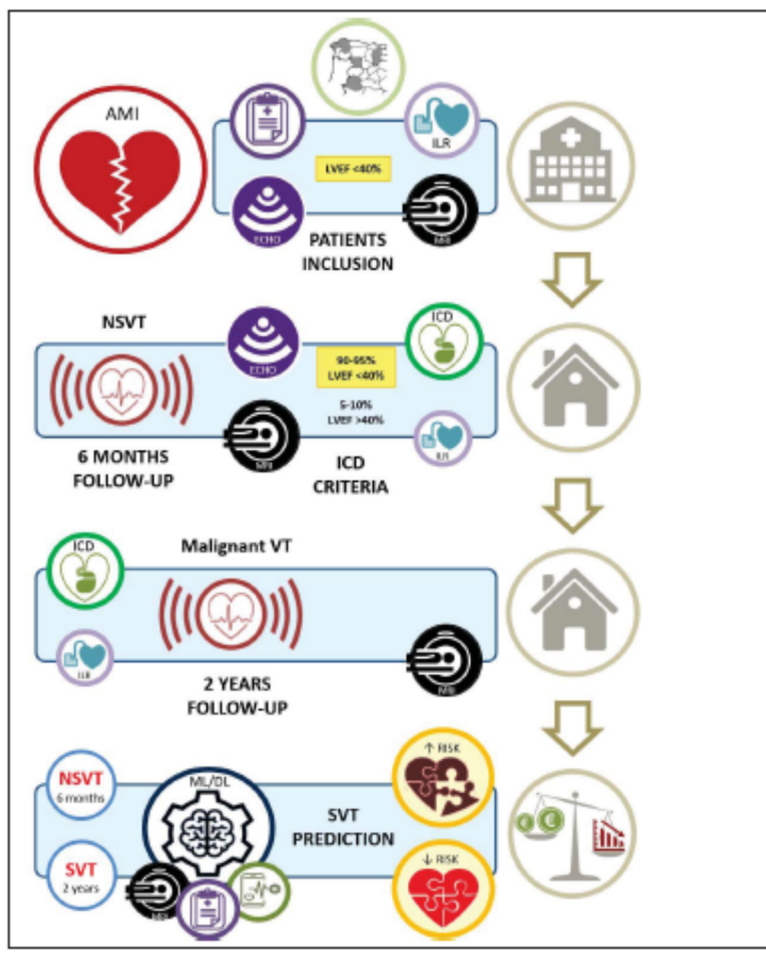# Analysis of the incidence, pathogeny and prognostic impact of the non-sustained VT registered by an Implantable Loop Recorder in the first 6 months after an AMI: TeVeO study.

INTRODUCTION

Worldwide, cardiovascular diseases (CVD) are the leading cause of death, being responsible for nearly one out of three demises (1), and including pathologies with a huge impact in patients' and their families' quality of life and a major sociosanitary burden for national health systems. Among them, ischemic heart diseases including mainly myocardial infarction are the leading cause of death (12-15% deaths globally), but with significative differences among countries (2). In Spain, and similarly in other European nations, prevention strategies, early and new therapeutic interventions and social awareness campaigns have contributed to reduce ischemic heart diseases death rate from 11% in 2001 to 7.6% (3, 4). However, its incidence has remained practically unaltered in last decades (5) due to the fact that the benefit from prevention strategies is being undermined by progressive population ageing. Since elder patients are at higher risk of developing these cardiovascular diseases (2), the impact and burden of heart failure in our society are expected to be increased during the next decades (6).

Nowadays, approximately 30% of the patients with an acute myocardial infarction (AMI) die before reaching the hospital. Among survivors, life-threatening sequels are highly common and account for secondary alterations in heart pacing, mainly ventricular tachycardia (VT), and contractility leading to heart failure. VT can be also presented as a consequence of other pathologies, but cardiac alteration following AMI is the underlying cause in most patients and it is often poorly tolerated leading to **sudden cardiac death (SCD)** in up to 30% of AMI survivors (7). Today SCD represents a relevant problem for national health systems (8) and it is expected to get worse in the future European society due to population aging.

According to the duration of the episodes, VT can be classified as non-sustained, when the altered rhythm is selfterminated within 30 seconds, and sustained if it lasts more than 30 secs. While non-sustained VT (NSVT) are frequently asymptomatic, sustained VT (SVT) are potentially lethal leading to SCD by haemodynamic destabilization, shock or ventricular fibrillation and usually an intervention is required to stop the arrythmia.

Interventions to avoid SCD following SVT are based on restoring sinus rhythm as soon as possible (9). Therefore, preventive strategies with **implantable cardioverter-defibrillator** (ICD) are the best clinical option for certain patients at higher risk of developing VT leading to life-threating events and, in fact, its implantation can rescue them from SCD.

Some patients more prone to suffer STV following AMI are those with prior history of SVT, poorly tolerated VT or previous aborted SCD. Prevention of further lethal VT by ICD implantation, a strategy known as **secondary prevention**, was proved beneficial by through 3 different early clinical trials, even when compared with antiarrhythmic drugs (10-12). The overall evidence clearly demonstrated that IDC reduce global and arrhythmic death and thus, its implantation is now a class I recommendation in the international guidelines for patients with aborted SCD, or potentially lethal VT (13, 14). On the other hand, despite the fact that NSVT are usually asymptomatic, they often precede SVT (15) especially when recurrent and monomorphic as an expression of a significant ventricular dysfunction. These NSVT are the clinical manifestation of an underlaying arrhythmogenic substrate and of the activation status of triggering factors (16). In fact, our group has published that the amount of NSVT is associated with the risk of medium and long-term clinically relevant events, especially with the risk of developing poorly tolerated and potentially lethal VT (17). Several multicentric prospective clinical studies (18-21) have demonstrated that ICD implantation improves overall survival of patients at high risk of developing a first episode of SVT after AMI, a strategy known as primary prevention. As a general conclusion, mortality is reduced around 20-30% and mainly due to SCD abortion. Although different approaches have been considered to identify those patients at higher risk, up to date, scientific evidence only support selection of ICD candidates for primary prevention according to following criteria: a) left ventricular ejection fraction (LVEF) and b) functional class by the New York Heart Association (NYHA) scale, both measured between 1-6 months after the AMI and under optimal pharmacological treatment with antiarrhythmic drugs (22). However, different guidelines do not agree on LVEF threshold to select primary ICD implantation, but it is generally accepted that a benefit is obtained in patients with functional class I-III and LVEF<35%. However, ICD devices not always produce benefits. On one hand, the apparition of a lethal SVT is not prevented, just aborted, and ICD implantation early after AMI is not translated into a better prognostic outcome for the patient. In fact, in the MADIT-II study, ICDs only produced a reduced mortality in patients implanted beyond 18 months after AMI (23). On the other, the device only responses to treat a VT in one every 10 patients implanted for primary prevention (24). Besides, ICD implantation requires an invasive surgery which implies the possibility of having a surgical complication and post-procedural infections in up to 3% of the patients, requiring sometimes to remove the IDC and replace it once the infection is cleared up (25). ICD malfunction and inappropriate shocks delivered by the device when no life-threatening arrythmia is present are additional problems that can be presented after the surgery. Therefore, device implantation and management accounts for a high

economic cost, with a relevant burden for the national health systems and, despite the fact that clear benefits are observed, patient selection for primary prevention of VT by IDC implantation should be further studied in order to first maximize the cost-effectiveness of the device and second minimize as much as possible associated complications and sociosanitary burden.

Implantable loop recorders (ILR) are small devices that are subcutaneously implanted requiring a minimally invasive procedure and work as a long-term Holter, monitoring for 24-hour a day patient's heart rhythm to detect arrythmias. ILR are compatible with remote monitoring systems (RMS), allowing the patients to send daily the information registered by the device to the healthcare center just using a conventional phone landline. This information can be immediately analyzed by the medical practitioner allowing to quickly adopt proper measures according to patient's clinical situation, which contributes to reduce the morbidity and mortality (26). Due to their safety and effectiveness, ILR are a valuable tool for the diagnosis of different clinical manifestations suspected to have a cardiac origin. However, up to date they have not been systematically used to detect NSVT in patients following an AMI, neither in their prognostic stratification, thus the viability of this strategy that could result in improving patients selection for IDC implantation need to be demonstrated. Though ILR monitoring, the TeVeO project aims to qualitative and quantitative characterize NSVT that take place during the first 6 months after an AMI, stablishing the relative importance of the two main factors influencing the arrhythmogenic mechanisms that can originate potentially lethal VT: substrate and triggers, which will allow us to advance in the proper treatment and prevention of these life-threatening events through patients stratification. The substrate for VT following AMI is the scar tissue, which extension and heterogeneity increase the risk. Prior studies have demonstrated that scar characterization by cardiac magnetic resonance imaging (cMRI) provides additional information to the LVEF and functional class to identify those patients at higher arrhythmic risk (27). However, little data are available regarding the underlying substrate and its evolution in chronic AMI with NSVT. Therefore, in addition to ILR monitoring, TeVeO study will evaluate the scar tissue by cMRI trying to identify further predictive markers associated to increased risk of developing SVT after AMI.

HYPOTHESIS

The project is grounded on the main assumption that the unsustained ventricular tachycardias (NSVT) that spontaneously occur during the first 6 months after an AMI can predict short and long-term functional outcome, specifically the risk of experiencing a potentially lethal VT. Therefore, the

study of theses arrhythmic events can contribute to patient stratification and help to develop further improvements for their management.

TeVeO project assume the following further hypothesis for the study of the NSVT following an AMI:

- The implantable loop recorders (ILRs) are able to accurately detect the NSVTs that patients submitted to coronary revascularization experiment after the medical discharge and during the first 6 months after an acute myocardial infarction (AMI).

- There are differences in the arrhythmogenic substrate of patients presenting NSVT in the 6 first months after an AMI with depressed left ventricular ejection fraction (LVEF) that can be determined by the study of the scar tissue by cardiac MRI (cMRI).

OBJECTIVES

The main objective of TeVeO study is to qualitative and quantitative characterize NSVTs that take place during the first 6 months after an AMI in patients with LVEF ≤40%, and to discriminate the short- and long-term risks of developing potentially lethal arrhythmic events, which will contribute to tailor patients' treatment and prevention according to identified risks and will improve patient selection for implantable cardioverter-defibrillator (ICD) implantation, improving the cost-effectiveness of these devices and minimizing its associated problems and sociosanitary burden.

To achieve main purpose, secondary and specific objectives have been stablished.

Secondary objectives:

- To determine the feasibility and accuracy of ILR devices to register NSVT following an AMI in patients with a relevant systolic dysfunction.

- To determine the number of medical interventions after an arrhythmic event registered by ILR and transmitted by RMS.

Specific objectives:

- To determine if there are differences in the substrate in patients with/without NSVT following an AMI (scar, compact necrosis and heterogeneous tissue extensions) by cMRI and gadolinium delayed enhancement.

- To determine la incidence of NSVT during the first 6 months after an AMI in patients with an LVEF ≤40%.

- To determine the medium-term prognostic impact (2 years) of the episodes of NSVT produced during the 6 first months after AMI: cardiovascular mortality, hospitalizations due to heart failure and SVT in patients implanted with ICD.

METHODS.

1. **Characteristics:**

Type: prospective clinical study, multicentric, Observational study.

Participating centres: Hospital Universitario de Salamanca, Complejo Asistencial Universitario de Burgos, Hospital Universitario San Pedro de Alcántara, Complejo Asistencial Universitario de Santiago de Compostela and Complejo Asistencial Universitario de Lugo.

Comparing groups: Acquired data within the first 6 months after an AMI will be study in order to stablish possible associations with the patient outcome in the first 2 years after an AMI.

Definitions:

- NSVT: Any rhythm with a wide QRS from a ventricular origin that is self-terminated within 30 second, with a heart rate over 100 bpm and over 5 beats.

- SVT: Any rhythm with a wide QRS from a ventricular origin with a heart rate over 100 bpm, that lasts over 30 seconds or that needs an intervention to be finished.

- Monomorphic VT: All QRS complex present the same morphology

- Polymorphic VT: QRS morphology changes in any heartbeat.

- Appropriate therapy: Any therapy (antitachycardia pacing or discharge) applied by ICD due to a ventricular tachycarrhythmia.

- Inappropriate therapy: Any ICD therapy that is not due to a ventricular tachyarrhythmia.

- Ischemic left ventricular dysfunction: The systolic dysfunction due to a previous coronary artery disease with myocardial necrosis with previous demonstration of at least one obstructed epicardial coronary artery, and presence of ischemic scar in MRI with characteristic distribution of late-enhancement of gadolinium.

2. **Study subjects:**

Inclusion criteria:

- AMI patients over 18 years old.

- LVEF equal or under 40% determined by a transthoracic echocardiography 4 days after the onset of the AMI.

- Revascularization during hospitalization according to the clinical practice guidelines

- Signed informed consent.

Exclusion criteria:

- Non-ischemic etiology of left ventricular dysfunction by cMRI.

- Patient already implanted with a cardiac device (pacemaker, ICD or ICD-TRC).

- Indication of pacemaker, ICD or ICD-TRC implantation during hospitalization.

- Allergy or hypersensitivity to any implatable device component.

- Contraindication for cMRI performance.

- Life expectancy under 1 year due to a non-cardiac cause.

- Concomitant valvulopathy with indication for surgery.

- High functional class (NYHA IV).

- No possibility to connect to the remote monitoring.

Sample size calculation: Study aims to include around 200 AMI patients. Sample size has been estimated for a confidence level of 95%, defined by a coefficient $Z_a = 1.96$ and taking into account a prevalence (p) of NSVT (< 5 episodes in 6 months) of 15% and a precision level (d) of 5%. According to the following formula, in which q = 1-p:

$$n = Z^2 * a * p * q / d^2$$
$$n = 3.84 * 0.15 * 0.85 / 0.0025 = 196 \text{ patients to be included.}$$

3. Study design:

- Epidemiological and basic clinical data of all the patients hospitalized in the participating hospitals after an episode of AMI will be collected.

- Patients accomplishing inclusion and exclusion criteria will be submitted to continuous electrocardiographic monitoring until medical discharge.

- Before discharge a cMRI (days 6-10 after AMI) will be performed and after an ILR will be implanted.

- Following medical discharge, enrolled patients will daily transmit the device register, which will be analyzed by specialized personnel. An intervention will take place if any arrhythmic event is registered following the current recommendations of scientific society.

- Patients will be reevaluated 6 months after the coronary revascularization performed during hospitalization. This clinical evaluation will include, at least, the clinical and functional status (NYHA scale), pharmacological treatment and LVEF determination by echocardiography. Besides, ILR will be explanted to cMRI acquisition. If the patient fulfills current criteria of the European

Society of Cardiology according to LVEF criteria, an ICD will be then implanted without resynchronization therapy. If the patient does not fulfill ICD criteria, ILR monitoring will continue for 18 months more (2 years after the AMI event). Periodic clinical checkup will take place according to the protocols specified by our center. According to the scientific evidence, 5-10% of subjects with LVEF ≤40% in the first week post revascularized AMI will recover part of the ventricular function, falling outside of ICD implantation criteria.

- Patients will be followed-up during the first 2 years after the AMI. Periodic checkups will be programmed according to the protocols of our center. ICD and ILR implanted patients will daily transmit the device register that will be weekly reviewed.

- After the 2 years follow-up, the ILR, in those patients without an ILR, will be explanted and a cMRI will be performed.

ICD programming:

Detection and therapy programming will be standardized and included two zones: Ventricular Fibrillation (VF) (Cycle Length [CL] < 250 ms) and Ventricular Tachycardia Zone 1 (CL from 250 to 320 ms). In both cases tachycardia detection will require that 30 of the last 40 R-R intervals had to have a CL bellow the cutoff point. Episodes classified as VF will receive a sequence of high-energy shocks. Otherwise, episodes detected in Ventricular Tachycardia Zone 1 will be initially treated by a single ATP sequence (an 8-pulse-burst train at 88%). Failed ATP will be followed by shock and then other shocks as necessary. An additional monitoring zone (Ventricular Tachycardia Zone 2) will be programmed for episodes with a CL from 321 to 400 ms.

All devices will be programmed to store the far-field electrograms before the onset of the episodes detected to aid in rhythm classification.

MRI protocol:

All patients will undergo contrast-enhanced MRI with a 1.5-T or 3 T scanner. All images will be obtained with electrocardiographic gating and breath-holding. The MRI study will consist of cine steady-state free precession imaging of left ventricular function and late enhancement imaging of myocardial scar tissue. Late Enhancement images will be obtained 10 to 15 min after an injection of 0.2 mmol/kg of gadodiamide. Late-enhanced images will be used for infarct characterization. Infarct and heterogeneous tissue (i.e., gray zone) mass will be quantified by 2 methods: 1) the full width at half maximum; and 2) on the basis of Standard Deviations (SD) of the signal intensity from

the remote mean healthy myocardium (>2SDs defined the total infarct mass,>3SDs the core infarct and HT between 2 and 3 SDs).

4. Data collection and statistical analysis

Data collection:

No personal data will be collected or processed without prior formal authorization. Once informed consent has been signed, data will be collected, stored and managed according to current local, national and EU legislation on this matter. In particular, the Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data and on the free movement of such data
will be carefully fulfilled. Any further ethical issue that may arise within the project will be properly consulted and addressed by participating entities.

Clinical variables:

a) Clinical variables from hospitalization phase:

- Date of AMI index.
- AMI location.
- Demographic data: age, gender, profession.
- Weight and height.
- Cardiovascular risk factors: Hypertension, dyslipemia, diabetes, smoking, obesity, peripheral vascular disease, drug abuse.
- Electrocardiographic variables:

o Atrial rhythm (sinus, atrial fibrillation/flutter, paced).

o Number of Q waves.

o Duration of QRS complex.

o Presence of complete bundle branch block.

- Number of epicardial coronary arteries with stenosis >70%.
- Coronary revascularization: type (percutaneous and surgical) and affected arteries.
- NSVT incidence during hospitalization.
- LVEF measured 5-7 days following the AMI: %.
- Date of ILR implantation.
- Pharmacological treatment at medical discharge.

b) Clinical variables from ILR monitoring phase:

- Qualitative (heartbeats number, polymorphic/monomorphic) and quantitative (event number) incidence of NSVT.

- Functional Class (NYHA) and LVEF (by echo) 6 months after revascularization.

- Unplanned medical interventions as a consequence of data collected from the ILR within the 6 first months post-AMI.

- After six months of ILR monitoring, among non-appropriate patients for ICD implant, clinical events will be recorded: hospitalization due to cardiac causes, syncope, pacemaker of ICD implant, aborted SCD, cardiovascular death.

c) Clinical variables from post-ICD implant phase:

- ICD or ICD-TRC implant date.

- Complications related to ICD or ICD-TRC implant.

- Clinical events after ICD implant: appropriate therapies, appropriate discharges, inappropriate therapies, hospitalization due to heart failure, cardiovascular death.

Variables from ILR recording:

- Relevant arrhythmias: sinus pause >3 seconds, second- or third-degree AV block, NSVT, SVT.

- For NSVT:

o Data: day and hour.

o Number of beats.

o Duration, seconds

o Cycle Length.

o Morphology: monomorphic or polymorphic.

- For SVT:

o Data: day and hour.

o Duration, seconds.

o Cycle Length.

o Morphology: monomorphic or polymorphic.

Variables from cMRI studies:

- Left ventricular dimensions.

- LVEF.

- Extension of scar.

- Extension of dense scar.

- Extension of heterogeneous tissue.

Statistical analysis:

Statistical analysis will be performed using the SPSS programme 11.0 or further. Normal and continuous variables will be described by means and standard deviations, whereas categorical variables will be summarized by the number of patients and percentages. Comparison of the categorical variables will be performed with the Chi-square test (or Fisher's exact test if n<5). Comparison of 2 normal variables (determined with the Kolgomorov-Smirnov test) and continuous variables will be done with Student's t test. Comparison of >2 continuous variables will be performed using the ANOVA test. Multivariate analysis will be accomplished by a logistic regression or Cox regression tests. To determine the individual mean of proportions adjusted per multiple episodes per patient, the Generalized Estimating Equations Method will be used in the calculations and comparisons. A p value <0.05 will be considered statistically significant.

Machine learning and Deep learning:

Due to the great amount of data to be collected by the ILR during the first 6 months after an AMI and by the ICD/ILR up to 2 years following the AMI, a Machine Learning analysis will be also performed to determine the association between the incidence, burden and temporal distribution of NSVTs registered by ILRs with the occurrence of ICD appropriate therapies.

Machine Learning techniques to be used will consist in supervised since the response variable is identified. The usual algorithms (random forest, xgboost, SVM, etc.) will be combined in order to find the balance between bias and variance, avoiding overfitting the available data, so that the model can be successfully generalized to further populations. In cases where the response variable is represented by a few cases, we will use subsampling and oversampling techniques such as bagging balance. All the Machine Learning analysis will be carried out using the Python programming language and libraries like scikit-learn, which include proper algorithms and techniques for the project.

Project will also acquire 2/3 cMRI of ICD/ILR implanted patients. Together with the abovementioned statistical analysis, cMRI images will be analyzed by deep learning (neural networks) in order to detect any possible pattern and their evolution. Raw images could be a reliable

predictor of patient's evolution. For the implementation of deep learning techniques Keras and TensorFlow programs will be used.

WORK PLAN

Participating centres and colaborators: Patients will be included in the study from 5 different hospitals of 3 regions of the national territory. Project will be led by Javier Jiménez Candil, from the Hospital Universitario de Salamanca, who will be in charge of project management and will coordinate actions between involved investigators within his hospital (8 collaborators) and from other entities (8 collaborators). The rest of participating hospitals are: Complejo Asistencial Universitario de Burgos (4 col.); Hospital Universitario San Pedro de Alcántara, from Cáceres (1 col.); Complejo Asistencial Universitario de Santiago de Compostela (1 col.), and Complejo Asistencial Universitario de Lugo (2 col.). All investigators collaborating within TeVeO study will facilitate to properly address the administrative management within their own entity and will ensure that protocol specifications are followed across the study, paying especial attention in data management and any ethical issue that may arise along the lifetime of the project.

Development stages:

1. <u>Project preparation and launching (M1-M2):</u> This activity will aim at first preparing the required documents needed for conducting the study, including mainly protocol approval by Ethic Committees from participating hospitals, registration and the design of data bases for data collection. Once conditions have been stablished, all participating investigators will receive instructions to properly conduct the study. Participant: JJC, JFP, JGS, ODB, JGF.

2. <u>Patients' inclusion and initial ILR monitoring (M2-M13):</u> According to stablished inclusion and exclusion criteria, AMI patients will be included in the study after obtaining the informed consent signed. ILR will be implanted and monitoring NSVT weekly during the following 6 months according to established protocol of every participating unit.
Participants: JJC, JFP, JGS, ODB, JET, JGF, JMG, NSM, RSA, JHH, JLM, MSF, FMH, LBC.

3. <u>Evaluation of ICD implantation and patient's follow-up (M7-M36):</u> 6 months after ILR implantation patients will be evaluated for ICD implantation according to previously established guidelines. Both, ICD and ILR implanted patients will be monitored up to 2 years after AMI. cMRI images will be acquired at 6 months after AMI (for the evaluation of ICD implantation) and at the

end of the follow-up period in ILR implanted patients. Participants: JJC, JFP, JGS, ODB, JET, JGF, JMG, NSM, RSA, JHH, JLM, MSF, FMH, LBC.

4. <u>Analysis of results: (M24-M36):</u> ILR data acquired during the first 6 months after the AMI will be processed as well as ILR and ICD data acquired in the following 18 months. cMRI images will be processed. Main results obtained from the project will be evaluated for publication in scientific journals, being estimated that 2 publications could be derived from this project. Participants: JJC, all investigators.

Researchers:

<u>Hospital Universitario San Pedro de Alcántara:</u> JFP (Javier Fernández Portales).

<u>Complejo Asistencial Universitario de Santiago:</u> JGS (Javier García Seara).

<u>Complejo Asistencial Universitario de Lugo:</u> ODB (Olga Durán Bobin), JET (Juliana Elices Teja).

<u>Complejo Asistencial Universitario de Burgos:</u> JGF (Javier García Fernández), JMG (Javier Martín González), NSM (Nuria Sánchez Mata), RSA (Ricardo Salgado Aranda).

<u>Hospital Universitario de Salamanca:</u> JJC (Javier Jiménez Candil), JHH (Jesús Hernández Hernández), JLM (José Luis Moríñigo), MSF (Manuel Sánchez Flores), PID (Pedro Ignacio Dorado), JMS (Jesús Manuel Sampedro), ASP (Antonio Sánchez Puente), FMH (Francisco Martín Herrero), LBC (Loreto Bravo Calero).

Timeline

SCHEDULE/TIMELINE

ACTIVITY / TASK	PERSON/S INVOLVED		MONTHS
			J F M A M J J A S O N D
PROJECT PREPARATION AND LAUNCHING	JJC, JFP, JGS, ODB, JGF	1° year	✓ ✓ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
		2° year	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
		3° year	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

ACTIVITY / TASK	PERSON/S INVOLVED		MONTHS
			J F M A M J J A S O N D
PATIENTS' INCLUSION AND INITIAL ILR MONITORING	jjc,jfp,jgs,odb,jet,jgf, jmg,nsm,rsa,jhh,jlm, msf,fmh,lbc	1° year	☐ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓
		2° year	✓ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
		3° year	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

ACTIVITY / TASK	PERSON/S INVOLVED		MONTHS
			J F M A M J J A S O N D
EVALUATION OF ICD IMPLANTATION AND PATIENTS' FOLLOW-UP	jjc,jfp,jgs,odb,jet,jgf, jmg,nsm,rsa,jhh,jlm, msf,fmh,lbc	1° year	☐ ☐ ☐ ☐ ☐ ☐ ✓ ✓ ✓ ✓ ✓ ✓
		2° year	✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓
		3° year	✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓

ACTIVITY / TASK	PERSON/S INVOLVED		MONTHS
			J F M A M J J A S O N D
ANALYSIS OF RESULTS	ALL INVESTIGATORS	1° year	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
		2° year	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ✓
		3° year	✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓

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