INSIDE-HEART

INSIDE-HEART: multI-discipliNary, multi-Sectoral and multi-national trainIng network on Digital biomarkErs for supraventricular arrHythmia charactErizAtion and Risk assessment

Project N°: 101119941

Start date of the project: 01/11/2023 Duration: 48 months

Project Coordinator: Valentina Corino

Individual research projects

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC1	POLIMI	Yes	May-July 2024	36 months	~39,000 €

Project Title and Work Package(s) to which it is related: Integration of novel contact and non-contact digital biomarkers for SVAs screening (WP1-T1.1)

Objectives:
- To acquire contact and non-contact biosignals using smartphones, webcams, thumb-ECG or other largely diffused digital devices.
- To study AI-based signal processing methods for the extraction of digital biomarkers in terms of signature.
- To assess novel risk stratification indexes for SVAs based on the new digital biomarkers.

Expected Results (project-KPI1.1, project-KPI1.2):
- AI-based reconstruction methods for the extraction of a digital biomarker signature from acquired recordings (KPI: one digital biomarker signature for project-KPI1.1).
- Integration of contact and non-contact digital biomarkers to improve SVA detection (KPI: SVA detection from 1-min recordings).
- A signature derived from the digital biomarkers able to stratify subjects for SVA risk (KPI: stratification signature with accuracy >0.90).

Planned secondments:
CCM M14 (2m) – Dr. Carbucicchio: Data collection from SVAs patients.
UTU M19 (3m) – Prof. Liljeberg: Complementary assessment of IoT for SVA detection.
PREC M22 (2m) – Eng. Juuso Blomster: Hands-on experience on the design and development of mobile apps dedicated to SVAs.
EMP M36 (3m) – Eng. Giulia Regalia: Integration of contact and non-contact technologies for SVA detection.

Notes:
The candidates must comply with the Italian laws and Politecnico rules for signing the contract. In particular, they have to provide the original academic diploma or a true copy of the same made by an Italian authority.
Non-EU candidates must legally stay in Italy at the starting date of the activities. Please read carefully the file "Additional information of employment POLIMI" for further restrictions and information.
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The hosting group: POLIMI is the largest Technical University in Italy and the Dipartimento di Elettronica, Informazione e Bioingegneria (DEIB) is the department involved in INSIDE-HEART. Within the DEIB, the Biosignals-Bioimaging-Bioinformatics (BBB) Group will participate to this network. The Group has long standing expertise in the processing of vital signals, feature extraction, system modeling as well as in the implementation of these methodologies in wearable or portable devices.

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC2	UTU	Yes	May-July 2024	36 months	~48,000 €

Project Title and Work Package(s) to which it is related: IoT-based system to detect and monitor the progress of infant's SVAs (WP1-T1.2)

Objectives:
- To acquire ballistocardiogram bed sensor and wearable ECG data from infants at in-hospital (control and SVA group) and out-of-hospital settings. To acquire spot smartphone data from infants at in-hospital settings.
- To design a remote application for detection and monitoring of SVA.
- To study signal processing methods and AI-based algorithms for the detection and monitoring of SVA.

Expected Results (project-KPI1.1, project-KPI1.2):
- Extraction of a digital biomarker signature for SVAs from clinical recordings (KPI: one digital biomarker for project-KPI1.1).
- An algorithm to detect and monitor infant's SVA via bed sensor (KPI: > 95% accuracy using motion free 30-s signal segment, normal rhythm vs. SVA).
- An algorithm to detect SVA with smartphone (KPI: > 90% accuracy using motion free 5-s signal segment, normal rhythm vs. SVA).

Planned secondments:
NU M15 (2m) – Dr. Gonzálvez: Experience on ICT infrastructures for SVA management.
POLIMI M24 (3m) – Prof. Corino: signal processing methods for non-contact monitoring of SVA.
BRC M33 (2m) – Eng. Schneider: accelerometer signal processing for implantable device.

Notes:
Please read carefully the file "Additional information of employment UTU" for further restrictions and information. www.inside-heart.eu
English language requirements: Applicants must have good English language skills and a certificate that proves those skills. Please read more about the language requirements:
https://www.utu.fi/en/research/utugs/how-to-apply/language
The person selected for the position must separately apply for the Doctoral degree study right at the Faculty of Technology, University of Turku. See also: www.inside-heart.eu

The hosting group:
University of Turku is an active academic community of more than 25,000 students and staff members from over 100 different countries. We welcome you cordially to our working community. In case you are arriving in Finland for the first time, we are offering you good orientation support. Please read further information at the website https://www.utu.fi/en/university/come-work-with-us.
- Please learn more about the culture and the people Working culture
- This is Finland   https://finland.fi/
- More information about why choose Turku as a place to study and work https://www.turku.fi/en/study-turku/welcome-turku/5-reasons-choose-turku

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC3	BRC	Yes	May-July 2024	36 months	~44,000 €

Project Title and Work Package(s) to which it is related: AI biomarker identification to assess SVA evolution as comorbidity of respiration diseases through continuous monitoring with innovative sensors (WP1-T1.3)

Objectives:
- To investigate the possibility of quantifying relevant AI-based biomarkers through innovative sensors (e.g., implantable devices, patches, smartwatches) to detect SVAs, using data from available pilot studies.
- To study how these biomarkers would help to predict SVA occurrence and prevent progression.
- To investigate the potential of those biomarkers for a comprehensive assessment of respiratory disease progression and the implication on SVA evolution.

Expected Results (project-KPI1.1, project-KPI1.2):
- Definition of 3 clinical application scenarios of the innovative sensors (KPI: one digital biomarker per application project-KPI1.1).
- Innovative algorithms for the quantification of AI biomarkers (KPI: SVA detection from 1-min recordings).
- A risk score combining the AI biomarkers for the risk assessment of patients with respiratory diseases in combination with cardiac disease (KPI: positive predictive value > 85%).

Planned secondments:
POLIMI M16-M31 (3m-1m) – Prof. Corino: Experience in sensor networks and data integration and attendance of mandatory PhD courses (POLIMI will award the PhD degree).
LU M24 (3m) – Prof. Stridh: Experience in automated analysis for cardiovascular data.
CCM M32 (3m) – Dr. Carbucicchio: Data collection for early phase clinical validation.
UMIL M40 (2m) – Prof. Sassi: Integration of AI-models with innovative sensors.

Notes:
This DC will pursue the PhD program at Politecnico di Milano. Therefore, the candidates must comply with the Politecnico requirements for joining the PhD program.
The candidates must comply with the Italian laws and Politecnico rules for signing the contract. In particular, they have to provide the original academic diploma or a true copy of the same made by an Italian authority.
Non-EU candidates must legally stay in Italy at the starting date of the activities. Please read carefully the file "Additional information of employment POLIMI" for further restrictions and information.
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Non-EU candidates must legally stay in The Netherlands at the starting date of the activities.

The hosting group: Medtronic Bakken Research Center (BRC) was founded in Maastricht in 1987 as a research facility (350 employees) for Medtronic in Europe. The BRC played a major role in the creation and realization of several world class therapies, like Deep Brain Stimulation and Cardiac Resynchronization Therapy and collaborated with Maastricht University Hospital in the definition of Atrial Fibrillation models. POLIMI is the largest Technical University in Italy and the Dipartimento di Elettronica, Informazione e Bioingegneria (DEIB) is one of the departments involved in INSIDE-HEART. Within the DEIB, the Biosignals-Bioimaging-Bioinformatics (BBB) Group will participate to this network. The Group has long standing expertise in the processing of vital signals, feature extraction, system modeling as well as in the implementation of these methodologies in wearable or portable devices.

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC4	CCM	Yes	May-July 2024	36 months	~39,000 €

Project Title and Work Package(s) to which it is related: Digital biomarkers identification and AI-based analysis for early diagnosis of SVAs in the young and adult population (WP1-T1.4)

Objectives:
- To acquire a dataset of signals provided by sensor devices of last generation (wearable sensors, smartphones, i-watches) during daily life in patients with SVAs.
- To identify digital biomarkers for specific rhythm patterns and neurohumoral parameters for the discrimination of different SVAs (atrial tachycardia vs. AF vs. atrial flutter) during continuous monitoring (facilitated by the analysis of the burden of atrial premature beats, heart rate variability, P wave, non-sustained atrial tachycardias and respiratory arrhythmias).
- To validate an AI-based algorithm for diagnosis and assessment of progression of the SVAs.

Expected Results (project-KPI1.1, project-KPI1.3):
- Identification of a digital biomarker for SVA diagnosis in young and adult population (KPI: one digital biomarker for project-KPI1.1).
- Better understanding of SVA etiopathogenesis (with implications on prevention and therapy) by digital biomarkers for the discrimination of different SVAs (KPI: accuracy > 80%).
- AI-based algorithm for early detection and progression characterization of SVAs (KPI: one digital biomarker for SVA progression).

Planned secondment(s):
POLIMI M18-M21-M31 (1m-3m-1m) – Prof. Corino: to develop algorithms for SVA discrimination and attendance of mandatory PhD courses (POLIMI will award the PhD degree).
CC M27 (3m) – Dr. Badilini: to validate an AI-based algorithm for assessment of SVA progression.

Notes:
This DC will pursue the PhD program at Politecnico di Milano. Therefore, the candidates must comply with the Politecnico requirements for joining the PhD program.
The candidates must comply with the Italian laws and Politecnico rules for signing the contract. In particular, they have to provide the original academic diploma or a true copy of the same made by an Italian authority.
Non-EU candidates must legally stay in Italy at the starting date of the activities. Please read carefully the file "Additional information of employment POLIMI" for further restrictions and information.
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The hosting group: CCM is the first Scientific Institute for Research and Treatment in Europe focused exclusively on cardiovascular disease, dedicated to adult patients.
CCM is a teaching hospital that hosts the courses for the Degree in Medicine and Surgery the Schools of Specialisation in Cardiology and Heart Surgery and courses for the Degree in Cardiocirculatory Pathophysiology of the University of Milan. Clinical, research and educational activities are combined in a "multidisciplinary approach" with the mission to achieve "Research for Care". Every year more than 1.500 surgical interventions are performed, along with 7.000 Electrophysiology Haemodynamic and Cardioversion procedures, 72.000 Medical Examinations and 55.000 Major diagnostic tests of which 2.400 for research protocols.
CCM has created and coordinates the CARDIOLOGY NETWORK of the Italian Ministry of Health. Main objects of this network are to promote scientific and technological research, create common clinical and experimental platforms, improve treatment standards and promote common educational and career programs.

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC5	EMP	Yes	May-July 2024	36 months	~39,000 €

Project Title and Work Package(s) to which it is related: AI-based monitoring platform for arrhythmia detection through smartwatch devices (WP1-T1.5)

Objectives:
- To design and validate a continuous monitoring system suitable for SVA events.
- To develop a digital biomarker able to detect SVA events with accuracy comparable or better than state-of-the-art.
- To identify low-cost alternatives for the algorithm components and system integration.

Expected Results (project-KPI1.1, project-KPI1.3):
- Continuous monitoring through smartwatch to detect SVAs (KPI: one digital platform for SVA monitoring).
- AI-based digital biomarkers for SVA identification (KPI: one digital biomarker for prokect-KPI1.1)
- Optimization of the computational cost to embed the algorithm on the EMP EmbracePlus (KPI: release in production of the algorithm)

Planned secondment(s):
CCM M16 (2m) – Dr. Carbucicchio: Data collection using EMP smartwatch from SVA patients.
UNIZAR M27 (3m) – Prof. Pueyo: Experience in algorithm development for SVA detection and attendance of mandatory PhD courses (UNIZAR will award the PhD degree).
UTU M36 (3m) – Prof. Liljeberg: Complementary experience in algorithm optimization on embedded systems.

Notes:
This DC will pursue the PhD program at University of Zaragoza. Therefore, the candidates must comply with the University of Zaragoza requirements for joining the PhD program. The candidates must comply with the Spanish laws and Zaragoza university rules for signing the contract. In particular, they have to provide the original academic diploma or a legalized copy of the same made by a Spanish authority. Please read carefully the file "Additional information of employment UNIZAR" for further restrictions and information" www.inside-heart-eu

The hosting group: EMP is a full-stack digital healthcare company headquartered in Boston, MA with offices in Milan, Italy, and Seoul, South Korea. Empatica is a pioneer in digital biomarker development and continuous patient monitoring driven by AI. Empatica's platform consists of medical-grade smartwatches, software, and physiological and behavioural digital biomarkers. Together they enable the continuous remote monitoring of human health across a range of conditions, through clinical-quality digital measurements.

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC6	NU	Yes	May-July 2024	36 months	~37,000 €

Project Title and Work Package(s) to which it is related: AI-based predictors of SVA development in patients with comorbidities and suspected SVAs (WP1-T1.6)

Objectives:
- To use deep learning on ECG data (long term Holter) to investigate the mechanisms behind SVA development in patients with comorbidities using data from available previous studies.
- To identify digital biomarkers which playing a central role in arrhythmia progression.
- To propose ECG-based biomarkers characterizing progression and compare them to non-ECG clinical biomarkers.

Expected Results (project-KPI1.1, project-KPI1.3):
- More accurate digital biomarkers for SVA detection in patients with comorbidities (KPI: accuracy > 0.8).
- New knowledge on arrhythmia progression with particular relevance to patients with comorbidities (stroke, syncope, TAVI's) (KPI: AI-based digital biomarker for early indication of SVA for project-KPI1.1).
- Agreement between ECG-based biomarkers and clinical ones (KPI: Cohen's kappa > 0.6).

Planned secondment(s):
CCM M15 (3m) – Dr. Carbucicchio: Data collection from patients with comorbidities and suspected SVAs.
UMIL M18-M32 (1m-2m) – Prof. Sassi: Algorithm validation for SVA prediction and attendance of mandatory PhD courses (UMIL will award the PhD degree).
UNIZAR M27 (3m) – Prof. Pueyo: Experience of complementary signal processing on SVA detection.

Notes:
This DC will pursue the PhD program at University of Milan. Therefore, the candidates must comply with the Italian laws and Università degli Studi di Milano rules for signing the contract.
In particular, they have to provide the original academic diploma or a legalized copy of the same made by an Italian authority. Non-EU candidates must legally stay in Italy at the starting date of the activities. Please read carefully the file "Additional information of employment UMIL" for further restrictions and information. www.inside-heart.eu

The hosting group: Nuubo is a Spanish medical device manufacturer with expertise in the development of wearable textile solutions. The company develops its own textile with electrodes integrated into the fabric, the electronics to record the ECG and also develops internally the software and algorithms to process the data and diagnose arrhythmias of long term monitoring (30 days). The product is CE marked and FDA approved . The company is also developing new algorithms using deep learning techniques and its proprietary dataset of long term ECG recordings.

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC7	TECH	Yes	May-July 2024	36 months	~43,000 €

Project Title and Work Package(s) to which it is related: Digital biomarkers and deep learning for cardiovascular risk prediction in patients with SVAs from continuous long term ECG recordings (WP2-T2.1)

Objectives:
- To develop deep learning and feature-based digital biomarkers for cardiovascular risk prediction in patients with SVAs from long term continuous ECG (~24 hours) using a novel large database totaling ~40,000 Holter ECG recordings from multiple centers.
- To compare the predictive power of deep learning and feature-based digital biomarkers, using class activation maps for the former and feature importance for the latter.
- To study how the performances of the deep learning algorithms vary with demographic differences such as sex, race and ethnicity.

Expected Results (project-KPI2.1, project-KPI2.2):
- Cardiovascular risk prediction in SVA patients learning (KPI: Area Under the Curve (AUC) > 0.8).
- Interpretability of feature-based digital biomarkers (using feature importance) and deep learning patterns (using activation maps) learnt for the risk prediction tasks (KPI: one digital biomarker for project-KPI2.1).
- Assessment of demographic differences on the deep learning performance (KPI: quantitative comparison).

Planned secondment(s):
UNIZAR M18 (3m) – Prof. Pueyo: experience on ECG waveform analysis.
RDS M33 (3m) – Eng. Mayaud: validation of algorithms on data acquired using RDS innovative ECG patch system.
BRC M39 (3m) – Eng. Schneider: validation of algorithms on data acquired using BRC implantable device.

Notes:
Doctorate in Israel and at the Technion lasts for 3.5 years. Please read carefully the file "Additional information of employment TECH" for further restrictions and information"
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The hosting group: The AIMLab. develops artificial intelligence algorithms for basic medical & clinical research which will lead to significantly improved patient care. URL: https://aim-lab.github.io/

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC8	UNIZAR	Yes	May-July 2024	36 months	~37,000 €

Project Title and Work Package(s) to which it is related: ECG prediction of AF recurrence rate guided by AI and mechanistic computational modelling (WP2-T2.2)

Objectives:
- To establish a relationship between spatial patterns of fibrotic distribution and characteristics of electrical propagation in atrial tissues.
- To identify atrial fibrotic patterns associated with high AF recurrence rate after ablation.
- To propose non-invasive ECG markers that improve the capacity to identify risk for AF recurrence after ablation when combined with other clinical variables.

Expected Results (project-KPI2.1, project-KPI2.3):
- Characterization of the association between atrial fibrotic tissue patterns and electrical propagation properties by combined image processing and in silico modelling (KPI: correlation coefficient > 0.75).
- AI-based identification of fibrotic patterns associated with high likelihood for AF recurrence after ablation (KPI: AI-based architecture with accuracy > 0.85).
- A digital biomarker obtained from integration of ECG markers correlated to fibrosis properties, allowing accurate prediction of AF recurrence after ablation (KPI: one digital biomarker for project-KPI2.1).

Planned secondment(s):
IISA M19 (2m) – Dr. Ramos Maqueda: To get training on electrophysiology and on ablation procedures in AF patients.
TECH M28 (3m) – Prof. Behar: To develop AI-based methods for classification of atrial fibrotic patterns.
NU M37 (2m) – Dr. Gonzálvez: To investigate techniques for monitoring of AF recurrence from long-term ECG recordings.

Notes:
The candidates must have a university degree in engineering, mathematics or physics plus master of science degree in related disciplines. Experience in signal processing, statistical data analysis and numerical simulations is advantageous. The candidates must comply with the Spanish laws and Zaragoza university rules for signing the contract. In particular, they have to provide the original academic diploma or a legalized copy of the same made by a Spanish authority. Please read carefully the file "Additional information of employment UNIZAR" for further restrictions and information"
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The hosting group: The Aragon Institute of Engineering Research (I3A), within the University of Zaragoza, comprises more than 500 researchers and a vibrant environment for multidisciplinary research. I3A has gained notable national and international recognition. Every year I3A participates in more than 300 research projects funded with over 10 M€ and more than 200 contracts with industry with 5 M€ turnover. Around 50 PhD theses supervised by I3A members are defended and nearly 300 papers are published in JCR journals every year. The Biomedical Signal Interpretation and Computational Simulation group at I3A, University of Zaragoza, comprising around 40 members, is a leading expert in the development of signal processing tools to aid in the diagnosis, prognosis and treatment of cardiovascular diseases and conditions. The expertise in processing of invasive and non-invasive signals is combined with modelling and simulation of cardiac electrophysiology to provide insight into the mechanisms underlying phenomena observed from the processed signals.

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC9	LU	Yes	May-July 2024	36 months	~51,000 €

Project Title and Work Package(s) to which it is related: AI-based outcome prediction of arrhythmia progression in elderly cardiac patients (WP2-T2.3)

Objectives:
- To use AI on big screening data to investigate the mechanisms behind SVA risk, using available large databases including thousands of recordings from elderly patients, reducing false positive rate.
- To identify digital biomarkers which play a central role in cardiovascular risk prediction.
- To compare ECG-based and non-ECG clinical biomarkers characterizing SVA risk.

Expected Results (project-KPI2.1, project-KPI2.2):
- Assessment of SVA risk in patients with short episodes of supraventricular tachycardia (KPI: one digital biomarker for project-KPI2.1).
- A digital biomarker for cardiovascular risk prediction in the elderly (KPI: one digital biomarker for project-KPI2.1).
- Agreement between ECG-based biomarkers and clinical ones (KPI: correlation coefficient > 0.75).

Planned secondment(s):
IISA M19 (2m) – Dr. Ramos Maqueda: To take part in data collection and writing of applications for ethical approvals.
UMIL M25 (3m) – Prof. Sassi: Experience on complementary AI approaches in relation to available data.
BRC M39 (1m) – Eng. Schneider: To study how AI can be used in relation to medical device regulation, and how research becomes products in this field.

Notes:
Please read carefully the file "Additional information of employment LU" for further restrictions and information" www.inside-heart.eu
See https://www.phd.lth.se/english/ and
https://www.phd.lth.se/fileadmin/phd/files/allm_studieplaner/Biomedicinsk_teknik_en.pdf.
The duration of the PhD program at Lund University is four years.
For further information visit www.inside-heart.eu

The hosting group: Lund University (LU) is the largest in Scandinavia, and houses the Department of Biomedical Engineering participating in this project. Within the department there are research groups covering a wide array of biomedical engineering related research topics including biomechanics, biomedical signal processing, biomedical imaging, nanobiotechnology, neural engineering, and ultrasound. The present project is performed within the well-known research group in biomedical signal processing. Analysis of cardiac signal represents the main research focus of the group, reflected by about 100 journal papers published. The group has long-standing collaboration with Swedish medical industry which to date has led to 10 patents. The group collaborates with Karolinska University Hospital (Stockholm) regarding ECG screening data (the StrokeStop project) as well as with other European universities. The research group is connected to the profile area Engineering Health at the Faculty of Engineering of Lund University (https://portal.research.lu.se/en/organisations/lth-profile-area-engineering-health).

Fellow	Host institution	PhD enrolment	Start date	Duration	Gross salary
DC10	UMIL	Yes	May-July 2024	36 months	~39,000 €

Project Title and Work Package(s) to which it is related: Assessment of ventricular repolarization during AF and risk prediction from clinical and wearable ECG (WP2-T2.4)

Objectives (project-KPI2.1, project-KPI2.3):
- To investigate on changes of ventricular repolarization during AF via computational model.
- To propose an advanced signal processing algorithm for digital biomarkers related to repolarization and AF.
- To propose AI-based digital biomarkers related to repolarization and AF, using data from previous studies.

Expected Results:
- Quantification of the relationship between repolarization time and action potential amplitude and digital biomarkers (KPI: correlation coefficient > 0.75).
- Development of robust signal processing algorithms to assess ventricular repolarization during AF (KPI: reliability test for the algorithms, p-value < 0.05).
- An AI-based digital biomarker to assess the risk of adverse events (KPI: one digital biomarker for project-KPI2.1).

Planned secondment(s):
UNIZAR M18 (2m) – Prof. Pueyo: Experience of high resolution computational models for ventricular repolarization during AF.
IISA M20 (1m) – Dr. Ramos Maqueda: Data acquisition for algorithm validation in conjunction with UNIZAR.
TECH M28 (3m) – Prof. Behar: Experience on complementary signal processing and machine learning algorithm for SVA analysis.
CC M37 (2m) – Dr. Badilini: Hands-on activity on the development of production-level software for clinical and wearable ECG automated processing.

Notes:
The candidates must comply with the Italian laws and Università degli Studi di Milano rules for signing the contract. In particular, they have to provide the original academic diploma or a legalized copy of the same made by an Italian authority. Non-EU candidates must legally stay in Italy at the starting date of the activities. Please read carefully the file "Additional information of employment UMIL" for further restrictions and information. www.inside-heart.eu

The hosting group: Università degli Studi di Milano (UMIL), member of the League of European Research Universities (LERU), is a public teaching and research university, distinguished by its wide variety of disciplinary fields and the largest university in the region (65000 students and a teaching staff of about 2200 professors). The Department of Computer Science (DCS) is the unit directly involved in INSIDE-HEART. Within the DCS, the BiSP (Biomedical image and Signal Processing) group will participate to the INSIDE-HEART network. The BiSP group has a significant expertise in biomedical signal processing, computer simulations, information processing technology and systems, applied mathematics, and wearable technologies. The Department of Clinical Sciences and Health Community (DCSHC) will also be involved in the education of the Ph.D. student, with specific regard to the acquisition of medical signals and definition of the medical experimental protocols. DCSHC has a long-lasting experience in the autonomic regulation of cardiovascular system.