br>**Adjusting inclusion criteria**; typo's, data collection, timelines aligned with SOC, clarifications | Correction of typo's and inconsistencies and addition of clarifications across the document<br>Need for adjusting inclusion and exclusion criteria |

# Revision History

| Revision Number | Release Date | Template number and version | Section | Change | Reason for Change |
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| | | | 9.3 | **Removing and adjusting exclusion criteria;** removal of exclusion criteria for non-device cohort, clarifications | |
| | | | 10.1 | **Clarification added** for eligibility criteria handling between protocol version C and D | |
| | | | Table 11.1-1 | **Adjustment** of wording across the document | |
| | | | 11.4 | **Adjustments** to content for data collection and timelines to align with SOC | |
| | | | 8., 11.1, 11.4, 11.5, 11.8, 11.9, 17.4, 20.4, 27.1 | **Adjustments** to wording | |
| | | | 21. | **Adjustments** to content regarding legally authorized representative | |
| | | | 2., 8.1, 8.2, 12.2.2, 27.1 | **Adjustment** to content regarding Korea participation as Korea will not join the study | |

## 2. Synopsis

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
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| **Study Objectives** | The purpose of this cohort therapy study is to collect clinical event and outcome data in a study population with a majority of Japanese subjects on sudden cardiac death (SCD), heart failure (HF) events, and appropriately treated ventricular adverse events in predefined subject cohorts. These event rates will be compared with available data mainly from Europe and the United States. It is the intention to add evidence in treatment with implanted Implantable cardioverter-defibrillator (ICD) and treatment with cardiac resynchronization therapy-defibrillator (CRT-D) devices.<br>**Selected Subject Cohorts:**<br>1. Selected subject cohort with criteria for SCD (without spontaneous prior ventricular sustained arrhythmia) and de novo ICD device treatment.<br>2. Selected subject cohort with criteria for SCD and widely accepted standard cardiac resynchronization therapy (CRT) indication who received a de novo CRT-D device treatment.<br>3. Selected subject cohort who are clinically expected to require >40% right ventricular pacing with a left ventricular ejection fraction (LVEF) ≤50%, any determined New York Heart Association (NYHA) Class, and receiving pacemaker (PM) or CRT-pacemaker (CRT-P) therapy despite previous device history (de novo, box changes, system revisions or upgrades).<br>4. Selected subject cohort with criteria for SCD fulfilling European Society of Cardiology (ESC) ICD or CRT-D therapy guidelines (2016) with an LVEF ≤35%, having 2 to 5 predefined SCD risk factors but do not have or had have a cardiac implanted defibrillator, CRT-D, PM, or CRT-P. |
| **Test Device** | Implanted subjects will receive one of 4 types of Boston Scientific (BSC) devices prior to enrolment in the study:<br>1. ICD (only magnetic resonance imaging [MRI] conditionally safe systems) + Latitude |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
|---|---|
| **Test Device (continued)** | 2. CRT-D (IS4 connector only, MRI conditionally safe systems) + Latitude<br>3. PM + Latitude<br>or<br>CRT-P + Latitude<br>All device systems are on the market in Japan, and will be implanted per standard of care (SOC) and BSC Instructions for Use (IFU) for the respective devices should be followed.<br>Neither the devices nor the implant procedure are part of this study. The decision as to which device any subject receives is to be determined by the investigator and is not part of this study.<br>Device system use and programming will need to follow SOC, devices IFUs and must follow CIP programming requirements. All devices in the study must be intended to be connected to the Latitude system. |
| **Study Design** | This is a prospective, non-randomized, multicenter, multi-cohort clinical outcome registry study to evaluate SOC. |
| **Planned Number of Subjects** | It is planned to enroll a minimum of 556 to power all primary endpoint for each cohort.<br>As soon as a minimum of 556 eligible subjects are entered into the study database, the closure of enrolment can begin. The maximum number of followed study subjects is 950.<br>The event dependent character of the study, and the calculated necessary minimum sample size may allow early enrollment closure of the study enrollment. |
| **Planned Number of Investigational Sites / Countries** | Approximately 40 investigational sites in Japan will be included. If a site does not enroll a subject within a 3-month time period, the site may be closed for enrolment and replaced at the discretion of the sponsor. |
| **Primary Safety Endpoint(s)** | Not applicable |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**d**e**n** Cardiac Death Prevention Trial Japan **HINODE** | |
|---|---|
| **Primary Effectiveness Endpoints** | **Defibrillator Cohort (including ICD and CRT-D Cohorts):**<br>Composite rate of first appropriately treated ventricular arrhythmia (by anti-tachycardia pacing [ATP] or shock) or life-threatening symptoms associated to ventricular arrhythmia (defined as hemodynamic instability which requires treatment), whichever comes first under MADIT Arm B or C programming conditions in a study population with a majority of Japanese subjects<br>**PM/CRT-P Cohort:**<br>All-cause mortality in subjects with a maximum of 3 risk factors (analyzed for MADIT II data)<br>**Non-device Cohort (ESC Guideline 2016 Indicated but not implanted):**<br>All-cause mortality in the subject cohort with 2 to 5 predefined SCD driving risk factors |
| **Secondary Endpoints** | **Defibrillator Cohort (including ICD and CRT-D Cohorts):**<br>• All-cause mortality rate<br>**ICD, CRT-D, and PM/CRT-P Cohorts:**<br>• Composite rate of HF events, which require intravenous (IV) treatment and/or HF related hospitalization, or which led to HF death<br>• Therapeutic sustainability at 1 year, defined as free of qualified serious adverse device events (SADEs) post successful implantation in comparison to data from MADIT CRT, MADIT RIT, Optimind and Rally X4 studies<br>Examples for qualified SADEs are: re-implant procedure, required invasive procedure related to the device system, pacing exit block, all-cause infection, and death due to therapy failure<br>**ICD, CRT-D, and Non-device Cohorts:**<br>• Comparison of rate of sudden cardiac death in the non-device cohort with the rate of appropriately treated ventricular arrhythmias or sudden cardiac death in the defibrillator cohort (including ICD and CRT-D Cohorts) |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
|---|---|
| **Additional Endpoints** | • Subject medical assessment collected pre-enrolment (post implant) and at Close-out:<br>– NYHA functional classification<br>– LVEF<br>– QRS duration<br>– Physician's judgment on therapy outcome<br>– Body mass index<br>– Diabetes mellitus type I and II<br>• Cross-over in device therapies<br>• Cause of death (SCD, cardiac related, other reasons, unknown)<br>• Impact of age and gender<br>• MRI observations in association with reported clinical events<br>• Analysis of device data coming from Latitude data reports<br>• Health care utilization under Latitude<br>• Standard biomarkers for heart failure and other morbidities |
| **Method of Assigning Patients to Treatment** | Subjects will be assigned to one of the 3 following Subject Cohorts according to device implanted:<br>1. ICD: 117 to 270 subjects<br>2. CRT-D: 95 to 250 subjects<br>3. PM/CRT-P: 172 to 200 subjects<br>A fourth cohort of non-implanted subjects will also be enrolled:<br>4. Non-device: 172 to 300 subjects<br>(ESC Guideline 2016 indicated but not implanted) |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
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| **Follow-up Schedule** | Clinic visits will occur at:<br>• Enrolment and Consenting Clinic Visit (Day 0, 0 to 45 days post implant procedure, alternative >90 days post myocardial infarction (MI)) (Required)<br>• 6-monthly Visit (180 ± 60 days post enrolment and multiplies until Close-out Visit) (required)<br>• Re-implant or New Device Implant post Enrolment (optional)<br>• Interim Visit and Event Report (serious adverse events/SADE related clinical care visit)<br>• Close-out Clinic Visit (see Figure 8.1-1) (Required)<br>• During the trial all adverse device effects, deaths, and changes in the device system must be reported<br>• Devices will be followed by the BSC Latitude team. Device Data as defined in the Clinical Investigation Plan (CIP), device alerts, and diagnostic data from the standard Latitude database may be collected and entered into the study database at any time. |
| **Study Duration** | Enrolment is expected to take approximately 18 months. The total study duration with all follow-up data collected will take up to 50 months. |
| **Key Inclusion Criteria** | <u>General Inclusion Criteria:</u><br>1. Subject is aged 20 or above<br>2. Subject is willing and capable of providing informed consent<br>3. Subject is willing and capable of participating in all visits associated with this study at an approved clinical study site and at the intervals defined by this CIP<br>4. Measured Ejection fraction value obtained by echocardiography or equivalent method as SOC:<br>• Device cohorts: within the last 3 months prior to enrolment<br>• Non-device cohort: latest available within the last 12 months prior to enrollment in case there was no documented HF decompensation, MI or revascularization, otherwise within the last 3 months prior to enrollment<br>And 12 lead ECG recording available as SOC:<br>• Device cohorts: pre-implant ECG maximum 45 days before implant; post-implant ECG<br>• Non-device cohort: latest available maximum 12 months prior to enrollment<br>and subject agrees in the data being used for this study |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
|---|---|
| **Key Inclusion Criteria** | Additional Inclusion Criteria for the ICD Cohort:<br>1. De novo ICD system implanted successfully 45 days prior enrollment in subjects with symptomatic HF (NYHA Class II–III), and an LVEF ≤35%<br>2. Subjects are on OMT ≥3 months<br>3. Provided that the subjects are expected to survive substantially longer than one year with good functional status<br>4. Subjects have ischemic heart disease or DCM (dilated cardiomyopathy)<br>5. Subject was implanted with a BSC MRI Conditional System<br>6. 2 to 5 risk factors out of the following prior device implant:<br>• LVEF ≤35%<br>• NYHA Class III or IV<br>• Left bundle branch block (LBBB) with QRS >130 ms or any QRS >150 ms<br>• Renal dysfunction (blood urea nitrogen chronically [BUN] >26 mg/dL / ≥9.28 mmol/L)<br>• Diabetes type I and II<br>• Chronic atrial fibrillation (permanent or persistent according to ESC Guideline 2016[11])<br>• Prior MI<br>• Age >70 years<br>• Smoking today or during last 5 years<br>7. Clinical subject conditions allow programming of defibrillation therapy according to the principals of the MADIT RIT study programming<br>8. Subjects' devices are currently intended to be followed on Latitude system. |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
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| **Key Inclusion Criteria (continued)** | Additional Inclusion Criteria for the CRT-D Cohort:<br>1. De novo CRT-D (BSC device system with IS4 connector and MRI conditionally safe) implanted successfully during the last 45 days prior enrollment in symptomatic subjects with HF<br>2. A: Sinus rhythm and one of the following conditions:<br>• QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT<br>• QRS duration ≥150 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT<br>• QRS duration of 130 to 149 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT<br>or<br>B: CRT-D implanted subjects in atrial fibrillation with LVEF ≤35% in NYHA Class III despite OMT and a QRS duration ≥130 ms<br>3. Subjects have 2 to 5 risk factors out of the following prior to device implant:<br>• LVEF ≤35%<br>• NYHA Class III or IV<br>• LBBB with QRS >130 ms or any QRS >150 ms<br>• Renal dysfunction (chronically BUN >26 mg/dL / ≥9.28 mmol/L)<br>• Diabetes type I and II<br>• Chronic atrial fibrillation (permanent or persistent according to ESC Guideline 2016[11])<br>• Prior MI<br>• Age >70 years<br>• Smoking today or during last 5 years<br>4. Defibrillator therapy will be programmed following MADIT RIT study programming principles (e.g. cutoff rate ≥ 200 bpm or 170 bpm with 60 seconds delayed therapy programming)<br>5. Subjects' devices are currently intended to be followed on Latitude system.<br>Additional Inclusion Criteria for the PM/CRT-P Cohort:<br>1. Subjects with a PM or CRT-P implanted during last 45 days prior enrollment (only BSC PG devices).<br>2. Subjects who are estimated to require right ventricle (RV) pacing >40%<br>3. PM subjects with LVEF ≤50% |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
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| **Key Inclusion Criteria (continued)** | 4. Paced or intrinsic QRS >90 ms, and any determined NYHA Class (symptoms of HF) or any previous HF admission (HF admission comprises the following conditions: admission to hospital because of HF and/or IV therapy for HF and/or upgrade of the PM/CRT-P)<br>5. Subjects' devices are currently intended to be followed on Latitude system.<br><br><u>Additional Inclusion Criteria for the Non-device Cohort (ESC Guideline 2016 Indicated but not implanted)</u><br><br>• Subjects with symptomatic HF (NYHA Class II-III), and an LVEF ≤35%<br>• Subjects are on OMT ≥3 months<br>• Subjects are expected to survive substantially longer than 1 year with good functional status<br>• Subjects have ischemic heart disease or DCM (dilated cardiomyopathy).<br><br>**<u>OR</u>**<br><br>• LBBB with QRS ≥130 ms and LVEF ≤35% despite OMT<br>or<br>• QRS ≥150 ms and non-LBBB QRS morphology and LVEF ≤35% despite OMT<br><br>**<u>AND</u>**<br><br>1. No present or past implanted device ICD, CRT-D, PM, or CRT-P<br>2. 2 to 5 risk factors out of the following:<br>• LVEF ≤35%<br>• NYHA Class III or IV<br>• LBBB with QRS > 130 ms or any QRS >150 ms<br>• Renal dysfunction (chronically BUN >26 mg/dL / ≥9.28 mmol/L)<br>• Diabetes type I and II<br>• Chronic atrial fibrillation (permanent or persistent according to ESC Guideline 2016[11])<br>• Prior MI<br>• Age >70 years<br>• Smoking today or during last 5 years |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
|---|---|
| **Key Exclusion Criteria** | General Exclusion Criteria:<br>1. Subject is enrolled in any other concurrent study without prior written approval from BSC, with the exception of local mandatory governmental registries and observational studies/registries that are not in conflict and do not affect the following:<br>• Schedule of procedures for the HINODE Study (i.e. should not cause additional or missed visits)<br>• HINODE Study outcome<br>• Conduct of the HINODE Study per Good Clinical Practice /International Standard Organization 14155:2011/local regulations as applicable<br>2. Device implant revision is scheduled due to unstable result of an implant <45 days prior enrolment<br>3. Subjects with more than 5 of the following risk factors: LVEF <35%, NYHA Class III or IV, LBBB with QRS > 130 ms or QRS ≥150 ms, renal dysfunction (chronically BUN >26 mg/dL / ≥9.28 mmol/L), diabetes type I and II, chronic atrial fibrillation (permanent or persistent according to ESC Guideline 2016), prior MI, age >70 years, smoking today or during last 5 years<br>4. Subjects with chronic renal disease with chronic BUN ≥50mg/dL or creatinine ≥2.5 mg/dL<br>5. Subjects with coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) within the past three calendar months prior to enrollment<br>6. Subjects with enzyme-positive myocardial infarction within the past three calendar months prior to enrollment<br>7. Subjects who are expected to survive for <1 year with good functional status<br>8. Subject's physician does not allow participation<br>9. Subject is not willing and capable of participating in all testing or visits associated with this clinical study at an approved clinical study center and at the intervals defined by this CIP<br>10. Unwilling to sign the consent for participation<br>11. Women of childbearing potential who are or might be pregnant at the time of study enrolment<br>12. ICD and CRT-D cohorts: implanted with a non-BSC device system. PM/CRT-P cohorts: implanted with a non-BSC PG device. |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
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| **Key Exclusion Criteria (continued)** | Additional Exclusion Criteria for the ICD and CRT-D Cohorts:<br>1. CRT implanted in subjects with a QRS duration <130 ms<br>2. Subjects who have recovered from a ventricular arrhythmia causing hemodynamic instability.<br>3. NYHA Class IV (for ICD subjects only)<br>4. Existing or previously implanted ICD, CRT-P, CRT-D, or pacemaker device system.<br>Additional Exclusion Criteria for the PM/CRT-P Cohort:<br>No additional Exclusion Criteria for the PM/CRT-P Cohort.<br>Additional Exclusion Criteria for the Non-device Cohort (ESC Guideline 2016 Indicated but not implanted):<br>1. Subjects who have recovered from a ventricular arrhythmia causing hemodynamic instability<br>2. Any ICD or CRT-D, PM or CRT-P device implanted at any time prior to enrollment. |
| **Statistical Methods** | |
| **Primary Statistical Hypothesis** | ICD Treated Subjects:<br>Ventricular arrhythmia associated symptoms free-rate from implant through 12 months post implant is greater than the pre-specified performance goal of 85.0%<br>$H_o$: $\pi \leq 85.0\%$<br>$H_A$: $\pi > 85.0\%$<br>CRT-D Treated Subjects:<br>Ventricular arrhythmia associated symptoms free-rate from implant through 12 months post implant is greater than the pre-specified performance goal of 87.0%<br>$H_o$: $\pi \leq 87.0\%$<br>$H_A$: $\pi > 87.0\%$ |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
|---|---|
| **Primary Statistical Hypothesis (continued)** | PM/CRT-P Treated Subjects:<br>All-cause mortality free-rate (survival rate) from implant through 12 months post implant is greater than the pre-specified performance goal of 80.0%<br>$H_o : \pi \leq 80.0\%$<br>$H_A : \pi > 80.0\%$<br>Non-device Subjects (ESC Guideline 2016 Indicated but not implanted)<br>All-cause mortality free-rate (survival rate) from enrolment through 12 months after enrolment is greater than the pre-specified performance goal of 80.0%<br>$H_o: \pi \leq 80.0\%$<br>$H_A: \pi > 80.0\%$ |
| **Statistical Test Method** | **Sample Size Methodology:**<br>• Sample size for each primary endpoint was calculated using exact binomial methods for comparison of a single proportion to a performance goal.<br><br>**Analysis Methods:**<br>• For ICD treated subjects, the ventricular arrhythmia associated symptoms free-rate from implant will be calculated as the proportion of actively enrolled subjects without an appropriately treated ventricular arrhythmia associated symptom through 12 months after implant. The null hypothesis will be rejected and the endpoint considered met if the lower one-sided 97.5% confidence bound for the proportion of subjects with no appropriately treated ventricular arrhythmia associated symptoms is greater than 85.0%.<br>• For CRT-D treated subjects, the ventricular arrhythmia associated symptoms free-rate from implant will be calculated as the proportion of actively enrolled subjects without an appropriately treated ventricular arrhythmia associated symptom through 12 months after implant. The null hypothesis will be rejected and the endpoint considered met if the lower one-sided 97.5% confidence bound for the proportion of subjects with no appropriately treated ventricular arrhythmia associated symptoms is greater than 87.0%. |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
|---|---|
| **Statistical Test Method (continued)** | • The primary endpoints above will be performed for ICD and CRT-D cohorts combined (primary analysis) as well as for ICD and CRT-D treated subjects separately (for descriptive purpose).<br>• For PM/CRT-P treated subjects, the all-cause mortality free-rate (survival rate) from implant will be calculated as the proportion of actively enrolled subjects who are alive 12 months after implant. The null hypothesis will be rejected and the endpoint considered met if the lower one-sided 97.5% confidence bound for the proportion of subjects with no death is greater than 80.0%.<br>• For Non-device subjects (ESC Guideline 2016 Indicated but not implanted), the all-cause mortality free-rate (survival rate) from enrolment will be calculated as the proportion of actively enrolled subjects who are alive 12 months after enrolment. The null hypothesis will be rejected and the endpoint considered met if the lower one-sided 97.5% confidence bound for the proportion of subjects with no death is greater than 80.0%.<br>• Exploratory analyses for ICD and CRT-D Cohorts combined versus Non-Device Cohort (ESC Guideline 2016 Indicated but not implanted): propensity score matching comparison of all-cause mortality rate and composite rate of HF events between pooled cohorts with device (ICD and CRT-D) versus the Non-Device Cohort regarding 7 risk factors at baseline (NYHA Class III or IV, renal dysfunction [chronically BUN >26 mg/dL / ≥9.28 mmol/L], diabetes type I and II, chronic atrial fibrillation [permanent or persisting according to ESC Guideline 2016], prior MI, age >70 years, smoking today or during last 5 years).<br>Further details on analytical methods can be found in Section 12 of the CIP |
| **Sample Size Parameters** | <u>ICD Treated Subjects:</u><br>The minimum required sample size to statistically power the ventricular arrhythmia associated symptoms free-rate through 12 months post implant is 117 subjects. Sample size was calculated assuming a 95.0% ventricular arrhythmia associated symptoms free-rate, a performance goal of 85.0%, one-sided alpha level of 0.025, 90% power, and 20% attrition. |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
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| **Sample Size Parameters (continued)** | Although the final sample size of 117-270 for ICD treated subjects is higher than that required to power the primary endpoint, a sample size of up to 270 ensures that there will be a sufficient number of subjects to evaluate the primary endpoint, as well as provide ample data to characterize the safety, performance and efficacy profiles based on secondary and additional endpoints.<br><br>CRT-D Treated Subjects:<br><br>The minimum required sample size to statistically power the ventricular arrhythmia associated symptoms free-rate through 12 months post implant is 95 subjects. Sample size was calculated assuming a 97.0% ventricular arrhythmia associated symptoms free-rate, a performance goal of 87.0%, one-sided alpha level of 0.025, 90% power, and 20% attrition.<br><br>Although the final adjustable sample size of 95-250 for CRT-D treated subjects is higher than that required to power the primary endpoint of the study arm, a sample size of up to 250 ensures that there will be a sufficient number of subjects to evaluate the primary endpoint, as well as provide ample data in the study arm to characterize the safety, performance and efficacy profiles based on secondary and additional endpoints.<br><br>PM/CRT-P Treated Subjects:<br><br>The minimum required sample size to statistically power the all-cause mortality free-rate (survival rate) through 12 months post implant is 172 subjects. Sample size was calculated assuming a 90.0% all-cause mortality free-rate (survival rate), a performance goal of 80.0%, one-sided alpha level of 0.025, 90% power, and 20% attrition.<br><br>Although the final sample size of 200 for PM/CRT-P treated subjects is higher than that required to power the primary endpoint, a sample size of 200 ensures that there will be a sufficient number of subjects to evaluate the primary endpoint, as well as provide ample data to characterize the safety, performance and efficacy profiles based on secondary and additional endpoints. |

| **H**eart Fa**i**lure I**n**dicati**o**n and Sud**de**n Cardiac Death Prevention Trial Japan **HINODE** | |
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| **Sample Size Parameters (continued)** | Non-device Subjects (ESC Guideline 2016 Indicated but not implanted):<br>The minimum required sample size to statistically power the all-cause mortality free-rate (survival rate) through 12 months after enrolment is 172 subjects. Sample size was calculated assuming a 90.0% all-cause mortality free-rate, a performance goal of 80.0%, one-sided alpha level of 0.025, 90% power, and 20% attrition.<br>The final sample size of 300 for Non-device subjects is higher than that required to power the primary endpoint in order to ensure that there will be a sufficient number of subjects to compare the rate of sudden cardiac death in the non-device cohort with the rate of appropriately treated ventricular arrhythmias or sudden cardiac death in the defibrillator cohort (ICD, CRT-D).<br>In case of low enrollment rates, enrollment may be closed after the statistically required calculated minimum sample size for each cohort. |

# 3. Table of Contents

### 3.1. *Table of Figures*



### 3.2. *Table of Tables*

# 4. Introduction

The prevalence of chronic heart failure (CHF) will rapidly increase in the next decades in many industrialized countries, including Japan[1]. Large cohort studies with CHF patients are useful for risk stratification and determination of preventive measures for the disorder. Large-scale, randomized treatment trials also are needed, especially in Japan, in order to obtain further evidence on prevention of sudden cardiac death (SCD) with defibrillation therapy[2] and to improve the management of patients with CHF.

The present study is intended to evaluate the risk of SCD and heart failure (HF) events in known high risk subject cohorts. Implantation of pacing and defibrillation devices that provide cardiac resynchronization therapy (CRT) is proven to be a highly effective treatment for selected subjects with cardiac arrhythmia and HF. However, the question remains whether study data from the United States (US) and Europe are fully applicable in Japan despite genetic and cultural differences. Implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy-defibrillator (CRT-D) devices for many patients with high risk on SCD have not been studied in a prospective study in Japan. Therefore, this registry study intends to collect clinical data in defined ICD and CRT-D treatment cohorts in a study population with a majority of Japanese subjects so that further knowledge is added to improve medical device treatment options.

An optimized ICD treatment was studied in the Automatic Defibrillator Implantation Trial (MADIT) Reduce Inappropriate Therapy (RIT) trial[3,4] where 1500 subjects from US and Europe have been enrolled in 3 arms. Arm B and Arm C, with a high cut off rate of >200 bpm and with a prolonged delay in therapy at 170 bpm have shown a significant reduction in unnecessary and inappropriate treatment.[4]

The mortality rate in pacemaker cohorts is usually very high and it is the question whether a different device therapy may help selected patient cohorts. The defined cohort in this HINODE study is selecting especially subjects with a heart failure background which have a high incidence of further progression of the disease.[6] It is the question whether those subjects can be identified during de novo implants or during device replacement so that a different device therapy would have the potential to impact the progression of the disease. The selected cohort has at least 3 risk factors which may lead to an increased incidence of Non-sustained ventricular tachycardia (NSVT) or other ventricular arrhythmia. The use of a risk score in a PM population may help to identify subjects who may benefit from CRT-P or CRT-D.

The outlined risk factor MI in the HINODE study is used for subjects with one or more clinically documented, enzyme-positive myocardial infarctions, or clear evidence of pathologic Q waves or generally accepted imaging techniques.

The rate of appropriate first treatments (anti-tachycardia pacing [ATP] or shock) will be considered as treatment of potential life-threatening arrhythmias. The present study will use the MADIT RIT ICD programming for ICD and CRT-D devices and will compare the rate of appropriate treatments in MADIT RIT[4] with the rate observed under the same programming conditions in the present study. The study results will be compared with data from

multicenter automatic defibrillator implantation trials (MADITs) conducted in US and Europe.

In addition to the evaluation of first appropriate treatment, life-threatening ventricular arrhythmias, clinical HF events will be evaluated.

Special attention will be given to known risk markers at enrolment throughout the study so that a risk score may be developed to provide guidance in optimized therapy decisions.

The sample size will provide sufficient data to allow the identification of high risk subgroups, especially in the ICD and pacemaker (PM) cohorts. These data will also allow an assessment of European and US study data being transferable to the Japanese specific environment due to similar clinical observations.

The selected cohort of PM subjects has an expected and unstudied elevated risk of developing increased HF symptoms or may be at risk of SCD. The required home monitoring system will allow early detection of ventricular arrhythmias and may serve as early indicator for left ventricular ejection fraction (LVEF) and QRS evaluation. The same LVEF and QRS evaluations will be associated with HF admissions ('HF admission' comprises the following conditions: admission to hospital because of HF and/or intravenous (IV) therapy of HF and/or upgrade of the PM/CRT-P) so that an unknown need for changed device therapy can be identified. CRT is recommended for subjects with HF with reduced ejection fraction (HFrEF; LVEF: <40%) and QRS >130 ms; ICD therapy is recommended for subjects with LVEF ≤35% especially if this is associated with additional risk factors e.g. prior MI, diabetes type I and II, etc.

In large European registries and European diabetes guidelines, it has been described that diabetic post myocardial infarction (MI) patients with a mid-range LVEF of 40-49% (HFmrEF) have an elevated risk of SCD. Since there are no event data available for Japanese patients, this registry will also include a group of subjects who have combined risk factors of post MI, diabetes type I and II, and an LVEF ≤35% but have not received device treatment to collect baseline data on event rates and disease progression in a study population with a majority of Japanese subjects.

## 5. Device Description

Implanted subjects will receive one of 4 types of Boston Scientific (BSC) devices prior to enrolment in the study:

1. ICD (only MRI conditionally safe systems) + Latitude
2. CRT-D (IS4 connector only, MRI conditionally safe systems) + Latitude
3. PM + Latitude

   or

4. CRT-pacemaker (CRT-P) + Latitude

All device systems are on the market in Japan, and will be implanted per standard of care (SOC) and BSC Instructions for Use (IFU) for the respective devices should be followed.

Neither the devices nor the implant procedure are part of this study. The decision as to which device any subject receives is to be determined by the investigator and is not part of this study.

Device system use will need to follow SOC, devices IFUs and must follow CIP programming requirements.

The programming of the devices is to be documented in the subject's electronic Case Report Form (eCRF) as part of the enrolment criteria (Section 9). As part of the programming, all subjects must be intended to be connected to the Latitude system.

If patients cannot be connected to Latitude more than 6 months after enrolment, a deviation needs to be completed and a reason needs to be given. In addition, endpoint related data can be uploaded into the database by the site (e.g. electrogram (EGM) for ventricular arrhythmias).

A device deficiency reporting might need to be completed.

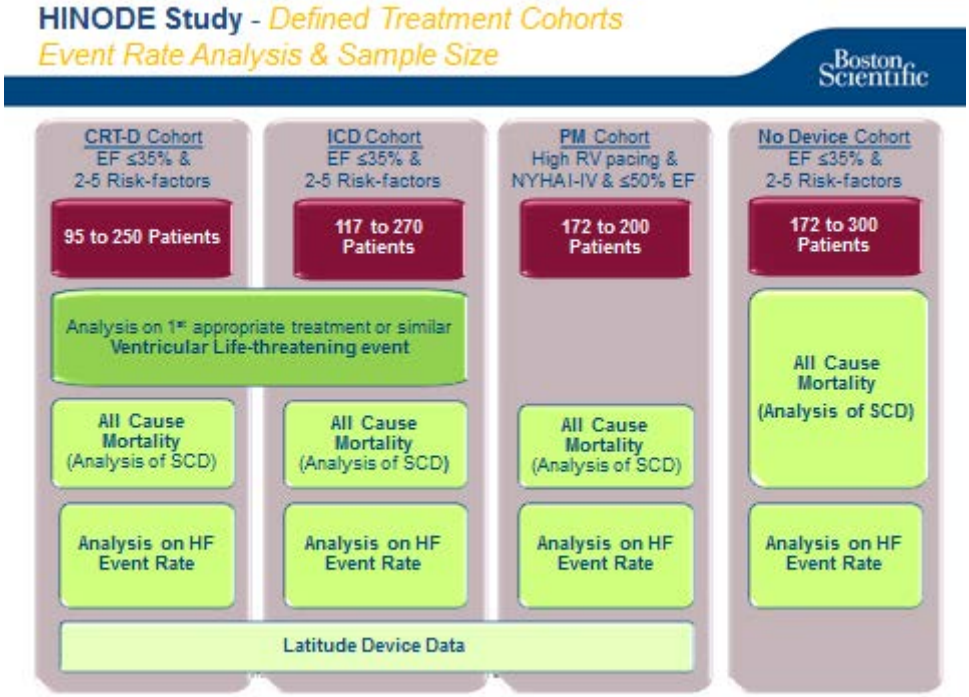
## 6. Study Objectives

The purpose of this cohort therapy study is to collect clinical event and outcome data in a study population with a majority of Japanese subjects on SCD, HF events, and appropriately treated ventricular adverse events in predefined subject cohorts. These event rates will be compared with available data mainly from Europe and the United States. It is the intention to add evidence in Defibrillator treatment and treatment with CRT-D devices.

**Selected Subject Cohorts:**

1. Selected subject cohort with of criteria for SCD (without spontaneous prior ventricular sustained arrhythmia) and de novo implanted Defibrillator device treatment (ICD).
2. Selected subject cohort with criteria for SCD and widely accepted standard CRT indication who received a de novo implanted CRT-D device treatment.
3. Selected subject cohort who are clinically expected to require >40% right ventricular pacing with an LVEF ≤50%, any determined New York Heart Association (NYHA) Class, and receiving PM or CRT-P therapy despite previous device history (de novo, box changes, system revisions or upgrades).
4. Selected subject cohort with criteria for SCD fulfilling European Society of Cardiology (ESC) ICD or CRT-D therapy guidelines (2016) with an LVEF ≤35%, having 2 to 5 predefined risk factors but do not have or have had a cardiac implanted device ICD, CRT-D, PM, or CRT-P.

**Figure 3.2-1: HINODE Sample Size**




# 7. Study Endpoints

## 7.1. *Primary Endpoints*

**Defibrillator Cohort (including ICD and CRT-D Cohorts):**

- Composite rate of first appropriately treated ventricular arrhythmia (by ATP or shock) or life-threatening symptoms associated to ventricular arrhythmia (defined as hemodynamic instability which requires treatment), whichever comes first under MADIT Arm B or C programming conditions in a study population with a majority of Japanese subjects

**PM/CRT-P Cohort:**

- All-cause mortality in subjects with a maximum of 3 risk factors (analyzed for MADIT II data[7])

**Non-device Cohort (ESC Guideline 2016 Indicated but not implanted subjects):**

- All-cause mortality in the subject cohort with 2 to 5 predefined SCD driving risk factors

## 7.2. *Secondary Endpoints*

- All-cause mortality rate for subjects implanted with ICD/CRT-D (= ICD cohort plus CRT-D cohort = defibrillator cohort)

- Composite rate of HF events in ICD, CRT-D, and PM/CRT-P cohorts, which require IV treatment, HF related hospitalization, or led to HF death
- Therapeutic sustainability at 1 year in ICD, CRT-D, and PM/CRT-P cohorts, defined as free of qualified serious adverse device events (SADEs) post successful implantation in comparison to data from MADIT CRT, MADIT RIT, Optimind and Rally X4 studies

  Examples for qualified SADEs: re-implant procedure, required invasive procedure related to the device system, pacing exit block, all-cause infection, and death due to therapy failure.
- Comparison of rate of sudden cardiac death in the non-device cohort with the rate of appropriately treated ventricular arrhythmias or sudden cardiac death in subjects implanted with ICD-CRT-D (defibrillator cohort)

### 7.3. *Additional Endpoints*

The ancillary assessments will include:

- Subject medical assessment collected pre-enrolment (post implant) and at Close-out:
  - NYHA functional classification
  - LVEF
  - QRS duration
  - Physician's judgment on therapy outcome
  - Body mass index (BMI)
  - Diabetes mellitus type I and II
- Cross-over in device therapies
- Cause of death (SCD, Cardiac related, other reasons, unknown)
- Incidence and development of Atrial fibrillation in different patient cohorts during the cause of the study
- Impact of gender and age
- Magnetic resonance imaging (MRI) observations in association with reported clinical events
- Analysis of device data coming from Latitude data reports
- Health care utilization under Latitude
- Standard biomarkers for heart failure and other morbidities

## 8. Study Design

This is a prospective, non-randomized, multicenter, multi-cohort clinical outcome registry study to evaluate SOC. Neither the devices nor the implant procedure are part of this study.

Subjects will be implanted with the device per SOC within 0 to 45 days prior to enrolment in this study.

The decision as to which subject gets which device is made by the implanting physician and is not part of this study. In addition, subjects with specified risk factors (Section 9.2.5) and with no device will also be enrolled.

Devices must be programmed (considered a non-invasive procedure and SOC operation of the device) per protocol and according to the respective BSC IFU, and must be connected to the Latitude system for the duration of the trial. If this is not possible, a deviation will be recorded.

The Latitude database will be reviewed by the BSC Latitude team on regular basis for all study subjects and inconsistencies will be discussed with the study data management.

### 8.1. *Scale and Duration*

As soon as a minimum of 556 eligible subjects are entered into the study database, the closure of enrolment can begin. After closure of enrolment, sites must obtain approval from the sponsor or the sponsor's delegated representative for all remaining subjects who are consented but who are not yet enrolled into the study database. The maximum number of followed study subjects is 950. Since this is an event dependent analysis, the total number of subjects might be considerably lowered in all different cohorts, depending on actual number of events. It would allow for an early closure of the study enrollment.

Approximately 40 investigational sites in Japan will be included. If a site does not enroll a sub

ject within a 3-month time period, the site may be closed for enrolment and replaced at the discretion of the sponsor.

Enrolment is expected to take approximately 18 months. The total study duration with all follow-up data collected will take up to 50 months. All subjects will remain in the study until the last subject completes his/her last visit. The maximum study duration for any subject will be 34 months (first subject first visit [FSFV] to last subject last visit [LSLV]); the minimum study duration will be the time of enrolment of the last subject enrolled (last subject first visit [LSFV] to LSLV) and is expected to be 16 months. Study completion and data analysis are anticipated in 2020.

**Figure 8.1-1: HINODE Study Design**

| TIME AXIS | PERIOD OF ENROLMENT OF SUBJECTS | | | | 1-YEAR FOLLOW-UP FOR ALL SUBJECTS ENROLLED | | CLOSE OUT VISIT |
|---|---|---|---|---|---|---|---|
| | 6 months | 6 months | 6 months | 6 months | 6 months | 6 months | |
| **FIRST SUBJECT** | Device implant or no device* | EV Day 0 | 1st 6-monthly visit | | | 5th 6-monthly visit | 2 months before** LSLV until 4 months LSLV |
| **FURTHER SUBJECTS** | Device implant or no device* | EV Day 0 | 1st 6-monthly visit | | | 4th 6-monthly visit | |
| **FURTHER SUBJECTS** | | Device implant or no device* | EV Day 0 | 1st | | 3rd 6-monthly visit | |
| **LAST SUBJECT** | | | Device implant or no device* | | EV Day 0 | 2nd 6-monthly visit = COV = LSLV *** | |

* device is BSC device, either ICD or CRT-D or CRT-P or PM; no device = no device implanted, but indicated according to ESC Guideline 2016
** if COV is done within 2 months before LSLV, the COV replaces the last 6-monthly visit
*** LSLV will be conducted within 12 months + 60 days post enrollment

Abbreviations: COV = Close out visit; EV = Enrolment visit; LSLV = last subject's last visit

### 8.2. *Treatment Assignment*

This is a non-randomized prospective registry study to collect clinical data in the real-life setting in Japan. Enrolled subjects will include those who have been implanted with BSC pacing or defibrillation devices as well as post MI subjects with preserved EF and no device treatment. Subjects will be assigned to one of the 3 following Subject Cohorts according to device implanted:

1. ICD: 117 to 270 subjects
2. CRT-D: 95 to 250 subjects
3. PM/CRT-P: 172 to 200 subjects

A fourth cohort of non-implanted subjects will also be enrolled:

4. Non-device172 to 300 subjects
   (ESC Guideline 2016 Indicated but not implanted)

### 8.3. *Justification for the Study Design*

The primary objective of this study is to collect clinical event data for selected patient cohorts who are at risk of ventricular tachy-arrhythmias and HF events. In order to obtain "real world" data, the study inclusion/exclusion criteria and follow-up schedule have been written generally enough to allow for study site specific SOC which should accurately capture the clinical data in a "standard" clinical setting. Additionally, by requiring study sites to follow their specific SOC, risk to the subject is minimized because the treatment received by the subject will be similar to the treatment the subject would receive if not participating in the study.

Requiring that all implanted devices be programmed per protocol and the respective BSC IFU, all devices must be intended to be connected to the Latitude system during study duration.

The determination of sample size is provided in Section 12.1.6.

## 9. Subject Selection

### 9.1. *Study Population and Eligibility*

Inclusion and exclusion criteria are listed in Sections 9.2 and 9.3 below.

Subjects who are enrolled but later determined to not fulfil all inclusion and exclusion criteria at the time of enrolment will be considered to have incurred a Clinical Investigation Plan (CIP) deviation. These subjects will be withdrawn from the study immediately and will not be included in the planned data analysis.

### 9.2. *Inclusion Criteria*

All inclusion criteria apply only at the time of enrolment into the study.

If a subject's medical conditions change after inclusion into the study so that one or several of the general inclusion criteria and inclusion criteria of the pertinent cohort are no longer met, the subject remains in the study.

If it turns out after enrolment into the study that one or several of the general inclusion criteria and inclusion criteria of the pertinent cohort were violated at the time of enrolment into the study, the study has to be ended in this subject.

### 9.2.1. General Inclusion Criteria

Subjects who meet all of the following criteria (Table 9.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3) is met.

**Table 9.2-1: General Inclusion Criteria**

1. Subject is aged 20 or above
2. Subject is willing and capable of providing informed consent
3. Subject is willing and capable of participating in all visits associated with this study at an approved clinical study site and at the intervals defined by this CIP
4. Measured Ejection fraction value obtained by echocardiography or equivalent method as SOC:
    - Device cohorts: within the last 3 months prior to enrolment
    - Non-device cohort: latest available within the last 12 months prior to enrollment in case there was no documented HF decompensation, MI or revascularization, otherwise within the last 3 months prior to enrollment

   And 12 lead ECG recording available as SOC:
    - Device cohorts: pre-implant ECG maximum 45 days before implant; post-implant ECG
    - Non-device cohort: latest available maximum 12 months prior to enrollment

   and subject agrees in the data being used for this study.

Abbreviations: CIP = Clinical Investigation Plan

### 9.2.2. Inclusion Criteria for the ICD Cohort

Subjects enrolled in the ICD group must also meet all of the following inclusion criteria (in addition to the General Inclusion Criteria):

**Table 9.2-2: Inclusion Criteria for the ICD Cohort**

1. De novo ICD system implanted successfully 45 days prior enrollment in subjects with symptomatic HF (NYHA Class II–III), and an LVEF ≤35%
2. Subjects are on OMT ≥3 months
3. Provided that the subjects are expected to survive substantially longer than one year with good functional status
4. Subjects have ischemic heart disease or DCM (dilated cardiomyopathy)
5. Subject was implanted with a BSC MRI Conditional System
6. Subjects have 2 to 5 risk factors out of the following prior device implant:
   - LVEF ≤35%
   - NYHA Class III or IV
   - Left bundle branch block (LBBB) with QRS >130 ms or any QRS >150 ms
   - Renal dysfunction (blood urea nitrogen chronically [BUN] >26 mg/dL)
   - Diabetes type I and II
   - Chronic atrial fibrillation (permanent or persistent according to ESC Guideline 2016[11])
   - Prior MI
   - Age >70 years
   - Smoking today or during last 5 years
7. Clinical subject conditions allow programming of defibrillation therapy according to the principals of the MADIT RIT study programming
8. Subjects' devices are currently intended to be followed on Latitude system

Abbreviations: BSC = Boston Scientific; BUN = blood urea nitrogen; ESC = European Society of Cardiology; HF = heart failure; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; NYHA = New York Heart Association; OMT = optimal medical therapy

### 9.2.3. Inclusion Criteria for the CRT-D Cohort

Subjects enrolled in the CRT-D Cohort of the study must also meet all of the following inclusion criteria (in addition to the General Inclusion Criteria):

**Table 9.2-3: Inclusion Criteria for the CRT-D Cohort**

1. De novo CRT-D (BSC device system with IS4 connector and MRI conditionally safe) implanted successfully during last 45 days prior enrollment in symptomatic subjects with HF
2. A: Sinus rhythm and one of the following conditions:
   - QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite optimal medical therapy (OMT)
   - QRS duration ≥150 ms and non-LBBB QRS morphology and LVEF ≤35% despite OMT
   - QRS duration of 130 to 149 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT

   or

   B: CRT-D implanted subjects in atrial fibrillation with LVEF ≤35% in NYHA Class III despite OMT and a QRS duration ≥130 ms
3. Subjects have 2 to 5 risk factors out of the following prior to device implant:
   - LVEF ≤35%
   - NYHA Class III or IV
   - LBBB with QRS >130 ms or any QRS >150 ms
   - Renal dysfunction (chronically BUN >26 mg/dL / >9.28 mmol/L)
   - Diabetes type I and II
   - Chronic atrial fibrillation (permanent or persistent according to ESC Guideline 2016[11])
   - Prior MI
   - Age >70 years
   - Smoking today or during last 5 years
4. ICD Defibrillation therapy will be programmed following MADIT RIT study programming principles (e.g. cut off rate ≥200 bpm or 170 bpm with 60 seconds delayed therapy programming)
5. Subjects devices are currently intended to be followed on Latitude system.

Abbreviations: BSC = Boston Scientific; BUN = blood urea nitrogen; CRT-D = cardiac resynchronization therapy-defibrillator; ESC = European Society of Cardiology; HF = heart failure; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; NYHA = New York Heart Association; OMT = optimal medical therapy

### 9.2.4. Inclusion Criteria for the PM/CRT-P Cohort

Subjects enrolled in the PM/CRT-P cohort must also meet all of the following inclusion criteria (in addition to the General Inclusion Criteria):

**Table 9.2-4: Inclusion Criteria for the PM/CRT-P Cohort**

| |
|---|
| 1. Subjects with a PM or CRT-P implanted during last 45 days prior enrollment (only BSC PG devices)<br>2. Subjects who are estimated to require right ventricle (RV) pacing >40%<br>3. PM subjects with LVEF ≤50%<br>4. Paced or intrinsic QRS >90 ms, and any determined NYHA Class (symptoms of HF) or any previous HF admission (HF admission comprises the following conditions: admission to hospital because of HF and/or IV therapy for HF and/or upgrade of the PM/CRT-P)<br>5. Subjects' devices are currently intended to be followed on Latitude system. |

Abbreviations: BSC = Boston Scientific; CRT-P = cardiac resynchronization therapy-pacemaker; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PM = pacemaker; RV = right ventricle

### 9.2.5. Inclusion Criteria for the Non-device Cohort (ESC Guideline 2016 Indicated but not implanted)

Subjects enrolled in the Non-device cohort (ESC Guideline 2016 indicated but not implanted) must also meet all of the following inclusion criteria (in addition to the General Inclusion Criteria):

**Table 9.2-5: Inclusion Criteria for the Non-device Cohort (ESC Guideline 2016 Indicated but not implanted)**

- Subjects with symptomatic HF (NYHA Class II-III), and an LVEF ≤35%
- Subjects are on OMT ≥3 months
- Subjects are expected to survive substantially longer than 1 year with good functional status
- Subjects have ischemic heart disease or DCM (dilated cardiomyopathy)

**OR**

- LBBB QRS (≥130 ms) morphology and with LVEF ≤35% despite OMT

or

- QRS duration ≥150 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT

**AND**

1. No present or past implant device ICD, CRT-D, PM, or CRT-P
2. 2 to 5 risk factors out of the following:
   - LVEF ≤35%
   - NYHA Class III or IV
   - LBBB with QRS >130 ms or any QRS >150 ms
   - Renal dysfunction (chronically BUN >26 mg/dL / >9.28 mmol/L)
   - Diabetes type I and II
   - Chronic atrial fibrillation (permanent or persistent according to ESC Guideline 2016[11])
   - Prior MI
   - Age >70 years
   - Smoking today or during last 5 years.

Abbreviations: BSC = Boston Scientific; BUN = blood urea nitrogen; CRT-D = cardiac resynchronization therapy-defibrillator; ESC = European Society of Cardiology; HF = heart failure; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; OMT = optimal medical therapy; PM = pacemaker

## 9.3. *Exclusion Criteria*

All exclusion criteria apply only at the time of enrolment into the study.

If a subject's medical conditions change after inclusion into the study so that one or several of the general exclusion criteria and exclusion criteria of the pertinent cohort are no longer met, the subject remains in the study.

If it turns out after enrolment into the study that one or several of the general exclusion criteria and exclusion criteria of the pertinent cohort were violated at the time of enrolment into the study, the study has to be ended in this subject.

### 9.3.1. General Exclusion Criteria

Subjects who meet any one of the following criteria (Table 9.3-1) are not allowed to be included in this clinical study. The exclusion criteria apply only at the time of enrolment into the study.

**Table 9.3-1: General Exclusion Criteria**

1. Subject is enrolled in any other concurrent study without prior written approval from BSC, with the exception of local mandatory governmental registries and observational studies/registries that are not in conflict and do not affect the following:
   - Schedule of procedures for the HINODE Study (i.e. should not cause additional or missed visits)
   - HINODE Study outcome
   - Conduct of the HINODE Study per Good Clinical Practice (GCP)/ International Standard Organization (ISO) 14155:2011/local regulations as applicable
2. Device implant revision is scheduled due to unstable result of an implant <45 days prior enrolment
3. Subjects with more than 5 of the following risk factors: LVEF ≤35%, NYHA Class III or IV, LBBB with QRS 130 ms or QRS >150 ms, renal dysfunction (chronically BUN >26 mg/dL / >9.28 mmol/L), diabetes type I and II, chronic atrial fibrillation (permanent or persistent according to ESC Guideline 2016[11]), prior MI, age >70 years, smoking today or during last 5 years
4. Subjects with chronic renal disease with chronic BUN ≥ 50mg/dL or creatinine ≥ 2.5 mg/dL
5. Subjects with coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) within the past three calendar months prior to enrollment
6. Subjects with enzyme-positive myocardial infarction within the past three calendar months prior to enrollment
7. Subjects who are expected to survive for <1 year with good functional status
8. Subject's physician does not allow participation
9. Subject is not willing and capable of participating in all testing or visits associated with this clinical study at an approved clinical study center and at the intervals defined by this CIP
10. Unwilling to sign the consent for participation
11. Women of childbearing potential who are or might be pregnant at the time of study enrolment
12. ICD and CRT-D cohorts: implanted with a non-BSC device system. PM/CRT-P cohorts: implanted with a non-BSC PG device.

Abbreviations: BSC = Boston Scientific; BUN = blood urea nitrogen; CIP = Clinical Investigation Plan; ESC = European Society of Cardiology; GCP = Good Clinical Practice; HF = heart failure; ISO = International Standard Organization; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association

### 9.3.2. Exclusion Criteria for the ICD and CRT-D Cohorts

Subjects who meet any one of the following criteria (Table 9.3-2) will be excluded from the ICD and CRT-D cohorts of the study.

**Table 9.3-2: Exclusion Criteria for the ICD and CRT-D Cohorts**

| |
|---|
| 1. CRT implanted in subjects with a QRS duration <130 ms<br>2. Subjects who have recovered from a ventricular arrhythmia causing hemodynamic instability<br>3. Subjects with NYHA Class IV (for ICD subjects)<br>4. Existing or previously implanted ICD, CRT-P, CRT-D, or pacemaker device system. |

Abbreviations: BSC = Boston Scientific; CRT = cardiac resynchronization therapy, CRT-D = cardiac resynchronization therapy-defibrillator; ICD = implantable cardioverter-defibrillator

### 9.3.3. Exclusion Criteria for the PM/CRT-P Cohort

No additional Exclusion Criteria for the PM/CRT-P Cohort.

### 9.3.4. Exclusion Criteria for the Non-device Cohort (ESC Guideline 2016 Indicated but not implanted)

Subjects who meet any one of the following criteria (Table 9.3-3) will be excluded from the Non-device cohort (ESC Guideline 2016 indicated but not implanted) of the study.

**Table 9.3-3: Exclusion Criteria for the Non-device Cohort (ESC Guideline 2016 Indicated but not implanted)**

| |
|---|
| 1. Subjects who have recovered from a ventricular arrhythmia causing hemodynamic instability<br>2. Subject with any ICD or CRT-D, PM or CRT-P device implanted at any time prior to enrollment. |

Abbreviations: CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; ICD = implantable cardioverter-defibrillator; PM = pacemaker

## 10. Subject Accountability

### 10.1. *Point of Enrolment*

Subjects will only be enrolled in this registry study if they meet all eligibility criteria and provide written informed consent. If a subject is found not to meet all applicable eligibility criteria, the subject will be withdrawn from the study; any points of ineligibility must be clearly documented in the enrolment/screening log. These subjects will be considered

consent ineligible as discussed in Section 10.3, and will not count towards the enrolment ceiling. Any subject that signs consent and meets all inclusion criteria and does not meet any Exclusion Criteria will be enrolled in the study. Any reportable events, as defined in Section 20 of this CIP, must be collected after written informed consent is obtained.

Subjects enrolled under protocol version C deviating from eligibility criteria of protocol version D will be withdrawn from the study. Other subjects previously not meeting eligibility criteria of protocol version C, but now meeting eligibility criteria of protocol version D, will be accepted under protocol version D and no protocol deviation will need to be documented in the eCRF.

### 10.2. *Withdrawal*

All subjects enrolled in this registry study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the study, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

All applicable eCRFs should be completed up to the point of subject withdrawal. Subjects who are "lost-to-follow-up" should have 3 documented failed phone call attempts to contact the subject as well as a certified letter sent to the subject without a response prior to study withdrawal or termination. A death note will need to be provided together with the serious adverse event (SAE) event description on the Adverse Event (AE) form. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open AEs should be closed or documented as chronic or continuing at the end of the study. Data collected up to the point of subject withdrawal may be used. A Study Withdrawal eCRF page should be completed at this time. A retrospective cancelling of subject data collection should be expressed explicitly by the subject so that all data can be removed from the database.

### 10.3. *Subject Status and Classification*

Consent ineligible subject
A study subject who has signed informed consent but is found to not meet eligibility criteria will be considered a consent ineligible subject and will not count towards the enrolment ceiling. There are no follow-up or AE reporting requirements for consent ineligible subjects. The original signed informed consent must be maintained in the center's administrative file as original or e-copy as part of the hospital patient chart.

Active enrolled subject
A study subject who meets the eligibility criteria as per Section 9.2 and Section 9.3 and has signed and dated the subject informed consent form (ICF) is considered actively enrolled in the study. These subjects are followed in accordance with the CIP follow-up schedule and included in the foreseen study analysis. The original signed subject ICF and any applicable documentation must be maintained in the center's subject paper or electronic file. All applicable electronic Case Report Form (eCRFs) per the CIP must be completed.

### 10.4. *Enrolment Controls*

Centers are allowed to enroll up to 20% of subjects in each of the 4 defined Subject Cohorts. This translates into the following allowed maximum subject numbers per center:

- ICD:23 to 54 subjects*
- CRT-D: 19 to 50 subjects*
- PM/CRT-P:34 to 40 subjects
- Non-device:34 to 60 subjects
  (ESC Guideline 2016 Indicated but not implanted)

* Variable; depending on the total number of enrolled subjects in this study cohort.

If a center wishes to exceed these limits, the center must obtain prior approval from the sponsor or sponsor's delegated representative.

As soon as a minimum of 556 eligible subjects are entered into the study database, the closure of enrolment can begin. All sites will be informed that enrolment has closed. After closure of enrolment has been communicated, sites must obtain approval from the sponsor or the sponsor's delegated representative for all remaining subjects who are consented but who are not yet enrolled into the study database.

A maximum of 950 subjects will be allowed to be followed and entered into the study database.

## 11. Study Methods

### 11.1. *Data Collection*

Details for data collection are shown in Table 11.1-1. Data collection will take place at the following time points:

- Enrolment and Consenting Clinic Visit (Day 0, 0 to 45 days post implant procedure, alternative minimum > 3months post MI, PCI, or CABG required). The date of signature on the informed consent form is the time point of enrolment.
- Six-monthly Visit (180 ± 60 days post enrolment and multiplies until Close-out Visit) (required)
- Re-implant or new device implant post enrolment (optional)
- Interim Visit and Event Report (SAE/SADE related clinical care visit) (Following study site specific SOC, optional)
- Close-out Clinic Visit (see table 8.1-1) (required)

All clinic visits that occur outside the specified protocol visit window will be classified as "Unscheduled CIP Visits". Unscheduled visits triggered by a specific event (e.g. adverse event, Latitude alert, patient request etc.) and not by standard routine control (e.g. device check-up standard by the institution, wound check, standard echo or ECG, blood analysis etc.) must be documented.

CIP defined visits that occur outside the specified visit window will be documented as a CIP deviation.

All data collected according to the Data Collection Requirements (Table 11.1-1) and specified in Sections 11.2 to 11.9 are to be appropriately noted in the eCRF.

**Table 11.1-1: Data Collection Requirements**

| Procedure/Assessment | Enrolment and Consenting Clinic Visit Day 0 (required) (0 to 45 days post implant procedure, or minimum ≥3 months post MI, PCI, or CABG) | Follow-Up Visits | | | |
|---|---|---|---|---|---|
| | | 6-monthly Visit (required) (180 ± 60 days post enrolment and multiplies until Close-out Visit) | Re-implant or New Device Implant post Enrolment (optional) | Interim/ Unscheduled Visit and Event Report (optional) (SAE/SADE related clinical care visit) | Close-out Clinic Visit (required) (see figure 8.1-1) |
| **Informed consent form, including informed consent signature and date** | X | -- | -- | -- | -- |
| **Inclusion criteria / exclusion criteria** | X | -- | -- | -- | -- |
| **Demographic data** | X | -- | -- | -- | -- |
| **Clinical assessment** | X | -- | X | -- | X |
| **Medical history/co-morbidities** | X | -- | X | -- | -- |
| **LVEF, intrinsic or paced** | X | SOC | SOC | -- | SOC |
| **QRS, intrinsic** | X | -- | -- | -- | -- |
| **QRS, intrinsic or paced** | -- | -- | -- | -- | X |
| **Current concomitant medications** | X | -- | X | -- | X |
| **Documentation of implanted devices** | X | -- | X | -- | -- |
| **ECG recording pre-implant upload** | SOC | -- | SOC | -- | -- |
| **ECG recording post implant (paced) upload** | SOC | | SOC | -- | SOC |
| **Echocardiography data collection** | SOC | SOC | SOC | -- | SOC |
| **Device assessment/Interrogation (for devices)** | SOC | SOC | SOC | -- | SOC |
| **Standard Biomarkers for heart failure+ other** | SOC | -- | -- | -- | SOC |
| **Adverse events assessment review** | -- | X | X | X | X |
| **Adverse events reporting (SAE, SADE, ADE, DD information)** | X | X | X | X | X |
| **Latitude device data collection (for subjects implanted with a device)** | X | X | X | X | X |

| Procedure/Assessment | Enrolment and Consenting Clinic Visit Day 0 (required) (0 to 45 days post implant procedure, or minimum ≥3 months post MI, PCI, or CABG) | Follow-Up Visits | | | |
|---|---|---|---|---|---|
| | | 6-monthly Visit (required) (180 ± 60 days post enrolment and multiplies until Close-out Visit) | Re-implant or New Device Implant post Enrolment (optional) | Interim/ Unscheduled Visit and Event Report (optional) (SAE/SADE related clinical care visit) | Close-out Clinic Visit (required) (see figure 8.1-1) |
| **MRI scan information** | SOC | SOC | SOC | SOC | SOC |
| **Physician's judgment on therapy status / outcome / CRT therapy delivery / defibrillator therapy** | X | X | X | -- | X |
| **Risk factor assessment** | X | X | X | X | X |
| **Protocol deviations** | X | X | X | X | X |

SOC = according to standard of care; X = required; -- = not required

Abbreviations: ADE = adverse device effect; CRT = cardiac resynchronization therapy; DD = device deficiency; ECG = electrocardiogram; LAT = Latitude reporting system; LSLV = last subject last visit; LVEF = Left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; NYHA = New York Heart Association; SADE = serious adverse device effect; SAE = serious adverse events; SOC = required if center's standard of care; X = required; -- = not required.

### 11.2. *Study Candidate Screening*

After approval by the investigator's Ethics Committee (EC) and the sponsor or delegated representative, the investigator will follow SOC practices to screen subjects for inclusion in the study.

### 11.3. *Informed Consent*

During the Enrolment and Consenting Visit (Section 11.4), a qualified center representative will review the consent with a potential subject. The subject will be encouraged to ask any questions about the study. All questions from the subject should be addressed prior to the subject signing the informed consent. If the subject signs the informed consent, a signed copy should be provided to the subject and the original should be filed in the electronic or paper medical records. Documentation of the consent process by the person obtaining consent should be filed in the subject study file. No study-specific data collection of any procedure should be conducted prior to consent.

### 11.4. *Enrolment and Consenting Visit (Day 0, 0 to 45 days post implant procedure, alternative >90 days post MI)*

Prior to initiating any study procedures, the investigator must ensure that appropriate informed consent has been signed and dated (Section 21). Subjects will sign and date the ICF post successful implant or minimum 3 months post MI, PCI, or CABG.

Subjects who meet all of the entry criteria and consent to the evaluation are eligible. The enrolment for this registry will occur up to 45 calendar days after the device system implantation.

Subjects are considered enrolled after they have met all inclusion criteria, none of the exclusion criteria, and provided written informed consent in accordance with applicable regulatory agency and EC requirements.

The data collection at enrolment includes: demographic data, clinical assessment, medical history and co-morbidities, subject information and medical history; subject status and clinical assessment per SOC; and details on previously/currently implanted devices.

<u>Subject information and medical history</u>

- **Demographic data:** age at time of consent; gender.
- **Clinical assessment**: weight, height, BMI, blood pressure, NYHA Class.
- **Medical history / co-morbidities:**
    - **Subject etiology:** ischemic cardiomyopathy; idiopathic cardiomyopathy; valvular cardiomyopathy; hypertrophic cardiomyopathy; congenital heart disease; infiltrative disease; neuromuscular disease (including myotonic dystrophy and Kearns-Sayre syndrome).

- **Associated diseases/risk factors:** previous MI; previous hospitalization for HF; hypertension; diabetes type I and II; renal disease (BUN); chronic pulmonary disease; smoking in the last 5 years, peripheral artery disease; other known malignancies (tumor, lymphoma or leukemia); other chronic diseases.
- **Additional rhythm disease:** information will be collected on additional relevant rhythm diseases: AV block; sinus node dysfunction; paroxysmal, chronic, persistent atrial fibrillation; chronotropic incompetence.
- **Other subject history:** previous stroke; shock; previous ablation (AV node, atrial fibrillation or atrial flutter).

- **LVEF:** measured or estimated within the last 12 months and documented in the subject's medical file: fully preserved (≥50%); partially preserved (40%-49%); reduced (<40%).
- **QRS:** intrinsic
- **Current/concomitant cardiac medication:** documentation of the following current/concomitant medication classes being administered: Angiotensin Converting Enzyme (ACE)-inhibitor/Angiotensin II (ATII) receptor antagonist; antiarrhythmic; anticoagulant; antiplatelet; Aldosterone-antagonist; beta-blocker; Digitalis; diuretics; statins; calcium antagonists.

Documentation of implanted devices

- **ICD, CRT-D, PM/CRT-P, etc. data**: Implant date, number of days implanted, model, serial number
- **Pacing lead data**: cardiac chamber (atrial and ventricular), number of days implanted and lead model (serial number) and manufacturer

Some subjects received a device system for the first time whereas others received a replacement procedure of existing systems (usually pulse generator due to battery depletion but may also include lead extractions due to lead failure or other reasons for system component replacement). Data (implant date, number of years implanted, model and manufacturer) for previous device systems will also be collected.

Defibrillator therapy for all ICD and CRT-D devices in the protocol must be programmed according to the specifications provided in Table 11.4-1, Table 11.4-2 and Table 11.4-3, respectively.

Any deviation from protocol requirements for medical reasons will need to be documented as an adverse event and as a deviation from the protocol. The programming is considered non-invasive; specifications are provided to ensure that the devices are operated per BSC IFU. Any programming not per the specifications below will be considered a CIP violation.

**Table 11.4-1: Programming Requirements for High Rate Cutoff**

| Parameters | Programming |
|---|---|
| Ventricular Tachy Therapy Zones | 2 and one optional high rate zone |
| Zone 1 (VT) Rate Cutoff | 170 bpm |
| Zone 1 (VT) Zone Rate Therapy | Monitor Only (No Therapy) |
| Zone 2 (VF) Zone Rate Cutoff | 200 bpm |
| Zone 2 (VF) Zone Duration | 2.5 seconds or longer |
| Zone 2 (VF) Zone Therapy | Defibrillator therapy (ATP (optional) + Shock) |
| Zone 3 (VF) | >200 bpm<br>Optional programming for all parameters |

**Table 11.4-2: Programming Requirements for Long Delay**

| Parameters | Programming |
|---|---|
| Ventricular Tachy Therapy Zones | 3 |
| Zone 1 (VT-1) Zone Rate Cutoff | 170 bpm |
| Zone 1 (VT-1) Zone Duration | 60 seconds |
| Rhythm Detection Enhancements (Rhythm ID): | ON; Program Passive and Active Methods ON with Fallback LRL |
| AF Threshold | 170 bpm |
| Stability | 20 ms |
| Post-Shock Detection: | ON |
| SRD | OFF |
| Zone 1 (VT-1) Zone Therapy | Defibrillator therapy (ATP (optional) + Shock) |
| Redetection Duration | Nominal |
| Zone 2 (VT) Zone Rate Cutoff | 200 bpm |
| Zone 2 (VT) Zone Duration | 12 seconds |
| Rhythm Detection Enhancements (Rhythm ID): | ON, Same as VT-1 Zone |
| Zone 2 (VT) Zone Therapy | Defibrillator therapy (Shock + ATP (Optional)) |
| Redetection Duration | Nominal |
| Zone 3 (VF) Zone Rate Cutoff | 250 bpm |

**Table 11.4-2: Programming Requirements for Long Delay**

| Parameters | Programming |
|---|---|
| Zone 3 (VF) Zone Duration | 2.5 seconds |
| Zone 3 (VF) Zone Therapy | Defibrillator therapy (ATP (optional) or Shock) |

Other parameters may be programmed following physician's discretion

**Table 11.4-3: ICD Programming Option 3 (if applicable for a specific device)**

| | |
|---|---|
| Conditional Shock Zone | 200 bpm |
| Shock Zone | 250 bpm |

Baseline subject status and clinical assessment data collection from if performed as standard of care

All uploaded data must be anonymous and de-identified to assure data confidentiality

- **12-lead ECG recording pre and post implant and at close-out (data collection and document upload in e.g. pdf format) as SOC**: date (pre-implant maximum 45 days before implant; latest available maximum 12 months prior to enrollment for non-device cohort); rhythm (normal sinus rhythm, junctional rhythm, atrial fibrillation, paced); resting heart rate; intrinsic or paced QRS width; PR interval, QT interval; QRS morphology (normal, right bundle branch block, LBBB, other conduction disorders).
- **Echocardiography or equivalent method as SOC:** will be used to determine basic measures: LVEF, diastolic diameters, volumes (Implant criteria and therapy efficacy data).
    - Device cohorts: data obtained within the last 3 months prior to enrolment are to be provided
    - Non-device cohort: latest data obtained within the last 12 months prior to enrollment in case there was no documented HF decompensation, MI or revascularization, otherwise within the last 3 months prior to enrollment are to be provided
- **MRI scan:** data on actual number of MRI scans performed according to center's SOC since the implant procedure, including information about scanned body parts, will be collected.
- **Physician's judgment:** judgment on therapy status / outcome / CRT therapy delivery (success yes/no) / defibrillator therapy (ATP/Shock delivered: yes/no).
- **Biomarkers for heart failure:** parameters as routinely evaluated prior to device implant or as part of standard visit for non-device subjects will be documented by the

site teams in the eCRF including name of parameter, date of analysis, result, and normal range according to local lab.

Collected standard biomarkers are: amino-terminal pro-peptide B-type natriuretic peptide (NT-proBNP), BNP, Troponin T, Troponin I, creatinine, BUN, and estimated glomerular filtration rate (eGFR)

Optional additional biomarkers collected from SOC diagnostics are: CK-MB, C-reactive protein, TNF-alpha, galectin-3 (Gal-3), parathyroid hormone (pTH), CA125, ST2

However, the identification of laboratory parameters as biomarkers for heart failure is left to the discretion of each individual investigator.

## Risk factor assessment

The following risk marker will need to be assessed (at all FU scheduled and unscheduled):

1. Myocardial infarction status
2. Last available EF status (value/ date)
3. Atrial fibrillation
4. Smoking
5. QRS morphology and width
6. Renal function
7. Diabetes type I and II
8. NYHA assessment
9. Age of subject

- Therapy judgment: appropriate, inappropriate, both, unclear
- CRT only: V-V timing of programmed vector
- MRI scan done during last 6 months observational period: yes/no
- Reason for MRI scan documented as related to diagnostics or related to a known SAE
- After any MRI, appropriate pacing and sensing need to be verified and documented as an unscheduled visit. In case of an increased pacing threshold or inappropriate sensing or any other device abnormality, an event report must be completed.

## Latitude

All Latitude alerts related to ventricular episodes and heart failure (if applicable) must be programmed on. All other alerts can be programmed on the physician's discretion or following hospital routine. If Latitude is available for a device, the device should be programmed ensuring that a Latitude report is created bi-weekly or at a higher frequency so that Latitude reports can be collected timely to corresponding clinical events.

Subjects will have their device performance and diagnostic data downloaded remotely into the Latitude database. The Latitude BSC team will collect device reports in the following cases:

- After all ventricular treatment Latitude alerts
- After all heart failure related Latitude alerts (if available)
- After the center reported serious adverse (device) events if these were related to ventricular episodes or heart failure events
- After the center reported SADE or ADE, including all inappropriate device treatments

The collected and anonymized Latitude reports will be uploaded into the study database for analysis.

If for any reason patients cannot be connected to Latitude, endpoint related data can be uploaded into the database by the site (e.g. electrogram (EGM) for ventricular arrhythmias).

### 11.5. *Six-monthly Visit*

Subjects will be visited every 6 months from enrolment (Day 0) until Close-out Visit. During the 6-monthly follow-up visit, device assessment/interrogation should be performed according to SOC practices. Details on the occurrence of any adverse device effects (ADEs), SAEs, SADEs, and device deficiency (DD), which have occurred since enrolment (Day 0), are to be recorded.

Echocardiography or equivalent method according to center's SOC will be used to determine basic measures: LVEF, diastolic diameters, and volumes. If the echo is not done per SOC, no deviation will be recorded.

Data on actual number of MRI scans performed according to center's SOC since the enrolment, including information about scanned body parts, reason for scan, etc., will be collected.

Subjects will have their device performance, all Latitude alerts on. Latitude report is requested every 14 days, and diagnostic data are downloaded remotely by the Latitude BSC team as Latitude report during this visit timeframe.

Latitude remote device interrogation is requested to be programmed every 2 weeks or more frequent.

Subjects that receive re-implant, repositioning, device upgrade or new device implant post enrolment, as determined by the investigator, will continue to follow same initial procedures and schedules as described for Day 0 at the initial enrolment. The reason for re-implant/ revision is to be documented as an Adverse Event in the eCRF.

Physician's judgment on therapy and risk factor assessment will be collected on standard follow-up CRF as planned at enrolment. In addition to the Re-implant CRF, the form for unscheduled visits will be used for event reporting.

If there were any protocol deviations since the last study visit, they have to be recorded.

### 11.6. *Re-implant, Device System Revision, Device Upgrades, or New Device Implant post Enrolment*

The Re-implant or New Device Implant post Enrolment visit is optional and needs to be performed only if re-implant (invasive procedure towards the evaluated therapy system), device system revision, device upgrade, or new device implant occurs while subjects are in the study.

Subjects that receive re-implant or new device implant post enrolment, as determined by the investigator, will undergo the same procedures as described for Day 0. The reason for re-implant/revision is to be documented in the eCRF.

Details on the occurrence of any adverse device effects (ADEs), SAEs, SADEs, and DD are to be recorded.

If there were any protocol deviations since the last study visit, they have to be recorded.

### 11.7. *Interim or Unscheduled Visit and Event Report (SAE/SADE related clinical care visit)*

The Interim Visit is optional and should be performed according to the SOC at the center. This visit can be completed in person at the clinic or over the phone at any time other than study scheduled visits.

All clinic visits that occur outside the specified protocol visit window will be classified as "Unscheduled CIP Visits". Unscheduled visits triggered by a specific event (e.g. adverse event, Latitude alert, patient request etc.) and not by standard routine control (e.g. device check-up standard by the institution, wound check, standard echo or ECG, blood analysis etc.) must be documented.

During this follow-up visit, details on the occurrence of any SAEs, SADEs, and DDs, which have occurred since the last visit, are to be recorded.

Events which already have been reported as part of an unscheduled visit do not need to be reported again during a CIP defined visit.

Data on actual number of MRI scans performed according to center's SOC since the last visit, including information about scanned body parts, will be collected.

Subjects will have their device performance, nominal alerts, and diagnostic data downloaded remotely from the Latitude BSC team during this visit. Risk factor assessment will be collected.

It is possible that more than one Interim Visit may occur if the SOC at the center requires more than one visit throughout the visit window. Any additional Interim Visits should be conducted similarly.

If there were any protocol deviations since the last study visit, they have to be recorded.

### 11.8. *Close-out Visit*

All subjects will remain in the study until the last subject completes his/her last visit. The maximum study duration for any subject will be 34 months (FSFV to LSLV). For the last subject enrolled, the study duration is 12 months.

As soon as the last subject was enrolled, planning of Close-out Visits for all subjects starts.

All close out visits will be documented on a specific Close out CRF. The time window for the Close-out Visits of all subjects starts 2 months before the last subject enrolled has completed 12 months and ends 4 months after the last subject enrolled has completed 12 months.

In case the time window for the Close-out Visits does not follow SOC, for HF subjects in a hospital, any follow-up appointment after 6 months which is closest to the study window might be defined as Close-out Visit.

During the Close-out Clinic Visit, a clinical assessment/physical exam should be performed in order to document the health status of the subject in addition to any ADEs, SA(D)Es, and DDs that may have occurred since the last visit. The physician's judgment on therapy outcome will be recorded. Current medication classes prescribed as well as a device assessment/interrogation should also be performed according to SOC practices.

The duration of QRS, intrinsic or paced, will be collected.

Full ECG recording is required at this visit if it is SOC of the center and data should be uploaded to the study database.

If Echocardiography or equivalent method is SOC of the center, it will be used to determine basic measures: LVEF, diastolic diameters, volumes.

Data on actual number of MRI scans performed according to site's SOC since the last visit, including information about scanned body parts, will be collected.

Subjects will have their device performance, nominal alerts and diagnostic data downloaded remotely from the Latitude BSC team during this visit timeframe.

Available results for heart failure related and other SOC biomarkers that were generated within the last 4 months prior each subject's individual close-out visit will be documented in the eCRF including name of parameter, date of analysis, result, and normal range according to local lab.

Once the subject completes the Close-out Clinic Visit, participation in this registry study has been completed. In case of premature termination of the study, data collection will stop accordingly. As this is an observational study, subjects will be managed according to center SOC following termination/completion of the study.

If a device-related event (unanticipated SADE [USADE], SADE, ADE) is ongoing at the time of study completion, the subject may be asked to remain enrolled in the study and provide additional information regarding the event until the event is resolved. The physician will provide treatment for any ongoing events according to SOC regardless of whether the subject agrees to continue participating in the study.

Physician's judgment on therapy and risk factor assessment will be done. Device therapy will be documented on an event form as well as all device deficiencies including false positive Latitude Alerts.

If there were any protocol deviations since the last study visit, they have to be recorded.

## 11.9. *Source Documents*

Table 11.9-1 summarizes all source data requirements for this CIP. Most source documents will be filed in the subject's hospital chart since all procedures will follow SOC. All source documents should be filed in the subject hospital chart since all procedures will follow SOC. Some source documents (ECG strips, Echo imaging, and Latitude recordings) may be stored electronically on a secured study database.

Only a copy of the subject consent will be kept in the administrative study binder and no subject study binder will be generated.

All personal information should be removed from all documents prior uploading into the study database and replaced by the study ID. In case this is not possible the database administrator will anonymize data as required.

**Table 11.9-1: Source Documentation Requirements**

| Requirement | Disposition |
|---|---|
| Subject Consent Form | 1-Retain subject file, 2 administrative study binder, 3-Subject copy |
| Enrolment and Baseline Data | Retain in subject hospital file |
| Implant Measurement | Retain in subject hospital file |
| Implant Procedure Medical Records | Retain in subject hospital file, |
| 6-monthly Clinic Visit Data | Retain in subject hospital file |
| Interim /Unscheduled CIP Visit Data | Retain in subject hospital file |
| Close-out Clinic Visit Data | Retain in subject hospital file |
| Adverse Events and Device Event Data | Retain in subject hospital file |
| CIP Deviation | Report in Study Database |
| Study Withdrawal Data | Retain in subject hospital file |
| ECG e-Recording | Retain in subject hospital file and copy upload to study database |
| Echocardiographic Imaging e-Recording | Retain in subject hospital file |
| Device Interrogation Printouts | Retain in subject hospital file |
| MRI pictures, videos, and reports | Retain in subject hospital file |
| Latitude device and alert data | Retain in subject hospital file<br>Latitude database and copy of the Latitude report upload into study database |

Abbreviations: CIP = Clinical Investigation Plan; ECG = electrocardiogram; MRI = magnetic resonance imaging

# 12. Statistical Considerations

## 12.1. *Endpoints*

### 12.1.1. Primary Endpoint for ICD Treated Subjects

The primary endpoint for ICD treated subjects is:

- Composite rate of first appropriately treated ventricular arrhythmia (by ATP or shock) or life-threatening symptoms associated to ventricular arrhythmia (defined as hemodynamic instability which requires treatment), whichever comes first under MADIT Arm B or C programming conditions in a study population with a majority of Japanese subjects

Based on the MADIT RIT study[4], we estimate that 5% of the ICD treated subjects will present an appropriately treated first ventricular arrhythmia associated symptom (by ATP or shock) within one year.

12.1.1.1. Hypotheses

The null and alternative hypotheses are as follows:

$H_0$: The ventricular arrhythmia associated symptoms free-rate from 0-12 months $\leq$85.0%

$H_A$: The ventricular arrhythmia associated symptoms free-rate from 0-12 months >85.0%

The null hypothesis ($H_0$) will be rejected if the lower one-sided 97.5% confidence bound for the ventricular arrhythmia associated symptoms free-rate is greater than the performance goal of 85.0%.

12.1.1.2. Statistical Methods

When the final study subject reaches the final CIP required follow-up visit, the primary analysis will be performed based on the Kaplan-Meier method for the estimation of the 12-month ventricular arrhythmia associated symptoms free-rate, including the lower 97.5% confidence bound (computed based on log-log methodology). This Kaplan-Meier analysis will begin at the time of implant. Subjects that withdraw consent or are lost-to-follow-up prior to the 12-month endpoint evaluation will be censored at their date of last contact. All subjects actively enrolled will be included in the endpoint analysis.

The null hypothesis will be rejected and the endpoint considered met if the lower 97.5% confidence bound for the ventricular arrhythmia associated symptoms free-rate at 12 months is greater than 85.0%.

Additionally, a Kaplan-Meier survival time-to-event curve along follow-up will be provided.

The primary analysis above will be performed for CRT-D and ICD cohorts combined as well as for ICD treated subjects separately.

### 12.1.2. Primary Endpoint for CRT-D Treated Subjects

The primary endpoint for CRT-D treated subjects is:

- Composite rate of first appropriately treated ventricular arrhythmia (by anti-tachycardia pacing [ATP] or shock) or life-threatening symptoms associated to ventricular arrhythmia (defined as hemodynamic instability which requires treatment), whichever comes first under MADIT Arm B or C programming conditions in a study population with a majority of Japanese subjects

Based on the MADIT RIT study[4], we estimate that 3% of the CRT-D treated subjects will present a first appropriately treated ventricular arrhythmia associated symptom (by ATP or shock) within one year.

#### 12.1.2.1. Hypotheses

The null and alternative hypotheses are as follows:

$H_0$: The ventricular arrhythmia associated symptoms free-rate from 0-12 months $\leq$87.0%

$H_A$: The ventricular arrhythmia associated symptoms free-rate from 0-12 months >87.0%

The null hypothesis ($H_0$) will be rejected if the lower one-sided 97.5% confidence bound for the ventricular arrhythmia associated symptoms free-rate is greater than the performance goal of 87.0%.

#### 12.1.2.2. Statistical Methods

When the final study subject reaches the final CIP required follow-up visit, the primary analysis will be performed based on the Kaplan-Meier method for the estimation of the 12-month ventricular arrhythmia associated symptoms free-rate, including the lower 97.5% confidence bound (computed based on log-log methodology). This Kaplan-Meier analysis will begin at the time of implant. Subjects that withdraw consent or are lost-to-follow-up prior to the 12-month endpoint evaluation will be censored at their date of last contact. All subjects actively enrolled will be included in the endpoint analysis.

The null hypothesis will be rejected and the endpoint considered met if the lower 97.5% confidence bound for the ventricular arrhythmia associated symptoms free-rate at 12-months is greater than 87.0%.

Additionally, a Kaplan-Meier survival time-to-event curve along follow-up will be provided.

The primary analysis above will be performed for CRT-D and ICD cohorts combined as well as for CRT-D treated subjects separately.

### 12.1.3. Primary Endpoint for PM/CRT-P Treated Subjects

The primary endpoint for PM/CRT-P treated subjects is:

- All-cause mortality in subjects with a maximum of 3 risk factors (analyzed for MADIT II data[7])

Based on previous CARE-HF study[8], we estimate that 10% of the PM/CRT-P treated subjects will present an all-cause mortality within one year.

12.1.3.1. Hypotheses

The null and alternative hypotheses are as follows:

$H_0$: The all-cause mortality free-rate (survival rate) from 0-12 months ≤80.0%

$H_A$: The all-cause mortality free-rate (survival rate) from 0-12 months >80.0%

The null hypothesis ($H_0$) will be rejected if the lower one-sided 97.5% confidence bound for the all-cause mortality free-rate is greater than the performance goal of 80.0%.

12.1.3.2. Statistical Methods

When the final study subject reaches the final CIP required follow-up visit, the primary analysis will be performed based on the Kaplan-Meier method for the estimation of the 12-month all-cause mortality free-rate (survival rate) including the lower 97.5% confidence bound (computed based on log-log methodology). This Kaplan-Meier analysis will begin at the time of implant. Subjects that withdraw consent or are lost-to-follow-up prior to the 12-month endpoint evaluation will be censored at their date of last contact. All subjects actively enrolled will be included in the endpoint analysis.

The null hypothesis will be rejected and the endpoint considered met if the lower 97.5% confidence bound for the all-cause mortality free-rate (survival rate) at 12 months is greater than 80.0%.

Additionally, a Kaplan-Meier survival time-to-event curve along follow-up will be provided.

### 12.1.4. Primary Endpoint for Non-device Subjects (ESC Guideline 2016 Indicated but not implanted)

The primary endpoint for Non-device subjects (ESC Guideline 2016 Indicated but not implanted) is:

- All-cause mortality in the subject cohort with 2 to 5 predefined SCD driving risk factors.

Based on the MADIT II study[2], we estimate that 10% of the Non-device subjects (ESC Guideline 2016 Indicated but not implanted) will present an all-cause mortality within one year.

12.1.4.1. Hypotheses

The null and alternative hypotheses are as follows:

$H_0$: The all-cause mortality free-rate (survival rate) from 0-12 months ≤80.0%

$H_A$: The all-cause mortality free-rate (survival rate) from 0-12 months >80.0%

The null hypothesis ($H_0$) will be rejected if the lower one-sided 97.5% confidence bound for the all-cause mortality free-rate is greater than the performance goal of 80.0%.

12.1.4.2. Statistical Methods

When the final study subject reaches the final CIP required follow-up visit, the primary analysis will be performed based on the Kaplan-Meier method for the estimation of the 12-month all-cause mortality free-rate (survival rate) including the lower 97.5% confidence bound (computed based on log-log methodology). This Kaplan-Meier analysis will begin at the time of enrolment. Subjects that withdraw consent or are lost-to-follow-up prior to the 12-month endpoint evaluation will be censored at their date of last contact. All subjects actively enrolled will be included in the endpoint analysis.

The null hypothesis will be rejected and the endpoint considered met if the lower 97.5% confidence bound for the all-cause mortality free-rate (survival rate) at 12 months is greater than 80.0%.

Additionally, a Kaplan-Meier survival time-to-event curve along follow-up will be provided.

### 12.1.5. Secondary Endpoints

- The secondary endpoint for subjects implanted with CRT-D/ICD is:
  - All-cause mortality rate
- The secondary HF endpoints for subjects with device implanted include:
  - Composite rate of HF events in ICD, CRT-D, and PM/CRT-P cohorts, which require IV treatment, HF related hospitalization, or led to HF death
  - Therapeutic sustainability at 1 year in ICD, CRT-D, and PM/CRT-P cohorts, defined as free of qualified SADEs post successful implantation, such as re-implant procedure, required invasive procedure related to the device system, pacing exit block, all-cause infection, and death due to therapy failure in comparison with data from MADIT CRT, MADIT RIT, Optimind, and Rally X4 studies.
- The secondary endpoint for subjects implanted with CRT-D/ICD and non-device subjects is:
  - Comparison of rate of sudden cardiac death in the non-device cohort with the rate of appropriately treated ventricular arrhythmias or sudden cardiac death in the defibrillator cohort (ICD cohort and CRT-D cohort)

Secondary analyses will be descriptive and exploratory. Detailed statistical methods for these endpoints will be presented in a Statistical Analysis Plan (SAP).

### 12.1.6. Sample Size

The pre-specified primary endpoints sample sizes are outlined in **Error! Reference source not found.**. The minimum required sample sizes to sufficiently power each primary endpoint at 90% and account for up to 20% attrition are lower than the final sample sizes.

The final sample sizes for the device cohorts (ICD: 117 to 270 subjects; CRT-D: 95 to 250 subjects; PM/CRT-P: 172 to 200 subjects) will ensure that there will be a sufficient number

of subjects to evaluate each primary endpoint, as well as provide ample data to characterize the safety, performance and efficacy profiles based on secondary and additional endpoints.

The final sample size for the non-device cohort (Non-device [ESC Guideline 2016 Indicated but not implanted]: 172 to 300 subjects) will ensure that there will be a sufficient number of subjects to compare the rate of sudden cardiac death in the non-device cohort with the rate of appropriately treated ventricular arrhythmias or sudden cardiac death in the defibrillator cohort (ICD, CRT-D).

In case of low enrollment rates, enrollment may be closed after the statistically required calculated minimum sample size was completed.

Table 12.1-1: Endpoint Sample Size Estimates

| Endpoint | Measurement | Performance Goal Hypotheses[1] | Expected Performance[2] | Power | Number of Subjects | |
|---|---|---|---|---|---|---|
| | | | | | Needed for Analysis | Required Minimum Sample size Enrolled for ≤20% Attrition |
| Primary Endpoint for ICD Treated Subjects | Ventricular arrhythmia[3] associated symptoms free-rate from 0 to 12 months | $H_0$: Rate ≤ 85.0%<br>$H_A$: Rate > 85.0% | 95.0% | 90% | 93 | 117 |
| Primary Endpoint for CRT-D Treated Subjects | Ventricular arrhythmia[3] associated symptoms free-rate from 0 to 12 months | $H_0$: Rate ≤ 87.0%<br>$H_A$: Rate > 87.0% | 97.0% | 90% | 76 | 95 |
| Primary Endpoint for PM/CRT-P Treated Subjects | All-cause mortality free-rate (survival rate) from 0 to 12 months | $H_0$: Rate ≤ 80.0%<br>$H_A$: Rate > 80.0% | 90.0% | 90% | 137 | 172 |
| Primary Endpoint for Non-device Subjects (ESC Guideline 2016 Indicated but not implanted) | All-cause mortality free-rate (survival rate) from 0 to 12 months | $H_0$: Rate ≤ 80.0%<br>$H_A$: Rate > 80.0% | 90.0% | 90% | 137 | 172 |

[1]Hypothesis test based on a one-sided alpha level of 0.025; clinically accepted delta of 10%, subtracted from expected performance
[2] Determined from prior comparable studies
[3] Appropriately treated
CRT-D = cardiac resynchronization therapy-defibrillator; ICD = implantable cardioverter-defibrillator; PM = pacemaker; CRT-P = cardiac resynchronization therapy-pacemaker.

Sample sizes for primary endpoints were calculated employing exact binomial methods in nQuery + nTerim 3.0.

## 12.2. *General Statistical Methods*

### 12.2.1. Analysis Sets

All subjects actively enrolled in the study (i.e. who meet all eligibility criteria at the time of enrolment into the study and who have given written informed consent) will be included in the primary endpoints analyses.

### 12.2.2. Number of Subjects per Investigative Site

Approximately 40 investigational sites in Japan will enroll a minimum of 556 to power all primary endpoint for each cohort and a maximum of 900 eligible subjects. If a site does not enroll a subject within a 3-month time period, the site may be replaced at the discretion of the sponsor.

### 12.2.3. Descriptive Statistical Methods

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for the primary endpoints. Unless otherwise stated, all statistical testing will be one-sided and will be performed using a significance (alpha) level of 0.025.

Continuous variables as a minimum will be described by number of non-missing observations (n), arithmetic mean (Mean), SD, minimum (Minimum), median (Median), and maximum (Maximum). One additional decimal point for mean and median and 2 additional decimal points for SD will be used.

Categorical variables will be presented using the number of non-missing observations (n) or the number of subjects in the population (N) as applicable and percentages (%). Percentages will be rounded to one decimal place. Unless otherwise stated, two-sided 95% confidence intervals (CIs) will be provided when relevant. The two-sided 95% CI will be presented as it provides the one-sided 97.5% lower (resp. upper) limit when the upper (resp. lower) bound is ignored to assess superiority.

## 12.3. *Data Analyses*

Exploratory analyses for the pooled ICD and CRT-D Cohorts versus Non-Device Cohort (ESC Guideline 2016 Indicated but not implanted) will be performed using propensity score matching method in order to compare the all-cause mortality rate and the composite rate of HF events between the pooled ICD and CRT-D Cohorts versus the Non-Device Cohort regarding 7 risk factors at baseline (age >70 years, smoking today or during last 5 years, prior MI, diabetes type I and II, chronic atrial fibrillation, renal dysfunction, NYHA Class III or IV).

A propensity matching score will be generated for each subject by logistic regression where the ‘device’ variable (device implantation Yes/No) is the dependent variable and the

covariates are the 7 risk factors in the model. Each subject in the pooled ICD and CRT-D Cohorts will be matched to a subject in the Non-Device Cohort based on the closest propensity score.

Subjects in the pooled ICD and CRT-D Cohorts will then be compared to those in the Non-Device Cohort before propensity score matching and after propensity score matching for each of the 7 risk factors using the Chi-square test. This technique enables evaluation of the success of propensity matching.

Finally, the all-cause mortality rate and the composite rate of HF events (outcomes) will be compared between the pooled ICD and CRT-D Cohorts and the Non-Device Cohort using the Chi-square test.

The detailed statistical method for propensity score matching will be presented in an SAP.

### 12.3.1. Other Endpoints/Measurements

The ancillary assessments will include:

- Subject medical assessment collected pre-enrolment (post implant) and at Close-out:
  - NYHA functional classification
  - LVEF
  - QRS duration
  - Physician's judgment on therapy outcome
  - BMI
  - Diabetes mellitus type I and II
- Cross-over in device therapies
- Cause of death (SCD, cardiac related, other reasons, unknown)
- Impact of gender and age
- MRI observations in association with reported clinical events
- Analysis of device data coming from Latitude data reports
- Health care utilization under Latitude
- Selected Biomarkers for heart failure and other morbidities

Additional analyses will be descriptive and exploratory. Detailed statistical methods for these endpoints will be presented in an SAP.

### 12.3.2. Interim Analyses

No interim analyses are planned.

### 12.3.3. Subgroup Analyses

Not applicable.

### 12.3.4. Justification of Pooling

The poolability of data by investigational site will be tested. This analysis will be performed to determine whether there are differences from center-to-center.

The center-to-center heterogeneity will be assessed for each primary endpoint by performing a random effects logistic regression analysis. Centers enrolling 10 subjects or fewer will be combined into pooled sites of 11 or more subjects for the purpose of this pooling analysis. Investigational center will be added into the model as a random effect. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to significantly differ from zero. A significance level of 10% will be used for each test.

### 12.3.5. Multivariable Analyses

Not applicable.

### 12.3.6. Other Analyses

Descriptive statistics of subject demographics and baseline characteristics will be presented. A list of potential baseline variables is categorized below:

- Demographics: age (numeric and % ≤70 years/ % >70 years), gender (%)
- Clinical: NYHA Class, chronic atrial fibrillation (%), paroxysmal atrial fibrillation (%), atrioventricular block (%), QRS morphology, intrinsic or paced QRS width, LVEF (numeric and % normal, fully preserved [≥ 50%]/ % partially preserved [40%-49%]/ % reduced [<40%]), blood pressure, BMI, heart rate
- Medical history/co-morbidities: single/multiple MI, hypertension, diabetes type I and II, current smoking, renal dysfunction
- Current medications: ACE-inhibitor, Angiotensin II receptor antagonist, antiarrhythmic, anticoagulant, antiplatelet, aldosterone-antagonist, beta-blocker, digitalis, diuretics, statins, calcium antagonists, oral hypoglycemic agent, non-insulin injectable, insulin.

### 12.3.7. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to database lock will be documented in an amended SAP approved prior to database lock. Changes from the planned statistical methods after database lock will be documented in the clinical study report along with a reason for the deviation.

## 13. Data Management

### 13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. The time periods for recording of study data (enrolment, implant data, etc.) are specified in the site guidelines.

The clinical database will reside on a production server hosted by EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

All echographic imaging (DICO format) and ECG readings (pdf format) should be uploaded to the study database.

All personal information must be removed prior to the upload.

### 13.2. *Data Retention*

The Principal Investigator or his/her designee or investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other country/regional/local regulations,

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

### 13.3. *Core Laboratories*

There will be no core laboratories involved in this registry.

## 14. Amendments

If a CIP revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., EC / Competent Authority) of the revised CIP must be obtained prior to implementation.

# 15. Deviations

An Investigator must not make any changes or deviate from this CIP, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the CIP, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using the eCRF. Sites may also be required to report deviations to the EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

# 16. Device/Equipment Accountability

Not applicable.

# 17. Compliance

## 17.1. *Statement of Compliance*

This study will be conducted in accordance with the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

## 17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the CIP/, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

All centers in Japan are asked to follow the recommended Ethics Guideline for Clinical Research on Human Subjects.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.

- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this CIP, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every AE as applicable per the CIP and observed device deficiency.
- Report to sponsor, per the CIP requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this CIP or by the EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this CIP and local EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of AEs, as described in the ICF.
- Inform the subject of the nature and possible cause of any AEs experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.

- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

#### 17.2.1. Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

### 17.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written EC and/or competent authority approval of the CIP (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual EC approval and renewals will be obtained throughout the duration of the study as required by local/country or EC requirements. Copies of the Investigator's reports and the EC continuance of approval must be provided to the sponsor.

### 17.4. *Sponsor Responsibilities*

Boston Scientific will serve as the sponsor of this clinical investigation. A sponsor is defined as individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation. It is the responsibility of BSC as the sponsor to ensure proper monitoring of the investigation and to see that all clinical requirements are

met. In addition, BSC representatives may participate in the conduct of the trial to the extent described in the following section that describes the role of the BSC representatives. BSC personnel may or may not be blinded to the study results. Participation in the study's conduct will be limited to BSC personnel who are appropriately qualified and trained such as those personnel with an engineering, technical or nursing degree or equivalent training, or who have significant experience in cardiology, electrophysiology or the implantable cardiovascular device industry. All personnel will be aware of general clinical study regulations and guidelines for medical device trials.

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study and publication.. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

### 17.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the CIP, and follow-ups. Support and assistance may include HCP training, addressing HCP questions, or providing clarifications to HCPs. Operation of BSC equipment/devices (including programmers, analyzers, and other support equipment) is not allowed per Japanese regulation.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to CIP compliance
- Reviewing collected data and study documentation for completeness and accuracy

**Boston Scientific personnel will not do the following:**

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

### 17.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage by BSC for subjects in the study will be obtained.

## 18. Monitoring

Monitoring will be performed during the study to assess continued compliance with the CIP and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

## 19. Potential Risks and Benefits

### 19.1. *Risks Associated with Participation in the Clinical Study*

This is a registration study and will therefore not increase the risks for the subject; after enrolment procedures are either SOC or eCRF documentation from Latitude uploads or the occurrence of any AEs.

Neither the device nor the implant procedure are part of this study; programming of the device has been specified as part of this study, but this is non-invasive and is specified to ensure compliance with the BSC device IFU. All subjects receive device as part of the SOC treatment, therefore there are no additional procedural risks to the subject for being included in this study.

### 19.2. *Anticipated Benefits*

There may be no benefit to the subject for being in this study. However, results from the data collected during this registry study may improve the medical device treatment options in the future, therefore the subjects enrolled in this registry may also benefit at a later stage.

Because device programming has been specified, it is ensured that the devices will be operated per BSC IFU.

### 19.3. *Risk to Benefit Rationale*

Subjects enrolled in the HINODE study will not be exposed to any additional testing, visits or risks as compared to subjects who are routinely implanted with any clinically approved

pulse generator (PG) system and not enrolled in this study. Standard device interrogation and testing that will be performed in the present study are part of routine procedures that occurs for each subject implanted with a PG who is followed up under standard clinical practice. Even if electronic devices such as PG are subject to random component failures that cannot be predicted, those risks are not affected by this CIP and would be equally applicable to all subjects implanted with a market released PG system. Risks can be minimized through adherence to the guidelines for subject selection, implementing BSC programming as specified by the CIP, close monitoring of the subject's physiologic status during visits and by promptly supplying BSC with all pertinent information required by this CIP.

# 20. Safety Reporting

## 20.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Serious Adverse Events
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- All Adverse Device Effects
- All ventricular episodes not followed by defibrillator therapy (ATP or Shock) but which have been associated to serious clinical symptoms (especially if medical intervention was necessary) must be documented as Adverse Event.
- All Cardiac Related AEs, including worsening in severity or frequency of pre-existing cardiac events and new onset of cardiac events (i.e. new onset Atrial Fibrillation)
    - For ICD/CRT-D - All ventricular arrhythmia which received therapy must be reported as an event.
    - Multiple ventricular arrhythmias on the same calendar day should be captured as a single event.
    - A pacemaker logbook on ventricular arrhythmias will be reviewed at any in clinic follow-up by the investigational center.
    - The Latitude database will be reviewed on ventricular arrhythmias at least annually. In case of arrhythmias that are not already reported by the study center, data management will query to add the arrhythmia as SAE.

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an AE and/or device deficiency.

Any AE event required by the CIP, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE (see Table 20.2-1 for AE definitions).

### 20.2. *Definitions and Classification*

Definitions are provided in Table 20.2-1 as reference only. Reportable events per this CIP are listed in the section above. Administrative edits were made on the definition of serious AEs from ISO 14155 and MEDDEV 2.7/4 for clarification purposes.

**Table 20.2-1: Safety Definitions**

| Term | Definition |
|---|---|
| Adverse Event (AE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/4* | Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.<br>NOTE 1: This includes events related to the investigational medical device or comparator.<br>NOTE 2: This definition includes events related to the procedures involved.<br>NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device. |
| Adverse Device Effect (ADE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/4* | Adverse event related to the use of an investigational medical device<br>NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.<br>NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device. |
| Serious Adverse Event (SAE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/4* | Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/4.<br>Adverse event that:<br>a) Led to death,<br>b) Led to serious deterioration in the health of the subject as defined by either:<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function, or<br>3) in-patient hospitalization or prolongation of existing hospitalization, or<br>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function<br>c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. |

**Table 20.2-1: Safety Definitions**

| Term | Definition |
|---|---|
| | **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event. |
| Serious Adverse Device Effect (SADE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/4* | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| Unanticipated Adverse Device Effect (UADE)<br><br>*Ref: 21 CFR Part 812* | Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. |
| Unanticipated Serious Adverse Device Effect (USADE)<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/4* | Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.<br>**NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. |
| Device Deficiency<br><br>*Ref: ISO 14155*<br><br>*Ref: MEDDEV 2.7/4* | An inadequacy of an investigational medical device-related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer. |

Abbreviations: ADE = Adverse Device Effect; AE = Adverse Event, ASADE = anticipated serious adverse device effect; EC=Ethics Committee; ISO = International Standard Organization, MEDDEV = medical device guidance; SAE = Serious Adverse Event; USADE = Unanticipated Serious Adverse Device Effect

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should be recorded as an SAE, and should include a detailed description of circumstances and expected cause.

Any AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

In case of shock or ATP treatment is noted by the subject or site, an SAE should be documented (life-threatening arrhythmia and corrective action is ATP or shock). Several shocks or ATP treatments on the same day are to be reported as one SAE. The event will be recorded as related to an arrhythmia. All events of shock will be captured by the Latitude system. If an event of shock is captured by the Latitude system, but has not been documented as an AE, the site will be asked to provide the documentation.

Any ATP treatment or shock that was inappropriate is to be documented as device deficiency. Multiple inappropriate ATP treatments or shocks on one day can be summarized in one device deficiency report.

Refer to the BSC Physician's Lead Manual for the known risks associated with the study devices.

All device-related AEs will be evaluated at least monthly during the trial and might be extracted from the database in order to pool those data with other available data sets (e.g. trials). Pooling of those datasets on product performance on a broader sample size will be done especially to support safety aspects of all medical devices in this trial.

### 20.3. *Relationship to Devices or Procedure*

The Investigator must assess the relationship of the AE to the device or procedure. See criteria in Table 20.3-1:

**Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event**

| Classification | Description |
|---|---|
| Not Related | Relationship to the device or procedures can be excluded when:<br>- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;<br>- the event has no temporal relationship with the use of the investigational device or the procedures;<br>- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;<br>- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;<br>- the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);<br>- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error;<br>- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. |
| Unlikely Related | The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| Possibly Related | The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| Probably Related | The relationship with the use of the investigational device seems relevant and/or the |

**Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event**

| Classification | Description |
|---|---|
| | event cannot reasonably explained by another cause, but additional information may be obtained. |
| Causal Relationship | The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:<br>- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;<br>- the event has a temporal relationship with investigational device use/application or procedures;<br>- the event involves a body-site or organ that<br>o the investigational device or procedures are applied to;<br>o the investigational device or procedures have an effect on;<br>- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);<br>- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);<br>- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;<br>- harm to the subject is due to error in use;<br>- the event depends on a false result given by the investigational device used for diagnosis, when applicable;<br>- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. |

### 20.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 20.4-1.

**Table 20.4-1: Investigator Reporting Requirements**

| Event Classification | Communication Method | Communication Timeline post-market studies (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM) |
|---|---|---|
| Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect | Complete AE eCRF page with all available new and updated information. | • Within 1 business day of first becoming aware of the event.<br>• Terminating at the end of the study |
| | Provide all relevant source documentation (unidentified) for reported event. | • At request of sponsor. |
| Serious Adverse Event | Complete AE eCRF page with | • Within 10 business days after |

**Table 20.4-1: Investigator Reporting Requirements**

| **Event Classification** | **Communication Method** | **Communication Timeline post-market studies** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM) |
|---|---|---|
| | all available new and updated information. | becoming aware of the event or as per local/regional regulations.<br>• Reporting required through end of the study |
| | Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor | • When documentation is available |
| Serious Adverse Device Effects | Complete AE eCRF page with all available new and updated information. | • Within 2 business days of first becoming aware of the event or as per local/regional regulations.<br>• Reporting required through the end of the study |
| | Provide all relevant source documentation (unidentified) for reported event | • When documentation is available<br>• At sponsor request. |
| Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities)<br>Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event. | Complete AE eCRF page with all available new and updated information. | • Within 2 business days of first becoming aware of the event. Reporting required through the end of the study |
| Adverse Event including Adverse Device Effects | Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device<br>Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor | • In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information<br>• Reporting required through end of study |

**Table 20.4-1: Investigator Reporting Requirements**

| Event Classification | Communication Method | Communication Timeline post-market studies (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM) |
|---|---|---|

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

### 20.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are to be reported in the eCRF but are not AEs. However, an AE that results from a device failure or malfunction would be recorded as an AE on the appropriate eCRF.

Any Device Deficiency that might have led to a serious AE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

Device deficiencies are to be reported from the study site to BSC or the study database within 2 business days of investigator awareness. Device deficiencies will be evaluated at routine intervals during the trial and might be extracted from the study database in order to pool those data with other available data sets (e.g. trials). Pooling of datasets on product performance on a broader sample size will be done especially to support safety aspects of all medical devices in this trial.

### 20.6. *Reporting to Regulatory Authorities / ECs / Investigators*

BSC is responsible for reporting AE information to all participating Principal Investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

### 20.7. *Subject Death Reporting*

A subject death during the study should be reported to BSC as soon as possible and, in any event, within 10 calendar days of site notification. The site's EC must be notified of any death in accordance with that site's EC policies and procedures.

Upon subject death, Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE.

An "End of Study" form must be completed for all deceased subjects, as well as the "Death CRF".

### 20.8. *Subject Death Classification*

The following definitions of each category, along with the Epstein article,[12] are to be used by the investigator when completing the Death Information section in the EDC.

I. **Primary Organ Cause** – The root problem that initiated the terminal event if multiple factors were involved, e.g., HF –primary, renal failure – secondary.

**A. Cardiac**

**1. Arrhythmic**

**2. Pump Failure** - Death occurring in a subject with severe heart failure, refractory to medical therapy, in whom death is anticipated within days to 2 months. Often such patients are referred for hospice care, comfort care is provided and aggressive treatment is curtailed. The terminal event could be sudden and may be arrhythmic. This does not change the non-sudden, non-arrhythmic course that preceded the terminal event.

**3. Ischemic**

**a. Acute MI** – Symptoms compatible with an acute coronary syndrome (chest pain, acute dyspnea etc.), with evidence of myocardial necrosis as defined by:

**i.** creatinine kinase (CK) ≥2x upper limit of normal (ULN) and CK-MB isoenzyme percent > ULN

**ii.** troponin level ≥2x ULN

Subjects with an acute coronary syndrome and diagnostic ST-T wave changes (>2 mm ST elevation in 2 contiguous leads) are included if death occurs prior to enzyme confirmation

**b. No Acute MI** – Subject has not met the enzymatic or electrocardiographic criteria for an acute myocardial infarction. The testing was done and came back negative. For example, a patient who survives an unstable angina episode long enough to provide documentation that they did NOT have an MI, e.g., cardiac enzyme confirmation.

**c. MI Unknown** – Myocardial infarction suspected but data to prove or disprove are not available. Used to capture the subject who is suspected of having probable MI but dies prior to the MI being documented. For example, chest pain >20 minutes, or chest pain with a non-diagnostic ECG (LBBB), or chest pain of unknown duration.

**4. Other Cardiac**

**5. Unknown**

**B. Noncardiac**

**C. Unknown**

**II. Temporal Course**

**A. Sudden** – death that occurred within one hour of onset of symptoms

**B. Non-Sudden** – death that occurred greater than one hour of onset of symptoms

**C. Unknown/Presumed Sudden** – This category should be used for subjects who were not expected to die of other causes, and were not witnessed at the time of death. There *must* be documentation of the subject's condition within 24 hours prior to the event and there should be no acute change in the subject's condition or circumstances leading up to the event. An example would be a stable subject who dies in his sleep. Subjects can have worsening heart failure prior to the event and be included in this category, as long as the severity of heart failure does not fit the definition of death due to pump failure.

**D. Unknown**

**III. Antecedent Worsening Heart Failure** – Patients with signs or symptoms of worsening heart failure within 2 weeks prior to death or the event that led to death (e.g. cardiac arrest and hypoxic encephalopathy from which the subject does not recover). In order to avoid recall bias, there *must* be documentation of a clinical evaluation documenting worsening signs or symptoms or a change in medication recommended for symptoms of worsening heart failure.

**A. N/A** (Not Applicable)

**B. Yes**

**C. No**

**D. Unknown** – Insufficient information to determine state of heart failure at time of the event

**IV. Death Witnessed** – Someone witnessed the death event (in the same room or within earshot)

**A. Yes**

**B. No**

**C. Unknown**

**V. Monitored** – The subject's rhythm at the onset of the terminal event (just prior to death) was documented. This may or may not be related to the actual cause of death.

**A. Yes**

1. **Ventricular Tachyarrhythmia**
2. **Bradyarrhythmia**
   a. **Sinus bradyarrhythmia**
   b. **High degree AV block with slow ventricular response**
   c. **Asystole**

3. **PEA (Pulseless Electrical Activity)**
4. **Other** (AF, SVT, sinus tachycardia, normal sinus rhythm)
5. **Unknown**

**B. No**

**C. Unknown**

**VI. Pulse Generator Related** – includes events associated with pulse generator's ability to detect and treat an arrhythmia.

**A. Yes**

**B. No** – including events where initiating event was non-arrhythmic

**C. Unknown**

**D. N/A**

## 21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's EC, or central EC, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's EC. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,

- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject and by the investigator and/or an authorized designee responsible for conducting the informed consent process. The original signed ICF will be retained by the site as original or as e-copy as part of the hospital patient chart and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements. Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, CIP, a change of the Principal Investigator, administrative changes, or following annual review by the EC. The new version of the ICF must be approved by the EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's EC. The EC will determine the subject population to be re-consented.

The ICF will note that the transmission of confidential subject data, such as copies of source documents, will be required and that by signing the consent, the subject gives permission for his/her confidential subject data to be transmitted to the sponsor.

# 22. Committees

### 22.1. *Safety Monitoring Process*

To promote early detection of safety issues and consistent coding across projects, an internal BSC Event Review Team (Technical Services, Clinical Cardiac Rhythm Management [a business division of BSC], Medical Safety, and assigned persons from ICON Plc) will provide routine and ongoing review and an overview of all events reported in the study database.

Review and event classification will be done to support device hazard analysis and monitoring of event rates. This process requires dynamic collection (as soon as the event is reported) of unmonitored data.

During scheduled monitoring visits, clinical research monitors and locally responsible BSC Technical Science Liaison will support the dynamic reporting process through their review of source document information.

### 22.2. *Event Committee*

The event committee will centrally assess events that are relevant for the primary endpoints (onset / treatment of all ventricular events and classifying those events towards endpoint relevance) of the study. The scope and the procedures to be followed will be defined in a separate document.

### 22.3. *ECG experts*

Experts will centrally assess the ECGs to determine whether subjects met ECG-related criteria for inclusion and exclusion at the time of enrolment.

## 23. Suspension or Termination

### *23.1Premature Termination of the Study*

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

#### 23.1.1Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of USADE or unusual trends of SAEs or SADEs that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrolment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of BSC to suspend or discontinue development of the device.

### *23.2Termination of Study Participation by the Investigator or Withdrawal of EC Approval*

Any investigator or EC in the HINODE Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to BSC. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

### *23.3Requirements for Documentation and Subject Follow-up*

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by BSC. The EC and

regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an EC terminates participation in the study, participating investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

### *23.4Criteria for Suspending/Terminating a Study Site*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after site initiation, or if the site has multiple or severe CIP violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed according to SOC of the center. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

## 24. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.

- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

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# 26. Abbreviations and Definitions

## 26.1. *Abbreviations*

Abbreviations are shown in Table 26.1-1.

**Table 26.1-1: Abbreviations**

| Abbreviation/Acronym | Term |
|---|---|
| ACE | Angiotensin Converting Enzyme |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| ATP | Anti-tachycardia pacing |
| AV | Atrioventricular |
| BSC | Boston Scientific |
| BMI | Body mass index |
| BUN | Blood urea nitrogen |
| CA125 | Carcinoma antigen 125 |
| CABG | Coronary artery bypass grafting |
| CHF | Chronic heart failure |
| CI | Confidence interval |
| CIP | Clinical Investigation Plan |
| CRT | Cardiac Resynchronization Therapy |
| CRT-D | CRT-Defibrillator |
| CRT-P | CRT-Pacemaker |
| CRO | Contract Research Organization |
| CRM | Cardiac Rhythm Management (a business division of Boston Scientific) |
| DCM | Dilated cardiomyopathy |
| DD | Device deficiency |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic data capture |
| EF | Ejection fraction |
| eGFR | Estimated glomerular filtration rate |
| ESC | European Society of Cardiology |
| FSFV | First subject first visit |
| GCP | Good Clinical Practice |
| HCP | Health Care Professional |
| HF | Heart Failure |
| HFmrEF | Heart failure with mid-range ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| ICD | Implantable Cardioverter-Defibrillator |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IFU | Instructions for Use |
| ISO | International Standard Organization |
| IV | intravenous |

**Table 26.1-1: Abbreviations**

| Abbreviation/Acronym | Term |
|---|---|
| LAT | Latitude reporting system |
| LBBB | Left bundle branch block |
| LSFV | Last subject first visit |
| LSLV | Last subject last visit |
| LV | Left ventricle/ventricular |
| LVEF | Left ventricular ejection fraction |
| MADIT | Automatic Defibrillator Implantation Trial |
| MEDDEV | Medical Device Guidance |
| MI | Myocardial infarction |
| MRI | Magnetic resonance imaging |
| ms | milli seconds |
| NYHA | New York Heart Association |
| OMT | Optimal medical therapy |
| PCI | Percutaneous coronary intervention |
| PG | Pulse generator |
| PM | Pacemaker |
| PSA | Pacing System Analyzer |
| pTH | Parathyroid hormone |
| RBBB | Right bundle branch block |
| RIT | Reduce Inappropriate Therapy |
| RV | Right ventricle/ventricular |
| s | seconds |
| SADE | Serious Adverse Device Effect |
| SAP | Statistical Analysis Plan |
| SAE | Serious Adverse Event |
| SCD | Sudden cardiac death |
| SD | Standard deviation |
| SOC | Standard of care |
| TNF | Tumor necrosis factor |
| US | United States |
| USADE | unanticipated serious adverse device effect |

### 26.2. *Definitions*

Terms are defined in Table 26.2-1.

**Table 26.2-1: Definitions**

| Term | Definition |
|---|---|
| Cardiac Perforation | Penetration of the lead tip through the myocardium to the pericardium or beyond (including micro-perforation), either clinically suspected by chest x-ray, fluoroscopy or, intra-cardiac electrogram and/or confirmed by echocardiogram, CT or visually at operation. |
| Cardiac Tamponade | Also known as pericardial tamponade is an acute type of pericardial effusion in which hemodynamic compromise results and urgent intervention is required. This will be considered a SADE. |
| Complication | An adverse event that resulted in: death, serious injury, a correction using invasive intervention, or permanent loss of device functions. |
| Conductor Fracture/Lead Fracture | A mechanical break/disruption within the lead conductor (includes connectors, coils and/or electrodes) observed visually, electrically or radiographically. |
| Device-related Complication | A complication (an AE that resulted in death, serious injury, a correction using invasive intervention, or permanent loss of device functions) assessed as related to the device. |
| Elevated Pacing Thresholds | At implant, pacing thresholds for the permanently programmed electrode that are greater than 3.0 volts and at follow-up pacing thresholds for the permanently programmed electrode that are either: (1) An observed increase of 2-fold over the first chronic threshold; or (2) An observed threshold greater than 3.5 volts. Please note that these elevations in pacing threshold values may be physiologic, pathologic or device-related. |
| Extra-cardiac Stimulation (e.g., phrenic, diaphragm) | Clinical observation of inadvertent muscle/nerve stimulation other than cardiac muscle. |
| Hematoma | If a hematoma requires invasive intervention to evacuate the hematoma, it will be considered a SAE. |
| Hemodynamic instability | A state requiring pharmacological or mechanical support to maintain a normal blood pressure or adequate cardiac output. |
| High Pacing Impedance | Pacing impedance is considered abnormal based on lead model and measurement range of the device. |
| High Shock Impedance | Shock impedance is considered abnormal based on lead model and measurement range of the device. |
| High Shock Impedance when attempting to deliver a shock | High shock impedance is considered abnormal based on lead model and measurement range of the device when attempting to deliver a shock. |

**Table 26.2-1: Definitions**

| Term | Definition |
|---|---|
| Inappropriate shock due to over-sensing | Shock delivered due to over-sensing resulting from either physiologic or non-physiologic causes. |
| Inappropriate shock | Shock delivered by the device which is not appropriate therapy/treatment per the device programming. |
| Infection | If oral antibiotics are prescribed for treatment of an infection, it will be considered as an adverse event. If IV antibiotics are required for treatment of the infection, then it will be considered a SAE.<br>Any confirmed pocket sepsis or lead endocarditis requiring device system (generator and lead) extraction will be considered a SAE. |
| Intermittent Sensing | Intermittent loss of sensing or failure to detect intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity settings. |
| Lead Abrasion | Upon returned product analysis, leads are analyzed for abrasion. Known examples of lead abrasion occur 1) proximal abrasions associated with lead-on-lead or lead-on-PG contact in the pocket; 2) mid-lead insulation damage caused by clavicle flex-fatigue or crush, suture or suture sleeve, insulation wear in the area of vein insertion and 3) distal region wear due to lead-on-lead (intra-cardiac), lead-on-heart valve or lead-on-another anatomy contact. |
| Lead Insulation Breach | A disruption or break in lead insulation observed visually, electrically or radiographically. |
| Lead Migration/Dislodgment | Radiographic and electrical evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing and/or lead performance. Micro-dislodgement is not included. |
| Lead Revision/Reposition | An invasive procedure that involves manipulation of the lead(s) to modify the anatomical implanted location of the intra-thoracic portion of the lead. |
| Loss-of-Capture | Intermittent or complete failure to stimulate cardiac stimulation (atrial or ventricular) at programmed output delivered outside of the cardiac refractory period. |
| Low Pacing Impedance | Pacing impedance is considered abnormal based on lead model and measurement range of the device. |
| Low Shock Impedance | Shock impedance is considered abnormal based on lead model and measurement range of the device. |
| Low shock impedance when attempting to deliver a shock | Low shock impedance is considered abnormal based on lead model and measurement range of the device) when attempting to deliver a shock. |
| Normal Battery Depletion | For pulse generators , the condition when a) a device is returned with no associated complaint and the device has reached its elective replacement indicator(s) with implant time that meets or exceeds the nominal (50 percentile) predicted longevity at default (labelled) settings, or b) the |

**Table 26.2-1: Definitions**

| Term | Definition |
|---|---|
| | device is returned and the device has reached it elective replacement indicator(s) with implant time exceeding 75% of the expected longevity using the longevity calculation tool available at the time of product introduction, calculated using the device's actual use conditions and settings. |
| Other, Lead related | Specific proprietary attributes of a lead, such as sensors which affect a leads ability to perform as designed and remain in service. |
| Other, Pulse Generator/Header related | Specific proprietary attributes of a pulse generator/header, which affect a device's ability to perform as designed and remain in service. |
| Over-sensing | The occurrence of cardiac or noncardiac events being misinterpreted as cardiac depolarization, (e.g., T waves, multiple counting, skeletal muscle potentials and extra-cardiac electromagnetic interference (EMI)). |
| Pacing Impedance Changes | Pacing impedance changes are considered clinically significant if the value changes by more than a 2:1 ratio from the previous value. |
| Pain | A pain requiring oral medication is not considered serious. Pain requiring IV analgesics or results in prolonged hospitalization will be considered a complication. |
| Pneumothorax | Is a collection of air in the pleural space, causing the lung to collapse. It will be considered a SAE if invasive intervention is needed for treatment. |
| Pocket Revision | Assuming that the subject continues to participate in the study, a pocket revision is an invasive procedure that involves modification in some manner to the extra-thoracic device pocket and/or lead(s) therein. There is no repositioning of the lead(s) tip in the heart. |
| Possible Malfunction | May be considered if neither of the 2 listed below occurred.<br>a) **Malfunction with compromised therapy, PG** – The condition when a device is found to have "malfunctioned" in a manner that compromised pacing or defibrillation therapy (including complete loss or partial degradation) while implanted and in service. Therapy is considered to have been compromised if no therapy is available or critical subject protective pacing or defibrillation therapy is not available<br>b) **Malfunction without compromised therapy, PG** - The condition when a device is found to have "malfunctioned" in a manner that did not compromise pacing or defibrillation therapy while implanted and in service. Therapy is not compromised as long as critical subject protective pacing or defibrillation therapies are available. Changes in device setting that occur as intended by design (i.e. Power-on-reset) that do not result in loss of critical subject protective therapies but are reported as reasons for explant shall be classified as malfunctions without compromised therapy. |
| Shock Impedance Changes | Shock impedance changes are considered clinically significant if the value changes by more than a 2:1 ratio from the previous value. |

**Table 26.2-1: Definitions**

| Term | Definition |
|---|---|
| Significant r-wave amplitude decrease over 2 weeks or less | A decrease in r-wave value is considered clinically significant if the value changes by more than a 2:1 ratio over the course of 2 (2) weeks or less. |
| Source Data | All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical study (original records or certified copies including electronic patient charts). |
| Source Document | Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, radiographs, records kept at the investigation site, and at the laboratories involved in the clinical study. |
| Suspected Lead Fracture | May be manifested by abnormal device measurements (i.e. RV lead impedance, thresholds, inappropriate shocks) which may be caused as a result of conductor/lead fracture. Investigators are requested to complete a through lead assessment; confirm through visual, radiographic and electrical analysis, and are strongly recommended to return the lead to for analysis. |
| Suspected Lead Abrasion | May be manifested by abnormal device measurements (i.e. RV lead impedance, thresholds) which may be as a result of unknown lead abrasion type (which are not already defined above). Investigators are requested to complete a through lead assessment; and strongly recommended to return the lead to for analysis. |
| Twiddler's Syndrome | A complication of pacemaker treatment, in which repeated torsional pocket forces applied to the generator cause rotation and, by a ratchet mechanism, lead retraction. This may potentially result in lead displacement and loss of device function. |
| Under sensing | Complete or intermittent loss of sensing or failure to detect the intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity. |

Abbreviations are defined in Table 26.1-1: Abbreviations

# 27. Appendices

## 27.1. *Clinical Trial Organization*

CRO

ICON Clinical Research Limited

South Country Business Park

Leopardstown

Dublin 18

Ireland

STUDY SITES

*In Japan will be documented and available upon request on a separate document.*

COORDINATING PRINCIPAL INVESTIGATOR

Professor Kazutaka Aonuma

Ibaraki

Japan

### 27.2. *NYHA Classification*

| NYHA Class | Symptoms |
|---|---|
| I | No limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea. |
| II | Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea. |
| III | Marked limitation of physical activity. Comfortable at rest, Less than ordinary activity causes fatigue, palpitation, or dyspnea. |
| IV | Unable to carry on any physical activity without discomfort. Symptoms of HF may be present even at rest. If any physical activity is undertaken, discomfort is increased. |

Source: Heart Failure Society of America. NYHA Classification: The Stages of Heart Failure. March 2012. Available at: http://www.abouthf.org/questions stages.htm.

### 27.3. *ESC Guidelines 2016: Patterns of Atrial Fibrillation*

**Table 5 Patterns of atrial fibrillation**

| AF pattern | Definition |
|---|---|
| First diagnosed AF | AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms. |
| Paroxysmal AF | Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days.[a] AF episodes that are cardioverted within 7 days should be considered paroxysmal.[a] |
| Persistent AF | AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more. |
| Long-standing persistent AF | Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy. |
| Permanent AF | AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'. |

AF = atrial fibrillation.
[a]The distinction between paroxysmal and persistent AF is often not made correctly without access to long-term monitoring.[163] Hence, this classification alone is often insufficient to select specific therapies. If both persistent and paroxysmal episodes are present, the predominant pattern should guide the classification.

Source: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal, doi: 10.1093/eurheart/ehw210

### 27.4. *Classification of LVEF*

**Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)**

| Type of HF | | HFrEF | HFmrEF | HFpEF |
|---|---|---|---|---|
| CRITERIA | 1 | Symptoms ± Signs[a] | Symptoms ± Signs[a] | Symptoms ± Signs[a] |
| | 2 | LVEF <40% | LVEF 40–49% | LVEF ≥50% |
| | 3 | – | 1. Elevated levels of natriuretic peptides[b];<br>2. At least one additional criterion:<br>a. relevant structural heart disease (LVH and/or LAE),<br>b. diastolic dysfunction (for details see Section 4.3.2). | 1. Elevated levels of natriuretic peptides[b];<br>2. At least one additional criterion:<br>a. relevant structural heart disease (LVH and/or LAE),<br>b. diastolic dysfunction (for details see Section 4.3.2). |

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.
[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.

Source: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, European Heart Journal, doi: 10.1093/eurheart/ehw128

### 27.5. *ESC Guidelines 2016: Recommendations for cardiac resynchronization therapy implantation in patients with heart failure*

**Recommendations for cardiac resynchronization therapy implantation in patients with heart failure**

| Recommendations | Class[a] | Level[b] | Ref[c] |
|---|---|---|---|
| CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality. | I | A | 261–272 |
| CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality. | IIa | B | 261–272 |
| CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality. | I | B | 266, 273 |
| CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality. | IIb | B | 266, 273 |
| CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1). | I | A | 274–277 |
| CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV[d] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm. | IIa | B | 275, 278–281 |
| Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF. | IIb | B | 282 |
| CRT is contra-indicated in patients with a QRS duration < 130 msec. | III | A | 266, 283–285 |

AF = atrial fibrillation; AV = atrio-ventricular; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OMT = optimal medical therapy; QRS = Q, R and S waves (combination of three of the graphical deflections); RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Use judgement for patients with end-stage HF who might be managed conservatively rather than with treatments to improve symptoms or prognosis.

Source: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, European Heart Journal, doi: 10.1093/eurheart/ehw128

### 27.6. *Declaration of Helsinki*

***DECLARATION OF HELSINKI***

**WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI - Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

**Preamble**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

**General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21 Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or

community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made

the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.