SEVENTH FRAMEWORK PROGRAMME

Health

HEALTH-2007-2.4.2-6 Organ imaging in CVD

Grant agreement for: Collaborative Project (i) Small or medium-scale focused research project

Annex I - "Description of Work"

Project acronym: EVINCI-study
Project full title: Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease
Grant agreement no.: 222915
Date of preparation of Annex I (latest version): 03/08/2011
Date of approval of Annex I by Commission:

List of Beneficiaries

Beneficiary Number	Beneficiary name	Beneficiary short name	Country	Date enter project	Date exit project
1(coordinator)	Consiglio Nazionale delle Ricerche	CNR	Italy	1	42
2	Turun yliopisto	U.Turku	Finland	1	42
3	Universitaet Zuerich	UZH	Switzerland	1	42
4	Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum	LUMC	Netherlands	1	42
6	Fundacio Privada Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	IR-HSCSP	Spain	1	42
7	Instytut Kardiologii Im. Prymasa Tysiaclecia Stefana Kardynala Wyszynskiego	NIC	Poland	1	42
8	Royal Brompton & Harefield National Health Service Trust	RBHT	United Kingdom	1	42
9	Assistance Publique – Hopitaux de Paris	AP-HP	France	1	42
10	Università degli Studi di Genova.	UniGE	Italy	1	42
11	Servicio Madrileño De La Salud	SERMAS	Spain	1	42
12	Università degli Studi di Napoli Federico II.	UniNA	Italy	1	42
13	Institut Catala de la Salut	HUVHEBRON	Spain	1	42
14	Société Européenne de Cardiologie	ESC	France	1	42
15	Inforsense Limited	INF	United Kingdom	1	15
16	CF Consulting Finanziamenti Unione Europea SRL	CFc	Italy	1	42
17	Fondazione toscana Gabriele Monasterio per la ricerca medica e di sanità pubblica.	FGM	Italy	1	42
18	Klinikum Rechts Der Isar Der Technischen Universitaet Munchen	KRITUM	Germany	1	42
19	Queen Mary and Westfield College, University of London	QMUL	United Kingdom	13	42
20	Azienda Ospedaliero-Universitaria Careggi	AOUC	Italy	13	42

21	Azienda U.S.L.N. 12 di Viareggio	Ospedale Versilia	Italy	13	42
22	Kliniken Des Landkreises Göppingen GGMBH	KAE	Germany	13	42

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PART A

A1. Budget breakdown and project summary

A.1 Overall budget breakdown for the project

Project Number [1]	222915	Project Acronym [2]	EVINCI-study

One Form per Project

Participant number in this project [3]	Participant short name	Estimated eligible costs (whole duration of the project)					Total receipts	Requested EU contribution
		RTD / Innovation (A)	Demonstration (B)	Management (C)	Other (D)	Total A+B+C+D		
1	CNR	604,366.53	0.00	69,856.67	31,704.23	705,927.43	0.00	554,835.80
2	U. Turku	571,611.20	0.00	19,154.69	2,160.00	592,925.89	0.00	450,023.09
3	UZH	107,586.98	0.00	5,760.00	6,255.76	119,602.74	0.00	92,706.00
4	LUMC	257,807.81	0.00	2,879.66	2,879.50	263,566.97	0.00	199,115.02
5 (DEL)	TUM	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6	IR - HSCSP	42,058.94	0.00	6,749.30	6,847.50	55,655.74	0.00	45,141.01
7	NIC	98,125.12	0.00	9,517.13	6,869.84	114,512.09	0.00	89,980.81
8	RBHT	72,636.00	0.00	29,806.10	10,989.02	113,431.12	0.00	95,272.12
9	AP-HP	108,844.21	0.00	1,440.00	1,440.00	111,724.21	0.00	84,513.16
10	UniGE	146,593.00	0.00	1,438.00	1,438.61	149,469.61	0.00	112,821.36
11	SERMAS	117,598.77	0.00	5,576.00	9,228.80	132,403.57	0.00	103,003.88
12	UniNA	46,129.58	0.00	5,302.38	5,132.80	56,564.76	0.00	45,032.36
13	HUVHEBRON	51,168.67	0.00	7,198.72	10,690.32	69,057.71	0.00	56,265.54
14	ESC	0.00	0.00	6,848.16	38,145.44	44,993.60	0.00	44,993.60
15	INF	62,321.20	0.00	2,034.18	0.00	64,355.38	0.00	48,775.08
16	CFc	0.00	0.00	54,105.69	56,574.77	110,680.46	0.00	110,680.46
17	FGM	310,709.12	0.00	0.00	0.00	310,709.12	0.00	233,031.84
18	KRITUM	115,347.95	0.00	6,981.55	5,470.48	127,799.98	0.00	98,962.99
19	QMUL	129,397.60	0.00	23,199.68	0.00	152,597.28	0.00	120,247.88
20	AOUC	47,238.40	0.00	2,285.60	2,285.60	51,809.60	0.00	40,000.00
21	Ospedale V	31,200.00	0.00	2,400.00	4,200.00	37,800.00	0.00	30,000.00
22	KAE	41,813.33	0.00	3,840.00	4,800.00	50,453.33	0.00	40,000.00
TOTAL		2,962,554.41	0.00	266,373.51	207,112.67	3,436,040.59	0.00	2,695,402.00

A.2 Project summary

A1:
Our project

Project Number [1]	222915	Project Acronym [2]	EVINCI-study

One form per project

General information

Project title [3]	Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease		
Starting date [4]	01/01/2009		
Duration in months [5]	42		
Call (part) identifier [6]	FP7-HEALTH-2007-B		
Activity code(s) most relevant to your topic [7]	HEALTH-2007-2.4.2-6: Organ imaging in CVD		

Abstract [9] (max. 3000 char.)

The main purpose of the EVINCI-study is to test the impact of combined "anatomo-functional" non invasive cardiac imaging for detection and characterization of Ischemic Heart Disease (IHD). The EVINCI-study is a prospective clinical European multicenter trial performed in a cohort of 700 patients with suspected IHD. Patients with intermediate pre-test probability will undergo clinical and biohumoral characterization, including novel circulating markers of cardiovascular risk. They will be admitted to a non-invasive cardiac evaluation, consisting of "anatomic" imaging, by multislice computerized tomography, combined with "functional" tests among radionuclide, magnetic resonance and ultrasound imaging. Heart catheterization will be performed to validate non-invasive diagnosis and follow-up to assess outcome. The diagnostic accuracy of combined non-invasive "anatomo-functional" imaging will be tested against reference methods for diagnosing epicardial coronary lesions (coronary angiography), vessel wall atherosclerosis (intracoronary ultrasound) and impaired coronary flow reserve (intracoronary doppler/pressure wire). The individual profiles from "anatomo-functional" cardiac imaging and "clinical-biohumoral" data will be combined and tested against outcome. A cost-benefit analysis (including an estimate of procedural/radiological risks) of the new diagnostic work-up will also be performed. A relevant part of the EVINCI-study will be dedicated to the development, in cooperation with the industry, of an advanced informatics' platform able to synthetically present to the end-user (patients, physicians, etc.) the integrated cardiological diagnostic profile of the individual patient as resulting from clinical-biohumoral and multi-imaging assessment. Overall results will be disseminated in cooperation with the European Society of Cardiology (ESC) and will guide the work of a dedicated ESC Commission which will release specific European Recommendations.

A.3 List of beneficiaries

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7	Instytut Kardiologii Im. Prymasa Tysiaclecia Stefana Kardynala Wyszynskiego	NIC	Poland	1	42
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PART B

B1. Concept and objectives, progress beyond state-of-the-art, S/T methodology and work plan

B 1.1 Concept and project objective(s)

In Europe the mortality due to cardiovascular diseases has progressively increased up to the last 20 years, when mortality flattened and then tended to decline[1]. It has been estimated that 42% of the decrease in cardiovascular mortality can be ascribed to new medical and interventional treatments (including secondary prevention, treatment of heart failure and acute myocardial infarction), while 58% can be ascribed to a reduction in some cardiovascular risk factors (as smoking cessation, improved blood pressure control and cholesterol reduction)[2]. While cardiovascular mortality rates, adjusted for age, continue to decline, the crude mortality rates remain approximately stable in most western European countries and even increase in most eastern countries. Hence, due to the ageing of the population, cardiovascular disease is still the major cause of death across Europe and a major cause of morbidity and loss of quality of life[1]. In particular, with the diffusion of new risk factors (physical inactivity, diabetes mellitus and obesity), the prevalence of **ischemic heart disease (IHD)**, the most frequent among cardiovascular diseases, is actually increasing[1]. Accordingly, better prevention and management of IHD is needed to further reduce early cardiovascular mortality and morbidity and to improve life expectancy and quality of life.

Further achievements in the fight against cardiovascular diseases could be obtained by developing and testing new strategies for the early detection and better characterization of IHD. These strategies should be based on non-invasive methods, should be cost-effective and ready for large scale clinical utilization in the next few years and should allow to identify new reliable end-points for prevention and treatment.

At present, invasive coronary arteriography (ICA) is widely considered the gold standard for the detection and characterization of IHD. However, ICA is not faultless. First of all it focuses on one specific "anatomical" feature of the disease, i.e. on the changes in coronary lumen caused by abnormalities in the wall of epicardial coronary arteries, but not on its functional correlates, namely the effect on myocardial perfusion and contraction. In addition, ICA has a limited sensitivity when compared to necropsy studies, where a significant gap was documented between the small number of angiographically visible lesions and the large number of occult plaques[3]. Furthermore, ICA does not allow to detect the early stages of coronary atherosclerosis and to study coronary microcirculation, increasingly recognized as independent determinants of impaired blood flow, disease progression and adverse prognosis and hence potential targets of early treatment. Further limitations of ICA are related to its cost and to procedural risks that prevent its utilization on a large scale in patients with intermediate-low pre-test probability of the disease.

The structure of the coronary arterial wall can be accurately studied by intra-vascular ultrasound (IVUS). This method is more sensitive than ICA in detecting early coronary atherosclerosis that can be found also at angiographically normal sites[4-6]; furthermore IVUS provides information on coronary remodelling and extraluminal plaques[7]. The functional significance of coronary lesions can be assessed by intra-coronary Doppler flow and pressure wires. When angiographic data were compared with the methods for functional assessment, only 36% of patients with angiographically normal coronary arteries were completely normal[8]. However, both IVUS and intra-coronary Doppler flow and pressure wires are again invasive, expensive and not routinely utilized.

Some of the limitations of ICA could be overcome by angiographic computed tomography of the coronary arteries (CTA), as it is non-invasive and enables the evaluation of both epicardial coronary lumen and arterial wall. The advantages of non-invasive coronary arteriography also carry some risks, mainly related to radiation exposure and to the contrast medium itself. Additionally, an intrinsic risk exists that a wide utilization of CTA, not supported by information on the functional significance of coronary lesions, could lead to an increase in the number of inappropriate invasive imaging procedures and even of unnecessary coronary interventions[9-10].

Several non-invasive "functional" tests, based on radionuclide (SPECT and PET), ultrasound (ECHO) or magnetic resonance imaging (MRI) methods, allow studying the functional correlates of coronary lesions. These techniques focus either on hemodynamic relevance (perfusion) or mechanical relevance (wall motion and contractility) of coronary stenoses. At present these "functional" tests and CTA can be utilized as gate-keepers to ICA. Recent surveys of the European Society of Cardiology have shown that non-invasive functional tests are under-utilized, with wide variability between different countries, so that several patients without significant IHD directly undergo ICA, as indirectly demonstrated by the large proportion of patients who do not receive any revascularization after ICA. On the other hand coronary lesions detected by ICA are often revascularized even if no demonstration that they affect either myocardial blood supply or mechanical function is provided[11-15].

We hypothesized that combining the "anatomical" information provided by CTA with the "functional" information provided by non-invasive tests could allow to early detect and better characterize the patients with suspected IHD. Since different non-invasive modalities provide different information, an integrated approach could improve our understanding of IHD, and could optimize patient management and utilization of health resources. Specifically, the number of invasive imaging procedures, the number of inappropriate revascularizations, and health costs due to inappropriate management could be reduced. Moreover, the recognition of patients with early disease could promote new prevention and early treatment programs. A possible risk of this approach could be an over-utilization and duplication of costly technologies. Accordingly, there is an urgent need to perform an intermodality comparison and to evaluate new integrated non-invasive diagnostic strategies for accuracy and cost-effectiveness against reference methods and patient outcome.

For the above reasons the European Society of Cardiology and its Working Group of "Nuclear Cardiology and Cardiac CT" endorse the application of the EVINCI-study. The EVINCI-study is a prospective, clinical, multi-centre, European trial in patients with suspected IHD. Patients with intermediate pre-test probability of the disease, defined after routine clinical screening including stress ECG, and fulfilling inclusion and exclusion criteria, will be enrolled. They will undergo laboratory characterization and non-invasive cardiac evaluation, consisting of "anatomic" coronary imaging by CTA, combined with "functional" imaging by radionuclide, ultrasound or magnetic resonance modalities. Subsequently, coronary arteriography, including invasive functional measurements, will be performed to validate non-invasive diagnosis. Follow-up data will be collected in each patient. A cost-benefit analysis of the new diagnostic work-up (including an estimate of procedural/radiological risks) will also be performed. Furthermore, an advanced informatics platform, able to synthetically present to the end-user the integrated information, will be developed in cooperation with the industry. The study results will be disseminated in cooperation with the European Society of Cardiology.

Main purpose of the study

To test the impact of a combined non invasive, "anatomo-functional" cardiac imaging strategy on the detection and management of IHD.

Specific objectives

Objective 1

To test the accuracy of "anatomo-functional" non-invasive cardiac imaging in the diagnosis of IHD. To this purpose the "anatomic" information provided by CTA will be combined in every patient with the "functional" information provided by radionuclide cardiac imaging (SPECT or PET) to assess the relevance of coronary disease by its effects on myocardial perfusion. Additionally, MRI or ECHO imaging will be performed to assess the relevance of coronary disease by its effects on myocardial contraction.

Non-invasive results will be tested against invasive reference standards. The latter will consist of ICA integrated by intra-coronary pressure wire (to assess the hemodynamic relevance of coronary stenoses), by IVUS (to detect early coronary artherosclerosis) and by Doppler flow wire (to recognize microvascular dysfunction).

Means of verification: I) number of patients enrolled (≥ 700 after 36 months [M0.2]) in whom non-invasive and/or invasive data have been collected according to the protocol; II) at least 70% of the number of patients with completed follow-up [M0.3] III) report on the overall results of multimodality non-invasive imaging in diagnosing and characterizing IHD available at 40 months [M4.1].

Objective 2

To evaluate the association of risk profiles assessed from clinical data and biomarkers with "anatomo-functional" patient characterization and outcome. To reach this goal the clinical characterization of patients (collected before non-invasive imaging) and the laboratory characterization (that will include novel biomarkers of cardiovascular risk) will be compared with patient characterization derived from "anatomo-functional" imaging and with patient outcome during the follow-up.

Means of verification: I) number of patients with complete clinical data and biomarkers collected at the time of non-invasive and/or invasive cardiac imaging, that is expected to exceed 70% of patients enrolled at 36 months [M1.1] II) report on results of models based on clinical data and biomarkers to predict diagnosis of IHD available at 40 months [M1.2] III) report on overall results of association between clinical, biomarkers and imaging profiles to predict outcome available at 40 months [M5.1].

Objective 3

To develop an advanced clinical and imaging reporting and integrated decision making tool in cardiology. In cooperation with InforSense (P15-INF), an informatics platform will be developed to synthetically and clearly present the integrated clinical and imaging diagnostic profile of individual patients. Specialized clinical decision making tools will be part of the platforms based on "image fusion" of different imaging modalities (CT, SPECT, PET, MRI) and their integrated analysis with other clinical data. The tools will target both researchers and physicians and would speed-up the deployment of the novel results obtained within EVINCI-study, and similar future studies, to clinicians at the point of care.

Means of verification: I) softwares for multimodality imaging registration/fusion and for integrating clinical and imaging information in a 3D heart model (ready to be tested by the participants) available at 40 months [M7.1].

Objective 4

To define the most cost-effective work-up for the diagnosis and characterization of IHD. To this purpose the costs and the procedural risks (including radiation exposure) of non-invasive and invasive diagnostic procedures will be prospectively collected. Cost-benefit and cost-effectiveness analyses will be conducted alongside the EVINCI-study clinical trial.

Means of verification: I) report on final results of safety, analysis of the entire study available after 40 months [M6.1].

Considering all the above, the EVINCI-study is in line with the FP7 application for several reasons:

1. It is based on the comparison of different imaging modalities.
2. All the tested imaging modalities are non-invasive. The invasive imaging modalities are the necessary gold standards.
3. A new diagnostic approach to the patients with suspected IHD (based on integrated non-invasive imaging) is proposed.
4. A new characterization of patients with suspected IHD (based on non-invasive imaging) is proposed.
5. Quantitative data are collected in every section of the study, from clinical characterization and laboratory examination, to non-invasive and invasive imaging, up to the follow-up.
6. A new tool will be set up to synthetically and clearly present to the end-user the integrated clinical and imaging diagnostic profile of individual patients and to help in the clinical decision making process.
7. The new characterization of patients derived from non-invasive imaging will be compared with patient outcome in an early clinical trial, and reliability of imaging data as surrogate endpoint to be used in trials will be investigated.
8. The cost/benefit ratio of the proposed approach will be evaluated.
9. The proposed approach could reduce the health costs caused by inappropriate management.
10. The proposed approach could improve our understanding of IHD and patient health.

B 1.2 Progress beyond the state of the art

1.2.1 Current diagnostic approach in patients with suspected IHD: pitfalls and risks

Before developing this issue, some words should be dedicated to the terminology adopted in this project. The abnormalities of myocardial perfusion, myocardial ischemia and its clinical manifestations will be identified as ischemic heart disease (IHD). Since IHD is commonly a more comprehensive definition, the abnormalities of epicardial coronary arteries, will be specifically referred to as coronary artery disease (CAD) while those of the coronary microcirculation, will be referred to as coronary microvascular disease (CMVD).

The state-of-the-art of diagnostic strategies in patients with suspected IHD is for many aspects unsatisfactory.

In everyday clinical practice, the main clinical manifestations of IHD (angina, myocardial infarction, cardiac sudden death and heart failure) are attributed to the effects of epicardial coronary lesions (CAD). In this view, stenotic or occluded coronary arteries hamper downstream blood flow, reduce myocardial perfusion and cause contractile dysfunction. This simplistic approach is largely incomplete for different reasons.

Many evidences [16-18] strongly suggest that the anatomical diagnosis of CAD, such as that based on detection of coronary stenoses, does not imply the presence of IHD and may not be related with outcome.

On the other side, patients with various diseases, such as arterial hypertension, diabetes mellitus, dyslipidemia, dilated cardiomyopathy and others, have myocardial perfusion defects in spite of normal coronary angiograms. These findings likely reflect primary changes in coronary microvascular function, i.e. CMVD[19]. These coronary microvascular alterations may coexist or not with epicardial coronary artery lesions and contribute to ischemia and to adverse prognosis[20]. Despite this complexity, the diagnostic work-up of patients with suspected IHD is still oriented mainly towards the detection of "anatomical" CAD as expressed by the degree of reduction in coronary lumen diameter at ICA.The "anatomically oriented" invasive approach may negatively impact patient management leading to suboptimal medical treatment, inappropriate revascularizations, additional risks and increased health costs [18, 21-23].

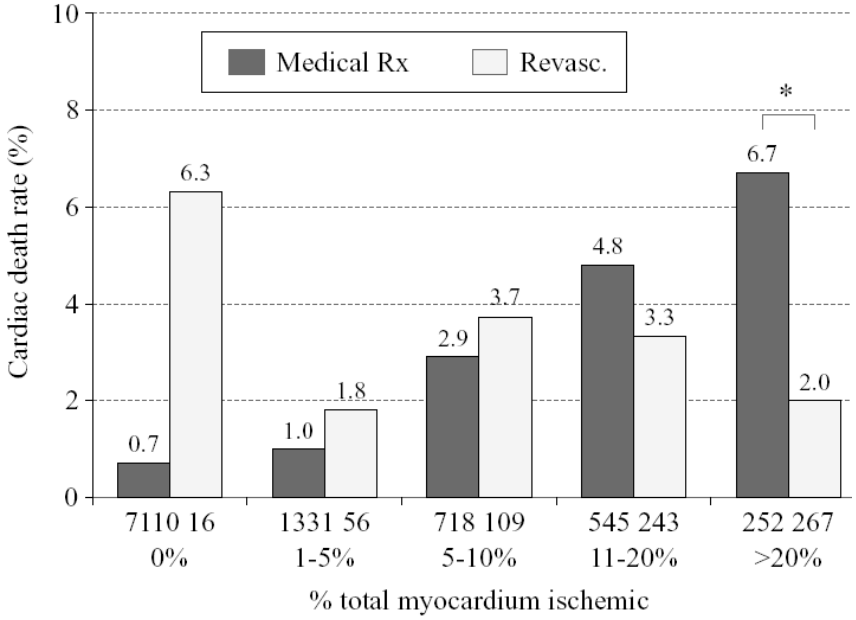

Figure 1. Differences in cardiac death rate at follow-up between patients treated medically (dark bars) or revascularized (white bars) subdivided according to the % extent of myocardial ischemia before treatment. Mortality is 6 times higher in patients revascularized with no evidence of ischemia while revascularization is associated with significant prognostic gain only in those patients previously showing substantial myocardial ischemia (REF 21).

1.2.2 Expected progress beyond the state-of-the-art (I): improved diagnosis and characterizationof IHD

Baseline

The baseline concept from which the EVINCI-study starts is that the introduction of multidetector CT scanners is revolutionizing the field of cardiac imaging by making "direct" non-invasive evaluation of the coronary anatomy possible. The application of this technology in the form of CTA, especially with 64-slices, provides excellent diagnostic sensitivity for identifying stenoses in the proximal and middle segments of main coronary arteries. Further application of CT includes the evaluation of non obstructive atherosclerotic plaque burden and its composition. Studies have been completed or are on-going in comparing the accuracy of CT against ICA for the "anatomical" detection of CAD. In the

opinion of the applicants, however, these potentialities of CT could further enhance a "paradox" of current clinical practice. Despite the availability of a variety of non-invasive imaging modalities which are able to provide information on "functional" correlates of CAD, this potentiality is not frequently utilized in the diagnostic work-up of IHD and it often serves merely as a gate-keeper to invasive assessment of coronary anatomy which dictates anyway the final medical decision. The introduction of CTA could further push the simple "anatomical" diagnostic approach which is inadequate for a correct management of IHD.

Progress

Starting from current development of non-invasive imaging technologies, the EVINCI-study will go further beyond this direction by combining "anatomical" with "functional" non-invasive imaging together with clinical and laboratory evaluation in patients with suspected IHD.

- ***The EVINCI-study will develop and validate a comprehensive non-invasive work-up, including clinical and laboratory evaluation together with "anatomic" and "functional" imaging, to provide a new mean for early detection and characterization of IHD.*** **[D1]**

1.2.3 Expected progress beyond the state-of-the-art (II): advancement in cardiac non-invasive imaging

Assessment of IHD by multimodality imaging

Baseline

The available meta-analyses refer to the accuracy of single non-invasive imaging modalities in detecting CAD, taking "anatomical" stenosis demonstrated at ICA as a gold standard[24-27]. However, the possibility to get multiple information from the same exam, as well as to use multimodality imaging to obtain complementary information on the anatomical and functional status of the coronary macro and micro vessels is a desirable goal for early detection and characterization of IHD. To better explain this issue, the relationship between the different stages of coronary disease (Figure 2), their possible clinical manifestations and their assessment are briefly reviewed. Early or minimal coronary atherosclerosis can be manifested by diffuse abnormalities of endothelial/microvascular function leading to myocardial perfusion abnormalities even in the absence of evident reduction in the coronary lumen. At these stages, cardiac CT could detect abnormal wall structure of the large coronaries and quantitative PET could evidence global impairment of myocardial flow reserve, expressing endothelial/microvascular dysfunction. The corresponding invasive assessment of these abnormalities would be provided by intracoronary ultrasound imaging as well as by measurement of coronary flow reserve (CFR) by Doppler flow wire. When atherosclerosis progresses, the coronary lumen narrows and this can be detected by non-invasive or invasive coronary angiography. A coronary stenosis becomes "functionally" relevant when it is able to limit blood flow. Accordingly, perfusion imaging, either with SPECT or PET (and more recently also with ECHO and MRI), would detect a perfusion defect in the myocardial territory subtended by the affected vessel. Invasive intracoronary measurements by pressure wire would show reduced fractional flow reserve (FFR). According to the concept of the "ischemic cascade", however, only when the flow limiting coronary lesion becomes severe enough, relatively to myocardial oxygen demand, it causes ischemic impairment of myocardial contraction, and hence can be also evidenced by stress induced regional wall motion abnormalities at ECHO or MRI.

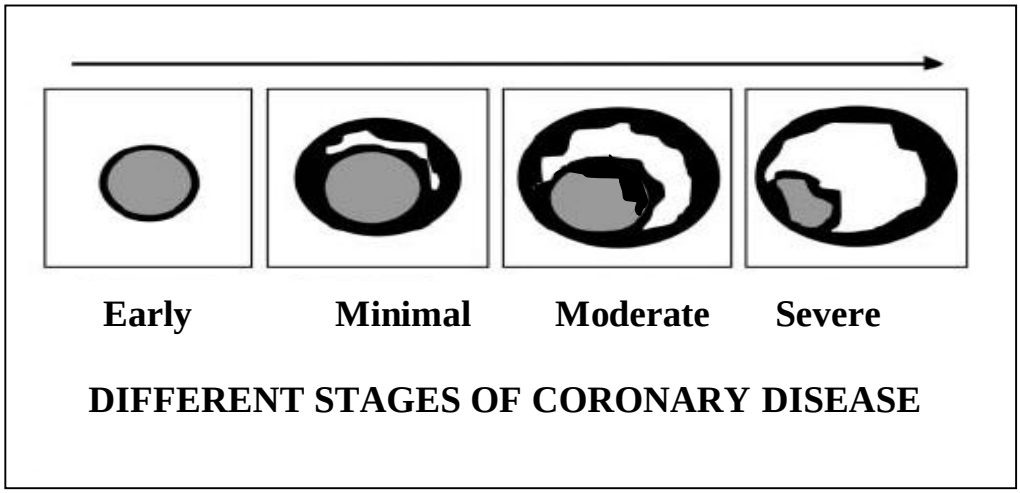

Figure 2. Different stages in the progression of coronary disease

From this brief review it should be evident that beyond the current utilization, the different non-invasive cardiac imaging modalities should be tested for their ability to provide complementary information on different aspects of the evolving coronary disease process.

Progress

Starting from this baseline data and from current European Guidelines for the management of patients with stable angina[28], the current project aims to achieve improvements for detection and characterization of IHD by multimodality non-invasive imaging.

- CT has relevant potentialities to assess early coronary anatomic lesions beyond simple detection of luminal stenosis. ***The EVINCI-study will develop new quantitative approaches for comprehensive assessment of anatomic coronary disease by CT including plaque characterization and coronary "atherosclerotic" burden.*** **[M2.1]**

- Radionuclide perfusion imaging (SPECT and PET) excels in detecting the early functional relevance of coronary abnormalities. In fact perfusion impairment is an early event in the "ischemic cascade" as it precedes myocardial contractile dysfunction. The more recent PET approach adds over SPECT the unique capability to quantify myocardial blood flow. This is a relevant property since it could increase the sensitivity and accuracy of radionuclide imaging in detecting functionally significant coronary disease either at the macro and micro vascular level. Disadvantages of PET are higher costs and lower availability of tracers and equipments. ***The EVINCI-study will evaluate the relative advantages of qualitative and quantitative assessment of myocardial perfusion by SPECT or PET radionuclide imaging for early detection and characterization of IHD.*** **[M3.1]**

- The other two modalities of functional cardiac imaging are based on ultrasound (ECHO) or magnetic fields (MRI). They excel in assessing the mechanical relevance of coronary abnormalities, i.e. the impairment of myocardial contraction caused by stress induced ischemia. According to the "ischemic cascade" concept, they are considered less sensitive than radionuclide methods for detection of the effects of intermediate or minor coronary lesions. On the other side, they do not expose the patients to ionizing radiations. Recently these techniques have been also developed to enable imaging of

myocardial perfusion. The combined perfusion-contraction analysis could potentially expand the diagnostic capabilities of non-invasive imaging. In fact, perfusion abnormalities (either qualitative or quantitative), in the absence of stress inducible contractile dysfunction, may identify subtle coronary lesions or microvascular dysfunction unable to cause manifest ischemia. Conversely, the presence of both stress inducible perfusion and contraction abnormalities would reinforce the non-invasive evidence of significant coronary lesions. ***The EVINCI-study will develop new protocols to obtain combined quantitative information on myocardial perfusion and contraction from single modality or multimodality functional imaging.*** **[M3.1]**

- Anatomical information from CT and functional information from stress imaging will be combined to provide alternative non-invasive strategies for the diagnosis and characterization of IHD to be tested against invasive reference. ***The EVINCI-study will provide data on standardization and validation of non-invasive, multimodality anatomo-functional imaging for the diagnosis of IHD.*** **[M4.1 and D4]**

Sustainability of cardiac imaging

Baseline

Wide clinical use of advanced diagnostic technologies poses problems of sustainability by the health systems. Sustainability is based on economic evaluation, benefits obtained and risks for the patient. Economical evaluations should provide a relevant framework for assessing the relative value of the possible different non-invasive imaging strategies in comparison with the current practice. Moreover, cardiological patients undergoing common radiological and nuclear medicine examinations often receive a significant radiation dose which is assumed to be linearly related to the long-term risk of developing cancer. In the framework of European imaging referral guidelines and legislation it is essential to inform patients of doses and risks with clear and informative consent forms and also to include the long-term risks in the risk-benefit assessment of the various competing techniques.

Progress

According to these considerations, the current project will obtain a significant progress in the evaluation of sustainability of cardiac imaging.

- ***The EVINCI-study protocol will allow to perform cost-benefit and cost- effectiveness analyses of the different strategies against diagnostic, clinical and prognostic end-points.*** **[D6]**

- ***The EVINCI-study will estimate directly cumulative radiological exposure for each patient, related risks and include them into the previous cost-benefit analysis.*** **[M6.1 and D6]**

Easy access and utilization of integrated multi imaging results

Baseline

The quantity and complexity of information derived from advanced multimodality cardiac imaging requires synthetic presentation of results in a simple and clinically meaningful form. Moreover, the additional value of cardiac imaging in the decision making process should always be combined with clinical and biological information easily available in the single patient. The challenges in achieving this are manifold including accessing data stored in different formats across multiple data sources; developing conceptual information models for integrating such heterogeneous data; using different statistical data and image analysis

softwares, and finally developing simplified decision making interfaces for both the researchers developing diagnostic tools and the physicians using such tools at the point of care.

Progress

By building on existing state-of-the-art data integration and analysis softwares, the EVINCI-study will produce, together with the Industrial partner, significant progresses for the utilization of the complex information coming from different imaging modalities.

- ***The EVINCI-study will develop specialized novel informatics tools for the integrated representation of information derived from multimodality cardiac imaging.*** [D7]

- ***The EVINCI-study will combine imaging data with biological, clinical information and outcome to develop a new computer assisted decision making engine.*** [D7]

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B 1.3 S/T Methodology and associated work plan

B 1.3.1 Overall strategy and general description:

i) Overall strategy

The project will be carried out over a period of 42 months and will involve 21 active partners from 9 countries, including eight European Member States (Spain, Italy, France, Poland, Finland, United Kingdom, Germany and Netherlands) and one Associated Country (Switzerland). Clinical partners have been chosen to represent the main European Centres dedicated to cardiac imaging.

The overall strategy of the work plan is to apply non-invasive, multimodality cardiac imaging approaches to the detection and characterization of ischemic heart disease (IHD) in patients with angina-like chest pain, under stable clinical conditions and with intermediate pre-test probability of the disease. The study is specifically designed to allow: a) the non-invasive detection of anatomical coronary lesions; b) the non-invasive quantification of functional correlates of abnormal coronary circulation (i.e.: stress inducible changes in myocardial perfusion and/or contraction); c) the integration of the anatomic with the functional information, and d) the comparison of the anatomic and functional information obtained non-invasively with invasive reference methods, clinical profiles, biomarkers and prognostic end-points.

It is important to emphasize that the EVINCI-study does not aim at evaluating the optimal treatment in patients with IHD. It attempts to define the best non-invasive imaging strategy to diagnose and fully characterize patients with suspected IHD. Patients enrolled into the protocol will be managed according to "best clinical practice" based on international guidelines[28]. The choice of treatment for a particular patient will remain the full responsibility of the referring clinician.

The major steps of the work plan are:

I) to standardize protocols for acquisition, analysis and reporting of non-invasive, multimodality cardiac imaging;

II) to define non-invasively new anatomo-functional categories of IHD, i.e.: IHD-CAD (IHD with functionally significant coronary artery disease), IHD-CMVD (IHD with functionally significant coronary microvascular disease), CAD (functionally non significant coronary artery disease), no disease;

III) to test the different non-invasive, multimodality imaging approaches in terms of:
   a. diagnostic accuracy against invasive reference methods;
   b. prognostic power;
   c. cost-benefit and cost-effectiveness analysis against diagnostic and prognostic end-points;

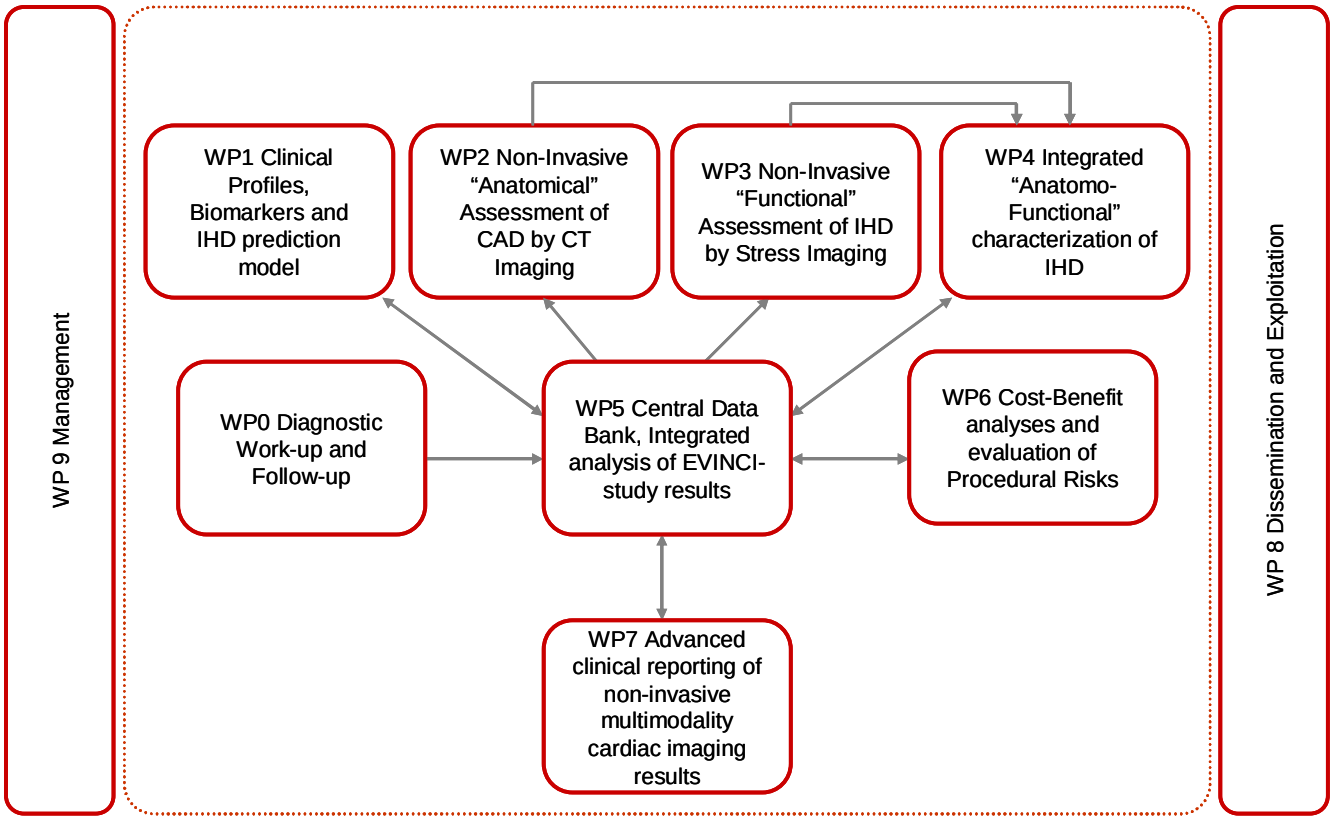
IV) to develop a novel informatic tool for the quantitative analysis and the integrated representation of anatomic and functional information, in order to assist in clinical decision making;

V) to combine the information obtained from non-invasive, multimodality imaging with that provided by clinical and laboratory evaluation of vascular damage in order to develop:
   a. a new risk stratification of anginal patients;
   b. novel, reliable end-points to be utilized in therapeutic trials.

To better tackle the complexity and the dimension of this project, activities have been grouped into 10 distinct workpackages (WPs) related to research activities (RTD),

dissemination activities (OTHER) and management activities (MNGT). Each WP is, in turn, subdivided in tasks. Each WP will be organised by a leader who will supervise the work into the WP in the different countries involved. Tasks will produce deliverables (Ds) and/or achieve milestones (Ms).

Graphical presentation of the components showing their interdependencies (Pert diagram)



WP0 - Diagnostic Work-up and Follow-up
WPLEADER: P1-CNR
PARTICIPANTS: P2-U. Turku, P3-UZH, P6-IR-HSCSP, P7-NIC, P8-RBHT, P9-APHP, P10-UniGe, P11-SERMAS, P12-UniNA, P13-HUVHEBRON, P17-FGM, P18-KRITUM, P19-QMUL, P20-AOUC,, P21-Ospedale Versilia, P22-KAE
DURATION: months 3-42

The general aim of WP0 is to perform a standardized diagnostic work-up and follow-up in a homogeneous population of patients, referred to clinical centres of the consortium because of angina-like chest pain or equivalents, in whom an intermediate pre-test probability of IHD will be estimated after clinical evaluation and ECG exercise test[28]. More specifically, the study will be performed in 700 patients referring angina-like chest pain (defined according to the guidelines of the European Society of Cardiology) or equivalents (dyspnea or fatigue on exertion). Patients will be selected independently of their sex and race. Patients younger than 30 or older than 75 years will be excluded. Patients with unstable clinical conditions (as acute myocardial infarction, hemodynamic or electrical instability), patients with severe systemic illness (as cancer or renal insufficiency under dialysis treatment), and patients unable to give their informed consent will be excluded from the study. Finally, patients who will present a low ($\leq$ 20%) or high ($\geq$ 90%) pre-test probability of coronary artery disease (estimated after clinical evaluation and ECG exercise test) will be excluded from the study. All patients, after fulfilling inclusion-exclusion criteria and signing an informed consent, will undergo blood sampling, non-invasive and invasive "anatomo-functional" coronary imaging and follow-up according to a specific flow-chart (see below).
At each step of the protocol the patient and his referring physician will receive by the local operators standard clinical reports of the performed examinations. In the case of incidental findings which preclude the fulfilment of the protocol or indicate a different clinical decision making, the patient will be managed according to good clinical practise and will be censored up to the time of the recognition of the specific condition.
Activities in WP0 will generate clinical and laboratory (biomarkers) data (processed in WP1), non-invasive imaging data (processed in WP2 and WP3), invasive data (processed in WP4), outcome and costs data (processed in WP5 and WP6). Such activities would require standardized procedures to acquire and transmit data which will be made available by P1-CNR. The specific Flow Chart which details the diagnostic work-up and follow-up is reported in Figure 3. Specific objectives of WP0 are: I) to standardize procedures to acquire and transmit data; II) to enrol patients eligible for the study and to obtain clinical data and blood samples for centralized analysis of biomarkers; III) to perform non-invasive multimodality imaging by CTA combined with perfusion (SPECT or PET) and contraction (ECHO or MRI) stress imaging; IV) to perform invasive anatomic imaging by ICA (and IVUS, wherever appropriate); V) to perform intracoronary measurements of FFR by pressure wire (or CFR by Doppler flow wire, wherever appropriate); VI) to follow-up patients at 1 month from enrolment and every 6 months.

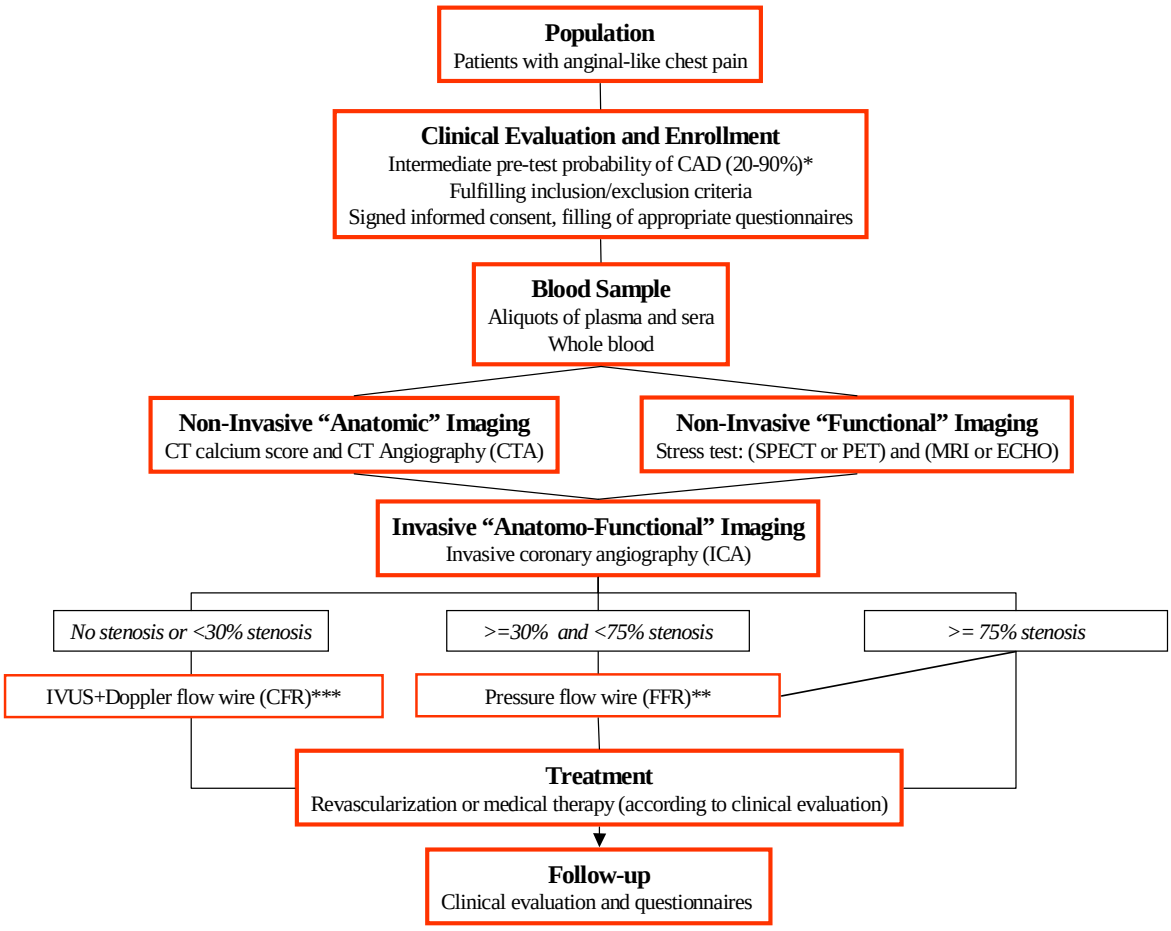


Figure 3. Flow-chart of the diagnostic work-up and Follow-up. *= Intermediate pre-test probability will be estimated based on age, gender and symptom classification and modified by ECG exercise test results according to European Guidelines on management of stable angina[28]. **=FFR will be performed in all main coronary vessels showing intermediate coronary lesions (30-75% stenosis) and also in vessels with tighter stenoses if judged clinically useful by the cath operator. ***=IVUS imaging and CFR measurements will be performed in the left anterior descending artery in patients with angiographycally normal coronary vessels or <30% coronary stenoses; IVUS imaging could be also performed in vessels with >=30% stenoses if judged clinically useful by the cath operator.

Power calculation

Based on the patient recruitment and imaging capacity of the different clinical partners, it was considered realistic to include in the EVINCI-study approximately 700 patients with intermediate pre-test probability of IHD over a period of 1.5 years. According to the study design all patients (N=700) will be submitted to CTA, all the patients will perform either ECHO (N=350) or MRI (N=350) and all the patients will perform either SPECT (N=350) or PET (N=350). In the single patient non invasive evaluation will consist of CTA plus one left ventricular function test (ECHO or MRI) plus one left ventricular perfusion test (SPECT or PET). As a result the combination of CTA with each of the four other different modalities

will be obtained in groups consisting of 350 patients each. Whether a patient could be submitted to only one stress test (either a function test or a perfusion test) together with CTA an additional patient will be enrolled throughout the consortium and will be submitted to the combination of CTA and the other test (the one that could not be performed in the previous patient). Monitoring of patients enrolment throughout the study will allow to ensure that an equal number of patients will be assigned to each modality. Given this sample size, a statistical power analysis was performed in order to define the likelihood of finding significantly differences between alternative non-invasive anatomo-functional imaging strategies (CTA+PET or CTA+SPECT or CTA+ECHO or CTA+MRI) in terms of their accuracy to identify hemodynamically significant coronary lesions at the invasive evaluation. Hemodynamically significant coronary lesions are defined in the presence of >=30% coronary stenosis at ICA associated (if required) with reduced FFR (<0.75) as stated in international guidelines[28]. Calculations were done taking into account average values and variability of sensitivity, specificity and accuracy for the detection of anatomic CAD published for each non-invasive imaging technique in the most recent meta-analyses[24-27]. The proportion of patients that will show hemodynamically significant coronary lesions was estimated as follows: 1) among the 700 patients enrolled with intermediate probability of anatomical CAD, roughly 350 will actually demonstrate >=30% stenosis at ICA; 2) among this 350 patients, roughly 50% are expected to show >=75% stenoses and/or reduced FFR (Pijls NHJ et al. Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis 5-Year Follow-Up of the DEFER Study. JACC 2007;49:2105-2111), i.e. 175 patients will represent the diagnostic end-point for power calculation.

The correlation between each combination of non-invasive tests in a patient was computed by simulation using average sensitivity and specificity reported in the literature[24-27].

The hypotheses being tested are:
Null hypothesis H0: $A1 = A2 = T$
Alternative hypothesis H1: $A2 = A1 + \Delta$
with the expected difference $\Delta \neq 0$. Statistical power was calculated for varying values of T and Δ and plotted versus T for Δ=0.01, 0.02, 0.03, etc.

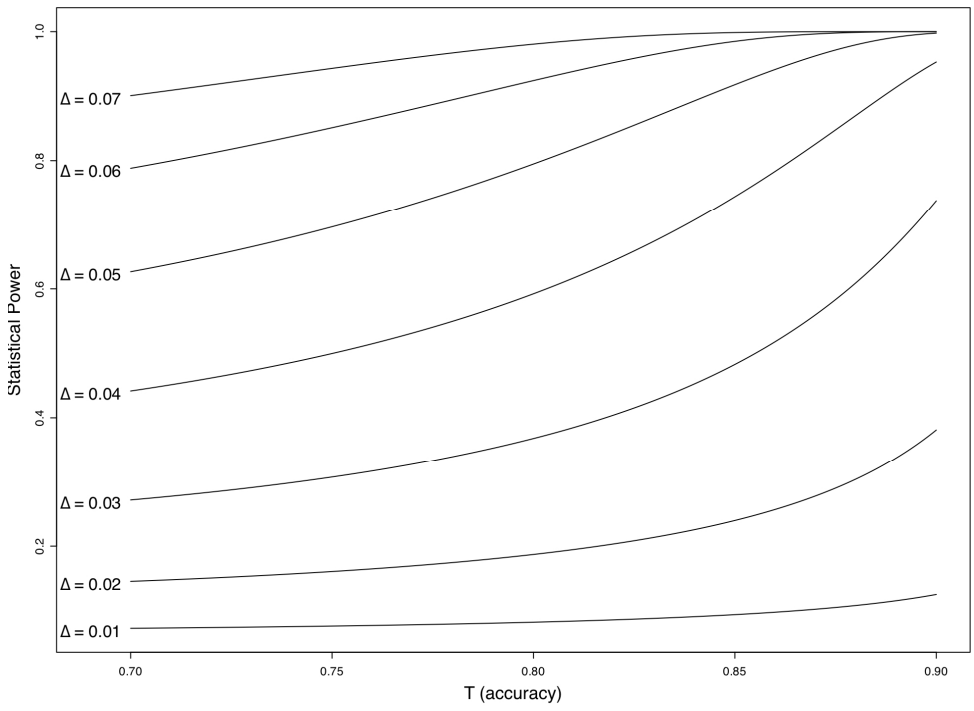


Figure 4: Statistical power of EVINCI Study to detect a statistically significant difference (Δ) in accuracy between different strategies of non-invasive tests showing an accuracy T. The 6 different combinations showed similar covariances. The individual accuracy of the 4 different strategies (CTA+PET or CTA+SPECT or CTA+ECHO or CTA+MRI) was estimated in a range between 0.75 and 0.85.

Using 80% statistical power as a threshold, it was concluded that 700 patients would be sufficient in order to detect a 6% difference in accuracy amongst each of 4 non-invasive strategies to be tested. This was considered appropriate for the objectives of the EVINCI-study since we expect an ample margin of numerosity to get statistically meaningful information for each modality.

WP1- Clinical Profiles, Biomarkers and IHD prediction model
WPLEADER: P1-CNR
PARTICIPANTS: P12-UniNA
DURATION: months 1-3 and 3-42

In patients with angina-like chest pain or equivalents, who are candidates to diagnostic cardiac imaging, the pre-test probability of IHD is currently obtained according to patient age, sex and symptoms possibly integrated with ECG exercise test results (when evaluable). A more accurate pre-test probability of IHD has been estimated including cardiovascular risk factors into the prediction model. However, these models have been tested mainly against the anatomic evidence of CAD derived from ICA. The EVINCI-study will provide a new classification of IHD based on anatomo-functional categories which require a new predictive model.
The general aim of WP1 is to generate from the analysis of clinical data and blood samples collected in patients enrolled into the EVINCI-study, a novel prediction model of pre-test probability of anatomo-functional categories of IHD.
The specific objectives of WP1 are: I) to elaborate the format for the collection of relevant clinical information, II) to define the procedures for blood specimens sampling, storage and shipment; III) to organize and manage the biological bank; IV) to perform central laboratory analysis in order to measure the main biomarkers of vascular damage including parameters describing systemic metabolism, inflammation and neurohormonal activation; V) to build-up a novel prediction model based on combined clinical data and biomarkers.

WP2 - Non-Invasive "Anatomical" Assessment of CAD by CT imaging
WPLEADER: P4-LUMC
PARTICIPANTS: P2-U. Turku
DURATION: months 1 – 42

Multislice cardiac CT has been recently introduced for the non-invasive screening of CAD. A complete examination includes determination of coronary calcium score (CCS) and CT angiography (CTA). Optimization of acquisition protocols is a matter of current investigation and should mainly take into account available equipments, patient characteristics and radiation exposure. Methods for quantitative analysis of CT imaging, able to assess not only coronary luminal diameter but also the atherosclerotic "burden" of the vascular walls, are under evaluation.
The general aim of WP2 is to perform central analysis of CT examinations and deliver quantitative parameters of "anatomic" coronary damage to be validated against invasive reference methods in WP4. Such activity would require standardized procedures for CT data

acquisition and transmission throughout the consortium, which will be made available by P4-LUMC.

Specific objectives of WP2 are: I) to define the procedures for CT acquisitions to be diffused to clinical centres; II) to perform central CCS and CTA readings; III) to develop new standards for comprehensive assessment of anatomic coronary damage from multislice CT.

WP3 - Non-Invasive "Functional" Assessment of IHD by Stress Imaging

WPLEADER: P1-CNR

PARTICIPANTS: P2-U. Turku, P3-UZH, P8-RBHT, P9-APHP, P11-SERMAS, P18-KRITUM

DURATION: months 1-42

Four different modalities of stress imaging are currently available for non-invasive screening of IHD. Two methods are based on radioisotopes (SPECT and PET) and mainly assess stress induced changes in myocardial perfusion. The other two methods are based on ultrasound (ECHO) or magnetic fields (MRI) and mainly assess stress induced changes in myocardial contraction caused by myocardial ischemia. However, ECHO and MRI also can provide data on coronary flow reserve and perfusion that will be acquired in the EVINCI Study using dedicated protocols.

Stress imaging modalities will be combined for better non-invasive assessment of functionally significant coronary disease. In particular, every patient will undergo a radionuclide stress study (either SPECT or PET) combined with either ECHO or MRI stress imaging. The central monitoring of patients enrolment throughout the study (see WP5) will allow to ensure that an equal number of patients will be submitted to each stress imaging modality. This protocol would allow to compare the diagnostic performance of each imaging modality against invasive reference standards. Moreover, it would allow to perform combined perfusion-contraction analysis (obtained either by single modality or by multimodality approach) and quantitative evaluation of myocardial perfusion (by PET) as new integrated strategies potentially able to expand the diagnostic capabilities of non-invasive stress imaging.

The general aim of WP3 is to perform central analysis of examinations by experts in each modality and to deliver qualitative and quantitative parameters for "functional" IHD characterization extracted from single or multimodality approaches to be validated against invasive reference methods in WP4. Such activity would require standardized procedures for stress imaging data acquisition and transmission throughout the consortium, which will be made available by P3-UZH. In particular, stress echocardiography is a more operator-dependent technique that need a specific training. Intra-observer variability will be reduced with two different approaches: A. training: all the centers enrolled respond to the criteria adopted by the European Association of Echocardiography expert consensus statement in the definition of expert operator; B. Central reading review: all the exams will be revised by a core lab in order to reduce inter-individual and inter-institutional variability.

Specific objectives of WP3 are: I) to define the procedures for SPECT, PET, ECHO and MRI stress imaging protocols and acquisitions to be diffused to the clinical participating centres; II) to perform central qualitative and quantitative readings of examinations; III) to develop new standards for combined perfusion-contraction analysis from single or multimodality stress imaging.

WP4 - Integrated "Anatomo-Functional" characterization of IHD
WPLEADER: P2-U. Turku
PARTICIPANTS: P1-CNR, P3-UZH, P4-LUMC, P7-NIC, P8-RBHT, P9-APHP, P11-SERMAS
DURATION: months 1-42

Invasive cardiac catheterization is currently the golden standard for the diagnosis and characterization of IHD. In most clinical centres, however, ICA is the only procedure performed at catheterization in order to assess the presence of luminal coronary stenosis. Significant CAD is consequently diagnosed on the basis of luminal reduction >= 50% and this is the morphological criterion often chosen to decide revascularization. This common approach has many limitations since luminal narrowing at ICA is not sufficient to describe the anatomic characteristics and severity of the coronary lesions and cannot predict their functional correlates. Moreover, dysfunction of the coronary microcirculation may cause severe impairment of flow reserve even in the absence of anatomically relevant epicardial coronary lesions. New technologies have been introduced to enhance the anatomic characterization of epicardial coronary vessels and to add functional measurements of coronary flow reserve in the presence of intermediate or minor coronary stenosis (< 75%). Pressure wires, combined with intracoronary infusion of adenosine, allow measurements of FFR as indicator of functional significance of coronary stenosis. Doppler flow wires allow measurements of CFR which, in the presence of minor or no stenosis, is able to assess the function of the coronary microcirculation. IVUS is able to reliably describe the extent and the characteristics of the atherosclerotic plaque not only in the coronary lumen but also in the vessel wall allowing to detect early coronary atherosclerosis.
The general aim of WP4 is to provide a reference anatomo-functional characterization of IHD by heart catheterization in order to validate non-invasive multimodality imaging approaches. Such activity would require standardized procedures of heart catheterization, acquisition and transmission of invasive data which will be made available by P2-U.Turku throughout the consortium.
Specific objectives of WP4 are: I) to standardize procedures of heart catheterization, acquisition and transmission of invasive data ; II) to perform central analysis of ICA and IVUS imaging to generate reference parameters of extent and characteristics of anatomic coronary lesions; III) to combine anatomic with flow reserve parameters (wherever appropriate) to generate reference IHD anatomo-functional categories; IV) to assess accuracy of non-invasive "anatomic" imaging by CTA against anatomic invasive parameters; V) to assess comparative intermodality accuracy of non-invasive "functional" stress imaging against invasive evidence of functionally significant coronary lesions or abnormal microvascular flow reserve; VI) to validate multimodality non-invasive approaches for characterization of IHD in anatomo-functional categories (Figure 5).

Coronary Flow	Coronary Anatomy: Normal vessels	Stenosis <30%	Stenosis >=30% and <75%	Stenosis >= 75%
Normal Flow	No Disease	CAD	CAD	IHD-CAD
Reduced Flow	IHD-CMVD	IHD-CMVD	IHD-CAD	

Figure 5. Anatomo-functional categories of IHD. Note: In case of >= 75% coronary stenosis associated to normal FFR (if measured) the patient is assigned to the category of CAD.

WP5 – Central Data Bank, Integrated analysis of EVINCI-study results
WPLEADER: P1-CNR
PARTICIPANTS: P2-U. Turku, P3-UZH, P4-LUMC, P8-RBHT, P11-SERMAS, P15-INF
DURATION: months 1-42

The overall organization of the EVINCI-study is centred on: a) generation of "raw data" in each clinical centre (consisting of questionnaires, blood samples, multimedia supports containing non-invasive imaging and invasive examinations) (WP0); b) transmission of "raw data" for central analysis; c) generation of "analysed data" in specific centres (WP 1-2-3-4); c) inclusion of "analysed data" in a central data bank accessible to the consortium; d) integrated analysis of data to generate overall results. This organization requires a central management of data fluxes.
The first aim of WP5 is to manage "raw data" transmission to specific centres dedicated to data analysis and to include "analysed data" in a central database. P1-CNR is responsible for ensuring a timely (according to EVINCI-study time schedule) and secured (in the respect of patient privacy) exchange and storage of data..
Specific objectives of this activity are: I) to establish an informatic platform (Central Server), accessible trough Internet, which allows participating clinical centres to enter patient's information, receive ID number (to assure anonymity) and to monitor the completion of diagnostic work-up, shipment of "raw data" and follow-up; II) to continuously monitor the state of patients' enrolment in each center and the number of patients assigned to each diagnostic modality in order to allow the study coordinator to ensure that an equal number of patients will be assigned to each non-invasive functional imaging modality; III) manage exchange of "raw data" among centres and to provide a central storage of hard copies of exams performed (Digital Bank); IV) to establish an informatic platform (Central Database) dedicated to organization in a digital format of clinical data, biomarkers, non-invasive and invasive parameters obtained from central readings to be available throughout the consortium for further analyses; V) to manage data entry, data quality control and make data available for final evaluation.
The second aim of WP5 is to assess the value of integrating clinical data and biomarkers with non-invasively defined anatomo-functional IHD categories to predict patient outcome. Moreover, the association between biomarkers and imaging indicators of coronary vascular

damage will be explored to provide new reliable end-points to be used in therapeutical trials in IHD.
Specific objectives of this activity are: I) to develop a new predictive model of outcome in patients with suspected IHD based on combined clinical-biomarkers-imaging information; II) to study the association of clinical hallmarks and laboratory biomarkers of vascular damage with anatomo-functional patterns of IHD.

WP6 – Cost-Benefit analyses and evaluation of Procedural Risks
WPLEADER: P10-UniGe
PARTICIPANTS: P1-CNR
DURATION: months 1-42

Economic evaluations will provide a relevant framework for assessing the comparative value of the multimodality non-invasive imaging strategies proposed in the EVINCI-study against current practice for detection and characterization of IHD. The social desirability of a health care program, relative to some other alternative, could be assessed by its inputs, such as costs, and outputs, as benefits and effects. Costs and benefits could be distinguished into three categories: direct, indirect and intangible. Direct refers to the health care system, community and family directly involved into the program (e.g. hospital care, physicians' services, nursing home care, interventions, drugs). Indirect includes earnings forgone or enhanced, as the value of production lost to, or gained by the rest of society. Intangible relates to the pain and suffering that are caused or alleviated by the health care intervention.
The first aim of WP6 is to perform cost-benefit analyses alongside the EVINCI-study clinical trial. A cost-benefit analysis uses benefits expressed in the same monetary units as the costs, a cost-effectiveness analysis considers the effects of the intervention measured in natural units and the cost-utility analysis estimates the satisfaction of the time that a person has left to live, the so called quality adjusted life year.
Specific objectives connected to this activity are: I) to develop a clinical standardized questionnaire (supported by an operating manual) to be filled at enrolment and at follow-up visits; besides socio-demographical and clinical characteristics, information on health costs for each patient enrolled in every centre will be included; II) once data will be collected, a series of checks for accuracy and completeness will be carried out; III) the benefit cost ratio (BCR), the incremental cost-effectiveness ratio (ICER), the incremental net benefit (INB) and the cost-effectiveness acceptability curve (CEAC) will be derived as summary measure of economic evaluations.
Cardiological patients undergoing common radiological and nuclear medicine examinations often receive a significant radiation dose which is assumed to be linearly related to the long-term risk of developing cancer. In the framework of European imaging referral guidelines and legislation it is essential to inform patients of doses and risks with clear and informative consent forms and also to include the long-term risks in the risk-benefit assessment of the various competing techniques. Radiological risks, in fact, should be evaluated against benefit provided by appropriate diagnosis.
Accordingly, the second general aim of WP6 is to estimate the overall procedural risks for the patient associated with the different non-invasive and invasive diagnostic approaches to be included in the previous cost-benefit analysis.
Specific objectives connected to this activity are: I) to develop and distribute to all patients a specific informed consent for each diagnostic modality specifying radiation doses and risks; II) to obtain actual (rather than estimated from reference values) patient dose data at the time of examinations; III) to produce an ongoing log of all previous (before study entry) and ongoing (during the study) log of cumulative effective doses (and corresponding estimated risks following the latest BEIR VII estimates); IV) to evaluate the acute diagnostic benefits

of the different techniques versus the acute (major life threatening effects of stress procedures, acute complications of catheterization, contrast-induced nephropathy) and long-term (cancer for ionizing testing) risks of the same procedures.

WP7 – Advanced clinical reporting of non-invasive multimodality cardiac imaging results
WPLEADER: P1-CNR
PARTICIPANTS: P2-U. Turku, P3-UZH, P18-KRITUM,
DURATION: months 24-42

Non-invasive multimodality cardiac imaging assessment of patients with suspected IHD poses new specific challenges to make it currently useful in the clinical practice. The quantity and complexity of information derived from advanced anatomo-functional cardiac imaging requires tools for synthetic presentation of results in a simple and clinically meaningful form. Moreover, the additional value of cardiac imaging in the decision making process should always be combined with clinical and biological information easily available in the single patient.
The general aim of WP7 is to develop a novel informatics tool supporting clinical decision making based on integrated representation of anatomo-functional information derived from multimodality cardiac imaging, combined to clinical and biological data. In addition to providing access to data stored in different formats across multiple data sources, the platform will be based on the development of conceptual information model for integrating such data together with access to statistical data and imaging software tools for its analysis.
Specific aims of WP7 are: I) to fuse the CT images with other imaging modalities into an enhanced overlay view including semiquantitative/quantitative data for improved interpretation; II) to create an environment allowing to present the imaging parametric information to the clinician in an ergonomically optimal fashion; III) to integrate all the available information (from clinical and imaging assessment) belonging to a single patient in a synthetic dynamic heart model, able to retrieve the origin and nature of each information, to synthetically summarize the disease status and to stratify predicted risk; IV) to develop simplified clinical decision making tools for use both by researchers developing the diagnostic methods and by the physicians using these tools at the point of care.

WP8 - Dissemination and Exploitation
WPLEADER: P14-ESC
PARTICIPANTS: P1-CNR, P2-U.Turku, P3-UZH, P4-LUMC, P6-IR-HSCSP, P7-NIC, P8-RBHT, P9-AP-HP, P10 UniGE, P11-SERMAS, P12 UniNA, P13-HUVHEBRON, P16-CFc, P20-AOUC, P21-Ospedale Versilia, P22-KAE
DURATION: months 1-42

The aim of this WP is to implement a set of actions devoted to spreading the results of EVINCI-study to the largest possible audience. These will comprise: educational initiatives, publication of information, workshop at internal and external level to the consortium and publication of results. P14-ESC will have the responsibility for co-ordinating and organizing initiatives connected to the dissemination activity.
A dissemination plan will be prepared during the first 6 months of the project. The table below summarises the target audience, the communication objectives and tools already identified.

target group	communication obj.	actions	tools
Scientific community (clinicians, researchers and clinical fellows)	To present the project; to provide information about project results, data and new knowledge acquired	To stay in touch with other FP7 projects in related areas; Participation in scientific events; Publications in peer-review cardiovascular/medical journals Meetings with national, regional, local authorities Mailing of reports to Scientific Societies	✓ Lectures ✓ Publications ✓ Project web site ✓ Reports ✓ Project summary ✓ Poster
Health authorities/ Health care services	To present the project to national, regional, local authorities To disseminate new knowledge on non-invasive detection and characterization of IHD and impact on care in order to modify health strategies		
Business community (biotechnological pharmaceutical, biomedical, industries)	To present the project (the methodology used, results, new perspectives etc.) to business community To steer research in imaging technology and to provide new end-points to be used in pharmacological trials in IHD	Publications in peer-review cardiovascular/medical journals; Participation in scientific events Meetings	✓ Lectures ✓ Publications ✓ Project web site ✓ Reports ✓ Project summary ✓ Poster
Patients/ General Public	To inform on advances in research on early detection of IHD	ESC e-newsletters in lay language	✓ Project web site ✓ Project summary

WP9 - Management
WPLEADER: P1-CNR
PARTICIPANTS: P2-U.Turku, P3-UZH, P4-LUMC, P6-IR-HSCSP, P7-NIC, P8-RBHT, P9-AP-HP, P10 UniGE, P11-SERMAS, P12-UniNA, P13-HUVHEBRON, P14-ESC, P16-CFc, P18-KRITUM, P19-QMUL, P20-AOUC, P21-Ospedale Versilia, P22-KAE
DURATION: months 1-42

The specific aims of this WP will be: I) to co-ordinate the various project components (financial, legal, administrative and logistic issues); II) to check progress of the project activities, ensuring adherence to project timetable, implementing corrective actions, if any, and preventing possible delays or unsuccessful results; III) to assure a timely reporting of the project to the EU; IV) to establish and adopt common operational procedures; V) to ensure respect of ethical issues and attention paid to gender issues; VI) to ensure high quality of scientific and technical results, verifying that each report covers all aspects required to meet the deliverables.

Risks contingency plan

A project like EVINCI-study can encounter a number of adverse situations that will generate risks. We define a risk as the product between an adverse event (or situation) and its consequences on the project's achievements of its objectives.
A correct procedure to minimise the overall risk of the project is taking into account and minimising the possible occurrence of adverse events in the construction of the project.

The envisaged risks can be organised in a number of classes:

1. technological and scientific risks;
2. dissemination risks;
3. management risks;
4. consortium related risks.

Technological and scientific risks table

Risk	WP	Probability	Contingency Plan
Excessive radiation exposure to patients enrolled in some centers as compared to a predefined maximum	0	Medium	Continuous central monitoring of actual cumulative radiation exposure per patient in each centre. Centers showing higher individual levels of radiation dose will be invited to adhere to the appropriate predefined protocols for imaging modalities involving radiations.
Insufficient number of patients with completed diagnostic work-up per centre.	0	Low	After checking the advancement of patients' enrolment in each centre at month 18, centres at higher enrolment rate will be asked to increase their allotted number in order to compensate for centres with lower enrolment rate.
Different numbers of patients submitted to each non invasive stress imaging modality	0, 5	Medium	After checking numbers of patients studied with each non invasive stress modality at month 18, centres will be asked to balance the successive enrolment in order to reach an equal distribution of patients for each non invasive stress imaging modality throughout the consortium. In particular additional patients over the predicted number of 700 could be enrolled to compensate for patients who could be submitted to only one stress modality.
Insufficient number of patients with invasive heart catheterization and intracoronary measurements (FFR, IVUS, CFR).	0	Medium	After checking numbers of invasive heart catheterization and intracoronary measurements performed in each centre at month 18, centres at lower performance will be asked to increase % of invasive studies integrated with intracoronary measurements within the enrolled population. Search for extra funding for this activity will be activated if needed.

Risk	WP	Probability	Contingency Plan
Insufficient number of patients with completed follow-up per centre.	0	Medium	After checking the advancement of patients follow-up in each centre at month 24, phone interviews to fill the questionnaires could be authorized.
Insufficient number of enrolled patients submitted to blood sampling.	1	Low	After checking the number of enrolled patients submitted to blood sampling in each centre at month 18, centres at lower performance will be helped to overcome difficulties encountered and will be asked to organize blood sample withdrawals at the first available follow-up visit.
Inaccurate determination of laboratory biomarkers due to a not suitable sample (e.g. hemolysis, inaccurate shipment).	1	Medium	To organize new blood sample withdrawal in the single patient at the first available follow-up visit.
Inhomogeneity of the image quality of datasets.	2, 3, 4	Medium	To ensure homogeneity of the image quality, WP2, 3 and 4 leaders will gather, prior to start of patient inclusion, test data-sets from the participating centres to review the image quality. This will allow timely optimization of data acquisition protocols. In addition, quality of the data (including image quality, appropriate phase reconstruction, kernel selection etc) will be monitored continuously throughout the project.
Diversity of stress protocols, lack of adherence to the delivered standardized protocol.	3	Low	After establishing the stress protocols all institutions will get strict instructions on how to adhere to guidelines provided.
Diversity of PET perfusion tracers, as cyclotrons are not widely available.	3	Low	Only few centers can participate with PET. They have all cyclotrons and can all produce either ^{15}O-labelled water or ^{13}N-labelled ammonia even if ^{82}Rubidium generators could be also used. Tracers use will be monitored so to allow a balanced number of studies performed with each tracer.

Risk	WP	Probability	Contingency Plan
Lack of centers who can deliver CFR by intracoronary Doppler together with PET to evaluate microvascular function.	3,4	High	There are only 3 centers that can perform both CFR by intracoronary Doppler and PET. They will be encouraged to preferentially perform PET over SPECT and CFR (wherever indicated) in their enrolled patients.
Difficulties in "raw" and "analysed" data exchanges among Centres.	5	Medium	The Central Server will allow to monitor in real time the completion of the procedures of data acquisition, informatic data entering and shipment of materials for each enrolled patient. Centres with a law performance will be continuously alerted of time delays.
Erroneous or incomplete or missing data on the questionnaires.	6	Medium	Any problems identified by general checks, range checks, logical checks and missing data will be conveyed back to each centre so that corrections can be made. Phone interviews will be performed to complete questionnaires.

Dissemination risks table

Risk	WP	Probability	Contingency Plan
IPR management blocks effective integration.	8	Low	Partners have experience in contributing to joint projects. The Steering Committee suggests to the General Assembly possible solutions.
Delay in the organization of the workshops or Final Conference	8	Medium	The P14-ESC has a longstanding experience and outstanding record of organizing international events. All possible channels of communication will be exploited in advance in order to inform the widest audience about the events.

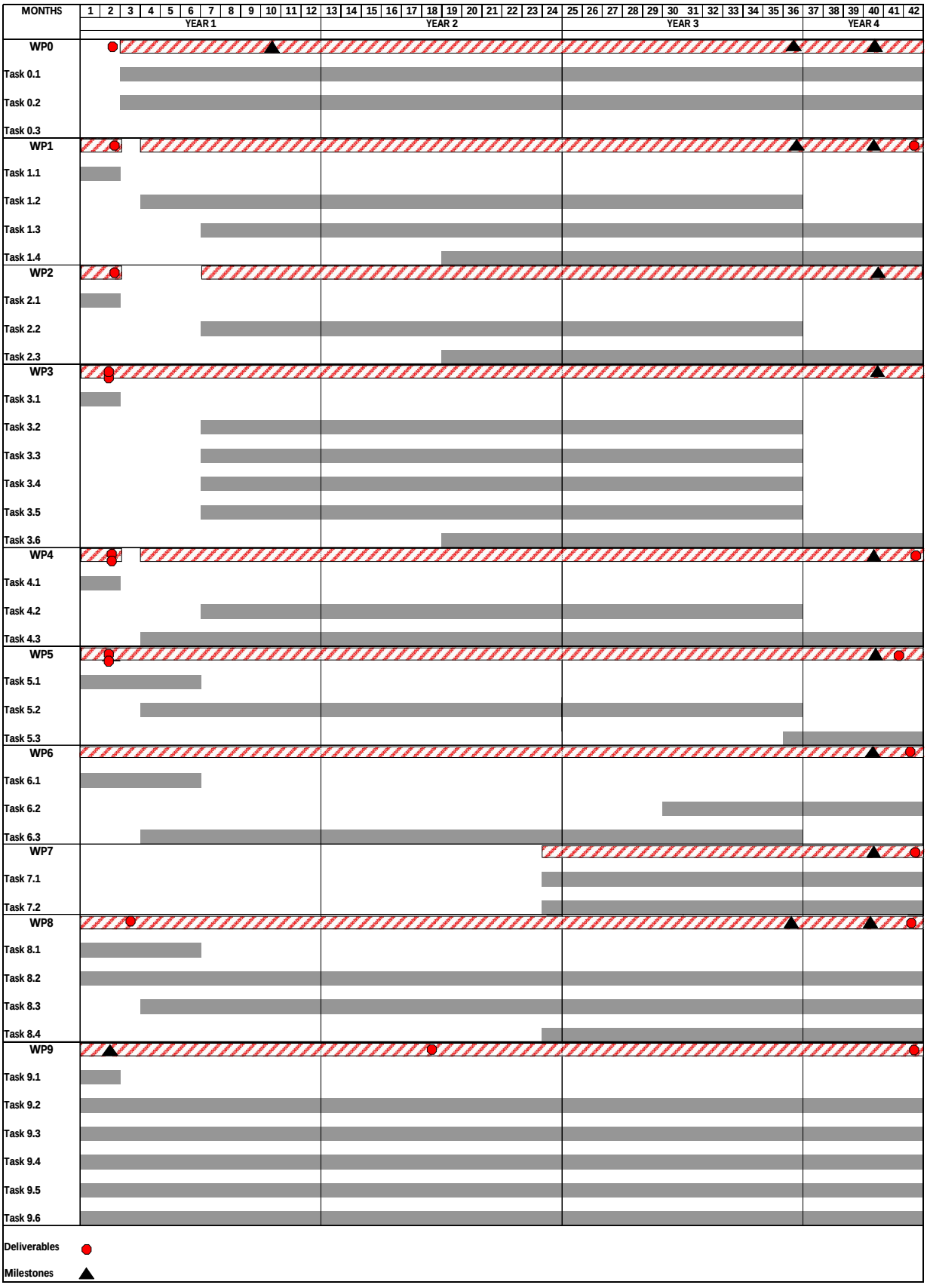
Management risks table

Risk	WP	Probability	Contingency Plan
Delays in report delivering by some partners.	9	Low	Partners are strongly committed to carry on the project. Consortium Agreement supplies the coordinator with the needed tools to assure a smooth project running.
Annual technical, financial and quality assessment.	9	Low	The annual assessment will cover technical, financial and quality issues. Main decision of potential reorientations will be taken so as to meet the objectives in the frame of the periodical meetings of the PSC.

Consortium risks table

Risk	Probability	Contingency Plan
Divergences among partners on project running.	Low Partners are accustomed to work together	Consortium Agreement rules every conflict situation.

B 1.3.2 Timing of work packages and their components:



B 1.3.3 Work package list / overview:

Work package list

Work package No	Work package title	Type of activity	Lead beneficiary No	Person-months	Start month	End month
0	Diagnostic Work-up and Follow-up	RTD	P1	135,4 (138)	3	42
1	Clinical Profiles, Biomarkers and IHD prediction model	RTD	P1	9 (7)	1 3	3 42
2	Non-Invasive "Anatomical" Assessment of CAD by CT Imaging	RTD	P4	22 (5)	1	42
3	Non-Invasive "Functional" Assessment of IHD by Stress Imaging	RTD	P1	34 (19)	1	42
4	Integrated "Anatomo-Functional" characterization of IHD	RTD	P2	24,5 (22)	1	42
5	Central data bank, integrated analysis of EVINCI-study results	RTD	P1	18,6 (13,5)	1	42
6	Cost-Benefit Analyses and Evaluation of Procedural Risks	RTD	P10	6 (7)	1	42
7	Advanced clinical reporting of non-invasive multimodality cardiac imaging results	RTD	P1	15 (14)	24	42
8	Dissemination and Exploitation	OTHER	P14	25,2 (28,5)	1	42
9	Management	MGT	P1	43,6 (19)	1	42
	TOTAL			333,3. (273)		

B 1.3.4 Deliverables list:

Del. no.	Deliverable name	WP no.	Lead bene-ficiary	Estimated Indicative Person-months	Nature	Dissemination level	Delivery date
D0.1	Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet.	0	P1-CNR	2	O	CO	Month 2
D1.1	Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet.	1	P1-CNR	2	O	CO	Month 2
D2.1	Standardized and optimised protocols for CT angiography acquisition and analysis	2	P4-LUMC	2	O	CO	Month 2
D3.1	Standardized and optimized protocols for performance of stress imaging, data acquisition and analysis	3	P3-UZH	2	O	CO	Month 2

Del. no.	Deliverable name	WP no.	Lead bene-ficiary	Estimated Indicative Person-months	Nature	Dissemination level	Delivery date
D3.2	Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet.	3	P3-UZH	2	O	CO	Month 2
D4.1	Standardized and optimised protocols for heart catheterisation	4	P2-U.Turku	2	O	CO	Month 2
D4.2	Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet.	4	P2-U.Turku	2	O	CO	Month 2
D5.1	Standardized protocols for access and secure transmission of data to the Central Server, Digital Bank and Data Base	5	P1-CNR	2	O	CO	Month 2
D5.2	Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet.	5	P17.FGM	2	O	CO	Month 2
D8.1	Web-site	8	P14-ESC	1	R	PU	Month 3
D9.1	Periodic Report	9	P1-CNR	3	R	CO	Month 18

Del.	Deliverable	WP	Lead	Estimated	Nature	Dissemination	Delivery

no.	name	no.	beneficiary	Indicative Person-months		level	date
D1.2	Report on standardisation and accuracy of integrated predictive model for diagnosis and prognosis of IHD based on clinical, laboratory and multi-imaging assessment	1	P1-CNR	4	R	PU	Month 42
D4.3	Report on standardization and validation of non-invasive multimodality anatomo-functional imaging for diagnosis of IHD	4	P2-U.Turku	4	R	PU	Month 42
D5.3	Report on results of association study between clinical profiles, biomarkers and imaging profiles of IHD and the integrated impact on outcome	5	P1-CNR	1	R	CO	Month 42
D6.1	Report on cost-benefit analysis of integrated non-invasive vs invasive strategies for the diagnosis of IHD (including radiation exposure and procedural risks)	6	P10-UniGE	4	R	PU	Month 42
D7.1	Software and graphical user interface for multi-imaging reporting and decision making in patients with suspected IHD	7	P1-CNR	10	R	CO	Month 42

D8.2	Final plan for the use and dissemination of foreground	8	P14-ESC	2	R	PU	Month 42
D9.2	Final Report	9	P1-CNR	5	R	CO	Month 42
			TOTAL	98			

B 1.3.5 Work package descriptions:

Work package description

Work package number	0			**Start date or starting event**		3		
Work package title	**Diagnostic Work-up and Follow-up**							
Activity Type	RTD							
Participant id	**P1-CNR**	P2-U. Turku	P3-UZH	P4-LUMC	P6-IR-HSCSP	P7-NIC	P8-RBHT	P9-APHP	P10-UniGE
Person-months per beneficiary:	13 (9)	21,5 (4)	0,5 (7)	(16)	14,5 (4)	4 (10)	1.5 (13)	6 (14)	2,5 (12)
Participant id	P11-SERMAS	P12-UniNA	P13-HUVHEBRON	P17-FGM	P18-KRITUM	P19-QMUL	P20-AOUC	P21-Ospedale Versilia	P22-KAE
Person-months per beneficiary	6 (2)	5,5 (10)	11,2 (12)	29,4	2,5 (12)	4,5	6	1,3	5,5 (13)

Objectives

- To enrol a homogeneous population of 700 patients with intermediate pre-test probability of IHD.
- To perform a standardized diagnostic work-up, and follow-up in each patient.
- To transmit clinical data, blood samples, non-invasive and invasive imaging data and measurements, outcome and costs data obtained in each patient for central analysis.

Description of work and role of participants

Task 0.1 Implementation of standardized procedures (P1-CNR, P2-U. Turku, P3-UZH, P4-LUMC, P6-IR-HSCSP, P7-NIC, P8-RBHT, P9-APHP, P10-UniGe, P11-SERMAS, P12-UniNA, P13-HUVHEBRON, P18 KRITUM) (month 3)

The objective of this task is to implement throughout the Consortium standardized procedures for patients' enrolment, diagnostic work-up, follow-up and for transmission of data and materials. These procedures will be standardized within specific WPs in the first two months of the project, validated by the PSC and implemented throughout the Consortium within the third month. Standardized procedures involve specifically: I) criteria of patients' enrolment; II) informed consent module; III) questionnaires for collection of clinical and quality of life data; IV) collection and storage of blood samples; V) execution of non-invasive and invasive exams, acquisition of imaging data, storage on digital support; VI) collection of data on follow-up, radiation exposure and

costs; VII) anonimization and data entry into the Central Server; VIII) shipment of blood samples and exams.

Task 0.2 Enrolment, diagnostic work up and treatment (P1-CNR, P2-U. Turku, P3-UZH, P4-LUMC, P6-IR-HSCSP, P7-NIC, P8-RBHT, P9-APHP, P10-UniGe, P11-SERMAS, P12-UniNA, P13-HUVHEBRON, P17-FGM, P18-KRITUM, P19-QMUL, P20-AOUC, P21-Ospedale Versilia P22-KAE,) (months 4 → 36)

The overall objective of this task is to allow generation of all clinical, biological and imaging "raw data" needed for the study in a population of 700 patients to be enrolled in the first 36 months of the project in the clinical centres participating to the Consortium.

0.2.1 Enrolment and informed consent

Patients with angina-like chest pain or equivalents, without known coronary artery disease and candidate to diagnostic work-up will be enrolled. General criteria for enrolment will be: a) intermediate probability of IHD (20-90%), as assessed from symptoms, age and sex and modified after ECG Exercise test (if evaluable); b) fulfilment of specific inclusion and exclusion criteria; c) signed informed consent.

At each step of the protocol the patient and his referring physician will receive by the local operators standard clinical reports of the performed examinations. In the case of incidental findings which preclude the fulfilment of the protocol or indicate a different clinical decision making, the patient will be managed according to good clinical practise and will be censored up to the time of the recognition of the specific condition.

0.2.2 Anonimization and opening of a "patient record" into the Central Server

Patients fulfilling inclusion and exclusion criteria, after giving informed consent, will be officially enrolled into the study after connecting through Internet to the Central Server and receiving an ID number which will anonymously identify the patient throughout the Consortium. A central "patient record" file will be created in the Server allowing entering of patients data and check-marks for completion of the relevant procedures required for that patient: enrolment, informed consent, questionnaires, blood samples, non-invasive imaging (detailing which exams have been performed), invasive evaluation, treatment, follow-up visits, follow-up questionnaires, radiation exposure data and events. All data to be entered into the Central Server, blood samples and exams to be shipped will be labelled by the same ID number without any reference to the actual patient's name. Data will be saved for 10 years after the end of the study.

0.2.3 Patients data collection and transmission

Clinical assessment will be completed by fulfilling dedicated questionnaires exploring patient clinical history, actual health status and quality of life. Questionnaires will be filled by the patient and the physician in paper formats, to be entered in dedicated electronic pages into the Central Server.

0.2.4 Blood Samples

Blood samples will be obtained within one week from the catheterization procedure. Blood will be centrifugated to extract plasma and sera aliquots (for analysis of biomarkers) which will be stored in a refrigerator (-80°). Plasma and sera will be shipped to P1-CNR for analysis and final storage.

0.2.5 Non-invasive diagnostic work-up

Stress ECG will be performed and its results (when evaluable) will be utilized to concur in identification of patients with intermediate pre-test probability to be enrolled.

All included patients will undergo: a) CT angiography (CTA) to assess the presence of "anatomical" correlates of IHD, i.e. epicardial coronary lesions; b) stress imaging with stress radionuclide (SPECT or PET) and stress MRI or stress ECHO studies, to assess the presence of "functional" correlates of IHD, i.e. abnormal myocardial perfusion and contraction. All studies will be performed within two months from enrolment, according to standardized protocols; they will be

registered on multimedial support (DVD) in standardized format and shipped for central readings. Records of measured radiation dose to the patient (when applicable) will be entered in the "patient record" into the Central Server. Patients who will not be able to perform one of the two non invasive stress tests will be kept into the study (with missing data). Patients who will refuse to perform invasive coronary angiography but will be submitted to CTA and functional stress tests (in particular in the case of normal non-invasive tests and/or CTA) will be kept into the study (with missing data). Patients who will refuse CTA but will perform functional stress tests and invasive coronary angiography will be kept into the study (with missing data). All patients will be encouraged to complete the whole protocol but, according to the above statements, a minimum of a functional stress test and an anatomic test will be considered sufficient to keep a patient into the study. Additional patients will be enrolled throughout the consortium to keep stable the final number of patients submitted to each combination of anatomo-functional non invasive modalities.
Regarding the stress Echo and stress MRI studies, dobutamine will be used as a stressor in the majority of centers. High dose dipyridamole Echo or MRI will be performed in a minority of patients to allow the contemporary analysis of ventricular function and epicardial coronary flow reserve by Echo or myocardial perfusion by MRI. As far as the accuracy in the detection of ischemic wall motion abnormalities are concerned the 2 stressors are very similar (see References below) allowing to pool the data when accuracy of Echo-Stress or MRI-Stress will be compared with other stress imaging approaches. See references below.

0.2.6 Invasive diagnostic work-up

Within two months from enrolment and after the completion of the non invasive work-up, patients will undergo invasive study. Coronary angiography (ICA) will be proposed to all patients since it is currently accepted in patients with intermediate pre-test probability of IHD even without further non invasive testing. Patients who will refuse ICA, in particular in the case of negative non-invasive testing, will be kept into the study. Intracoronary estimate of fractional flow reserve (FFR) by pressure wire will be performed as golden standard to assess the "functional" significance of an intermediate coronary lesion >=30% (obligatory in stenoses 30%-70%) and as a guide to indicate revascularization (also in stenoses >70% if judged clinically useful by the cath operator). Intracoronary ultrasound (IVUS) will be performed in patients with angiographycally normal coronary vessels or <30% coronary stenoses for accurate evaluation of early epicardial coronary atherosclerosis. For lower than 30% stenosis, coronary flow reserve (by Doppler wire) will be also measured to assess coronary microvascular function. All studies will be performed according to standardized protocols, registered on multimedial support (DVD) in standardized formats and shipped for central analysis. Records of measured radiation dose to the patient will be entered in the "patient record" into the Central Server.

0.2.7 Treatment

Coronary revascularization as well as medical treatment will be decided by the attending physician on a clinical basis, taking into account all available data, and registered. However, revascularization of invasively documented hemodynamically significant stenosis will be highly recommended.

Task 0.3 Follow-up (P1-CNR, P2-U. Turku, P3-UZH, P4-LUMC, P6-IR-HSCSP, P7-NIC, P8-RBHT, P9-APHP, P10-UniGe, P11-SERMAS, P12-UniNA, P13-HUVHEBRON, P17-FGM, P18-KRITUM, P19-QMUL, P20-AOUC, P21-Ospedale Versilia, P22-KAE) (months 5 → 42)

All patients will be admitted to a clinical follow-up consisting of regular visits at 1 month and at 6 months from enrolment and every 6 months afterwards. Follow-up data will be obtained by filling dedicated questionnaires which explore patient health status, relevant follow-up events and quality of life. Questionnaires will be filled by the patient and the physician in paper formats, to be entered in dedicated electronic pages into the Central Server. Records of measured radiation dose to the patient in the follow-up (when applicable) will be entered in the "patient record" into the Central Server.

Deliverables

D0.1 Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet **(Month 2)**

Milestones

M0.1 To issue implementation and harmonization of validated procedures for central analysis throughout the consortium **(Month 10)**

M0.2 700 patients enrolled with completed diagnostic work-up per centre and at least 70% of the patients with both invasive data collected according to the protocol **(Month 36)**

M0.3 At least 70% of the patients with completed follow-up **(Month 40)**

References:

1. Picano E, et al. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. Cardiovasc Ultrasound. 2008 Jun 19;6:30

2. Heijenbrok-Kal et al. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. Am Heart J. 2007;154:415-23.

3.Sicari R, et al. European Association of Echocardiography. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2008 Jul;9(4):415-37

4. Pingitore A, et al. Head to head comparison between perfusion and function during accelerated high-dose dipyridamole magnetic resonance stress for the detection of coronary artery disease. Am J Cardiol. 2008 Jan 1;101(1):8-14

Work package description

Work package number	1	**Start date or starting event**				1	
Work package title	**Clinical Profiles, Biomarkers and IHD prediction model**						
Activity Type	RTD						
Participant id	**P1-CNR**	P12-UniNA					
Person-months per beneficiary	9 (4)	(3)					

Objectives

- To analyse blood samples.
- To deliver biomarkers of vascular damage.
- To develop a novel prediction model to establish pre-test probability of IHD.

Description of work and role of participants

Task 1.1 Standardization of clinical data, blood samples and parameters to be analysed (P1-CNR) (months 1 → 2)

1.1.1 Format for the collection of relevant clinical information

To standardize the procedure for collection of clinical data, a format will be prepared by P1-CNR within the first 2 months. In each patient the following variables will be collected according to pre-defined criteria:

- Symptoms (categorized as typical/definite angina, at rest and/or on effort, atypical/probable angina, anginal-like chest pain at rest, epigastric pain, chest pain associated with dyspeptic symptoms, non-anginal chest pain, sharp chest pain, chest pain exacerbated by cuff and/or respiration, exertional dyspnea or fatigue)
- Cardiovascular risk factors (including family history of premature CAD, smoking within the last year and pack/years, diabetes mellitus (type 1 or 2), hypercholesterolemia, hypertriglyceridemia, arterial hypertension, obesity, sedentary habit, stress)
- 12-lead ECG (categorized as normal, left bundle branch block, left ventricular hypertrophy, other)
- Exercise stress test (including exercise tolerance, chest pain on effort, hypotension on effort, ST segment changes)
- Echocardiogram (left ventricular ejection fraction, left ventricular end-diastolic diameter)

1.1.2 Procedures for blood specimens sampling, storage and shipment

In order to standardize the procedure for collection of biological samples, a well defined protocol containing the detailed procedure for blood sample withdrawn, pre-analytical treatment, storage and shipment will be prepared by P1-CNR within the first 2 months. All the participating centres will receive this document which has to be strictly followed. The pre-analytical handling of the haematic samples is of pivotal importance for reliable determination of the chosen biomarkers, specifically for the molecules with problems of stability over time. Thus, a tight control of the schedule of the different steps of sample management will be recommended for the more sensitive parameters. In particular, the protocol will contain the instruction relative to 1. Patient conditions at the blood withdrawing (i.e.: time of fasting); 2. Conditions for blood collection (i.e.: kind and

number of tubes, kind of anti-coagulant, volume of blood to be withdrawn, the need to keep the samples at 4°C in an ice bath); 3. Plasma or serum preparation (conditions for blood centrifugation); 4. Number and size of aliquots; 5. Labelling (allowing sample identification and anonymization); 6. Storage conditions; 7. Conditions for shipping to P1-CNR for specific assays.

Task 1.2 Biological bank (P1-CNR) (months 4 → 36)

The processing of blood samples of the patients enrolled will be performed at every clinical centre labs, while the collection, cataloguing, and definitive cryoconservation will be done at the Biological Bank of P1-CNR. The Biological Bank of P1-CNR is an operational facility for the collection, conservation, and management of biological samples, with sampling procedures that are standardized. The ID number associated to the single patient by the Central Server (see WP5) will also label the biological samples. A dedicated database manages the applications for the positioning and the retrieval of the aliquots inside the set of freezers at -80°C that are monitored centrally through a computerised system capable of sending out information on the status of each freezer on the Institute's internet system. The bank access is allowed only to specialized and authorized personnel.

Task 1.3 Central biohumoral analysis (P1-CNR) (months 7 → 42)

The biological variables chosen will include the main indicators of the metabolic and inflammatory individual profiles, as well as specific markers of cardiovascular damage. In particular: I) the lipid profile will be evaluated by total cholesterol, triglycerides, HDL, Apolipoprotein A1, B, Lipoprotein (a); II) the glicidic profile will be evaluated by glucose, HbA1, insulin; III) the systemic inflammatory profile by C-reactive protein and Interleukin-6. Specific markers of cardiovascular damage will include: I) adhesion molecules, NT-pro-CNP and endothelin-1 as markers of endothelial/microvascular activation; II) osteopontin to evaluate vascular remodelling; III) NT-proBNP as marker of myocardial damage; IV) Heat Shock Proteins (HO-1, HSP72) and adiponectin as protective factors against ischemia/reperfusion injury.

— The methods that will be utilized for the determination of the above mentioned biomarkers have been previously standardized in the laboratories of CNR as to sensitivity, accuracy, reproducibility and working range (analyte determination with an imprecision < 10%). All determinations will be made in duplicate to reduce the analytical variability.

Task 1.4 Diagnostic predictive model based on clinical profiles and biomarkers (P1-CNR, P12-UniNA) (months 19 → 42)

Both the clinical and laboratory data will be entered into the Central Database at P1-CNR, as soon as the data are available. The results of non-invasive anatomo-functional imaging will also be entered into the same data base. To develop a predictive model clinical and laboratory variables will be tested against the novel patient categories derived from non-invasive imaging using logistic regression. A preliminary version of the model will be available after the second year of the project. The validity of this model will be tested against actual data in the third year.

Deliverables

D1.1 Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet **(Month 2)**

D1.2 Report on standardisation and accuracy of integrated predictive model for diagnosis and prognosis of IHD based on clinical, laboratory and multi-imaging assessment (**Month 42**)

Milestones

M1.1 At least 70% of patients enrolled with completed centralized analysis of laboratory data **(Month 36)**

M1.2 Results of models based on clinical profiles and biomarkers to predict diagnosis of IHD **(Month 40)**

Work package description

Work package number	2	**Start date or starting event**				1	
Work package title	**Non-Invasive "Anatomical" Assessment of CAD by CT imaging**						
Activity Type	RTD						
Participant id	**P4-LUMC**	P2-U.Turku					
Person-months per beneficiary	22	(5)					

Objectives

- To perform central analysis of CT examinations
- To deliver quantitative parameters of "anatomic" coronary disease to be validated against invasive reference methods
- To develop new strategies for comprehensive assessment of anatomic coronary disease by CT.

Description of work and role of participants

Task 2.1 Standardization of exams procedures and parameters to be analysed (P4-LUMC) (months 1 → 2)

The WP2 leader will develop standardized procedures for CT acquisition protocols and minimization of radiation dose within month 2 to be implemented by the participating centers in month 3. To ensure homogeneity of the image quality, the WP2 leader will gather prior to start of patient inclusion test data-sets from the participating centers to review the image quality. This will allow timely optimization of data acquisition protocols. In addition, quality of the data (including image quality, appropriate phase reconstruction, kernel selection, etc.) will be monitored continuously throughout the project. The WP2 leader, within month 2, will also develop standardized procedures for CT analysis and will define relevant parameters to be entered into the Central Database.

Task 2.2 Central CT imaging analysis (P2-U. Turku, P4-LUMC) (months 7 → 36)

Participating centres will send the original axial data sets to Central Digital Bank at CNR that will forward them to the leader of WP2 at Leiden (P4-LUMC). At Leiden, the data sets will then be further analysed and reconstructed. For this purpose, a dedicated researcher- with several years of experience in performing and reading CT angiography - will view the axial data sets and select the appropriate phases for the different coronary arteries. Subsequently, curved multiplanar reformat in different angulations will be obtained for all coronary arteries and side-branches. Coronary calcium scoring will be performed by an experienced observer with the application of dedicated software. Agatston and Volume calcium scores will be obtained per coronary artery and per patient.

The processed data for the CT angiography studies will be read by a cardiologist together with a dedicated researcher. A maximum of 250 scans will be re-evaluated to assess inter- and intra-observer variability (together with P2-U. Turku).

A Local Database for entering the CT angiography data will be constructed, continuously updated and interfaced with Central Database. Data will be checked by the WP2 leader for consistency

throughout the project.

Task 2.3 Comprehensive assessment of "anatomic" coronary disease by CT (P4-LUMC) (months 19 → 42)

In addition to the diagnostic accuracy reading, the CTA studies will be evaluated for plaque characterization, both visually and quantitatively. This is a time-consuming process, which will be performed by dedicated researchers, supervised by participating cardiologists. Also, to evaluate inter- and intra- observer variability, a maximum of 250 scans will be re-evaluated. For the quantitative analyses, dedicated software that is currently under development will be obtained.

These data will then be used to explore and develop new approaches to evaluate and report CT angiography studies in a more comprehensive manner. While at present only limited data is used in reporting CT angiography, a wealth of data is potentially available that could be extracted from the original data. Indeed, not only information on coronary luminal diameter but also the atherosclerotic "burden" can potentially be obtained, improving both diagnosis and prognosis.

Deliverables

D2.1 Standardized and optimised protocols for CT angiography acquisition and analysis **(Month 2)**

Milestones

M2.1 Results of comprehensive assessment of anatomic coronary disease by CT **(Month 40)**

Work package description

Work package number	3	**Start date or starting event**		1		
Work package title	**Non-Invasive "Functional" Assessment of IHD by Stress Imaging**					
Activity Type	RTD					
Participant id	**P1-CNR**	P2-U.Turku	P3-UZH	P8-RBHT	P9-APHP	P11-SERMAS	P18-KRITUM
Person-months per beneficiary	3,5 (3)	11 (2)	3,5 (7)	3	(2)	8 (2)	5 (3)

Objectives

- To perform central analysis of Stress Imaging examinations by experts in each modality
- To deliver quantitative parameters of "functional" coronary disease to be validated against invasive reference methods
- To develop new strategies for comprehensive assessment of "functional" coronary disease by single and multimodality stress imaging

Description of work and role of participants

Task 3.1 Standardization of exams procedures and parameters to be analysed (P1-CNR) (months 1 →2)

The WP3 leader, in agreement with centres which will act as core labs for each imaging modality, will develop, within month 2, standardized procedures for imaging acquisition protocols including: scanning parameters, stress protocols, data acquisition and storage, minimization of radiation dose as well as transferring process to the respective core labs. In particular stressors for each imaging modality will be standardized according to the following indications: 1. bycicle exercise or pharmacologic vasodilation (i.v. adenosine/dipyridamole) for SPECT; 2. pharmacologic vasodilation (i.v. adenosine/dipyridamole) for PET; 3. pharmacologic stress (i.v. dobutamine) for ECHO or MRI studies including only wall motion and contractility assessment; 4. pharmacologic vasodilation (i.v. dipyridamole) for ECHO or MRI studies including wall motion/contractility and perfusion assessment in the same study (as an alternative to dobutamine in selected centres). These guidelines will be implemented by the participating centres in month 3. To ensure homogeneity of the image quality, the WP3 leader will gather prior to start of patient inclusion test data-sets from the participating centres and will forward them to the core labs to review the image quality. This will allow timely optimization of data acquisition protocols. In addition, quality of the data will be monitored continuously throughout the project as well as number of patients studied with each modality and stressor so to issue corrections in order to allow a balanced distribution of the number of patients to each modality and stress protocol. The WP3 leader, within month 2, in agreement with centres which will act as core labs for each imaging modality, will also develop standardized procedures for imaging analysis, to allow extraction of complete "state of the art" parameters from each modality to be entered into the Central Database.

Task 3.2 Central SPECT imaging analysis (P8-RBHT) (months 7 → 36)

3.2.1 Central SPECT imaging readings with regard to perfusion.

Analysis will provide visual as well as semiquantitative scoring. Presence versus absence of perfusion abnormalities as well as its severity and extent will be assessed. Wherever appropriate

gated-SPECT acquisitions have been performed, quantitative analysis of wall motion and wall thickening will be included to assess "contractile function"

3.2.2 Data entry of the centrally evaluated SPECT scans into the central database
Exams which will meet all established quality control criteria will be included. The data base has to be set up in order to allow meaningful intermodality comparison per patient, per artery and per segment versus the other techniques, i.e. invasive and non-invasive.

Task 3.3 Central PET imaging analysis (P2-U. Turku, P18-KRITUM) (months 7 → 36)

3.3.1 Central PET imaging readings with regard to perfusion
This part is analogous to the SPECT reading see above Task 3.2. Wherever appropriate gated-PET acquisitions have been performed, quantitative analysis of wall motion and wall thickening will be included to assess "contractile function". In addition, quantitative analysis of PET scans will be performed to provide absolute myocardial blood flow (MBF) values at rest and at stress, including MBF reserve.

3.3.2 Data entry of the centrally evaluated PET scans into the central database
Quality controlled PET imaging results obtained in each patient will be entered into the central database as described in Task 3.2.

Task 3.4 Central ECHO imaging analysis (P1-CNR, P11-SERMAS) (months 7 → 36)

3.4.1 Central ECHO imaging readings
The primary goal is to read the wall motion at rest and to assess the wall motion abnormalities induced during the stress protocol. Wall motion abnormalities will be graded and scored as defined in the guidelines prepared as for Task 3.1. Besides the conventional stress echocardiographic parameters of regional function such as rest WMSI, and peak WMSI, their variation expressed by the delta WMSI, global function parameters will also be evaluated at rest and at peak stress: ejection fraction (measured by the Simpson's rule), end-systolic and end-diastolic volumes. On the basis these parameters it will be possible to provide indexes of global contractility during stress echocardiography (i.e. Bombardini T, et al.. Force-frequency relationship in the echocardiography laboratory: a noninvasive assessment of Bowditch treppe? J Am Soc Echocardiogr. 2003 Jun;16(6):646-55).
In a subpopulation transthoracic assessment of proximal coronary flow and flow reserve at baseline and during stress will also be performed. Such data will be included in the analysis where available as a secondary endpoint.

3.4.2 Data entry of the centrally evaluated ECHO exams into the central database
Quality controlled ECHO imaging results obtained in each patient will be entered into the central database which has to meet the same criteria mentioned in Task 3.2 as will be predefined in Task 3.1 to allow intermodality comparison.

Task 3.5 Central MRI imaging analysis (P1-CNR) (months 7 → 36)

3.5.1 Central MRI imaging readings
In analogy to Task 3.4 (ECHO) the primary goal is to read the wall motion at rest and to assess the wall motion abnormalities induced during the stress protocol. Wall motion and contractility abnormalities will be graded and scored as defined in the guidelines prepared in Task 3.1. Besides the conventional stress MRI parameters of regional function, drawing the epicardial and endocardial LV contours will allow to obtain quantitative estimation of wall motion and wall thickening during rest and stress together with parameters of global LV function.
In a subpopulation myocardial perfusion will also be assessed at baseline and during stress. Such data will be included in the analysis where available as a secondary endpoint.

3.5.2 Data entry of the centrally evaluated MRI exams into the central database
Quality controlled MRI imaging results obtained in each patient will be entered into the central database which has to meet the criteria mentioned in Task 3.2 as will be predefined in Task 3.1 to allow intermodality comparison.

Task 3.6 Comprehensive assessment of "functional" coronary disease by non-invasive stress imaging (P1-CNR and the other participants) (months 19 → 42)
The individual patients data included in the central database for all the non-invasive imaging modalities will be merged. An integrated diagnostic profile, as obtained from non-invasive single or multimodality "functional" imaging combining perfusion and contraction information, will be created for each patient and analysed in the whole study population. New risk adapted and patient tailored strategies for comprehensive assessment of functional coronary disease by single and multimodality stress imaging will be developed.

Deliverables

D3.1 Standardized and optimized protocols for performance of stress imaging, data acquisition and analysis **(Month 2)**

D3.2 Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet. **(Month 2)**

Milestones

M3.1 Results of comprehensive assessment of "functional" coronary disease by non-invasive stress imaging **(Month 40)**

Work package description

Work package number	4	**Start date or starting event**		1			
Work package title	**Integrated "Anatomo-Functional" characterization of IHD**						
Activity Type	RTD						
Participant id	**P2- U.Turku**	P1- CNR	P3- UZH	P4- LUMC	P7- NIC	P8- RBHT	P9- APHP	P11- SERMAS
Person-months per beneficiary	17 (2)	3,5 (3)	(2)	(6)	1 (3)	(2)	(3)	3 (1)

Objectives

- To perform central analysis of "invasive" coronary imaging
- To deliver reference quantitative parameters of anatomo-functional coronary disease
- To develop a validation model of non-invasive multimodality imaging approaches

Description of work and role of participants

Task 4.1 Standardization of exams procedures and parameters to be analysed (P2- U. Turku) (months 1 → 2)

The WP4 leader will develop standardized procedures for heart catheterization within month 2 to be implemented by the participating centers in month 3. To ensure homogeneity of the image acquisitions at invasive coronary angiography (ICA), the WP4 leader will gather prior to start of patient inclusion, test exams from the participating centers to review the image quality. In addition, the results of the coronary pressure measurements (FFR), Doppler flow velocity measurements (CFR) and intravascular ultrasound (IVUS) measurements of the first patients in each centre will be evaluated immediately to ensure that also these procedures will be appropriately acquired. The WP4 leader, within month 2, will also develop standardized procedures for ICA, FFR, CFR and IVUS analysis and will define relevant parameters to be entered into the Central Database.

Task 4.2 Central invasive exams analysis (P2- U. Turku) (months 7 → 36)

Participating centres will send the original heart catheterization data sets to Central Digital Bank at CNR that will forward them to the leader of WP4 at Turku. At Turku, the data sets will then be further analysed. For this purpose, dedicated researchers, with several years of experience in performing and reading ICA, FFR, CFR and IVUS exams, will review and analyse the original data.

A maximum of 250 exams will be re-evaluated to assess inter- and intra- observer variability. In particular IVUS and CFR data, obtained in patients with <30% coronary stenoses, will be specifically analysed to obtain a complete characterization of early coronary atherosclerosis and to detect coronary microvascular dysfunction (together with P1-CNR and P7-NIC).

A Local Database for entering the invasive data will be constructed, continuously updated and interfaced with Central Database. Data will be checked by the WP4 leader for consistency throughout the project.

Task 4.3 Validation model of non-invasive multimodality imaging (P1-CNR, P2- U. Turku, P3-

UZH, P4-LUMC, P7-NIC, P8-RBHT, P9-APHP, P11-SERMAS) (months 4 → 42)

4.3.1 Validation of single non-invasive modality against invasive standards
Accuracy of non-invasive "anatomic" imaging by CTA will be assessed against anatomic invasive parameters from ICA and IVUS. Comparative intermodality accuracy of non-invasive "functional" stress imaging will be assessed against invasive evidence of functionally significant coronary lesions (>=30% with abnormal FFR) or of abnormal microvascular function (coronary stenoses <30% or no stenoses with abnormal CFR).

4.3.2 Validation of multimodality non-invasive approaches for characterization of IHD in anatomo-functional categories against invasive standards
This task will create and validate comprehensive understanding and interpretation of various non-invasive imaging strategies. In particular the accuracy of different non-invasive integrated imaging modalities (CTA+PET, CTA+SPECT, CTA+ECHO, CTA+MRI) will be assessed against reference anatomo-functional invasive characterization of IHD. This task will be performed from month 19 to month 30.

Deliverables

D4.1 Standardized and optimised protocols for heart catheterisation **(Month 2)**

D4.2 Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet. **(Month 2)**

D4.3 Report on standardisation and validation of non-invasive multimodality anatomo-functional imaging for diagnosis of IHD (**Month 42)**

Milestones

M4.1 Results of multimodality non-invasive imaging in diagnosing and characterizing IHD **(Month 40)**

Work package description

Work package number	5	**Start date or starting event:**				1
Work package title	**Central data bank, integrated analysis of EVINCI-study results**					
Activity Type	RTD					
Participant id	**P1-CNR**	P2-U.Turku	P3-UZH	P4-LUMC	P8-RBHT	P11-SERMAS	P15-INF
Person-months per beneficiary	9 (3)	(1)	(3)	(3)	(3)	2,5 (0,5)	7,08

Objectives:

- To develop an informatics platform accessible trough Internet, which allows clinical centres to enter patients information, receive ID number (for anonymization) and monitor the completion of diagnostic work-up, shipment of "raw data" and follow-up.
- To manage "raw data" transmission to specific centres dedicated to central readings and to include "analysed data" in a central database.
- To assess the value of integrating clinical profiles and biomarkers with non-invasively defined anatomo-functional IHD categories to predict patient outcome.
- To investigate the association between biomarkers and imaging indicators of coronary vascular damage in order to provide new reliable end-points to be used in therapeutical trials in IHD.

Description of work and role of participants

Task 5.1 Development of Central Server, Digital Bank and Database. (P1-CNR, P15-INF) (months 1 → 6)

An informatics platform for the Central Server will be developed within month 2 to monitor the process of patients' enrolment and to allow collection of the main data related to clinical evaluation, follow-up, costs, risks assessment and quality of life. The Central Server will be available to the consortium via a website with a password protected area. A dedicated space for exchange of organizational information will be available within the restricted area of the web site, moderated by P1-CNR. The web site will be the main media for communication and coordination among partners.

An informatics platform for the Digital Bank will be developed within month 2 to allow storage in a readily accessible format of the "raw data" of the imaging exams.

An informatics platform for the Central Database will be developed within month 6 to provide storage of the relevant parameters derived as outputs of central readings in a format which will allow comparison among different sources, access throughout the Consortium and statistical analysis.

Task 5.2. Management of Central Server, Digital Bank and Database (P1-CNR, P2- U. Turku, P3-UZH, P4-LUMC, P8-RBHT, P11-SERMAS) (months 4 → 36)

5.2.1 Management of Central Server

In order to ensure the respect of patients' privacy, all centres will enter a code including the centre identification, the progressive number of enrolment, the initials of the patient followed by his/her date of birth (e.g. center 1, pt #5, AD, 03-10-43). All enrolled patients will be identified automatically in the Central Server and will receive a progressive ID number visible to the entire

consortium (without any reference to the actual patient's name for complete anonimization). After the enrolment and the receipt of the ID number, each patient will be monitored automatically for the completion of diagnostic work-up and follow-up (informed consent, blood samples, exams performed, follow-up visits). Information about clinical history, treatment, radiation exposure, costs, adverse events and quality of life will be collected by filling dedicated electronic questionnaires available in the Central Server. An E-mail alert service will be created to evidence incomplete procedures or delayed shipment of "raw data" for central readings.

Subtask 5.2.2 Management of Central Digital Bank
Imaging exams of each patient, identified by the ID number, will be registered on CD-DVD in Dicom format and then sent by surface mail to P1-CNR who will provide to store a copy of the raw data in a Central Digital Bank, accessible to the consortium on request, and to send specific material to participating centres which will perform central readings according to the specific WPs.

Subtask 5.2.3 Management of Central Database
In order to allow a comparison of data from different imaging techniques, main parameters derived from central readings will be entered into the Database according to the standard 17 segments heart model with identification of the three main vascular territories. Parameters will be organized in dedicated sections including: patient's status data (clinical, costs, risks, and follow-up data from Central Server), biohumoral data (from WP1), semiquantitative and quantitative data on myocardial perfusion, myocardial function, coronary anatomy and coronary flow reserve (from WP2-3-4).

Task 5.3 Outcome predictive model and association study (P1-CNR, P2- U. Turku, P3-UZH, P4-LUMC, P8-RBHT, P11-SERMAS) (months 36 → 42)
Clinical profiles and biomarkers will be combined with non-invasively defined anatomo-functional IHD categories in a new model to predict patient outcome. Moreover, the association between specific biomarkers and imaging indicators of coronary vascular damage will be analysed to provide new insight into the pathophysiology of IHD and new reliable end-points to be used in therapeutical trials.

Deliverables

D5.1 Standardized protocols for access and secure transmission of data to the Central Server, Digital Bank and Data Base **(Month 2)**

D5.2 Authorisation of the study by the relevant ethical committees, informed consent forms and information sheet. **(Month 2)**

D5.3 Report on results of association study between clinical profiles, biomarkers and imaging profiles of IHD and the integrated impact on outcome **(Month 42)**

Milestones

M5.1 Number of patients with completed transmission of clinical data, blood samples, non-invasive and invasive imaging raw data **(Month 40)**

Work package description

Work package number	6	**Start date or starting event:**			1		
Work package title	**Cost-Benefit analysis and evaluation of Procedural Risks**						
Activity Type	RTD						
Participant id	**P10-UniGE**	P1-CNR					
Person-months per beneficiary:	3,5 (3)	2,5 (4)					

Objectives

- To perform cost-benefit analyses alongside the EVINCI-study.
- To estimate the overall procedural risks for the patient associated with the different non-invasive and invasive diagnostic approaches.

Description of work and role of participants

Task 6.1 Standardization of questionnaires and parameters to be analysed (P1-CNR, P10-UniGe) (months 1 → 6)

The WP6 leader, and P1-CNR, will develop standardized questionnaires (supported by an operating manual) for collection of relevant data concerning cost-benefit analyses and procedural risks evaluation within month 2. In particular standardized questionnaires to be filled at enrolment and at follow-up visits, will include, besides socio-demographical and clinical characteristics, information on health costs for each patient enrolled in every centre, quality of life and perceived health status. Information on actual (rather than estimated from reference values) patient dose data at the time of examinations as well as on previous and follow-up exposure will be included. A specific informed consent for each diagnostic modality specifying radiation doses and risks will be standardized. Questionnaires will be available in digital format on the Central data-base. To ensure quality control of the data a series of checks for accuracy and completeness will be carried out alongside the EVINCI-study.

The WP6 leader, within month 6, will also define relevant parameters to be extracted form questionnaires and entered into the Central Database.

Task 6.2 Cost-benefit models (P10-UniGe) (months 30 → 42)

Cost-benefit, cost-effectiveness and cost-utility analyses will be performed alongside the EVINCI-study clinical trial. The cost-benefit analysis will use benefits expressed in the same monetary units as the costs, the cost-effectiveness analysis will consider the effects of the intervention measured in natural units and the cost utility analysis will estimate the satisfaction of the time that a person has left to live, the so called quality adjusted life year. The benefit cost ratio (BCR), the incremental cost-effectiveness ratio (ICER), the incremental net benefit (INB) and the cost-effectiveness acceptability curve (CEAC) will be derived as summary measure of economic evaluations.

Task 6.3 Procedural Risks evaluation (P1-CNR, P10-UniGe) (months 4 → 36)

A log of all previous (before study entry) and ongoing (during the study) cumulative effective doses (and corresponding estimated risks following the latest BEIR VII estimates) will be produced. The acute diagnostic benefits of the different techniques versus the acute (major life threatening effects of stress procedures, acute complications of catheterization, contrast-induced nephropathy) and predicted long-term risks of the same procedures will be evaluated.

Deliverables

D6.1 Report on cost-benefit analysis of integrated non-invasive vs invasive strategies for the diagnosis of IHD (including radiation exposure and procedural risks) (**Month 42**)

Milestones

M6.1 Final results of safety analysis of the entire study **(Month 40)**

Work package description

Work package number	7	Start date or starting event		24			
Work package title	**Advanced clinical reporting of non-invasive multimodality cardiac imaging results**						
Activity Type	RTD						
Participant id	**P1-CNR**	P2-U.Turku	P3-UZH	P18-KRITUM			
Person-months per beneficiary	15 (5)	(1)	(3)	(5)			

Objectives

- To develop software for the integrated representation of anatomo-functional information derived from multimodality non-invasive cardiac imaging
- To develop a novel informatics tool to combine integrated imaging information with clinical and biological data in order to assist in clinical decision making

Description of work and role of participants

Task 7.1 Image fusion analysis (P1-CNR, P2-U. Turku, P3-UZH, P18-KRITUM) (months 24 → 42)

The objective of this Task is to provide the clinician with a user interface that integrates the various image data obtained from different modalities utilized in the project in order to present them in an intuitive, easy to use graphical form to the clinician for interpretation.

7.1.1 Image standardization

Tomographic 3D images (CT, MRI, PET, SPECT) will be available in DICOM standard format, this file format includes information about image resolution, orientation and image acquisition modality characteristics. Standardized acquisition protocols (WP3, Task 3.1) will be used in order to optimise the image fusion process. The independency of the DICOM image format, allows to store images in any DICOM image manager component of a modern PACS (Picture Archiving and Communication System) and to retrieve them by standardized DICOM clients, independently from the used platform (Windows, Macintosh, UNIX).

7.1.2 Image registration and fusion

Image registration is necessary where the same region of interest is captured with different sensors (i.e. multimodal) or at different imaging sessions (i.e. unimodal). In the context of the present project, accurate registration among different modalities is necessary to obtain a geometric alignment of heart structures visualized with different characteristics and different resolutions. The geometric alignment of 3D cardiac data sets of the same patient, will be obtained with dedicated registration algorithms. P1-CNR has a consolidate experience in registering unimodal (especially MRI) and multi-modal (MRI combined with SPECT and PET) imaging modalities. This approach will be extended to incorporate CT modality. An interesting point is the possibility to use CT as a "bridge" to register MR images with PET images acquired by a CT-PET scanner. A peculiarity of the present project is the involvement of dynamic, cardiac images with different time resolution among the cardiac cycle. Hence, the registration process should be applied not only in the spatial domain but in the time domain as well. A crucial aspect of image registration is the evaluation of the algorithms accuracy. Such task will be reached performing single and multimodal registration

on phantoms created to be sensitive to a couple of imaging modalities. After the registration, images coming from different session/modalities can be fused in a unique graphical representation and displayed in an appropriate GUI, as described in task 7.1.4.

7.1.3 Quantitative information

Quantitative data extracted from each modality involved in the project will be integrated in the image fusion representation. Effective comparison of indices provided by each modality must be provided as well in the project framework taking into account the standards used in the clinical/experimental practice. In heart studies, the AHA left ventricle model (i.e. 17 sectors) is widely accepted and will represent the reference model for quantitative parameters mapping. This model also provides a validate mapping of coronary arteries on heart sectors. Quantitative parameters will be also converted in colour maps that will be integrated in the GUI environment.

7.1.4 Graphical user interface for multimodality imaging fusion

The Graphical User Interface (GUI) will provide an effective way to deal with different image modalities and quantitative data. Basically, the GUI will allow performing visual comparative analysis of images and comparison of numerical quantitative clinical indices. The GUI will allow to extract corresponding slices from two or more modalities with the same spatial orientation and related to the same phase of the cardiac cycle. The extracted images can be examined by the user side-by-side or by an appropriate image fusion algorithm. It will also allow to map on a reference model quantitative, segmental data provided by the different image modalities. Two kinds of models will be available in the final GUI: a standard, "graphical" model (i.e. 17-sectors AHA) and a "true", anatomical model represented by CT images. In the second case, quantitative indices will be mapped on CT by rigid or warp transformations.

Task 7.2 Synthetic 4D dynamic heart model (P1-CNR) (months 24 → 42)

Medical decision is the result of a complex mental process integrating available clinical and instrumental information. The number and heterogeneity of information, which is frequently obtained by different techniques, at different times and by different specialists, whose knowledge of the patient may also be fragmentary, often make this process difficult. The need for integration and synthesis of anatomo-functional information and multimodal data as well as the need of user-friendly specialist reports for communication is widely acknowledged. Purpose of the task is to integrate all the available information (from clinical and imaging assessment) belonging to a single patient in a synthetic dynamic heart model, able to retrieve the origin and nature of each information, to synthetically summarize the disease status and to stratify the predicted risk.

Additional aims of the project are to obtain a picture of the patient's status easy to be shared among different subjects (cardiologist, cardiac surgeon, family doctor and the patient himself), appreciated as graphical support for decision making and follow-up (description of the evolution of the disease by successive frames) and also suitable for educational purposes.

7.2.1. 3D Model

The main target of the model is to simultaneously represent left ventricular dimensions, global and regional function, presence, site and extension of ischemia or necrosis and their spatial correlation with coronary anatomy and disease.

In brief, the left ventricle will be subdivided into 17 segments, according to the widely used AHA 17 segments model. Each segment is free of moving according to a wall motion parameter scored from normal to dyskinesia. In addition each segment is differently colored depending on the presence of ischemia and/or necrosis. The ventricle is surrounded by the coronary branches subdivided into 18 segments. For each coronary segment, presence and severity of stenosis, presence, degree and origin of feeding collateral circulation and type and outcome of revascularization procedures (CABG, PTCA, and stent) are graphically represented. Each coronary segment will be color coded in order to render wall vessel and obstructive materials properties. The

LV shape is made similar to a paraboloid. The myocardium is included in 2 paraboloids outlining the inner and outer ventricle surfaces. The diameters of LV in diastole and in systole are derived from the resting echocardiogram, MRI or CT images. Asymmetry of wall thickness is accomplished by shifting the inner paraboloid. Systolic wall thickness is calculated keeping constant the myocardial mass in systole and diastole. Coronary tree is constructed according to the anatomical distribution in each patient.
The physician conclusive diagnosis and all the information derived from the different modalities are forced to be organized according to the model schema. Additional information will be available as text report.

7.2.2 Integrating clinical and imaging data
Non-imaging clinical data is typically stored in a combination of RDBMS and flat text files, and may include current as well as historical clinical measurements for each patient. An information model and data schema will be developed to simplify querying such data as well as integrating it with measurements and parameters derived from imaging analysis, and to simplify the presentation and usage of such data in the decision making tools.

7.2.3 Graphics user interface for 3D heart model
To simplify viewing and correlating the patient data with the imaging data in an intuitive manner, a graphical user interface will be organized into a tabbed pane. In the center, the main pane will show the 3D heart and the visual exploration tools. Information sources will be displayed on the left as a sequence of reports and tabular data. Planar bull's eye will be included in the source pane to aid quick reading and visual comparison. A variety of visual analysis tools will be provided to automatically evidence conflicting and missing data. The exploration of the model will be possible by rotation, zooming, fixed points of view, show or hide functionalities and stop or run the contraction procedure.

7.2.4 Integrated decision making tool (4D model)
The integrated analysis of the clinical data and 3D heart model will provide the basis for building an integrated decision making tool (4D model). The tool will incorporate the use of the predictive models developed in WP 5. The final decision making tool will be presented to the users as an intuitive wizard environment that guides them through the different stages of the predictive model development and usage.

Deliverables

D7.1 Software and graphical user interface for multi-imaging reporting and decision making in patients with suspected IHD (**Month 42**)

Milestones

M7.1 Software for multimodality imaging registration and fusion and for integrating clinical and imaging information into a 3D heart model **(Month 40)**

Work package description

Work package number				8			**Start date or starting event:**	**1**		
Work package title				**Dissemination and Exploitation**						
Activity Type				OTH						
Participant id	**P14-ESC**	P1-CNR	P2-U.Turku	P3-UZH	P4-LUMC	P6-IR-HSCSP	P7-NIC	P8-RBHT	P9-APHP	P10-UniGE
Person-months per beneficiary:	2,5 (9,5)	3 (3)	(2)	0,3 (1)	(2)	1,5 (0,5)	1 (1)	0,4 (1,5)	(2)	(2)
Participant id	P11-SERMAS	P12-UniNA	P13-HUVHEBRON	P16-CFc	P20-AOUC	P21-Ospedale Versilia	P22-KAE			
Person-months per beneficiary	(1)	0,5 (2)	2,3	12,3	0,5	0,4	0,5 (1)			

Objectives:

- To disseminate the results generated in the EVINCI-study.
- To reach all the potential audiences, in particular, scientific community, patient organisations and public health authorities.
- To manage the foreground and intellectual property.

Description of work and role of participants

Task 8.1 Design of a dissemination plan (P1-CNR, P14-ESC) (months 1 → 6)
A dissemination plan will be designed during the first 6 months of the project. Target groups will be identified in all member states and in the other European countries. For each target group, the route to establish contact will be decided; to identify a strategy to reach the target; to set rules for dissemination: what knowledge and to what level it is worth disseminating (according to the rules settled in the Consortium agreement)

Task 8.2 Creation and maintenance of the EVINCI-study web site (All partners) (months 1 → 42)
During the first 3 months, the EVINCI-study web site will be designed and will present the project objectives and methodologies. The scientific content, including the state of advancement of the project and the major results, will be updated regularly. Each partner will contribute to the scientific contents of the site which will be collected, organised and formatted at the P14-ESC site and, after approval of the Programme Steering Committee (PSC), published on the web. The site will be hosted and managed by the P14-ESC. The website will facilitate the visibility of the project to EU.

Task 8.3 Organization of Workshops and Final Conference* (*All partners) (months 4 → 42)
Workshops internal to the consortium (but opened to the health authorities and to the industry) will be organized at month 6 to present the results of standardization procedures, at month 18 to present the results of enrolment and at month 30 to present the results of central analysis. Communications on the progresses of the EVINCI-study to the scientific community will be issued by presentations to the annual ESC and other scientific meetings and will be submitted to other medical society's annual meetings.

Task 8.4 Definition of a final use and dissemination plan (All partners) (months 24→ 42)
Prepare the final plan for using and disseminating the foreground, at the end of the project, to provide complete picture of all activities undertaken and most importantly information on the future route to full use (exploitation or use in further research) and dissemination of the foreground.
Expected results to be commercially exploited include: I) predictive models of pre-test probability of IHD, post-test cardiovascular risk stratification and cost-benefits evaluation to be included in non-invasive imaging modalities users' manuals; II) softwares for multimodality imaging analysis and display; III) 4D heart dynamic model for clinical decision making in cardiology; IV) new end-points to be used in pharmacological trials in IHD.

Deliverables

D8.1 Web-site (**Month 3)**

D8.2 Final plan for the use and dissemination of foreground (**Month 42**)

Milestones

M8.1 Published web-site **(Month 3)**

M8.2 Organization final conference **(Month 42)**

Work package description

Work package number		9		**Start date or starting event:**			**1**			
Work package title		**Management**								
Activity Type		MGT								
Participant id	**P1-CNR**	P2-U.Turku	P3-UZH	P4-LUMC	P6-IR-HSCSP	P7-NIC	P8-RBHT	P9-APHP	P10-UniGE	P11-SERMAS
Person-months per beneficiary:	14 (6)	2,5	0,3 (0,5)	(1,5)	1,5	1,5 (1)	1,7	(4)	(1,5)	2 (1)
Participant id	P12-UniNA	P13-HUVHEBRON	P14-ESC	P16-CFc	P18-KRITUM	P19-QMUL	P20-AOUC	P21-Osp. Ver.	P22 KAE	
Person-months per beneficiary:	0,5 (1)	1,5	1 (0,5)	12,3	2	1,5	0,5	0,3	0,5 (2)	

Objectives:

- To co-ordinate the various project components (research activity, legal, administrative and logistic issues).
- To assure a timely reporting of the project to the EU.
- To establish and adopt common operational procedures; to check progress of the project activities, ensuring adherence to project timetable, implementing corrective actions, if any, and preventing possible delays or unsuccessful results; to ensure respect of ethical issues and attention paid to gender issues; to ensure high quality of scientific and technical results, verifying that each report covers all aspects required to meet the deliverables.

Description of work and role of participants

Task 9.1 Standardization of research procedures and co-ordination of activity (P1-CNR, P2-U. Turku, P3-UZH, P4-LUMC, P10-UniGe, P14-ESC) (months 1→ 2)

The Project Steering Committee (PSC) coordinates and validates, during months 1-2, all the research operational tools and procedures to be used by the partners. The GA members, as team leaders in their own centres, are then charged with implementing the day-to-day co-ordination and monitoring of the activity.

Task 9.2 Logistics (P1-CNR, P14-ESC) (months 1 → 42)

This task deals with the organisation of the management meetings and periodical scientific meetings.

Task 9.3 Assessment of results (PSC) (months 1 → 42)

- To agree on final research Work-Plan **(Month 1)**
- To issue implementation and harmonization of final research Work-Plan **(Month 3)**

- To discuss results of implementation and harmonization of validated procedures for acquisition and analysis of imaging data throughout the consortium **(Month 10)**
- To discuss results of patients' enrolment: population characteristics, exams performed, treatment **(Month 25)**
- To discuss results of diagnostic models: clinical-biomarkers prediction model of IHD, anatomic assessment of CAD, functional assessment of IHD, integrated anatomo-functional assessment of IHD **(Month 31)**
- To discuss overall results of the EVINCI-study and to present them to an enlarged audience **(Month 42)**

Task 9.4 Legal & Administrative issues (P1-CNR) (months 1 → 42)

This task mainly deals with the following actions:

1) Definition of access rights to the project knowledge base. The PSC establishes the rules for the access and exploitation of the pre-existing knowledge of the individual partners and of the results obtained so far. The PSC maintains the Consortium Agreement, dealing with technical (contribution of each partner, technical resources, scheduling), commercial (confidentiality, ownership of results, et cetera), organisational (composition and rules of the PSC), financial (Certificates on the Financial Statements, collective responsibility), legal (penalties, settlement of disputes, et cetera) and provisions. Any modification to the Consortium Agreement is approved by the General Assembly (GA).

Task 9.5 Reporting (All Partners) (months 1 → 42)

- Activity reporting: Based on the reports provided by the coordinators of the WPs, the activity report at months 18-42 is issued. The reports contain an overview of the activities undertaken during the period, a summary of the S&T results achieved during the period, a list of the deliverables generated and of the milestones reached during the period, a description of the monitoring actions (measurement/evaluation/corrective actions) undertaken to assure adherence to the project workplan, a summary of the risk analysis performed and a chapter on ethical issues.
- Financial reporting. At months 18-42, the financial reports are issued. They contain the cost statements, cost justifications and cost certification provided by each participant and a summary financial report.

Task 9.6 Harmonization of procedures and documentation (P1-CNR, P2-U. Turku, P3-UZH, P4-LUMC, P11-SERMAS, P16-CFc, P18-KRITUM) (months 1 → 42)

EVINCI-study brings together researchers from different institutes and different countries. Taking into account the enlarged EVINCI-study partnership, in order to establish standardized operational procedures and a "common" language, the PSC:

- **Reviews and validates the standardized procedures provided by each Workpackage and assures their implementation**
- **Reviews and validates the informatic platforms to be accessed by the partners (Central Server, Central Digital Bank, Central Data Base) for data transmission and sharing**

Prepares templates, forms, and modules to be used by each participant and by WPs Coordinators for reporting activity (both scientific and administrative/financial). For example: a common format for all the project deliverables, cost statement forms, risk analysis templates, task activity evaluation, et cetera.

Deliverables

D9.1 Periodic Report **(Month 18)**

D9.2 Final Report **(Month 42)**

Milestones
M9.1 Kick-off meeting **(Month 1)**

B 1.3.6 Efforts for the full duration of the project:

Template: Project Effort Form 1 - Indicative efforts per beneficiary per WP

Participants	WP0		WP1		WP2		WP3		WP4		WP5		WP6		WP7		WP8		WP9		Total per Beneficiary	
CO1-CNR	**13**	(9)	**9**	(4)			3,5	(3)	3,5	(3)	**9**	(3)	2,5	(4)	**15**	(5)	3	(3)	**14**	(6)	**72,5**	**(40,0)**
P2-U.Turku	21,5	(4)				(5)	11	(2)	**17**	(2)		(1)				(1)		(2)	2,5		**52,0**	**(17,0)**
P3-UZH	0,5	(7)					**3,5**	(7)		(2)		(3)				(3)	0,3	(1)	0,3	(0,5)	**4,6**	**(23,5)**
P4-LUMC		(16)			**22**					(6)		(3)						(2)		(1,5)	**22,0**	**(28,5)**
P6-IRHSCSP	14,5	(4)															1,5	(0,5)	1,5		**17,5**	**(4,5)**
P7-NIC	4	(10)							1	(3)							1	(1)	1,5	(1)	**7,5**	**(15,0)**
P8-RBHT	1,5	(13)					3			(2)		(3)					0,4	(1,5)	1,7		**6,6**	**(19,5)**
P9-AP-HP	6	(14)						(2)		(3)								(2)		(4)	**6,0**	**(25,0)**
P10-UniGe	2,5	(12)											**3,5**	(3)				(2)		(1,5)	**6,0**	**(18,5)**
P11-SERMAS	6	(2)					8	(2)	3	(1)	2,5	(0,5)						(1)	2	(1)	**21,5**	**(7,5)**
P12-UniNA	5,5	(10)		(3)													0,5	(2)	0,5	(1)	**6,5**	**(16,0)**
P13-HUVHEBRON	11,2	(12)															2,3		1,5		**15,0**	**(12,0)**
P14-ESC																	**2,5**	(9,5)	1	(0,5)	**3,5**	**(10,0)**
P15-INF											7,08										**7,1**	**(0,0)**
P16-CFc																	12,3		12,3		**24,6**	**(0,0)**
P17-FGM	29,4																				**29,4**	**(0,0)**
P18-KRITUM	2,5	(12)					5	(3)								(5)			2		**9,5**	**(20,0)**
P19-QMUL	4,5																		1,5		**6,0**	**(0,0)**
P20-AOUC	6																0,5		0,5		**7,0**	**(0,0)**
P21-Ospedale Versilia	1,3																0,4		0,3		**2,0**	**(0,0)**
P22-KAE	5,5	(13)															0,5	(1)	0,5	(2)	**6,5**	**(16,0)**
TOTAL	**135,4**	(138)	**9**	(7)	**22**	(5)	**34,0**	(19)	**24,5**	(22)	**18,6**	(13,5)	**6,0**	(7,0)	**15**	(14)	**25,20**	(28,5)	**43,60**	(19)	**333,3**	**(273,0)**

In brackets (…) non EC funded man months

B 1.3.7 List of milestones and planning of reviews:

Template: Milestones List and planned reviews

List and schedule of milestones					
Milestone no.	**Milestone name**	**WPs no's.**	**Lead beneficiary**	**Delivery date from Annex I**	***Comments***
M9.1	Kick-off meeting	WP9	1	1	PSC Minutes
M8.1	Published web-site	WP8	14	3	Web-Site
M0.1	To issue implementation and harmonization of validated procedures for central analysis throughout the consortium	WP0	1	10	GA meeting
M0.2	700 patients enrolled with completed diagnostic work-up per centre and at last 70% of the patients with both invasive and non-invasive data collected according to the protocol	WP0	1	30	Patients' data available in the Central Database
M0.3	At last 70% of the patients with completed follow-up	WP0	1	36	Patients' data available in the Central Database
M1.1	At last 70% of patients enrolled with completed centralized analysis of laboratory data	WP1	1	36	Patients' data available in the Central Database
M1.2	Results of models based on clinical profiles and biomarkers to predict diagnosis of IHD	WP1	1	40	Validity of the model tested against actual data in the third year

Milestone no.	Milestone name	WPs no's.	Lead beneficiary	Delivery date from Annex I	*Comments*
M2.1	Results of comprehensive assessment of anatomic coronary disease by CT	WP2	4	40	New quantitative approaches for comprehensive assessment of anatomic coronary disease by CT including plaque characterization and coronary “atherosclerotic” burden will be available
M3.1	Results of comprehensive assessment of “functional” coronary disease by non-invasive stress imaging	WP3	3	40	Based on these results, new protocols to obtain combined quantitative information on myocardial perfusion and contraction from single modality or multimodality functional imaging will be developed
M4.1	Results of multimodality non-invasive imaging in diagnosing and characterizing IHD	WP4	2	40	Achievements of D4.1
M5.1	Number of patients with completed transmission of clinical data, blood samples, non-invasive and invasive imaging raw data	WP5	1	40	Achievements of D1.1
M6.1	Final results of safety analysis of the entire study	WP6	10	40	Achievements of D6.1

Milestone no.	Milestone name	WPs no's.	Lead beneficiary	Delivery date from Annex I	*Comments*
M7.1	Software for multimodality imaging registration and fusion and for integrating clinical and imaging information into a 3D heart model	WP7	1	40	Software available and working
M8.2	Organization final conference	WP8	14	40	Publications related to the Final Conference and Conference Program available

B2. Implementation

B 2.1 Management structure and procedures

The EVINCI-study management structure consists of three decision-making bodies:

- the Project Co-ordinator (P1-CNR). The Institute of Clinical Physiology, National Research Council (CNR) will be represented by Dr. Danilo Neglia, who acts as project Co-ordinator; Dr. Neglia will be assisted by Dr. Daniele Rovai, who acts as Senior Project Manager and an administrative team. The EVINCI-study administrative headquarters will be located at the Institute of Clinical Physiology, National Research Council (ICP-CNR) (P1-CNR).
- the General Assembly (GA) composed by 21 active persons, being the Principal Investigators (PIs), or representatives designed by the PIs, of the 21 active partners of the EVINCI-study programme (P1-CNR, P2–U. Turku, P3–UZH; P4–LUMC, P6– IR-HSCSP, P7-NIC, P8-RBHT, P9-APHP, P10-UniGe, P11-SERMAS, P12-UniNA, P13-HUVHEBRON, P14-ESC, P15-INF, P16-CFC, P17-FGM, P18-KRITUM, P19-QMUL, P20-AOUC, P21-Ospedale Versilia, P22-KAE). Each member of the GA is entitled to nominate an alternate to attend any meeting which such member is unable to attend. The GA will meet within 1 month of the project starting date and thereafter on a predefined schedule. It will also meet to consider any matter that requires an urgent consideration. The GA will be convened and chaired by the Project Co-ordinator;
- the Programme Steering Committee (PSC) is formed by P1-CNR which is represented by Dr. Danilo Neglia and Dr. Daniele Rovai, and 6 additional members designed on the basis of recognized international expertise in major research activities as defined in the principal WPs and in coordinating roles within the ESC with specific reference to “organ imaging in cardiovascular diseases”. In particular experts in multimodality quantitative cardiac imaging-Dr. Knuuti (P2-U. Turku), CT angiography- Dr. Bax (P4-LUMC), nuclear cardiology - Dr. Kaufmann (P3-UZH), non-nuclear cardiac imaging-Dr. Zamorano (P11-SERMAS), clinics/pathophysiology of coronary disease- Dr. L’Abbate (P1-CNR) and informatics applied to cardiac imaging Dr. Nekolla (P18-KRITUM). Each organization has the right to one vote. Each member of the PSC is entitled to nominate an alternate to attend any meeting which such member is unable to attend. The PSC will meet within 1 month of the project starting date and thereafter on a predefined schedule. It will also meet upon the request of any PSC member or of the P1-CNR to consider any matter which in the opinion of such member or of the P1 requires an urgent consideration of the PSC. The PSC will be convened and chaired by the Project Co-ordinator.

At every level, decisions will be made by consensus whenever possible. When a major dispute arises it will be referred to the PSC. A decision will be made by simple majority.

Tasks and responsibilities

The management structure is the guarantee for the prompt and proper implementation of activities. It ensures that the project operates at the highest standards in both organisational and financial terms. In the following, the major tasks and responsibilities are presented.

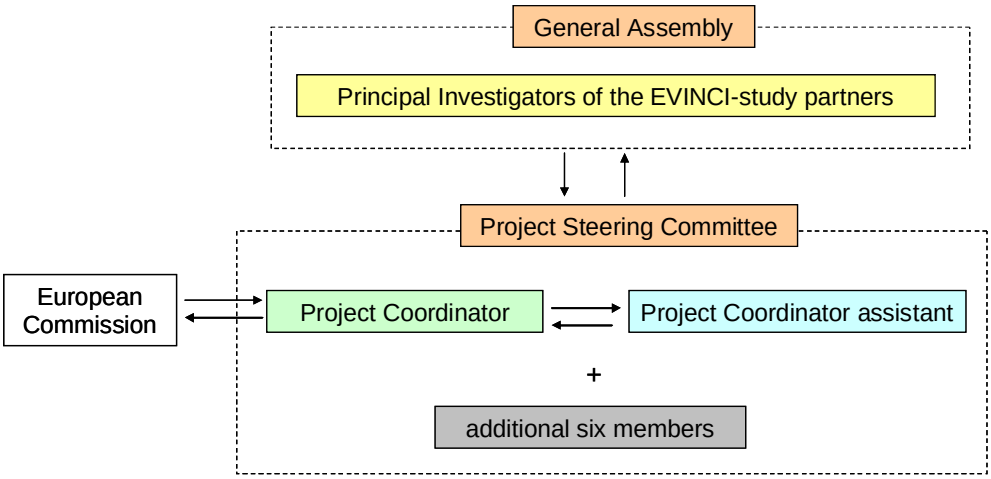
P1-CNR is responsible for:

- representing the EVINCI-study Consortium in the communication with the EC;
- communicating and negotiating with the EC after approval of the PSC;
- distributing funds among partners;
- preparing the periodic technical reports and submitting them to the EC;
- collecting and preparing the administrative and financial reports and submitting them to the EC;
- monitoring the appointment of Financial Auditors by the partners, if applicable;

- organising, convening (with no less than 15 days' notice) and participating in the PSC meetings;
- supervising the central database;
- supporting the WP8, led by P14-ESC in the management and monitoring of the dissemination actions foreseen during the project, which include presentation of the EVINCI-study project to welfare authorities, assisting promotion of public awareness campaigns, etc.

The **GA** will be the ultimate decision-making body of EVINCI-study and as such it shall have decision-making powers in all fundamental questions of project execution, such as:
- allocation of budget;
- approval of any modification to the Consortium Agreement;
- proposals for any amendments to the Grant agreement;
- actions with regard to a defaulting party;
- decisions about any modification to the technical specifications into the workplan.

The **PSC** will have the responsibility for:
- supervising and controlling the research programme, including control of research progress towards the milestones;
- validating the standardized protocols provided by each Workpackage and assuring their implementation;
- supervising the informatics platforms;
- ensuring the adherence to the project timetable;
- setting the scientific priorities, within the existing objectives and budget framework;
- maintaining and implementing the Consortium Agreement;
- setting the guidelines of the risk management analysis;
- monitoring and reporting processes and results, based on deliverables accomplished by the Consortium.



Flow of activities

From a functional point of view, management will deal with the following sub-processes:
- implementation of the project components;
- quality assurance & risk management;
- knowledge management & reporting.

In the following, a brief description of the main objectives, activities and the responsibilities associated with the management processes is given.

PROCESS 1: IMPLEMENTATION

Objective 1: to establish common operational procedures

1. PSC will control the standardized protocols provided by each Workpackage and assuring their implementation The PSC develops common templates, forms, and modules to be used by each participant in order to provide the whole project documentation (both scientific and administrative/financial). For example: common format for all the project deliverables, cost statement forms, risk analysis templates, task activity evaluation forms, etc. For some of these activities it is also supported by P16-CFc.
2. The PSC approves the templates described in point 1 and distributes them to all the partners.

Objective 2: to ensure integration of the different research teams

1. The PSC establishes the rules for the day-to-day activities of the different research groups.
2. The PSC defines the proper tools and infrastructures for implementing the co-operation between the different research groups.

Objective 3: to prepare and agree on the IPR and access rights and to maintain the Consortium Agreement

1. The PSC agrees on IPR, exploitation rights of the projects results, common knowledge access rights, etc.
2. The partners adhere to the Consortium Agreement proposed by the PSC and approved by the GA.

Objective 4: to organise periodic meetings of the PSC

P1-CNR takes care of the organisation of periodic meetings of the various project components.

Based on the reports and deliverables of the project, and possibly also with the support of presentations made by Consortium members, the Commission may conduct a review of project progress with the assistance of an independent expert. This is used by the Commission to assess the project's progress and to decide if Community financial support for the project should be continued. In the event of a negative outcome of a review, the Commission may decide to suspend the project - pending corrective action, or to terminate the grant agreement. The review may also lead the Consortium, or the Commission, to require changes to the work plan. In these cases, the Consortium will be required to revise Annex I.

The table below gives a provisional overview of the previewed meetings.

Frequency	Type of meeting	Scope	Participants
Month 1	**PSC Meeting**	**To agree on final research Work-Plan**	**PSC Members**
	Kick-off meeting	**To issue implementation and harmonization of final research Work-Plan**	**GA**
Month 2	PSC meeting (validation)	To validate: I) standardized procedures for "raw data" acquisition and transmission generated in WPs 1-2-3-4-6; II) informatic platform of Central Server generated in WP5	PSC Members
Month 3	**Implementation meeting**	**To issue implementation and harmonization of validated procedures for "raw data" acquisition and transmission throughout the consortium (WP0)**	**GA**

Month 9	PSC meeting (validation)	To validate: I) standardized parameters, to be measured in central analysis of "raw data", generated in WPs 1-2-3-4-6; and to be entered in Central Data Base; II) informatic platform of Central Data Base generated in WP5	PSC Members
Month 10	**Implementation meeting**	**To issue implementation and harmonization of validated procedures for central analysis of "raw data" and transmission of analysed data throughout the consortium (WP0)**	**GA**
Month 12	PSC and GA meeting Internal Scientific workshop	**To discuss results of patients' enrolment: population characteristics, exams performed, treatment**	PSC Members, GA
Month 30	PSC and GA meeting Internal Scientific workshop	**To discuss results of patients' enrolment: population characteristics, exams performed, treatment**	PSC Members, GA
Month 42	PSC meeting (final results)	To review results of outcome predictive model from WP5, cost-benefit analysis from WP6 and clinical reporting model and decision making tool from WP7 To review **overall results of the EVINCI-study** to be presented in the Final Conference and to be submitted to ESC for issuing of a European Consensus Document to be submitted for publication	PSC Members

PROCESS 2: QUALITY ASSURANCE (QA) AND MONITORING

Objective 1: (I) To secure the correct and smooth flow of the project activities; (II) To check progression of the project activities, ensuring adherence to project timetable; (III) To implement corrective actions, if any.

1. The PSC clearly identifies the parameters to be checked (measured) for every specific scientific activity.
2. Based on the parameters identified at point 1, the PSC prepares progress evaluation forms (checklists). Key elements of these templates will be: type of parameter(s) to be measured – degree (level) of completion of the activity under examination – factors that have influenced the delay (if any) or the unsuccessful results (if any) of the specific activity – proposed corrective actions.
3. PSC determines the checkpoints for progress evaluation.
4. Every Partner analyses the state of its activity, completing the forms (progress reports) described at point 2 and transmitting them to the PSC.
5. The PSC evaluates the progress reports and takes decision upon corrective actions, if required.
6. Every Partner implements the actions decided at point 5 and evaluates its results.

Objective 2: (I) To ensure high quality of the scientific and technical results; (II) To verify that all arguments presented and conclusions reached are logical and consistent, (III) To verify that each report covers all aspects required to meet the deliverables.

1. The PSC defines a number of "critical" S&T issues.
2. The PSC defines the requirements of potential external independent experts (peer reviewers)

3. Peer reviewers perform a qualitative evaluation of the scientific results and transmit their output to the PSC.
4. The Peer Reviewers' evaluation are then collected by P1-CNR and incorporated into the deliverable submitted to the Commission. Also, a summary of the evaluation will be incorporated into the periodic progress reports.

Objective 3: to monitor the project financial status

1. Every reporting period, each partner prepares:
- a financial statement, which declares the sustained costs broken down by type of activity;
- a justification of its overall costs incurred, linking these costs to the resources deployed and to the activity performed during the period;
- a certificate on the Financial Statement, supervised by an external auditor (if applicable).
2. Each partner transmits to **P1-CNR** the information prepared at point 2.
- P1-CNR evaluates, with the support of P16-CFc, the financial statements received.
- P1-CNR collects the information and prepares the financial report for the EC.

PROCESS 3: KNOWLEDGE MANAGEMENT

Regarding management of knowledge, it is worth distinguishing between:
- "internal" knowledge, i.e. Consortium access to the information needed to carry out the research programme;
- spreading of knowledge toward the scientific community, i.e. enlargement of the researchers base and dissemination activity;
- knowledge transfer to the EC, i.e. reporting activity.

Objective 1: to guarantee that information is available where and when it is needed

1. The PSC defines and implements access rights provisions to the documentation and the results achieved during the project.
2. Within these provisions, P1-CNR is responsible for deciding what information is needed and for collecting it from the partners.
3. P1-CNR is responsible for the implementation and management, after the PSC approval, of the Central Server, the Central Digital Bank and the Central Data-Base.
4. P1-CNR supported by P14-ESC is then responsible for publishing internal documents, deliverables, reports, publications, brochures etc. on the website that can be used by each partner of the Consortium to download documents and run discussions. The website will be hosted and managed by P14-ESC.

Objective 2: to support the dissemination of the project results

1. The PSC approves the dissemination activities defined within the WP8.
2. The partners submit their contributions to P1-CNR.
3. P1-CNR, supported by P14-ESC collects and organises the information/reports/deliverables received from the partners.
4. P14-ESC publishes the "public" information.

Objective 3: to assure complete and timely reporting to EC

1. Every reporting period P1-CNR prepares:

a. the activity report for the previous 18 months. The activity report contains:
- an overview of the activities undertaken during the period;
- a summary of the S&T results achieved during the period;
- a list of the deliverables published and of the milestones reached during the period;
- a description of the actions carried out in the "Monitoring" process, i.e. the measurement/evaluation/corrective actions carried out to assure adherence to the project workplan.

- The PSC agrees on the final documents before submission to the EC;

b. the financial report, based on the output of the "Monitoring" process, which contains:
- financial statements, cost justifications and cost certification provided by each participant;
- a summary financial report.

2. P1-CNR submits them to EC.

B 2.2 Beneficiaries

P1 – Consiglio Nazionale delle Ricerche - Institute of Clinical Physiology- CNR

The Institute of Clinical Physiology (IFC-CNR) is the largest biomedical Institution of Italian CNR and is focused on translational research. Current research encompasses the investigation of genetic determinants of IHD (GENOCOR Study), the role of coronary microvascular dysfunction, the use of advanced imaging technologies, metabolic, hormonal and inflammatory profiles as risk factors and markers of coronary and heart diseases. Recently, starting on November 1st, 2007, CNR and Regione Toscana through formal decisions of the respective governing bodies, have decided to confer the responsibilities and costs of running the hospital activities of IFC-CNR to "Fondazione toscana Gabriele Monasterio per la ricerca medica e di sanità pubblica" (P17-FGM). Cardiology, Cardiosurgery, and Cardiovascular Imaging Departments are equipped with complete laboratory setting, non invasive and invasive technologies, ICU, fully computerized outpatient and inpatient clinics and data base.

Main tasks attributed to the organisation: Coordination and monitoring the study; store and analyse blood samples; receive and redistribute exams for central readings; perform central reading of Echo and MRI; evaluate imaging procedural risks; manage the data bank; perform the outcome analysis; develop a novel Report and Decision making Tool.

Previous experience related to those tasks: IFC-CNR is coordinating the GENOCOR study. It has coordinated different multicentre studies on cardiovascular imaging. IFC-CNR has patented original software for Clinical Data Base in Cardiology and Cardiovascular Imaging.

Staff involved: Danilo Neglia (M). MD, PhD. Nucleus Member of WG5 of Nuclear Cardiology and Cardiac CT of ESC. Responsible for CT-PET. Res.: applications of cardiovascular imaging and intracoronary measurements for evaluation of coronary microvascular function; application of CT-PET for diagnosis of coronary artery disease. **Ornella Rimoldi** (F). MD. International expert of Cardiac Imaging. Res. applications of cardiovascular imaging in patients with coronary artery disease. **Antonio L'Abbate** (M). MD. FACC, FESC. Scientific Director. Coordinator of GENOCOR. Res.: pathophysiology of CV diseases, microcirculation. **Oberdan Parodi** (M) MD: Research director. Res: Nuclear Cardiology. **Daniele Rovai** (M). MD, Cardiology Board, Fellow of the ESC. Research Director. Res.: clinical cardiology, prognosis. **Paolo Marraccini** (M), MD. Head of Heart Catheterization Unit. Research Director. Res.: coronary plaque by CT and IVUS; invasive coronary flow reserve. **Eugenio Picano** (M), MD, PhD. Head of the Echocardiography Unit. Research Director. Res.: echocardiography, sustainability of cardiovascular imaging. **Rosa Sicari** (F), MD. Nucleus Member of the "Echocardiography" WG of ESC. Senior researcher. Res.: coronary flow reserve from transthoracic echo. **Massimo Lombardi** (M), MD. ViceChairman of the "Magnetic Resonance Imaging" WG of ESC. Head of the MRI Unit. Res.: MRI for the study of myocardial perfusion, viability and metabolism. **Alessandro Pingitore** (M), MD Cardiac MRI Unit. Res: MRI for the study of myocardial perfusion, viability and metabolism. **Paolo Marzullo** (M), MD**:** Past-chairman of WG5 of the ESC. Responsible of Nuclear Medicine Unit. Res.: SPECT for the diagnosis of coronary artery disease. **Luigi Landini** (M), Head of the Bioengeneering Unit. Res.: MRI cardiovascular imaging developments, image fusion in cardiology. **Vincenzo Positano** (M), Staff member of the Bioengneering Unit. Res.: MRI image acquisition and processing, MRI-PET fusion. **Martina Marinelli** (F), PhD Student. Res.: multimodality cardiological imaging and image fusion. **Ezio Maria Ferdeghini** (M) Dr. Staff member of the Computer Science Unit. Res.: reporting tools in nuclear imaging. **Giuseppe Andrea L'Abbate** (M), Dr. Staff member of the Computer Science Unit. Res.: development of multiparametric Report Tools in Cardiology. **Daniela Giannessi** (F), ChD. Senior staff member of Laboratory Unit. Res.: circulating biomarkers of vascular/myocardial damage. **Silvia del Ry** (F), ChD. Staff member of Laboratory Unit. Res.: circulating biomarkers of vascular/myocardial damage. **Tiziana Sampietro** (F), MD. Head Lipidology Unit. Res.: dyslipidemias and atherosclerosis. **Oreste Sorace** (M). Radiology

Technician. Res.: cardiac PET. **Silvia Bernardi** (F), assistant project coordinator. **Natalia Esposito** (F), Technician. Res: Postprocessing Cardiac Imaging.

1. Neglia D, et al. Effects of long-term treatment with carvedilol on myocardial blood flow in idiopathic dilated cardiomyopathy. Heart 2007;93:808-13.
2. Picano E, et al. A gatekeeper for the gatekeeper: inappropriate referrals to stress echocardiography. Am Heart J. 2007;154:285-90.
3. Sampietro T, et al. Inflammatory markers and Serum Lipid in Idiopathic Dilated Cardiomyopathy. Am J Cardiol. 2006;96:1718-1720.
4. Neglia D, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. Circulation. 2002;105:186-93.
5. L'Abbate A, et al. Myocardial perfusion and coronary microcirculation: from pathophysiology to clinical application. J Nucl Cardiol. 2002;9:328-37.

P2 - Turun yliopisto – U. Turku

Turku PET Centre at the University of Turku is Finnish National Research Institute. The scientific activities include all non-invasive imaging methods especially molecular imaging. The centre employs 110 persons and consists of 3 cyclotrons, radiochemistry laboratory with 16 hot-cells, 5 PET scanners, MRI, 64-slice CT and digital echocardiography devices. The cardio-metabolic research group has earned the status of Finnish Centre of Excellence by the Academy of Finland. The group has published several hundreds of original papers in high-rank journals about cardio-metabolic multimodality imaging in preclinical and clinical settings.

Main tasks attributed to the organisation: Coordination of WP3 Integrated anatomo-functional Assessment of Disease. Standardization, Central Reading CA Exams and FFR. Intergrated analysis of anatomo-functional imaging against ICA diagnosis. Standardization, central reading, Quantitation PET exams. Patient data acquisition

Previous experience related to those tasks: These tasks are those in which the U. Turku/Turku PET Centre has long experience. P2-U. Turku has standardized the imaging protocols, developed/improved some of the techniques as well as data analysis methods. Recently similar study protocols that are included in the EVINCI-study trial have been running at Turku PET Centre.

Staff involved: Juhani Knuuti (M). Professor, he is the acting director of Turku PET Centre (since 1996). He has been working in cardiac imaging since 1989 and has published over 200 original papers. The research interests are: A. The regulation of cardiac perfusion and substrate utilization in vivo. B. Coronary and peripheral artery reactivity and endothelial function. C. Myocardial metabolism, oxygen consumption and sympathetic innervation in heart failure. D. Imaging of vulnerable coronary plaques. **Heikki Ukkonen** (M), MD, PhD, is staff clinical cardiologist who has been focused on cardiac imaging. He has also worked at Ottawa Heart Center in the imaging laboratory. He has been working in cardiac imaging for over 10 years. **Mikko Pietilä** (M), MD, PhD, is clinical staff cardiologist who is responsible of invasive cardiac laboratory of Turku University hospital. Before that he has been working at Turku PET Centre as imaging scientist. **Sami Kajander** (M). Physician who is performing his PhD studies in the project.

1. Sundell J, et al (2004) The effects of cardiac resynchronization therapy on left ventricular function, myocardial energetics and metabolic reserve in patients with dilated cardiomyopathy and heart failure. Journal of American College of Cardiology 17;43(6):1027-33
2. Pitkänen O-P, et al (1996) Coronary flow reserve is Impaired in young adults with hypercholesterolemia. J Am Coll Cardiol 28:1705-1711
3. Tuunanen H, et al. (2006) Free Fatty Acid Depletion Acutely Decreases Cardiac Work and Efficiency in Cardiomyopathic Heart Failure. Circulation 14;114(20):2130-7
4. Pitkänen O-P, et al. Coronary flow reserve in young men with familial combined hyperlilidemia. Circulation 1999; 99: 1678-84.
5. Sakuma H, et al. Assessment of coronary flow reserve using fast velocity-encoded cine MR imaging: validation study using positron emission tomography. Am J Roentgenol. 2000 Oct;175(4):1029-33
6. Parkka JP, et al. Comparison of MRI and positron emission tomography for measuring myocardial perfusion reserve in healthy humans. Magn Reson Med. 2006 Apr;55(4):772-9.
7. Knuuti J. Clinical Cardiac PET in the Future. Eur J Nucl Med Mol Imaging 2004 Apr;31(4):467-8.

P3 - Universitaet Zuerich - UZH

The University Hospital Zurich is the largest University Hospital in Switzerland. The Nuclear Cardiology scientifically deals mainly with new developments in the field of cardiac perfusion scanning with several Isotopes such as ammonia, water and rubidium and has several collaborations with other national and international centers. The current research activities in the Nuclear Cardiology are focused on improvement of integrating cardiac imaging. The most advanced software for fusion of perfusion and CT-coronary anatomy has been developed here. Cardiac CT imaging has therefore emerged as additional new focus on the scientific work. Nuclear Cardiology is well settled as interdisciplinary Division between Radiology, Nuclear Medicine and Cardiology. The Department of Radiology and Nuclear Medicine has a fully equipped PET Center with a Cyclotron and 2 PET/CT scanners, and with two SPECT/CTs and several multislice CT. In addition, there is a MRI center with 5 MR scanners. Cardiology is equipped with 2 latest generation cath labs and an EP lab.

Main tasks attributed to the organisation: Apart from performing catheterization including FFR the Center will perform PET and/or SPECT and MSCT or MR exams.

Previous experience related to those tasks: Nuclear Cardiology Zurich has a long and published experience in quantitative measurement of myocardial blood flow with PET and water or ammonia. Repeatability has been established for several stimuli such as adenosine, dobutamine, bicycle exercise stress and cold pressor test. Impact of drugs and food additives (vitamin C, caffeine) on myocardial blood flow have been studied. Zurich has also pioneered hybrid imaging by developing and validating the currently widely used software for PET/CT and SPECT/CT hybrid imaging

Staff involved: Philipp Antonio Kaufmann (M). Professorship of the Swiss National Science Foundation (SNSF) since 2003. Degree in Medicine (1990) Board Certification in Internal Medicine (1996), Cardiology (1998), Nuclear Medicine (2006). Director of Nuclear Cardiology, University Hospital Zurich since 1999. Working in the field since 1995. Research interests: a) Multimodality and hybrid imaging using PET/CT, SPECT/CT;CT b) development of new algorithm for evaluation of CAD; c) regulatory mechanisms and pathophysiology of myocardial perfusion, d) CT coronary angiography. **Lars Husmann** (M). Degree in Medicine Research Fellow Nuclear Cardiology Zurich. Past position: Research Fellow Radiology Zurich. Working in the field since 2005. **Costantina Manes** (F) Degree in Medicine, University Bologna. PhD Universtiy Bologna. Diploma of Specialty in Cardiology, University Bologna. MRI Specialty Fellowship, Royal Brompton. **Ulf Landmesser** (M) Degree in Medicine and PhD, University Hannover. Assistant Professorship Hannover. Director of Translational research/ Staff Interventional Cardiology

1. M.Namdar, P.Koepfli, R.Grathwohl, P.T.Siegrist, M.Klainguti, T.Schepis, R.Delaloye, C.A.Wyss, S.P.Fleischmann, P.A.Kaufmann. (2006) Caffeine decreases exercise-induced coronary flow reserve. Journal of the American College of Cardiology, 47:405-410
2. P.A.Kaufmann, M.Namdar, M.Roffi, S.V.Aschkenasy, B.van der Loo, G.Sutsch, F.Mathews, T.F.Luscher, R.Jenni. (2005) Novel Doppler-based method for intracoronary volumetric flow reserve: validation against PET in humans with and without flow-mediatied dilation. Journal of Nuclear Medicine 46:1272-1277
3. O.Gaemperli, T.Schepis, P.Koepfli, V.Kalff, I.Valenta, L.Stefani, S.Leschka, L.Husmann, H.Alkadhi, P.A.Kaufmann (2007) Validation of a new cardiac image fusion software for three-dimensional integration of myocardial perfusion SPECT and standalone 64-slice CT angiography. European Journal of Nuclear Medicine, 48:1097-1106
4. L.Husmann, I.Valenta, O.Gaemperli, O.Adda, C.A.Wyss, P.Veit-Haibach, F.Tasugami, G.K.von Schulthess, P.A.Kaufmann. Feasibility of low-dose coronary CT angiography: first experience with prospective ECG-gating.
   Eur Heart J. 2008;29:191-197

P4 – Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum– LUMC

The Department of Cardiology of the Leiden University Medical Center is the reference field for multi-modality non-invasive imaging in the Netherlands. Other main topics include Vascular Biology and Intervention, Cardiac Dysfunction and Arhythmias. The Department is involved in many research projects, thereby collaborating with multiple sites around Europe, including the Cardiovascular Center Aalst amongst others.

For the project the following equipment will be used: Toshiba Aquilion 64 or 320, Toshiba, Japan (for the MSCT studies), GCA 9300/HG, Toshiba, Japan (for the SPECT studies) and Eagle Eye, Volcano, Belgium (for the IVUS studies).

Main tasks attributed to the organisation: The department will serve as the central core lab for the MSCT studies.

Previous experience related to those tasks: The department has extensive experience in both performing and reading of MSCT coronary angiograms. In addition, we have published extensively on this topic.

Staff involved: Jeroen Bax (M). Prof. Director of Non-invasive imaging and Director of the Echo-lab at the department of Cardiology of the Leiden University Medical Center, the Netherlands. He has authored numerous papers and holds several positions in national and international scientific organizations. In addition he is the President of the ESC congress program committee for 2007 - 2008 and also serves on many editorial boards of different journals including associate editor for the Journal of the American College of Cardiology and Heart. **Joanne Schuijf** (F). Dr. Coordinator of the Cardiac CT-lab at the Leiden University Medical Center, the Netherlands. She has authored several papers and serves as reviewer for a number of international journals. She has extensive experience in performing and analyzing MSCT coronary angiography studies. In addition, she has participated in the scientific program committee of the International Conference of Nuclear Cardiology 2007.

1. Pundziute, G. (2007) Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J Am Coll Cardiol. 2007;49:62-70.
2. Schuijf, J. D. (2006) Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. J Am Coll Cardiol. 2006;48:2508-14.
3. Schuijf, J.D. (2006) A comparative regional analysis of coronary atherosclerosis and calcium score on multislice CT versus myocardial perfusion on SPECT J Nucl Med. 2006;47:1749-55

P6 – Fundacio Privada Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau - IR-HSCSP

Nulcear Medicine Department of the Hospital de la Santa Creu i Sant Pau, which is a University hospital, performs all types of nuclear medicine studies. It is involved in research projects mainly regarding cardiology, neurology and oncology.

Main tasks attributed to the organisation: IR-HSCSP will participate in WP0: Diagnostic Work-up and Follow-up; WP8: Dissemination and Exploitation; WP9: Management.

Previous experience related to those tasks: Nuclear Medicine and molecular imaging of cardiovascular diseases mainly using SPECT and PET.

Staff involved: Albert Flotats (M). M.D. FEBNM, DCBNC. Associate Professor of Nuclear Medicine. Senior Physician of the Nuclear Medicine Department. Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona. Working in the field since 1995. Research interests in cardiology and nuclear medicine. **Ignasi Carrio** (M). M.D. FEBNM, FRCP. Chair Professor of Nuclear Medicine. Director of the Nuclear Medicine Department. Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona. Working in the field since 1985. Research interests in cardiology and nuclear medicine. **Montserrat Estorch** (M). M.D. Associate Professor of Nuclear Medicine. Consultant Physician of the Nuclear Medicine Department. Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona. Working in the field since 1987. Research interests in cardiology and nuclear medicine. **Ato Rodríguez-Revuelto** (M). M.D. Physician of the Nuclear Medicine Department. Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona. Working in the field since 2004. Research interests in cardiology and nuclear medicine.

1. Ballester-Rodes M, Flotats A, Torrent-Guasp F, Carrio-Gasset I, Ballester-Alomar M, Carreras F, Ferreira A, Narula J (2006). The sequence of regional ventricular motion. Eur J Cardiothorac Surg;29 Suppl 1:S139-44.
2. Flotats A, Serra-Grima R, Camacho V, Mena E, Borràs X, Estorch M, Tembl A, Fuertes J, Cinca J, Carrió I (2005). Left ventricular end-diastolic volume is decreased at maximal exercise in athletes with marked repolarisation abnormalities: a continuous radionuclide monitoring study. Eur J Nucl Med Mol Imaging;32:203-10.
3. Estorch M, Carrió I, Mena E, Flotats A, Camacho V, Fuertes J, Kulisewsky J, Narula J (2004). Challenging the neuronal MIBG uptake by pharmacological intervention: effect of a single dose of oral amitriptyline on regional cardiac MIBG uptake. J Eur J Nucl Med Mol Imaging;31:1575-80.

P7 – Instytut Kardiologii Im. Prymasa Tysiaclecia Stefana Kardynala Wyszynskiego– NIC
Institute of Cardiology in Warsaw (NIC) is the reference centre in the area of cardiology in Poland. Fields of excellence include: treatment of acute coronary syndroms (ACS), electrophysiology (esp. ablation-treatment of arrhythmias), diagnosis of CAD (invasive-esp.IVUS & non-invasive), diagnosis&treatment of cardiomyopathies, diagnosis of secondary hypertension. The most specific activity of the Nuclear Medicine Dept. (DNM) is 24-hr service for acute myocardial infarction (AMI) to assess the risk area, before primary PCI. Current research activities of DNM: efficacy of primary-PCI techniques and revascularisation techniques, assessment of cardiac viability, perfusion, function, innervation. Eqipment: 2 SPECT-cameras (1-head: Orbiter-Siemens; 2-head: Axis-Picker), networked with Odyssey-Picker computer system.
Main tasks attributed to the organisation: Contribution to WP0, WP4, WP8 and WP9.
Previous experience related to those tasks: I. RECENT INTERNATIONAL TRIALS: 1. 'Euroinject-One': randomized program of therapeutic angiogenesis by using intramyocardial injections of VEGF-A165; 2002-3; 2.'STICH': randomized trial "Surgical Treatment for Ischemic Heart Failure"; since 2002; 3.'OAT-NUC': Viability and Remodelling in the Occluded Artery Trial: An Ancillary Study; since 2004; 4.'DELTA MI Trial': project to limit reperfusion injury following PCI for AMI (sponsor-KAI Pharmaceuticals); since 2005; 5.'MBG311': an open-label, phase 3 study evaluating the prognostic value of I123-mIBG scintigraphy (sponsor-GE Healthcare); since 2005. II. STATE COMMITTEE FOR SCIENTIFIC RESEARCH PROJECTS - numerous 3-years long projects including clinical evaluation, enrollment and randomization, SPECT, CA, IVUS, follow-up.
Staff involved: Anna Teresinska (F). PhD in med. sciences(1993), MSc in med. physics (1981). Assistant. Prof., Head of the Nucl. Med. Dept. (s. 1994). In the field s. 1981. Research: myocardial perfusion, viability, innervation; efficacy of cardiac revascularisation. **Adam Witkowski** (M). MD, PhD & habilitation in cardiology. Associate Prof., Deputy Director of Haemodynamics Dept. In the field s. 1983. Research: coronary interventions (PCI, DES, carotid stenting, in-stent restenosis, brachytherapy). **Jacek Kadziela** (M). MD, PhD. Assistant in Clinic of CAD. In the field s. 1998. Reasearch: CAD, cardiac hemodynamics (FFR). **Tomasz Deptuch** (M). MD, PhD. Asisstant in Clinic of CAD. In the field s. 1999. Reasearch: ACS, invasive cardiovascular imaging (IVUS) and treatment (stenting). **Jacek Wnuk** (M). MD Nuclear med. specialist in NMD. In the field s. 1987. Research: diagnostic cardiology. **Mariusz Kruk** (M). MD, PhD. Assistant Prof. in Clinic of CAD. In the field s.1997. Reasearch: ACS, coronary imaging (IVUS, VH, CTA). **Anna Klisiewicz** (F). MD, PhD & habilitation in cardiology. Associate Prof., Head of Clinical ECHO Lab. In the field s.1983. Research: CAD diagnosis (esp. DOB Stress ECHO). **Arkadiusz Dabrowski** (M). MD. Internal med. specialist in NMD. During specialisation and before Ph.D. from nuclear cardiology. In the field s. 1994. Research: diagnostic cardiology. **Andrzej Czerwiec** (M). Eng. in biomechatronics. Research: image processing, quantification of scintigraphic images, image fusion, data archiving.

1. Gyongyosi M., Khorsand A., Zamini S., Sperker W., Strehblow C., Kastrup J., Jorgensen E., Hesse B., Tagil K., Botjer H.E., Ruzyllo W., Teresinska A., et al (2005). NOGA-guided analysis of regional myocardial perfusion abnormalities treated with intramyocardial injections of plasmid encoding vascular endothelial growth factor A-165 in patients with chronic myocardial ischemia. Circulation, 112, I-157-65.
2. Kruk M., Przyluski J., Kalinczuk L., Pregowski J., Chmielak Z., Debski A., Demkow M., Jodkowski J., Bilinska Z., Witkowski A., Ruzyllo W. (2005). Cumulative incidence of coronary lesions with vulnerable characteristics in patients with stable angina pectoris: an intravascularultrasound and angiographic study. Int J Cardiol, 102, 201-6.
3. Pregowski J., Tyczynski P., Mintz G., Sang-Wook K., Witkowski A., Waksman R., Pichard A., Satler L., Kent K., Kruk M., et al. (2005). Incidence and clinical correlates of ruptured plaques in saphenous vein grafts: an intravascular ultrasound study. J Am Coll Cardiol, 45 (12), 1974-9.

P8 - Royal Brompton and Harefield NHS Trust - RBHT

Royal Brompton & Harefield NHS Trust is the largest cardio-thoracic centre in the UK. The invasive and non-invasive cardiology units are leading international centres performing innovative procedures whilst maintaining at the same time strong collaborative links with other national and International centres. The research activities include development, validation and application of techniques assessing myocardial perfusion and ventricular function. Investigation of clinical and sub-clinical atherosclerosis and physiology of myocardial perfusion utilising the combined strengths of radionuclide perfusion imaging and CT is another area of interest as it is the exploration of the role of non-invasive imaging in the field of Heart failure. The department of Nuclear Medicine/Cardiology has four gamma cameras: Philips Forté, Philips CardioMD, GE Infinia, and GE Ventri whilst the cardiac Radiology unit is equipped with a 64 slice CT scanner, Sensation 64, Siemens.

Main tasks attributed to the organisation: Contribution to WP0, WP3, WP4, WP5, WP8 and WP9.

Previous experience related to those tasks: The research group has an extensive clinical, training and research experience in the fields of both invasive and non-invasive cardiololgy with numerous publications in journals with high impact factor. The investigators have attracted research funds both from commercial and non commercial sponsors and have taken part in relevant task and guideline committees. Research interests include imaging of ischaemic left ventricular dysfunction, development of nuclear imaging techniques, cost effectiveness studies and also coronary imaging and calcification for the diagnosis of coronary artery disease and the management of coronary risk factors. Additional areas are Rubidium-82 kinetics and quantitative assessment of myocardial perfusion (collaboration with Harvard Medical School), effect of anti-anginal medication on the action of the vasodilator adenosine and novel angiographic techniques for functional assessment of coronary lesions.

Staff involved: Richard Underwood (M). Prof. FRCP, FRCR, FESC, FASNC. Professor of Cardiac Imaging. Research interests include heart failure Imaging, attenuation correction and coincidence imaging of positron emitting radiopharmaceuticals using a conventional gamma camera and cost effectiveness of strategies of investigation for the diagnosis and management of patients with coronary heart disease. **Michael Rubens** (M), Dr. FRCR. Consultant Radiologist. Research interests: coronary artery calcification/imaging and diffuse lung disease. **Carlo Di Mario** (M). Prof. M.D, FRCP. Prof. of Cardiology, Consultant in Invasive Interventional Cardiology. Research interests: drug eluting stents, interventional devices, application of robotic surgery, pharmacological and interventional approaches in coronary heart disease. **Reyes Eliana** (F) Dr. Research Registrar at the Department of Nuclear Medicine; on going PhD thesis on New Strategies in Pharmacological Myocardial Perfusion SPECT Imaging.

1. C. Anagnostopoulos, JJ Bax, P. Nihoyannopoulos, and E van der Wall, “Non-invasive Imaging of myocardial ischaemia” (Springer-Verlag,) 2006, pages 314.
2. C Anagnostopoulos, A Almonacid, Georges El Fakhri et al. Quantitative Relationship Between Coronary Vasodilator Reserve Assessed by Rubidium-82 PET Imaging and Coronary Artery Stenosis Severity. Eur J Nucl Med Mol Imaging 2008 Apr 19. [Epub ahead of print]
3. SR Underwood, C. Anagnostopoulos , M Cerqueira, PJ Ell, J Flint, M Harbinson, A Kelion, A Al Mohammad, EM Prvulovich, LJ Shaw, AC Tweddel. Myocardial Perfusion Scintigraphy – the Evidence. A consensus conference organised by the British Cardiac Society, the British Nuclear Cardiology Society and the British Nuclear Medicine Society, endorsed by the Royal College of Physicians of London and the Royal College of Radiologists. Eur J Nucl Med Mol Imaging (2003) Nov 25 [Epub ahead of print].

P9 – Assistence Publique – Hopitaux de Paris – AP-HP

The Nuclear Medicine department of Bichat Hospital (tertiary care centre) is one of the leading centres of Nuclear Cardiology in France. Its medical staff include 5 senior cardiologists and others in training. Cardiology represents 60% of the global activity of the depatment. Patients are referred to us by the cardiology department of our institution and others institutions in Paris. In the clinical field, the specific activities of the Nuclear Medicine department relates to specific indications of radionuclide angiography such as diagnosis and follow-up of arrhythmogenic right ventricular dysplasia and the assessment of ventricular dyssynchrony. We are also involved in the development and evaluation of new devices, tracers and softwares. In the preclinical field, our group is a part of a small-animal imaging platform and our research activity relates to the development of new tracers of the thrombus. The department is equipped with 3 dual-head gamma-cameras (1 of which is a hybrid SPECT/CT camera) and will be equipped with a PET/CT (64-slices) in 2008.

Main tasks attributed to the organisation: Assessment of myocardial perfusion using radionuclide SPECT, PET and hybrid SPECT/CT and PET/CT devices - PET imaging for absolute quantitative evaluation of coronary and microvascular function - Standardized protocols for quantification of coronary/microvascular flow - MRI and echocardiography for the assessment of stress induced myocardial dysfunction/perfusion.

Previous experience related to those tasks: The Nuclear Medicine department performs 3700 myocardial perfusion studies per year, and is used with hybrid SPECT/CT acquisitions. Some members of the medical staff are experienced with cardiac PET, including perfusion studies. The Cardiology department of the institution performs more than 1400 coronary angiographies and about 140 stress echocardiographies per year, and angiographists are experienced with intracoronary studies. The Radiology department is equipped with a 1.5T MRI and a 64-slices CT on which is routinely performed cardiac imaging.

Staff involved: Dominique Le Guludec (F), MD, PhD. Nuclear Physician, Cardiologist. Head of the Nuclear Medicine department of Bichat Hospital. Member of the European Council of Nuclear Cardiology. Member of the Editorial Board of the Journal of Nuclear Medicine and of the European Journal of Nuclear Medicine and Molecular Imaging. Working in nuclear cardiology since 1994. Research interests are: quantification of cardiac receptors using PET and SPECT, Equilibrium radionuclide angiography in arrhythmogenic right ventricular cardiomyopathy, Assessment of bloodpool tomography softwares, small animal imaging, funtional imaging of the thrombus. **Francois Rouzet** (M), MD. Nuclear Physician, Cardiologist. Associate Professor. Working in nuclear cardiology since 2001. Research interests are: Equilibrium radionuclide angiography in ventricular dyssynchrony and arrhythmogenic right ventricular cardiomyopathy, small animal imaging, functional imaging of the thrombus. **Laurent Feldman** (M), MD, PhD. Professor of Cardiology. Working in Cardiology since 1990. Research interests are: coronary angiography, angioplasty, intravascular ultrasound, mechanisms of restenosis. **Jean-Pierre Laissy** (M), MD, PhD. Professor of Radiology. Working in Radiology since 1990. Research interests are: perfusion imaging using cardiac magnetic resonance imaging, detection of inflammatory diseases of the heart using MRI. **Eric Brochet** (M), MD. Cardiologist. Research interests are: echography in valvular heart diseases.

1. Rouzet F, Dominguez Hernandez M, Hervatin F, Sarda-Mantel L, Lefort A, Duval X, Louedec L, Fantin B, Le Guludec D, Michel JB. Technetium 99m-labeled annexin V scintigraphy of platelet activation in vegetations of experimental endocarditis. Circulation. 2008 Feb 12;117(6):781-9.
2. Feldman LJ, Coste P, Furber A, Dupouy P, Slama MS, Monassier JP, Tron C, Lafont A, Faraggi M, Le Guludec D, Dubois-Rande JL, Steg PG; FRench Optimal STenting-2 Invest. Incomplete resolution of ST-segment elevation is a marker of transient microcirculatory dysfunction after stenting for acute myocardial infarction. Circulation. 2003 Jun 3;107(21):2684-9.

3. Le Guludec D, Gauthier H, Porcher R, Frank R, Daou D, Benelhadj S, Leenhardt A, Lavergne T, Faraggi M, Slama MS. Prognostic value of radionuclide angiography in patients with right ventricular arrhythmias. Circulation. 2001 Apr 17;103(15):1972-6.
4. Lasalarie JC, Serfaty JM, Carre C, Messika-Zeitoun D, Jeannot C, Schouman-Claeys E, Laissy JP. Accuracy of contrast-enhanced cine-MR sequences in the assessment of left ventricular function: comparison with precontrast cine-MR sequences. Results of a bicentric study. Eur Radiol. 2007 Nov;17(11):2838-44.

P10 – Università degli Studi di Genova – UniGE

The group of Genoa Unit (UniGE) is located in the University of Genoa, Italy. It is part of a larger Research Hospital campus which encompasses regulated scientific relationships with the Scientific Institute of Cancer in Genoa and with the C.N.R.- Institute of Clinical Phisiology in Pisa as well as scientific relations with the Scuola. Superiore S. Anna in Pisa. In the labs of Nuclear Medicine and Radiology of our Unit, there is the availability of all the equipments necessary for imaging studies, including gamma camera, radiochemistry labs, cyclotron and PET/CT facilities, as well as 1.5 and 3 T MRI systems. The group has long time expertise in the methodology of nuclear cardiology as well as in invasive studies of coronary circulation. In particular, this center already developed a close cooperation between the teams of the different departments (radiology, cardiology and nuclear medicine) focusing on the topic of coronary anatomy and physiology relationships. It serves one of the largest European hospitals providing a large database of patients and expertizes.

Main tasks attributed to the organisation: Apart from performing catheterization including FFR, UniGE will coordinate the WP6. UniGE will participate in WP0, WP8 and WP9.

Previous experience related to those tasks: The University Hospital of San Martino di Genova and the University of Genoa already participated to several multicenter studies focused on cardiovascular imaging.

Staff involved: Gianmario Sambuceti (M), principal investigator. He is the head of the Nuclear Medicine Unit at the University Hospital San Martino in Genoa. Since 20 years, he has worked in the field of nuclear cardiology and, mostly, in application of nuclear methods in studying cardiovascular pathophysiology, with about 80 papers published on peer review Journals. He served as chairman of the Working Group 5 Nuclear Cardiology of the European Society of Cardiology and is now fellow of this same society. Prof. Sambuceti will spend 20% of his time on the project. **Lorenzo Derchi** (M). Full professor of Radiology at the University of Genoa, who has experience in MRI applications to molecular imaging. **Manrico Balbi** (M). Associate professor at the Cardiology Unit of our departement who worked in molecular cardiology since a long time and with a prolonged work experience at the University in St Louis, (US).

1. Sambuceti G. Differences and similarities between coronary atherosclerosis and ischaemic heart disease: implications for cardiac imaging. Eur J Nucl Med Mol Imaging. 2005;32:385-8.
2. Marini C, Giorgetti A, Gimelli A, Kusch A, Sereni N, L'abbate A, Marzullo P, Sambuceti G. Extension of myocardial necrosis differently affects MIBG retention in heart failure caused by ischaemic heart disease or by dilated cardiomyopathy. Eur J Nucl Med Mol Imaging. 2005;32(6):682-8.
3. Sambuceti G, Marzilli M, Mari A, Marini C, Schluter M, Testa R, Papini M, Marraccini P, Ciriello G, Marzullo P, L'Abbate A. Coronary microcirculatory vasoconstriction is heterogeneously distributed in acutely ischemic myocardium. Am J Physiol Heart Circ Physiol. 2005;288(5):H2298-305.
4. Sambuceti G, Marzilli M, Fedele S, Marini C, L'Abbate A. Paradoxical increase in microvascular resistance during tachycardia downstream from a severe stenosis in patients with coronary artery disease. Reversal by angioplasty. Circulation 2001; 103:2352-2360.
5. Sambuceti G, Marzullo P, Giorgetti A, Neglia D, Marzilli M, Salvadori P, L'Abbate A, Parodi O. Global alteration in perfusion response to increasing oxygen consumption in patients with single-vessel coronary artery disease. Circulation. 1994;90:1696-705.

P11 – Servicio Madrileno del la Salud – SERMAS

Cardiovascular Institute of the HCSC in Madrid is one of the reference center in Spain in interventional cardiology, electrophisiology and cardic imaging. Cardiovascular Imaging Unit integrated in the Cardiovascular Institute of the HCSC is the reference center in the field of 3D echocardiography, stress echo, perfusión echo, strain and development of new cardiovascular softwares in Spain. Along with clinical assistance and research proyects, the unit is involved in diffrente educational aspects: fellow programs, post-grade courses, specific courses (stress echo, transesofagueal echo).Currently the Unit is involved in different research proyects on 3D echocardiography, cardiac MR and development of new softwares. The laboratory is equipped with 14 echos. HP sonos 4.500 and 5,500, 2 Phillips iE 33. A 64 multidetector Phillips TC, and 2 GE MR 1,5T is also available for cardiovascular studies in colaboration with the radiology department.

Main tasks attributed to the organisation: Clinical assistance: transtoracic echos, stress echo, intraoperative transesofagueal echos, transesofagueal echos. Along with radiology department, cardic MR and cardiac coronary TC performance and reading. Involvement in different research projects and national trials. Post-grade courses and fellow training. 3D echocardiography.

Previous experience related to those tasks: Some of the research work developed in the laboratory: differences in Regional Systolic and Diastolic Function by Tissue Doppler in Patients with Hypertrophic Cardiomyopathy and Hypertrophy due to Hypertension; Myocardial Contrast Echocardiography in Coronary Artery Disease; Negative predictive value of dipyridamole vs. dobutamine stress echocardiography in the long-term follow-up of patients undergoing major vascular surgery; Role of echocardiography in the assessment of mechanical dyssynchrony; Real-time three-dimensional echocardiographic quantification of left ventricular volumes using a rapid tissue tracking algorithm.

Staff involved: Jose Luis Zamorano (M), MD,FESC,PhD, Profesor in Cardiology. Director Non-Invasive Cardiovascular Imaging Unit. HCSC. Working in the field since 1993. Research interest: heart failure, ischemic heart disease, CV risk factors,CV imaging modalities. Active member of different international and national editorial board and committes on cardiac imaging. **Covadonga Fernández-Golfín** (F), MD. Consultant in Cardiology. Non-invasive Cardiovascular Imaging Unit. HCSC. Working in the field since 2005. Research interest: cardiovascular MR, cardiac CT, heart failure. **Leopoldo Pérez de Isla** (M), MD, PhD. Consultant in Cardiology. Non- invasive Cardiovascular Imaging Unit.HCSC. Working in the field since 2002. Reserch interest: heart failure, ischemic heart disease, CV risk factors, CV imaging modalities.

1. Leopoldo Pérez de Isla, José Zamorano, Carlos Almería, José Luis Rodrigo, David Villagómez, José Florit, Adalia Aubele and Carlos Macaya. Long-term Prognostic Importance of Transient Left Ventricular Dilation during Pharmacological Stress Echocardiography. J Am Soc Echocardiogr 2005 Jan; 18(1):57-62.
2. Gutierrez-Chico JL, Zamorano JL, Pérez de Isla L, Orejas M, Almería C, Rodrigo JL, Ferreirós J, Serra V, Macaya C.Comparison of left ventricular volumen and ejection fraction measured by three-dimensional echocardiography and cardiac magnetic resonance in patients with various cardiomyopathies. Am J Cardiol. 2005 Mar 15;95(6):809-13.
3. Serra V, de Isla LP, Ferro MP, Rodrigo JL, Almeria C, Fernandez-Ortiz A, Garcia-Rubira JC, Zamorano J, Macaya C.Identification of stunned myocardium with parametric imaging-based, quantitative myocardial contrast echocardiography after acute myocardial infarction. Am J Cardiol. 2005 Jul 15;96(2):167-72.

P12 – Università degli Studi di Napoli Federico II – UniNA

Integrated department of cardiology and internal medicine. The division of cardiolggy is working in clinical and basic research activities, with particular attention on the fields of coronary artery disease and heart failure. Research activities includes clinical trials and basic science (molecular biology). The Institution provides invasive and non-invasive care, including electrophysiology and percuteneous treatment of non coronary arterial disease

Main tasks attributed to the organisation: Invasive and non-invasive evaluation of patients

Previous experience related to those tasks: Long term involvement on clinical research in the field of coronary artery disease using imaging techniques in patients with left ventricular dysfunction.

Staff involved: Pasquale Perrone-Filardi (M), Prof. Degree in Medicine and Surgery. Currently Associate Professor of Cardiology. Fogarty Fellow from 1989 through 1992 at The Cardiology Section of the National Institutes of Health in Bethesda, MD, USA. Working on the field of cardiac imaging since graduation in 1983. Board certified on Cardiology and on Internal Medicine. Main research interests: myocardial viability evaluation in patients with left ventricular dysfunction, nuclear cardiology, MRI, cardiovascular risk assessment. **Alberto Cuocolo** (M). Full Professor of Nuclear Medicine at the Federico II University of Naples, Elected President of the European Association of Nuclear Medicine, Director of the Specialty School of Nuclera Medicine at the Federico II University, Past Fellow at the National Hart Lung and Blood Institute of Bethesda, MD, USA, Author or Co-Author of more than 80 full papers in peer review journals. Main research fields: hypertension, coronary artery disease, risk stratification. **Wanda Acampa** (F). Researcher at the Cuoncil for National Research in Naples, Italy. Board in Nuclear Medicine, deeply involved in research activity using imaging modalities under the supervion of Prof. Cuocolo.

1. Sorrentino, Acampa, Petretta, Mainolfi, Salvatore, Cuocolo. Comparison of the prognostic value of SPECT after nitrate administration and metabolic imaging in patients with ischemic left ventricular dysfunction. Eur J Nucl Med Mol Im 2007;34:558
2. Perrone-Filardi P, Cuocolo A, Brevetti G, Silvestro A, Storto G, Dellegrottaglie S, Corrado L, Cafiero M, Camerino R, Polimeno M, Zarrilli A, Caiazzo G, Maglione A, Petretta A, Chiariello M
3. Ralation of artery flow-mediated vasodilation to significant coronary artery disease in patients with peripheral arterial disease. American Journal of Cardiology 96:1337-41, 2005
4. Perrone-Filardi P, Pace L, Prastaro M, Squame F, Betocchi S, Soricelli A, Piscione F, Indolfi C, Crisci T, Salvatore M, Chiariello M. Assessment of myocardial viability in patients with chronic coronary artery disease: rest-4 hour-24 hour 201thallium tomography vs dobutamine echocardiography. Circulation 94:2712-2719, 1996

P13 - Institut Catala de la Salut- HUVHEBRON

Institut Catala de la Salut, Hospital Universitari Vall d'Hebron, is the greatest hospital centre of Barcelona, is the reference centre for more than 500.000 persons in Barcelona and more in its influence area. The mainly deals of the hospital is Cardiology, Oncology, Paediatrics, Neurology and Neurosurgery, Transplantation and image diagnostics. The activities of Nuclear Medicine service was all nuclear procedures, with special dedication on Nuclear Cardiology, and direct collaboration with Radiologist, Cardiologist, Physics and Engineers, in the hospital and with others centres (we have the manager centre for Nuclear Cardiology on RECAVA - the cooperative web in Cardiac research in Spain). The current research activities include the participation in GE multicentic trial for MIBG 123I (MBG311 trial), the main centre of Spain multicentric trial for evaluation the gated-SPECT studies in atrial fibrillation, supported by RECAVA, and the using of fusion cardiac images SPECT-CT on diagnostic and prognostic value for CAD. The service equipment: 1 Siemens Ecam dual head, 2 GE infinia HK4, both prepared for cardiac use. In the hospital: 1 Siemens Somatron plus CT (16 slices) and a 1 Philips 64 slices CT.

Main tasks attributed to the organisation: Collection of patients with CAD and were studied with SPECT, SPECT/AngioCT and angiography. Image fusion and analysis of clinical images.

Previous experience related to those tasks: 24 years work in Nuclear Cardiology and made 23 Courses of Clinical Nuclear Cardiology (for training of NM physicians and cardiologist in Spain). From 1980 our group publicated more than 130 articles about Nuclear Cardiology, 6 books over Nuclear cardiology, and participated in 17 trials (7 as reference center). Makes more than 2000 studies of myocardial perfusion SPECT/year.

Staff involved: Santiago Aguade (M), Mr, PhD, Nuclear medicine staff from 1995. Dedicated to nuclear cardiology from 1986, and make 15 book chapters and published 4 books of nuclear cardiology. Presented 10 large communications and more of 100 oral presentations about nuclear cardiology. I was the principal investigator on GE MBG311 trial on Vall d'Hebron hospital. **Jaume Candell-Riera** (M), Dr. MD, Cardiologist staff master. Dedicated to Nuclear cardiology from 1984 and Echocardiography from 1989 to 2003. Has make 25 book chapters and published 6 books of nuclear cardiology. Presented 40 large communications and more of 130 oral presentations about cardiology and nuclear cardiology. **Montserrat Negre** (F), Mrs,PhD, Nuclear medicine staff from 2007. Dedicated to nuclear cardiology from 2005. Interest research in nuclear cardiology, theraphy and thiroid cancer. **Maria Boronat** (F), Ms, PhD, Partially dedicated to nuclear cardiology.

1. Jaume Candell-Riera, Guillermo Oller-Martínez, Gustavo de León, Joan Castell-Conesa, and Santiago Aguadé-Bruix. (2007) Yield of Early Rest and Stress Myocardial Perfusion SPECT and Electrocardiographic Exercise Test in Patients With Atypical Chest Pain, Nondiagnostic Electrocardiogram, and Negative Biochemical Markers in the Emergency Department. Am J Cardiol ;99:1662–1666
2. Ana P. Caresia-Aróztegui, Santiago Aguadé-Bruix, Joan Castell-Conesa, Paloma Pifarré-Montaner, Gemma Cuberas-Borrós, Jaume Casaldàliga, Josep Girona, Guillermo Romero-Farina, Jaume Candell-Riera. (2007). Gated-SPECT equilibrium radionuclide angiography in right ventricle assessment of patients with repaired tetralogy of Fallot. Nucl Med Commun ;28:159–164.
3. Pereztol-Valdes O, Candell-Riera J, Santana-Boado C, Angel J, Aguadé-Bruix S, Castell-Conesa J, Garcia EV, Soler-Soler J. (2005). Correspondence between left ventricular 17 myocardial segments and coronary arteries. European Heart J ; 26: 2637-2643.

P14 - Société Européenne de Cardiologie - ESC

The European Society of Cardiology (ESC) represents nearly 53,000 cardiology professionals across Europe and the Mediterranean. The ESC comprises 50 National Cardiac Societies, 19 Working Groups, 5 Associations and 3 Councils. It also includes the distinguished community of ESC Fellows and Nurse Fellows (Fellow, FESC; Nurse Fellow, NFESC).

To fulfil its mission of "reducing the burden of cardiovascular disease in Europe", the ESC provides an array of scientific and educational activities, such as the production and continuous updating of Clinical Practice Guidelines, the organisation of educational courses and initiatives, pan-European surveys on specific disease areas and the ESC Congress, the largest medical meeting in Europe. The ESC is proud to hold, in conjunction with its constituent bodies, 6 subspecialty congresses, which are becoming increasingly popular within the profession. The ESC also edits and publishes 7 of the world's leading journals on cardiology: the European Heart Journal, Cardiovascular Research, Heart Failure, Europace, Echocardiography, Cardiovascular Nursing and Cardiovascular Prevention and Rehabilitation**.**

Main tasks attributed to the organisation: The European Society publishes regular newletters, appropriate guidelines and recommendations. It also arranges meetings and participates in organising the main congress of the field on Europe, The International Congress of Nuclear Cardiology (ICNC). The working group also designs, coordinates and participates to appropriate surveys and multi-centre research trials.

The ESC Working Groups (WG) have important roles in the actions of ESC. The WGs participates in the composing the scientific program of the annual congress, they arranges educational courses, publishes position papers and pariticipates in the creation of quidelines. One of the main tasks is also to design and coordinate European multi-centre trials.

The ESC Working Group on Nuclear Cardiology and Cardiac CT aims to promote research, teaching and clinical activities in its field. The WG consists of experts of cardiac imaging. The current EVINCI-study project fits perfectly with the aims of this WG. WG can serve ideal contact to other cardiologists and non-cardiology medical imaging groups in disseminating the results of EVINCI-study trial.

Previous experience related to those tasks: WG 5 has been working with several multicentre trials and has published several recommenadations and guidelines.

Staff involved: Francoise Heraud (F). Finance Director of Working Group 5. **Juhani Knuuti** (M). Chairman of WG. **Pasquale Perrone-Filardi** (M). Vice-chair of WG

1. Underwood SR, et al (2004) Imaging techniques for the assessment of myocardial hibernation. Report of a Study Group of the European Society of Cardiology Eur Heart J May;25(10):815-36.
2. Fraser AG, et al. (2006) The future of cardiovascular imaging and non-invasive diagnosis : A joint statement from the European Association of Echocardiography, the Working Groups on Cardiovascular Magnetic Resonance, Computers in Cardiology, and Nuclear Cardiology, of the European Society of Cardiology, the European Association of Nuclear Medicine and the Association for European Paediatric Cardiology. Eur J Nucl Med Mol Imaging. Aug;33(8):955-9.
3. Hesse B, et al (2005). EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. Eur J Nucl Med Mol Imaging. Jul;32(7):855-97.

P15 – InforSense Ltd – INF

InforSense was founded in 1999 as a spin-off company of Imperial College London. Its products include InforSense core platform, InforSense ClincalSense, GenSense, BioSense and ChemSense targeting decision making applications in the cinical informatitcs and life science domains. The company has offices in UK, USA and China employing more than 100 people.

Main tasks attributed to the organisation: InforSense will lead the design and implementation of the EVINCI informatics platform for use in the project and will provide user support for the platform across different centers.

Previous experience related to those tasks: InforSense's software is used in a large number of Fortune 100 companies as well as major research organization. It also forms the basis for collaborations in four major EU-funded FP6 projects: SIMDAT, TOPCOMBI, ArguGRID and BRIGDE. Its technology was the winner of the IEEE high-performance computing challenge in 1998, 1999 and 2002, and the Best of Show Award in the BioIT World Exposition in 2005, and has been applied to many fields of scientific research including Life Science. Earthquake modelling and Environmental Monitoring (see underneath).

Staff involved: Moustafa Ghanem (M), Director of Research at InforSense leading its participation a number of FP6 funded. He was a co-author and project manager of the award winning Discovery Net e-Science Pilot Project at Imperial College London. His research interests include semantic service composition, large scale grid computing and text mining and he has published more than 50 papers in these areas. He holds a PhD and MSc in high performance computing from Imperial College London. Dr. Ghanem will lead the participation of InforSense in this project. **Jonathan Sheldon** (M), chief Scientific Officer at InforSense. Responsible for managing InforSense product development and delivery to meet customer needs in life sciences and healthcare. Prior to InforSense he was Chief Technology Officer for Confirmant where he was responsible for developing the company's proteomics products and services. Previously he established the first bioinformatics group and was Head of Bioinformatics for five years at Roche Welwyn, UK, participating in a number of global initiatives within the company. Dr Sheldon holds a PhD in Molecular Biology/Biochemistry from the University of Cambridge. **Mick Correll** (M), Director of Product Developme, Clincal Applications. Responsbile for ClinicalSense product and previously responsible for global service delivery to InforSense customers in clincal applications. **Yike Guo** (M), founder and Chief Executive Officer of InforSense and Professor in Computing Science at Imperial College London. Research interests: large-scale data analysis and grid computing especially in the field of life sciences. Prof. Guo has successfully led a large number of research projects funded by the EU, the UK research councils and industry and has extensive experience in leading the scientific and technical directions of large scale projects .

1. The discovery net system for high throughput bioinformatics. Anthony Rowe, Dimitrios Kalaitzopolous, Michelle Osmond, Moustafa Ghanem, Yike Guo. Bioinformatics. 2003
2. Bridging the Macro and Micro: A Computing Intensive Earthquake Study Using Discovery Net Yike Guo, Jian Guo Liu, Moustafa Ghanem, Kyran Mish, Vasa Curcin, Christian Haselwimmer, Dimosthenis Sotiriou, K. K. Muraleetharan, L. Taylor. 2005 ACM/IEEE conference on Supercomputing. November, 2005
3. Grid based analysis of air pollution data. Mark Richards, Moustafa Ghanem, Michelle Osmond, Yike Guo, John Hassard. Ecological Modelling. March, 2006

P16 – CF consulting s.r.l. – CFc

CF consulting is a SME composed in majority by women involved in research programmes, technological, environmental, financial, training and cultural issues, and innovation policies relevant at national and European level. CFc is based in Milan and in Bruxelles. CFc team gathers 12 consultants with complementary experience or training to innovation management. The company offers scientific, legal, economical, statistical and engineering competences, in order to give a concrete and complete support to: organization of training activities (courses, seminars and cross-sectional training academia-industry); organization of project meetings and workshop; market analysis and business plan definition; support to transfer of knowledge within and outside consortia; dissemination process targeted to economic authorities and politicians and public aimed to enlarge the awareness at European level on the project's results; design, implementation and maintenance of project's web sites; knowledge management and quality assurance, in order to ensure the proper information availability for all partners and the correct activities' progression. In particular, the creation of documentation aimed to describe research project flow, activities' correlations, milestones & deliverables.

Main tasks attributed to the organisation: In the frame of WP9 (Management) P16-CFc will support the Coordinator for: the communication with the EC, the reporting activities, the verification of consistency of the project costs and the tasks performed, the maintenance of the Consortium Agreement and the harmonisation of procedures, through the creation of guidelines and common templates to be provided to the partners for carrying out their activities.

Previous experience relevant to those tasks: CFc's past experience and network of contacts including several European organizations, research centres, universities, industries represent a useful vehicle for targeting and enhancing the dissemination actions foreseen during the project. In the last ten years, the company supported universities, R&D centres and companies in the up-dates of their management practices (financial planning and management, programmes for the valorisation of research results, support in the technology transfer, integration of information and communication technologies).

Staff involved: Carla Finocchiaro (F). Founder of the CFc company and currently General Manager, over 18 years experience in European research programmes and coordination of teams at international level. Training expertise on academia-industry cross-sectional transfer. **Grazia Pagano** (F). Senior Project Manager. Multiannual experience in European research programmes knowledge management, organisation of workshops and international conferences and dissemination activities. **Emilio Cigliano** (M). Law degree. External Consultant. Experience in Corporate and Litigation and arbitration practice. Drawing up of national and international agreements, **Sofia Cappellari (F)**. Assistant project manager in proposal preparation and management. **Enrico Rosa (M)**. Expert in financial management, controls and audits. **Sibilla Sorrentino (F)** Webmaster.

P17 – Fondazione toscana Gabriele Monasterio per la ricerca medica e di sanità pubblica – FGM

Clinical activity on both in- and outpatients in the field of cardiovascular diseases has been an essential component of the research programs of the Institute of Clinical Physiology of the Italian National Research Council (P1- CNR) founded in 1968. Due to the growing importance of the clinical activities of IFC-CNR in the two hospital units of Pisa and Massa both for the Regional Health System and the CNR research activities, CNR and Regione Toscana through formal decisions of the respective governing bodies, have decided to establish a new permanent entity, FGM (Fondazione toscana Gabriele Monasterio per la ricerca medica e di sanità pubblica) to which, starting November 1, 2007, have been conferred the responsibilities and costs of running the hospital activities of IFC-CNR. FGM activities remain in close connection with IFC-CNR research activities within the same hospital setting, by full integration of personnel and technology. Cardiology, Cardiosurgery, and Cardiovascular Imaging Departments are equipped with complete laboratory setting, non invasive and invasive technologies, ICU, fully computerized outpatient and inpatient clinics and data base.

Main tasks attributed to the organisation: Performing some clinical examinations requested by the EVINCI Study (in particular heart catheterization, IVUS and measurements of FFR and CFR) in the patients enrolled by P1-CNR.

Previous experience related to those tasks: FGM, with its two hospital units of Pisa and Massa, is a tertiary referral center for heart catheterization in Regione Toscana.

Staff involved: Alessia Gimelli (F), MD. Member of WG5 of the ESC. Senior staff member of Nuclear Medicine Unit. Res.: SPECT for the diagnosis of coronary artery disease. **Sergio Berti** (M), MD. Cardiologist. Head of Interventional Cardiology Unit of Massa. Res: PCI in coronary disease. **Marco Ciardetti** (M), MD. Cardiologist. Staff member Catheterization Unit. Res: invasive functional characterization of the coronary circulation in cardiovascular diseases. **Mathis Schluter** (M), MD. Cardiologist. Staff member Catheterization Unit. Res: ICA and CT in cardiology. **Dante Chiappino** (M), MD. Radiologist. Director Cardiac Imaging Department, Head of the Radiology Unit. Res.: ICA and CT in cardiology. **Paolo Marcheschi** (M), Dr. Staff member of the Computer Science Unit. Res.: standards in multimodality cardiac imaging. **Alessandra Perinazzo** (F). Radiology Technician. Res.: cardiac catheterization and CT. **Maurizio Mangione** (M), PhD, Staff member of the Computer Science Unit. Res.: standards in clinical informatics networks and data base. **Stefano Puzzuoli** (M), PhD, Staff member of the Computer Science Unit. Res.: standards in clinical informatics networks and data base.

1. Neglia D, De Caterina A, Marraccini P, Natali A, Ciardetti M, Vecoli C, Gastaldelli A, Ciociaro D, Pellegrini P, Testa R, Menichetti L, L'Abbate A, Stanley WC, Recchia FA. Impaired myocardial metabolic reserve and substrate selection flexibility during stress in patients with idiopathic dilated cardiomyopathy. Am J Physiol Heart Circ Physiol. 2007 Dec;293(6):H3270-8.
2. Gimelli A, et al. Cardiac imaging improves risk stratification in high-risk patients undergoing surgical revascularization. J Cardiovasc Med 2006;7:51-6.
3. Sambuceti G, Marzilli M, Mari A, Marini C, Schluter M, Testa R, Papini M, Marraccini P, Ciriello G, Marzullo P, L'Abbate A. Coronary microcirculatory vasoconstriction is heterogeneously distributed in acutely ischemic myocardium. Am J Physiol Heart Circ Physiol. 2005 May;288(5):H2298-305.
4. Bamoshmoosh M, Marraccini P, Pratali L, Ciriello G, Ciardetti M, Mazzarisi A."Reverse steal phenomenon" in a patient with coronary artery disease and coronary-left ventricular fistula. Int J Cardiol. 2007 Jan 31;115(1):e33-5. Epub 2006 Oct 16. pairment in idiopathic left ventricular dysfunction. Circulation. 2002;105:186-93.

P18 – Klinikum rechts der Isar der Technischen Universitaet Muenchen – KRITUM

The Department of Nuclear Medicine of the Klinikum rechts der Isar der Technischen Universität München is a worldwide recognised research center with a focus on multimodal, molecular imaging. The department operates a variety of tomographic imaging systems such as SPECT, SPECT/CT, PET, PET/CT and MRI. In addition animal imaging devices such as PET/CT and SPECT/CT are available. It is one of the largest centers in Germany and provides the full range of nuclear medicine tests and therapies. Research interests cover cardiac, oncological and neurological topics as well as instrumentation and software development. With respect to cardiac imaging the focus is on preclinical and clinical research ("mice to men") of myocardial viability, microcirculation, innervation, neoangiogenesis and gene imaging. A wide range of international research collaborations leverage these developments and facilitate the translation of preclinical to clinical results. A tight cooperation with the department of cardiology (Prof. Dr. Albert Schömig) facilitates our cardiac research. This lab actually performs the invasive testing for this project as it operates two catherization laboratories in close proximity of our center.

Main tasks attributed to the organisation: Contributing site for mono- and multimodal patient examinations (CTA, MRI, PET and PET/CT, PET quantification). Potential provider of multimodal quantification software.

Previous experience related to those tasks: The department operates core lab facilities for SPECT and MRI infarct quantification as part of longitudinal studies after cardiac interventions. Over the last ten years, several thousand studies from several European interventional centers were analyzed. The invasive and non-invasive interventions included various stents, medical therapy, and stem cells). In addition, software packages for quantification, coregistration and image fusion approaches for all imaging methodologies mentioned above were developed in close interaction with the optimization of the actual imaging process.

Staff involved: Stephan Nekolla (M), physicist, Ph.D. Head multimodal cardiac imaging. 20 years of imaging experience in MRI, PET, SPECT and CT for preclinical and clinical applications. Author or coauthor of more than 80 peer reviewed publications. Author of the internationally used cardiac analysis package MunichHeart. Primary research interest is the development and validation of optimal workflows consisting of the best suited image acquisitions (mono- or multimodal), maximal extraction and quantification of physiologicaly relevant information and efficient communication of the results. **Susanne Weismüller** (F), M.D.. Physician employed in the department of nuclear medicine at P18-KRITUM since 5 years. Involved in several projects concerning MRI, PET, SPECT and CT for preclinical and clinical imaging of cardiovascular diseases. Primary research interest is the imaging of cardiovascular diseases using a multimodal approach (MRI/PET/SPECT/CT). **Markus Schwaiger** (M), M.D. Prof. of Nuclear Medicine. Director of the department of nuclear medicine at P18-KRITUM. Internationally renowned scientist with three decade long experience in preclinical and clinical cardiac, oncological and neurological research with more than 500 peer reviewed publications.

1. Ibrahim T, Bulow HP, Hackl T, Hornke M, Nekolla SG, Breuer M, Schomig A, Schwaiger M. Diagnostic Value of Contrast-Enhanced Magnetic Resonance Imaging and Single-Photon Emission Computed Tomography for Detection of Myocardial Necrosis Early After Acute Myocardial Infarction. J Am Coll Cardiol. 2007 Jan 16;49(2):208-216.
2. Martinez-Möller A, Souvatzoglou M, Navab N, Schwaiger M, Nekolla SG. Artifacts from misaligned CT in cardiac perfusion PET/CT studies: frequency, effects, and potential solutions. J Nucl Med. 2007 Feb;48(2):188-93
3. Schomig A, Mehilli J, Antoniucci D, Ndrepepa G, Markwardt C, Di Pede F, Nekolla SG, Schlotterbeck K, Schuhlen H, Pache J, Seyfarth M, Martinoff S, Benzer W, Schmitt C, Dirschinger J, Schwaiger M, Kastrati A; Beyond 12 hours Reperfusion AlternatiVe Evaluation (BRAVE-2) Trial Investigators. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. JAMA. 2005 Jun 15;293(23):2865-7

P19- Queen Mary and Westfield College, University of London - QMUL

QMUL is one of London and the UK's leading research-focused higher education institutions. Amongst the largest of the colleges of the University of London, QMUL 3,000 staff deliver world class degree programmes and research across a wide range of subjects in Humanities, Social Sciences and Laws, in Medicine and Dentistry and in Science and Engineering.

Main tasks attributed to the organisation: The research group will recruit suitable individuals (from those scheduled for invasive coronary arteriography) to undergo (after signing an informed consent) the following; blood sampling (once) and one adenosine myocardial perfusion PET or SPECT study during their first visit. Within 2 weeks of the SPECT scans, the patients will undergo a second functional test in the form of adenosine myocardial perfusion MRI and on the same day, they will also undergo CTA for non invasive assessment of coronary anatomy. Follow up, in the form of an interview at Barts and the London NHS Trust will be performed according to the research protocol.

Previous experience relevant to those tasks: The research group has extensive clinical, training and research experience in the fields of both invasive and non invasive cardiololgy with numerous publications in journals with high impact factor. The investigators have attracted highly significant research funds both from commercial and non commercial sponsors and have taken part in relevant task and guideline committees. Research has focused on the following fields: stem cells, inflammation, tissue repefusion injury, validation of nuclear and cardiac MRI techniques for assessment of myocardial perfusion, viability and ventricular function. Other areas of research include assessment of pharmacological manipulation of myocardial perfusion and absolute perfusion quantification (in mls/min/gr) and assessment of vascular inflammation by PET and also multimodality Heart failure imaging.

Staff involved: Francesca Pugliese (F), (PI) M.D, PhD is a Senior Lecturer at Barts and The London NIHR Advanced Cardiovascular Imaging Unit. She has been trained in a number of prestigious centres in the US and Europe and worked as Consultant Cardiac Radiologist at the Essex Cardiothoracic Centre. Francesca has co-authored 38 published peer reviewed journal papers and 44 other papers (proceedings of meetings and chapters in books). **Constantinos Anagnostopoulos (M),** (Co-PI) M.D, PhD, FRCP, FRCR, FESC is a Senior Lecturer in Nuclear Medicine at the QMUL and Clinical Head of Service. He has received a number of commercial and non commercial grants and is a member of many guideline comittees. His research focuses on development, validation and application of radionuclide techniques assessing myocardial perfusion and ventricular function. Current research activities include investigation of clinical and sub-clinical atherosclerosis and physiology of myocardial perfusion using Positron Emission Tomography. **Ceri Davies (M)** (Co-inv) (MD, FRCP) is a general physician and cardiologist received training in advanced non invasive cardiac imaging at Addenbrooke's and Papworth Hospitals in Cambridge. He set up and helps run the cardiac MR Service at the London Chest Hospital and is currently clinical lead for the Cardiac CT service. **Anthony Mathur (M),** (Co-inv) (PHD, FRCP). Lead for Advanced Cardiac Imaging at Barts and the London NHS Trust and chairs the management board of one of the busiest units in the UK. Recently Prof Mathur has helped set up an advanced cardiac Imaging Biomedical research unit as co-Pi on a prestigious UK Department of Health Grant. He is also PI on the 3 largest interventional trials of cell therapy for heart disease in the UK. He has been Director of the Cardiac cath labs and also part of the live faculty for major interventional meetings (TCT and EuroPCR). **Steffen Petersen (M)** (Co-PI)(MD DPhil (Oxon) FESC) is the Centre lead for Advanced Cardiovascular Imaging at the Barts and The London. He is a Consultant Cardiologist and Reader in Advanced Cardiovascular imaging. He trained in Mainz, Germany and Oxford, UK and has co-authored over 50 peer reviewed original manuscripts. He has received substantial grant support for his research. He is scientific advisor to UK Biobank, a population based study, which plans to include cardiovascular imaging in 100,000 subjects. Dr Petersen won the British Cardiovascular Society Young Research Worker's prize in 2007. Dr Petersen regularly speaks at

international and national conferences, supports training activity in cardiovascular imaging (EuroCMR exam, London CMR, CMR stress imaging course etc) and has an active research programme using CMR as a tool to investigate inherited disease affecting the cardiovascular system and is currently setting up a programme of using CMR for surrogate endpoints in clinical trials. **Andrew Wragg (M)**, FRCP, is a consultant cardiologist at Barts and The London NHS Trust and is charge of the Rapid Acess Chest Pain Clinic. **Mark Westwood (M)**, FRCP, is a consultant cardiologist and trained in cardiac MRI at the Royal Brompton Hospital in London. Dr Westwood is the clinical lead of cardiac MRI at Barts and The London NHS Trust, and also is an interventional cardiologist. **Sam Mohiddin (M)**, FRCP, is a consultant cardiologist at Barts and The London NHS Trust involved in both cardiac MRI and cardiomyopathy. **Ian Goddard (M)**, FRCR, is a consultant radiologist in charge of the cardiac SPECT service at St. Bartholomew Hospital together with Dr Anagnostopoulos.

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P20- Azienda Ospedaliero-Universitaria Careggi - AOUC

The Azienda Ospedaliero Universitaria Careggi has been established by cooperation between the Tuscan Health Care System and the University of Florence. AOUC mission is characterized by medical care activity strictly linked with didactics and highly developed medical research. The Heart and Vessels Department, held by Professor G. F. Gensini, is a regional and national centre of excellence for the treatment of complex patients with cardio-vascular diseases. Moreover, the Heart And Vessels Department is a leader both in scientific research and in high and basic medical education.

Main tasks attributed to the organization: Collect blood samples and send them for central reading. Perform and store digitally ECHO and MRI images and send them for central reading.

Previous experience relevant to those tasks: the AOUC staff involved in EVINCI Study has a wide experience in the following research fields: coronary angiography, invasive coronary flow reserve, IVUS, coronary plaque by CT, Cardiac CT, SPECT and PET for diagnosis of coronary artery disease, Echocardiography and New technology in transthoracic echo

Staff involved: Gian Franco Gensini (M), Prof, director of Heart and Vessels department, head of Florence School of Medicine MD (M), **Serafina Valente** (F), MD staff member of Intensive Cardiac Care Unit; **Cristina Giglioli** (F), MD staff member of Post-Intensive Cardiac Care Unit; **Manlio Acquafresca** (M), cardiac CT MD, **Roberto Sciagra** (M), staff member of nuclear medicine unit MD, **Francesco Cappelli** (M) MD, staff member of Intensive Cardiac Care Unit.

1. Sciagrà R Sotgia B et al. Assesement of the influence of atrial fibrillation on gated SPECT perfusion data by comparison with simoultaneously acquired non gated spect. J Nucl. Med 2008 aug 49 (8)1283-1287.
2. Conti A, Vanni S, Sammicheli, L Raveggi S, Camaiti A, Pieralli F, Nozzoli C, Gallini C, Costanzo E, Gensini GF. Yeld of nuclear scan strategy in chest pain unit evaluation of special population. Nucl Med commun 2008 Dec;29 (12):1106-12
3. Sotgia B Sciagra R et al. Spatial relationshipbetwee coronary microvascular dysfunction and delayed contrast enhancement in patients with hypertrofic cardiomyopathy J Nucl Med 2008 jul;49(7):1090-6

P21 – Azienda U.S.L. N. 12 di Viareggio – Ospedale Versilia

The Cardiology Unit of the Versilia Hospital includes an Intensive Care Unit (4 beds), a Cardiollogy Ward (16 beds), an Invasive Cardiology Team, an Electrophysiology Team, a non-Invasive Cardiology Team. There are 15 Cardiologists and 35 Nurses. It serves a district population of about 180.000 inhabitants and provides ambulatory activities as well as a complete diagnostic service. The latter includes an interdipartimental activity of cardiac-MRI, coronary-cardiac MSCT. The annual volume of admission to the ward is around 1100/year. The annual number of coronary angiograms is around 500/yr, cardiac MRI 250/yr, cardac MSCT 280/yr, Pace Maker implants 300/yr. The Cardiologists of the Hospital also serve in the peripheral clinics all over the Versilia Area granting an homogenous activity.

Main tasks attributed to the organisation: During the study P21-Ospedale Versilia will evaluate patients with suspected coronary artery disease by means of noninvasive tools (stress-Echpo, MSCT, CMR) and compare the results with coronary angiography as the goal.

Previous experience related to those tasks: We are participating to some international studies. We are participating, among others, to the TRACER study (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome), TRILOGY study (Comparison of Prasugrel and Clopidogrel in Subjects with Unstable Angina / Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Acute Coronary Syndrome (ACS) who are Medically Managed.

Staff involved: Giancarlo Casolo (M), Director of the Cardiology Unit, Versilia Hospital since 2006. Former Senior Staff Cardiologist Careggi Hospital, Florence, Italy. MD, PhD, Fellow of the American College of Cardiology, Fellow of the Eurpean Society of Cardiology, Specialist in Cardiology, Specialist in Radiology. Over 150 publications on peer reviewed Journals. **Rosa Poddighe** (F), Senior Staff Cardiologist Versilia Hospital. MD. Specialist in Cardiology. Co-Author of several published paper. Non invasice Cardiologist with experience in echocardiography, pulmonary hypertension clinic, non-invasive evaluation of coronary flow.

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P22- Kliniken Des Landkreises Göppingen GGMBH - KAE

P22-KAE is General academic hospital affiliated to the University of Ulm, Germany. All invasive and non- invasive cardiac diagnostics and interventions are performed.

Main tasks attributed to the organisation: P22-KAE will participate in WP0, 5, 8 and 9.

Previous experience related to those tasks: Approximately 15 year of research in the field of interventional and non-invasive cardiology with app. 120 scientific publications..

Staff involved: Stephen Schröder, (M), M.D., FESC, Professor of Internal Medicine/ Cardiology, University of Tuebingen. Chair, Department of Cardiology, Angiology and Pneumology Klinik am Eichert, Göppingen. Working in the field since 1996. Research interests in invasive and non-invasive cardiology. **Josef Steindl** (M), M.D. Cardiologist, Head of Cath Lab, Research Interest: Interventional Cardiology, Partecipation in national and international studies, especially registiries since 15 years. **Franz Hofgärtner** (M), M.D. Cardiologist, Head of Electrophysiology, Research Interest: Interventional Cardiology, Electrophysiology. Partecipation in national and international studies since 20 years. 30 scientific publications**. Jürgen Hauber** (M), M.D. Cardiologist, Research Interest: Interventional Cardiology, Non-Invasive Diagnostics, Head of Echo Lab. Partecipation in national and international studies since 20 years. **Hans-Peter Hafner** (M), M.D. Cardiologist,Research Interest: Interventional Cardiology, Non-Invasive Diagnostics. **Tanja Drosch** (F), MD, Cardiologist,Research Interest: Interventional Cardiology, Non-Invasive Diagnostics, especially cardiac CT, staff member since years, ca 14 scientific publications**; Christiane Lopes** (F), MD, Cardiologist,Research Interest: Interventional Cardiology, Non-Invasive Diagnostics. **Thomas Zelesny** (M), MD, Radiologist, Head of Computed Tomography, Research Interest: Cardiac- CT**. Marion Steindl** (F), Scientific Secretary.

1. Schröder S, Baumbach A, Haase KK, Oberhoff M, Mahrholdt H, Herdeg C, Athanasiadis A, Karsch KR. Reduction of Restenosis by Vessel Size Adapted Percutaneous Transluminal Coronary Angioplasty Using Intravascular Ultrasound. Am J Cardiol 1999; 83:875-879, *IF: 3,059*
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B 2.3 Consortium as a whole

The composition of this consortium has been carefully selected in order to include all the expertises in IHD and especially cardiac imaging in order to faster accomplish of the main objectives of the proposed project. All groups participating in the consortium have the expertise and facilities to perform the proposed experiments.

Partners of the consortium have been selected for their following attributes:

- recognized world leading experts in their fields;
- facilities and technologies that allow performing high quality cardiac imaging;
- complementary to each other regarding the aims of the project;
- excellent scientific record;
- highly motivated to solve the challenges that the EVINCI-study project poses;
- demonstrated ability to successfully carry out international multi-centre projects.

The consortium is composed by top level European laboratories which are leaders in the field of cardiovascular diseases and key in the forefront research on the impact of combined "anatomo-functional" non invasive cardiac imaging especially for detection and characterization of IHD. They all use state-of-art technologies to address the scientific goals of the project.

A relevant part of the EVINCI-study will be dedicated to the development, in cooperation with the industry, of an advanced informatics' platform able to synthetically present to the end-user (patients, physicians, etc.) the integrated cardiological diagnostic profile of the individual patient, as resulting from clinical-biomarkers and multi-imaging assessment, and to help in the clinical decision making process.

The objectives of the EVINCI-study could be reached only if a large cohort of patients (500 to 700) will be enrolled and submitted to a standardized clinical, laboratory and multimodality imaging work-up. Due to the complexity and the costs of the project only a multicentre European study will have the potential of addressing these objectives.

The Consortium includes 21 active partners, of these 13 are international Centres which represent leading European sites for cardiovascular imaging and include in particular the following centres: P1-CNR; P2-U.Turku, P3-UZH, P4-LUMC and P18-KRITUM. These are units that operate a variety of tomographic imaging systems such as SPECT, SPECT/CT, PET, PET/CT, MRI and ECHO as well as invasive imaging techniques. P6-IR-HSCSP has expertise on nuclear medicine and molecular imaging of cardiovascular diseases mainly using SPECT and PET. P7- NIC is the reference centre in the field of cardiology in Poland. P8-RBHT is the largest cardio-thoracic centre in the UK and has very strong position especially in SPECT and MRI. P9- APHP is one of the leading centres of Nuclear Cardiology in France. P10-UniGe has all the equipments necessary for imaging studies, including gamma camera, radiochemistry labs, cyclotron and PET/CT facilities, as well as 1.5 and 3 T MRI systems. P11- SERMAS is one of the reference centre in Spain in interventional cardiology, electrophysiology and cardiac imaging. Cardiovascular Imaging Unit integrated in the Cardiovascular Institute of the SERMAS is the reference center in the field of 3D echocardiography, stress echo, perfusion echo, strain and development of new cardiovascular softwares in Spain. P12-UniNA provides complete invasive and non invasive carein cardiovascular diseases. P13- HUVHEBRON is expert on making image fusion and analyzing clinical images. P17 -FGM has a specific and certified record in heart catheterization. It will perform some clinical examinations requested by the EVINCI-study (in particular heart catheterization, IVUS and measurements of FFR and CFR) in the patients enrolled by P1-CNR.

P14-ESC which is the European Society of Cardiology represents nearly 53,000 cardiology professionals across Europe and the Mediterranean. The aim of ESC is to reduce the burden of cardiovascular disease in Europe, therefore ESC provides an array of scientific and educational activities, such as the production and continuous updating of Clinical Practice Guidelines, the organization of educational courses and initiatives, pan-European surveys on specific disease areas and the ESC Congress, the largest medical meeting in Europe. The Centers and the Researchers participating into the consortium have been since a long time cooperating with ESC for technological advancement, standardization of cardiovascular imaging and dissemination of knowledge and guidelines as also demonstrated by the high number of members of ESC WGs Nucleus among the participants.

P15-INF is a leading provider of integrative analytics and workflow technology for the life science, clinical informatics and business analytics industries.

The activities of P19-QMUL, P20-AOUC, P21-Ospedale Versilia and P22-KAE are to facilitate the clinical arm of the project by recruiting 150 patients according to the EVINCI protocol.

Such a technical experience is complemented by P16-CFc's 10-year experience in involvement in EC-funded projects for knowledge management, quality assurance procedures and dissemination actions in the context of research activities. P16-CFc's past experience and network of contacts including several European organizations, research centres, universities, industries represent a useful vehicle for targeting and enhancing the dissemination actions foreseen during the project.

The table below shows the complementarities of all the partners included in the consortium

	P1	P2	P3	P4	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22
WP0	●	●	●	●	●	●	●	●	●	●	●	●				●	●	●	●	●	●
WP1	●										●										
WP2		●		●																	
WP3	●	●	●				●	●		●							●				
WP4	●	●	●	●		●	●	●		●											
WP5	●	●	●	●			●			●				●							
WP6	●								●												
WP7	●	●	●														●				
WP8	●	●	●	●	●	●	●	●	●	●	●	●	●		●				●	●	●
WP9	●	●	●	●	●	●	●	●	●	●	●	●	●		●		●	●	●	●	●

Sub-contracting:
Six out of 21 active partners will have subcontractors. Subcontract is awarded on a transparent ground, based on the best bid offered taking into consideration price/quality ratio, national legislation in force and internal regulations.
The selection procedure takes the form of three different offers which will be evaluated against common established criteria, each of them being treated fairly and equitably. The estimation of costs will be made on the basis of correspondence to average market prices and of the available budget.

The following partners will have subcontractors:

P1-CNR, P2-U. Turku and P15-INF will subcontract to external auditors the preparation of certificates on financial statements.

CO1-CNR will also subcontract some of the activities related to statistical analysis of EVINCI-study results. The total cost of the subcontractor will be equal to 72.000 €.

P10-UniGe will subcontract cost-benefit analyses throughout the EVINCI-study. P10-UniGE will contact Scuola Superiore Sant'Anna (Pisa, Italy), with which it has a long standing cooperation, but other organizations will also be considered and the best bid will be selected.

P14-ESC will subcontract for website design and maintenance.

P19-QMUL will subcontract the patient recruitment arm of the study (WP0) to Bart's and The London NHS Trust. The subcontractor will recruit 40 patients for the purposes of the EVINCI-study. P19-QMUL has a long standing cooperation with Bart's and The London NHS Trust. However other organizations will be also considered and the best bid will be selected.

Third parties (other than subcontractors):

P6 - IR-HSCSP
The HOSPITAL DE LA SANTA CREU I SANT PAU acts as a 3rd part which provides only personnel resources. There is a signed agreement between HOSPITAL DE LA SANTA CREU I SANT PAU and INSTITUT DE RECERCA DE L'HOSPITAL DE LA SANTA CREU I SANT PAU, which regulates the relationship between both institutions regarding European Projects.

P11- SERMAS
"The Fundación para la Investigación Biomédica del Hospital Universitario Clínico San Carlos is a Third Party of Servicio Madrileño de la Salud in the project in order to manage the financial and administrative aspects of this entity relating to it. The Servicio Madrileño de la Salud (before named "Instituto Madrileño de la Salud") has a prior agreement (signed in 2004) with this non-profit fundation by means of which this entity is in charge of managing the research activities of Hospital Clínico San Carlos, Hospital which is part of Servicio Madrileño de la Salud.
Accordance to it, the coordinator pays the EC contribution directly to this foundation as a Third party and not to the beneficiary".

P13 - HUVHEBRON
FUNDACIO INSTITUT DE RECERCA DE L'HOSPITAL UNIVERSITARI VALL D'HEBRON provides, during the whole execution of the project, managerial and administrative services to Hospital de la Vall d'Hebron-Institut Catala de la Salut (HVH-ICS). FUNDACIO INSTITUT DE RECERCA DE L'HOSPITAL UNIVERSITARI VALL D'HEBRON is a non-profit foundation which has been created to provide such services for externally financed projects including EU framework projects. The FUNDACIO INSTITUT DE RECERCA DE L'HOSPITAL UNIVERSITARI VALL D'HEBRON is paid for its services from the overhead of the grant. The implementation of the research work, as described in the DoW, is done under the complete responsibility of HVH-ICS.

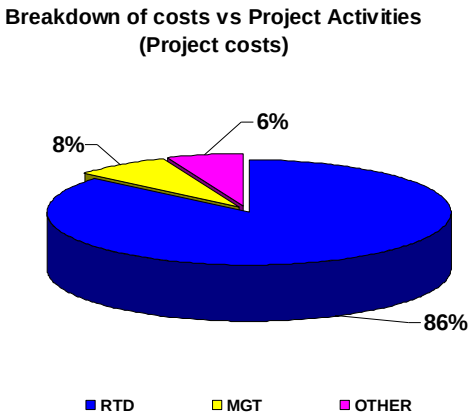
Funding for beneficiaries from "third" countries: Not applicable

Additional beneficiaries / Competitive calls: Not applicable

B 2.4 Resources to be committed

Setting a well balanced financial plan is a key issue for a research project; EVINCI-study partners collaborated to define the 42 months budget plan. EVINCI-study Consortium, in order to complete all the objectives of the proposal, decided to co-finance the project with several man months per activity. The final figures show that a big effort in terms of man-months will be mobilized and integrated to reach the project goal: **264,5** man-months will be devoted to the RTD activities (including scientific management), **43,6** man-months to the overall administrative and financial management of the Consortium, and finally **25,2** man-months for other activities. This will correspond to a total of **333,3 man-months**. In addition, the non-budgeted man/months contributed by project partners will be: **225,5** man/months for RTD, **19** man/months for management and **28,5** man/months for other activities, **273** man/months in total. The global man/months devoted to the project will therefore **be approximately 606,3 man/months**.

The EVINCI-study total costs' by type of activity are: € **2 962 554,41** for RTD; € **266 373,51** for Management (mostly administrative and secretarial personnel costs, and costs for travel, conference calls and certificates on the financial statement) and € **207 112,67** for other activities. All this will be equal to a cost of € **3 436 040,59** and consequently the total EC requested grant is equal to € **2 695 402**. The figures below show the distribution of costs per type of activities:

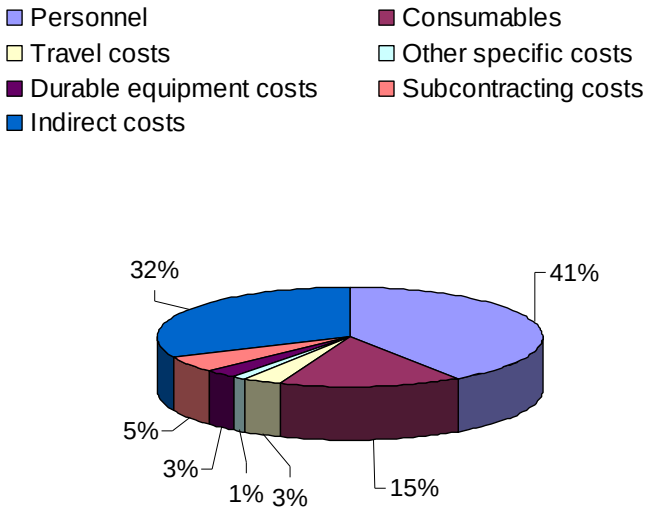


The global costs *vs* cost factors analysis denotes that about 41% of the total costs is for personnel, 15% for consumables, 3% for travels, 1% for other costs, 5% for sub-contracting, 3% for durable equipment and the remaining 32% for indirect costs.

All Partners calculated their EVINCI-study expenses on the basis of their actual costs.

Breakdown by type of activity

Personnel costs contribute the majority because the RTD programme is very labour intensive. Personnel costs equal to **€ 1 393 269**, mostly for the man/months in RTD programme and scientific management as above-mentioned, which accounts for the effort of the senior researchers, post-doctoral researchers, scientist/research assistants, PhDs, post-doctoral and technicians/programmers listed in the summary effort table. These numbers have been calculated on the basis of detailed work planning, taking into account the partners actual experience with related tasks and making use of any opportunities for research staff to take on more than one task. Without this work force, the programme would have to cut certain activities which would weaken the power of the analyses and render the programme less competitive.



Consumable costs amount to a total of about € **522 565** of the total costs they will be used to cover expenses for: contrast agents, drugs and related materials for additional (i.e. not funded by the National Insurance Systems) CT-MRI-Echo studies; radiotracers and related materials for additional SPECT-PET studies; kits and reagents for blood sample analysis, catheters and related materials for FFR/CFR/IVUS studies; data media (CD, DVD disks for results).

Travel costs will be equal to € **115 727** and these will be necessary to allow regular work package meetings, management meetings (including review meetings) and meetings in the context of dissemination activities.

Other costs equal to **€ 37 877** are envisaged for networking (e.g. through conference calls) dissemination (conference participation and scientific publications).

Durable Equipment costs will be equal to € **101 613**. The cost is relatively modest as the vast majority of necessary equipment is already in place. Equipment expenses will incur, including depreciation cost for: ThermoOption for the RadiAnalyser for the FFR (for CFR evaluation), ultrasound probe for stress echo, and finally workstations and several personal computers and servers.

Sub-contracting costs these will be equal to € **178 921**. P1-CNR, P2-U. Turku and P15-INF will subcontract to external auditors the preparation of certificates on financial statements.

CO1-CNR will also subcontract some of the activities related to statistical analysis of EVINCI-study results. The total cost of the subcontractor will be equal to 72.000 €.

P10-UniGe will subcontract in order to perform cost-benefit analyses throughout the EVINCI-study, at a cost of € 29 695. P10-UniGE will contact Scuola Superiore Sant'Anna (Pisa, Italy), with which it has a long standing cooperation, but other organizations will also be considered and the best bid will be selected. P14-ESC will subcontract website design and maintenance at a cost of approximately € 4 499. P19 QMUL will subcontract to Bart's and The London NHS Trust the patient recruitment arm of the study (WP0). Total subcontracting costs are equal to: 66.732 € and cover all the clinical aspects of the trial.

Indirect costs are calculated according to each partner's method for their calculation and are equal to € **1 086 0769 .**

B3. Impact

B 3.1 Strategic impact

The number of patients with suspected or documented IHD is steadily increasing. This is caused by the ageing of the population and by an increase in other cardiovascular risk factors as physical inactivity, diabetes mellitus and obesity. Thus, IHD remains still the leading cause of death and the main determinant of health costs in Europe. The fight against this trend includes developing and testing new strategies for the early detection and better characterization of the disease and, thus more accurate guidance of therapy.

Non-invasive imaging plays crucial role in IHD but the evidence-based and economically optimized use is challenging since there is limited data available to guide the usage of various advanced and often costly procedures. The rapid technical development has also produced new techniques that are often competitive or complementary to earlier methods. Therefore, European-wide multi-centre clinical trial is the only possibility to provide comprehensive information in larger populations.

This trial will definitely provide answer to most of the current burning questions in use of imaging in IHD. Based on the data created by the EVINCI-study one could e.g. answer the following questions:

1) Can anatomo-functional non-invasive imaging provide information accurate enough to replace invasive imaging in large fraction of patients and to enable focusing of invasive procedures on patients that need revascularization therapy?
2) How the newest non-invasive imaging of coronary arteries (X-ray computerized angiography) perform as a stand alone technique?
3) Which ones of the non-invasive functional techniques (SPECT, PET, ECHO, MRI) are performing the best by means of accuracy and risks?
4) Is combined use of non-invasive imaging feasible and useful?
5) What is the most cost-effective selection and sequence of imaging techniques in IHD.

Being able to answer these questions would make huge impact to the current clinical practises and consequently to the economical burden.

To reach the goals defined in the EVINCI-study plan, strong consortium with expertise and up-to-date technologies must be available. The current list of partners includes most of the European top cardiovascular imaging centres.

There are no comparable trials ongoing or even designed in any European country based on the best knowledge available. In USA there is multi-centre trial ongoing (SPARC) that is addressing similar questions. However, that study includes only X-ray computed tomography and nuclear perfusion imaging and compares these combined findings against prognosis but without ICA or any invasive functional measurements as well as other non-invasive imaging techniques (ECHO, MRI). Thus, the SPARC-study has much more limited scope and cannot provide comprehensive analysis of imaging in IHD as were the goals of the EVINCI-study.

To achieve the abovementioned impacts, the dissemination of study results must be carefully planned and performed. In general, changes in clinical practises takes time since these are often determined by local subjective opinions, earlier experience and logistical limitations. In this context

the primary target group in dissemination of study results is clinicians that in primary patient care determine which tests are used.

B 3.2 Plan for the use and dissemination of foreground

The EVINCI-study Consortium anticipates that this Project will generate innovative information and knowledge on organ imaging in CVD, in fact, through the cooperative effort of a multidisciplinary consortium the EVINCI-study will apply non-invasive, multimodality cardiac imaging approaches to the detection and characterization of ischemic heart disease (IHD) in patients with angina-like chest pain, under stable clinical conditions and with intermediate pre-test probability of the disease.

A continuous flow of information will be kept, not only within the members of the Consortium, but also with the scientific community, including representatives of the International, European and National scientific societies in the field, and patients' organisations. The creation of easy-access, wide-range flows of information will contribute to disseminate acquired data, stimulate research, educate stakeholders, increase awareness of the problem, and increase resources.

The EVINCI-study Consortium considers the dissemination of the project results as a highly strategic issue as it will boost strategies with other similar initiatives and provide a solid basis to start with the exploitation phase. In this view dissemination activities are not only a mere contractual obligation, but represent the strategic way in order to promote knowledge sharing, greater public awareness transparency and education.

At the same time a successfully communication can help to:

1) attract the interest of potential partners;
2) encouraging student to join the partner institutes;
3) enhancing the reputation of the participants at local national and international level;
4) draw the attention of national governments, regional authorities, and other public or private funding sources;
5) where appropriate aiding the search for financial backers, licensees or industrial to exploit the results.

The last aim to communicate is represented by the pursuit of the EU' objective to spread the results of the research projects to the wider possible interested public.
In order to do improvement the quality of life, the state of health of the European citizens and contemporarily decreasing the costs in term of human lives it is important to disseminate the EVINCI-study results.

- **Dissemination strategy**

The communication activity has consequence in term of both financial and time expenditure. It is therefore essential to establish a dissemination plan with predetermined scope, budget, priorities and goals. The project partners will delineate a dissemination plan whose main strengthening points can be summarized as follows:

1) Content to be disseminated in order to demonstrate:
    a. the credibility of the methodology used,
    b. the quality and the relevance of the outcomes.
2) Tools to be used, selected according to their:
    a. capacity to reach the target user,
    b. timelines of access,

c. accessibility and user friendliness,
d. flexibility, reliability and cost effectiveness.

3) Users to be target:
   a. presentation and level of information needed by the different typologies of users,
   b. most suitable tools to be used for each identified target group,
   c. capability of the user to use information.

EVINCI-study dissemination objectives are to:

a. diffuse interest in Health Care innovation technology,
b. pass on the information about EU' interest stimulating the research health market,
c. inform the target audiences of the existence of the project, and its benefits, use and applicability in the different market segments,
d. find potential customers and partnerships (hospital, ICT firm, pharmaceutical firm).

To reach these goals the Consortium singles out these stakeholders:

1. **Scientific Community**
2. **Health authorities/Health care services**
3. **Business community**
4. **General public.**

In support to its dissemination activities, the consortium will set up a specific project web site.
P14-ESC will have the responsibility to disseminate the project's results including the development of the web site of the project whose primary aim will be the provision of general purpose information about the project's objectives and goals and for the announcement of the major results of the project. The structure of this web site will depend on the project specific needs but should contain minimum information about the project, its objectives, work plan and involved partners. It will also acknowledge European Commission's FP7 support and display the EU flag and FP7 logo.

At the end of the project a demonstration activity will be organized in an appropriately chosen European Health Conference, dissemination strategy and activities will commence at an early stage in the project.
Four distinct steps are envisaged:

	Step 1: Awareness	Step 2 Information	Step 3 Knowledge	Step 4 Full Knowledge
What	The Consortium will decide on concrete actions to define a communication integrated plan. The first step is the decision concerning what to communicate (idea, partial results, all results, step-by-step results, generic information, Technical information). The	Once the communication contents and tools have been determined, the Consortium will issue the first package of dissemination activities. The goal is starting to find interested public in the project. This will be an informational phase.	Once first results will be available, dissemination activities will focus on informing the selected target (scientific community, health authorities, industry). The information in this phase becomes more scientific and technical. Through workshops	Dissemination activities will intensify in this phase to reach much more possible main publics. The Consortium would diffuse results. The communications becomes technical and accurate. The Consortium will decide on increasing publications

	second step is the decision concerning how to communicate (generic, informational, scientific, technical, approach).	The communication has generic-informational nature. The Consortium will refine the website, publish a Project brochure, issue and mail the first releases and attend selected events.	discussion the Consortium would reach a target more definite.	
Objective	To inform on advances in research on early detection of IHD	To bring about approval in the project.	To find interested industry and interested health care management.	To find interested industry and interested health care management

	Step 1: Awareness	Step 2 Information	Step 3 Knowledge	Step 4 Full Knowledge
Tool	✓ Publications ✓ Project web site ✓ Reports ✓ Project summary ✓ Brochure ✓ Poster ✓ Annual ESC meetings ✓ Final Conference		Workshop, Publications	Publications, Events, Final Conference.

Other action to be included in dissemination activity is **Consensus activity,** in order to create good relationships and visibility in the national and international context.
The main activities to be considered to develop this goal are:

− **Participation in concentration activities** organised by the European Commission;
− **Establishment of contacts** with European projects having complementary interests;
− **Identification and participation in national and international events** which can promote and amplify the awareness of the project in the reference market.

At the end of the project a Final Conference focused on the project progress will be instrumental to consensus activity. It will be organised to gather members from all participant countries. This Final Conference will be organized in order to maximize dissemination and finally deploy the results of the project.

Any dissemination activities and publications in the project will acknowledge European Commission's FP7 funding.

Standard communication material to be provided to the European Commission
In support to the communication activities of the Commission services, and in addition to a presentation leaflet that it may initiate, the consortium will provide the Commission, within 3 months after the start of the project, with a 2 pages information sheet (double sided A4) which will be drafted in a standard format communicated by the Commission. The consortium will also provide an updated version of this information sheet on an annual basis. The Commission services

may also request one illustration (picture, schema or drawing) to illustrate such communication material

Exploitation Strategy

A detailed exploitation plan will be defined during the project lifetime, based on a careful analysis of the IPR issues that may arise, which will be carried out by the PSC.
In month 42 inside the WP8 Dissemination and Exploitation the consortium will produce a **Dissemination Plan** which specifies how the Consortium members on their own or in collaboration with other partners, intend to exploit the results of the Project. At this stage, the prevailing attitude is towards an exploitation of the results through the Consortium members themselves.
Project activities and results will go alongside and will integrate those partners business strategy and this clear correlation will foster the effective use of project outcomes in their business scenario.
EVINCI-study system will be marked by its developers on the base of commercial agreements that emerge towards the end of the project.
In this case, the value chains are supposed to be collaborative partnerships between the consortium and the leading players on the referred market engaged in economic exchange.
The Consortium will further set up an Internet-based infrastructure easing interactions among the partners by enabling virtual meetings, collaborative work sessions and seminars.

Management of knowledge and of Intellectual Property (IPR)

The management of IPR is a very complex issue. The EVINCI-study Consortium will gave special consideration to Intellectual Property Rights (IPR) in order to identify all possible means protecting its research; at the same time EVINCI-study project is based on data provided by partners, thus, at the conclusive step of realization, consortium would have to manage also IPR of these data.
The strategy on which EVINCI-study IPR management will be based on the ones that are outlined by the Commission for the Seventh Framework Programme and in the Consortium Agreement, as appropriate. Considering that each partner can bring into the project two kinds of contributions, which are background (pre-existing to the project) and foreground (developed in the project), some basic rules of exploitation have been already set up and below we define the general principles through which we intend to manage all the Intellectual Property matters. The Consortium agreement will include well defined confidentiality clauses to be accepted and respected by all members.

Access to background
- Access to background for carrying out the project:
    a. Free if a participant needs them for carrying out the project.
    b. Background will be accessible to all the members of the consortium through a royalty free license for research purposes within the scope of the network.

Access to background can be excluded, at the sole discretion of the owner, through a written agreement included in the Consortium Agreement.

- Access to background for exploitation use
    a. Background can be accessible for commercial exploitation, to members of the network potentially interested, through a license agreement to be negotiated in good faith among the parties
    b. Free if a participant needs them for carrying out its own work inside the project.

Access to foreground
- for carrying out the project:

a. Free if a participant needs them for carrying out its own work inside the project.

Access to background for further use:

a. Free.
b. A commercial license, to all members of the network if it is needed for the commercial exploitation of their own technology. The parties involved shall negotiate in good faith the terms of such a "limited license" (limited in terms of field of application).
c. The same technology can be granted as a "limited license" to more than one member if the fields of application are different.
d. Members, will have a first right of negotiate a "exclusive license" (i.e. an exclusive license that is limited to certain fields of application on which other members might have obtained a limited license).

In case of disputes on IPR issues the PSC will intervene.

Who is the owner?

- The contributing member owns the Intellectual Property Right (IPR), regarding any original contribution or background knowledge brought into the consortium.
- The Intellectual Property Right (IPR) regarding any new knowledge (foreground) generated in the framework of the project as a result of a cooperative activity, is jointly owned by the members contributing to this knowledge. For joint ownership a default regime will facilitate the exploitation of jointly owned results in the absence of a clear agreement between parties.
- The Intellectual Property Right (IPR) regarding any new knowledge (foreground) generated in the framework of the project by each partner, is owned by the member that developed this knowledge.

Tools to manage IPR

The management of the Intellectual Property Rights will be considered within the Dissemination and exploitation WP and will consequently be under the responsibility of the ESC.

The Project will use a tool tailored to suit between others also the Intellectual Property management needs of the Consortium. This tool will be hosted in the project web site in a restricted access area.

B4. Ethical issues

ETHICAL ISSUES TABLE

	YES	PAGE
Informed Consent		
• Does the proposal involve children?		
• Does the proposal involve patients or persons not able to give consent?		
• Does the proposal involve adult healthy volunteers?		
• Does the proposal involve Human Genetic Material?		
• Does the proposal involve Human biological samples?	X	39-42
• Does the proposal involve Human data collection?	X	39-59
Research on Human embryo/foetus		
• Does the proposal involve Human Embryos?		
• Does the proposal involve Human Foetal Tissue / Cells?		
• Does the proposal involve Human Embryonic Stem Cells?		
Privacy		
• Does the proposal involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)	X	39-42
• Does the proposal involve tracking the location or observation of people?		
Research on Animals		
• Does the proposal involve research on animals?		
• Are those animals transgenic small laboratory animals?		
• Are those animals transgenic farm animals?		
• Are those animals cloning farm animals?		
• Are those animals non-human primates?		
Research Involving Developing Countries		
• Use of local resources (genetic, animal, plant etc)		
• Benefit to local community (capacity building ie access to healthcare, education etc)		
Dual Use		
• Research having potential military / terrorist application		
I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL		

Ethical, legal, social and safety issues that may be raised by the subject and activities of the proposal.

The EVINCI-study project raises ethical issues due to the involvement in research of human beings and collection of human biological samples. This research is highly sensitive to what is considered to be the ethical use of human beings and human biological samples by the scientific community and confidentiality issues with specific reference to information on patients.

The research and clinical service must also be carried out in accordance with the relevant guidelines and legislations. In addition to this, however, both the science and the clinical service must be founded on high ethical standards and take into account the good empirical evidence of the psychosocial aspects of clinical interventions.

National regulations and international codes of conduct

NATIONAL LEGISLATION

The research programme will be conducted in accordance with any relevant local or national rules and regulations of the country where the research shall be carried out and subject, as appropriate, to prior authorization of the project by competent research ethics or medico-ethical committee(s) of that country. For those of the partners who have not already obtained relevant authorization or opinion of local ethics committees, copies of authorization will be submitted to the Commission prior to the commencement of the relevant part of the research project.

Italy

- Law n.675 of 31 December 1996 Tutela delle persone e di altri soggetti rispetto al trattamento dei dati personali (published on the G.U. n.5 of8 January 1996
- C. M. n. 6 of 2 September 2002 , Attività dei comitati etici istituiti ai sensi del decreto ministeriale 18 marzo 1998. (published on the G.U. n. 214 of 12 September 2002)
- D.I.S.S. of 26 April 2002, Accertamento della composizione e innocuità dei farmaci di nuova istituzione prima della sperimentazione clinica sull'uomo. Individuazione della documentazione da sottoporre all'Istituto superiore di sanità ai sensi dell'art. 4, comma 2, del decreto del Presidente della Repubblica 21 settembre 2001, n. 439.
- D.P.R. n. 439 of 21 September 2001, Regolamento di semplificazione delle procedure per la verifica e il controllo di nuovi sistemi e protocolli terapeutici sperimentali
- D.M. of 23 November 1999, Composizione e determinazione delle funzioni del Comitato Etico nazionale per le sperimentazioni cliniche dei medicinali, ai sensi del decreto legislativo n. 220 del 19 giugno 1999
- D.M. of 18 March 1998, Decreto Ministeriale 18 marzo 1998 relativo alle Linee guida di riferimento per l'istituzione e il funzionamento dei Comitati etici (published on the G.U. n. 122 of 28 May 1998)
- D.M. of 18 March 1998, Decreto Ministeriale 18 marzo 1998, recante modalità per l’esenzione dagli accertamenti, di cui al Decreto del Presidente della Repubblica n°754 del 21 settembre 1994, sui medicinali utilizzati nelle sperimentazioni cliniche (published on the G.U. n. 122 of 28 May 1998)
- D.M. of 15 July 1997, Recepimento delle linee guida della U. E. di Buona Pratica Clinica per l’esecuzione delle sperimentazioni cliniche dei medicinali
- Regional Law of Lombardy, 20 June 1975 n. 97.

France

- Use of Personal data (loi informatique et liberté, article 10)

- Bioethics (loi de bioétique de 1994,articles 162-16)

United Kingdom

- The Human rights Act 1998
- The Data Protection Act 1998
- The Home Office The Animals (Scientific procedures) Act 1986
- The protection and Use of Patient information Department of Health 1996
- The Human tissue act 1961

The Netherlands

- Code of Practice welzijnsbewaking van proefdieren. Keuringsdienst van Waren 2000

Germany

- Paragraph 15, Berufsordnung der Ärtzekammer Westfalen Lippe vom 25. November 2000.Or translated: vocational regulations of the General Medical Council Westfalen Lippe, 25th of November 2000.
- Bundesdatenschutzgesetz 1990, last change 23. May 2001. The national German law provides protection for data on patients.

Spain

- Ley Organica 25/1990 de 20 de Diciembre (BOE n. 305 y 306 de 21 y 22 de Diciembre de 1990, "Ley del Medicamento";
- Real Decreto 561/1993 de 16 de Abril (BOE n. 114 de 13 de Mayo de 1993) "Requisitos para la realizacion de ensayos clinicos con medicamentos".
- Real Decreto 994/1999, de 11 de junio, Reglamento de medidas de seguridad de los ficheros automatizados que contengan datos personales, Ley Orgánica 15/1999, de 13 de diciembre, “Protección de datos de carácter personal”(BOE n. 298 de 14 de Diciembre de 1999)
- Ley 8/2001, de 13 de julio, Protección de datos de carácter personal en la comunidad de Madrid
- Real Decreto 951/1997 de 20 de Junio, por el que se desarrolla la ley 15/1994;
-

Finland

- *Act on the Status and Rights of Patients (785/1992, amendment 333/1998) established at the beginning of April, 1998 by the National Advisory Board on Health Care Ethics*
- Checklist for researchers and members of ethics committees National Advisory Board on Health Care Ethics (ETENE) Sub-Committee on Medical Research Ethics (14.5.2001)
- Guidelines by the sub-committee on medical research ethics: patient information and consent forms related to DNA samples taken in connection with pharmaceutical research (4 September 2000)
- Law (488/99) and regulation (986/99) on medical research
- Patient accident law (585/86)
- Personal register law (471/87)
- Personal register regulation (476/87)

Poland

- Polish Act on the protection of personal data published on 29th of August 1997 (Official Journal n.133, position 883) and successive modifications
- Polish Act on the Medical Profession published on 9th of December 1996 (Official Journal n. 28, position 152).

Switzerland

- Loi sur la Santé Publique from the 29th of May, 1985
- Loi Fédérale sur la Protection des Données of June 1992

EU LEGISLATIONS

Participants in the proposed EVINCI-study will conform to the relevant EU legislation, such as:

- the **EU Charter of Fundamental Rights**;
- **Directive 2001/20/EC** of the **European Parliament and of the Council of 4 April 2001** on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;
- **Directive 95/46/EC** of the European Parliament and of the council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data;
- **Commission Decision** on standard contractual clauses for the transfer of personal data to third countries, under Directive 95/46/EC - 15.06.01 (2001/497/EC)
- **Council Directive 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC** on the approximation laid down by law, regulation or administrative action relating to proprietary medicinal products;
- **Directive 98/44/EC** of the European Parliament and of the council of 6 July 1998 on the legal protection of biotechnology inventions;

INTERNATIONAL CONVENTIONS AND DECLARATIONS

- **Helsinki Declaration** (adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964; amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical Assembly, Venice, Italy, October 1983; the 41st World Medical Assembly Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000);
- **Convention for the Protection of Human Rights and Dignity of the Human Being** with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine, Oviedo, April 4th 1997);
- **Additional Protocol to the Convention for the Protection of Human Rights** and Dignity of the Human Being with regards to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings (signed in Paris, 12 January 1998);
- **UN convention on the Rights of the Child**;
- **Universal Declaration on the human genome and human rights adopted by UNESCO**;
- **Opinion N. 2 of the European Group on Ethics in Science and New Technologies of 12 March 1993 on Products derived from human blood or human plasma**;
- **Opinion n. 3 of the European Group on Ethics in Science and New Technologies of 30 September 1993 on ethical questions arising from the commission proposal for a Council directive for legal protection of biotechnological inventions**;
- **Opinion n. 4 of the European Group on Ethics in Science and New Technologies of 13 December 1994** on the ethical implications of gene therapy;
- **Opinion n. 7 of the European Group on Ethics in Science and New Technologies of 21 May 1996** on Ethical aspects of genetic modification of animals;
- **Opinion n. 8 of the European Group on Ethics in Science and New Technologies of 25 September 1996 on ethical aspects of patenting inventions involving elements of human origin**
- Recommendations of the **European Group on Ethics in Science and New Technologies** in their **Opinion No. 11** of 21 July 1998 on Ethical Aspects of Human Tissue Banking;

- principles expressed in the **Communication** from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the Regions **"Life sciences and biotechnology – a Strategy for Europe [COM(2002)27 final]** will be observed;
- **Directive 86/609/EEC related to animal experiments.**

INFORMED CONSENT

The Consortium has prepared a draft informed consent form (see Appendix A) that will be translated and enclosed in the Applications to the Local Ethical Committees. After local approval by the Ethical Committees and central validation by the EVINCI Programme Steering Committee the Informed Consent will be used in all the clinical centres participating into the project.

Fully informed valid consent will be obtained from all patients participating to the study. Participants will not be subject to any invasive procedures specifically designed to provide information for this project, except that of drawing venous blood samples and performing evaluation of early atherosclerotic and functional coronary abnormalities (by intravascular US and measurement of coronary flow reserve by intracoronary Doppler wire) in patients showing minor coronary lesions (as a substudy, in selected centres which commonly use this approach, see below).

Approval for protocols involved in this project will be sought both at the coordinating institution ethical committee for the protocol as a whole, as well as at the ethical committees of each partner unit. The coordinating centre CNR has experience of coordinating ethics approvals from multiple institutions. No one's medical treatment is being compromised and participants know that they can withdraw or refuse their participation without this affecting their treatment in any way**.**

The Ethical sensitive issues involved in the EVINCI-study are detailed below and discussed.

Human biological samples

Patients fulfilling inclusion and exclusion criteria, after giving informed consent, will be officially enrolled into the study after connecting through Internet to the Central Server and receiving an ID number which will anonymously identify the patient throughout the Consortium. Blood samples will be then obtained and in part locally processed to provide relevant clinical information for the single patient and in part shipped for central analysis (to P1-IFC-CNR) after labelling with the same ID number without any reference to the actual patient's name.

Main biohumoral variables that will be centrally measured and included in the EVINCI-study data base are listed below.

Type	Amount	Source	Target Parameters
BLOOD (serum, plasma)	40 ml	Venous Blood Samples	**- Lipid profile:** total cholesterol, triglycerides, HDL, Apolipoprotein A1, B, lipoprotein (a) **- Glicidic profile:** glucose, HbA1, insulin **- Inflammatory profile:** C-reactive protein, Interleukin-6. **- Markers of CV**

			damage: adhesion molecules, NT-pro-CNP, endothelin-1, osteopontin, NT-proBNP, Heat Shock Proteins (HO-1, HSP72), leptin and adiponectin

Human data collection

The new knowledge to be generated in EVINCI-study is expected to significantly contribute to improved prevention and treatment of Ischemic Heart Disease (IHD). The risks, discomfort and inconvenience to participants are very limited, considering that the design of the study follows a typical diagnostic work-up in patients with suspected IHD. Also, based on the extensive experience present within the partnership in the diagnosis and treatment of IHD, it is considered highly unlikely that participation would cause significant anxiety on the part of patients and/or relatives.

The functional imaging protocols

Patients will be submitted to non-invasive imaging stress tests commonly utilized in the EVINCI Participating Centres for non-invasive evaluation of suspected IHD. Standardized stressors and "state of the art" examinations and analyses will be used to ensure the best clinical quality of the results.
Specifically, the first 2 months of the study will be dedicated to the standardization of imaging/data acquisition and analysis protocols. Standardization will be pursued by consensus meetings chaired by the coordinator of the project and by the coordinators of core-labs for each imaging modality, who include several European opinion leaders. The acquisition protocols and the data analyses considered to have the highest accuracy for each modality will be chosen. Moreover, a quality control will be performed throughout the study allowing validation of all sites and core-labs for appropriateness of imaging protocols, data acquisition and analysis.

Minimization of radiation exposure in each individual case

Since some examinations in the common diagnostic work-up of a patient with suspected IHD include radiation exposure, the minimization of the radiation dose to the patient to obtain an accurate diagnosis is one of the goals of the EVINCI-study. The strategies to minimise radiation exposure throughout the protocol will be manifold, will be standardized in the first phase of the project and are summarized below.
1. Appropriate guidelines will be followed (i.e. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology).
2. After a recognition of the CT scanners available in each centre, it will be recommended to implement adequate software to reduce patient radiation exposure before starting the project.
3. In centres where both PET and SPECT are available it will be recommended to use PET for the majority of perfusion studies due to the fivefold less radiation exposure of this method as compared to SPECT.
4. When SPECT will be used , specific protocols will be applied to reduce the dose to the patient.

5. During the diagnostic work up the actual exposure of each patient will be registered for each test, when appropriate, in order to monitor the cumulative exposure to be kept below a predefined maximum.
6. Exclusion criteria will be applied to minimize the radiation risk (young women before the age of 50 years; young men before the age of 40 years; patients already submitted to other tests implying significant radiation exposure in the same year).

Intravascular US and measurement of coronary flow reserve by intracoronary Doppler wire

Patients enrolled in the EVINCI Study will be submitted to standard cardiac catheterization and wherever appropriate to measurement of Fractional Flow Reserve to detect the presence of hemodynamically significant coronary stenosis according to current methods and guidelines (ESC Guidelines on the management of stable angina pectoris, Eur Heart J, 2006).

During the catheterization procedure additional evaluation by intravascular US (IVUS) and measurement of coronary flow reserve (CFR) by intracoronary Doppler will be performed in those patients without significant coronary stenoses at standard evaluation. This additional procedure is not standard in some centers. Accordingly, it will be limited only to patients enrolled in those selected centres which commonly use this approach (as a substudy) and will be specifically mentioned in the informed consent. In these patients, IVUS and intracoronary Doppler investigation will be performed only in the presence of <30% coronary stenoses or apparently normal coronary arteries at angiography and only in the left anterior descending artery. The purpose of this procedure is to detect the presence and the functional relevance of early atherosclerosis and of microvascular dysfunction. These abnormalities are a recognized cause of symptoms and function/perfusion stress induced defects. As a matter of fact up to 36% of angiographically normal vessels may show reduced CFR. Patients with abnormal CFR due to early coronary atherosclerosis or microvascular dysfunction, documented by IVUS and Doppler flow wire, show a worse prognosis and deserve medical treatment and careful follow-up.

Every possible effort is performed to standardise the clinical decision making

It is important to emphasize that participation to the EVINCI Study does not imply any change in clinical decision making regarding the treatment of enrolled patients. In each individual patient the treatment will be optimized according to the “best clinical practice” and based on international guidelines (ESC Guidelines on the management of stable angina pectoris, Eur Heart J, 2006). The choice of treatment for a particular patient will therefore remain in the full responsibility of the local physician who could take into account all the information produced in the context of this study.
Moreover, at each step of the protocol the patient and his referring physician will receive by the local operators standard clinical reports of the performed examinations. In the case of incidental findings which preclude the fulfilment of the protocol or indicate a different clinical decision making, the patient will be managed according to good clinical practise and will be censored up to the time of the recognition of the specific condition.
Patients will be enrolled according to intermediate pre-test probability of IHD as defined after clinical evaluation and ECG exercise test. Thus, the first part of the diagnostic work-up will follow current diagnostic guidelines where patients with intermediate pre-test probability of IHD after a complete clinical evaluation, undergo an ECG exercise stress test (whenever feasible). Patients still showing intermediate probability of IHD after the exercise stress test will be enrolled into the EVINCI Study. Using these criteria and according to guidelines (ESC Guidelines on the management of stable angina pectoris, Eur Heart J, 2006)) non-invasive imaging is indicated and

even direct invasive coronary evaluation is acceptable also in the absence of non-invasive imaging testing (as often clinically performed throughout Europe). The referring physician will choose the first non-invasive test among those included in the EVINCI-study. Each patient will undergo two additional non invasive tests independently from the results of the first test. Additional non-invasive tests could be still indicated by current guidelines in the case of inconsistency of the results of the first test. In the other cases they will be performed "for research purposes" as will be clearly stated in the informed consent.
The most important clinical decision after coronary arteriography regards coronary revascularization. This process will be under the responsibility of the clinician according to international Guidelines. Particularly, decisions have to be made on whether coronary revascularization is indicated or not, which lesion has to be treated, the feasibility of coronary revascularization and the ideal method (surgical or percutaneous). In the case of severe lesions (visually estimated to exceed 70% of luminal diameter) coronary revascularization is considered to be indicated, provided that the revascularization is feasible, that the risk area is not trivial and that the downstream myocardium is viable. In the case of intermediate lesions (visually estimated 30-70% of luminal diameter) the hemodynamic significance of the stenosis will be also assessed invasively using pressure wire method and FFR calculation. In the EVINCI-study protocol FFR estimation is encouraged (unless technically unfeasible) in all vessels with stenoses above 30%. According to the literature, FFR measurement has been shown to be useful in differentiating between patients with favourable long-term outcome (i.e. patients with FFR>0.75) who do not need revascularization and patients who require early revascularization (i.e. patients with FFR<0.75) (Legalery P, et al. Eur Heart J 2005;26:2623-2629). This approach could meet one of the goals of the project, that is to evaluate the performance of different non invasive tests in identifying hemodynamically significant coronary lesions as assessed by FFR, the golden standard. The indication to coronary revascularization will be the presence of angina or anginal equivalent symptoms, the occurrence of myocardial ischemia and of lesion significance obtained invasively by FFR as indicated in current guidelines (ESC Guidelines on the management of stable angina pectoris, Eur Heart J, 2006).
It is clearly stated in the protocol that treatment strategies will be under the responsibility of the referring physician who could use all the data available. Clinicians will be strongly encouraged to revascularize hemodynamically significant stenoses as assessed during the invasive study. To facilitate the decision process all intermediate lesions will be evaluated by FFR by protocol but the cath operator could also extend FFR evaluation to >= 75% stenoses or apply IVUS investigation to >=30% stenoses if clinically useful.

DATA PROTECTION AND PRIVACY

The project activity will be carried on in respect of the following principles:
1. status of personal health data:

- The EVINCI-study activity takes into account the principle that personal health data form part of the personality of the individual, and must not be treated as mere objects of research interest;

2. confidentiality / privacy:

- during the EVINCI-study the collection of, and access to, personal health data is limited to treating medical practitioners and to those third parties (non-treating medical practitioners, healthcare and social security personnel, administrators) who can demonstrate a legitimate use;
- an informed consent of the individual is required for the collection and release of personnel health data. All legitimate users of personal health data have a duty of confidentiality equivalent to the professional duty of medical secrecy. Exceptions to this duty must be limited and provided for by legal rule;

- the EVINCI-study consortium comply with the principle that the respect for the confidentiality of health data continues after the death of the person;

3. self-determination:

- health data will be collected directly from the patient wherever possible;
- self-determination includes patients' right to know and to determine which personal health data are collected and recorded, to know who uses them for what purposes, and to correct data if necessary;
- the patient has the right to oppose, the use of her/his data for secondary purposes not provided for by law;

4. accountability:

- the networking of health institutions fosters new kinds of dependencies and responsibilities. This has to be reflected in new kinds of accountability;
- for all partners using health data an equivalent to the accountability of health professionals should be established;
- when health managers use health data for the purposes of health services planning and management, they should be accountable for such data uses;

5. principle of legitimate purpose:

- the principle of a strict relationship between the collection and processing of personal health data and handling and the legitimate purpose to which those data are used guides the collection of data;
- third parties, who do not form part of the public health system may require, during the EVINCI-study, access to medical information for their professional purposes, such as insurers and employers. Such third parties must in no case have direct access to personal health data;

6. security:

- the security of clinical, biological and imaging data in healthcare is an ethical imperative to ensure the respect for human rights and freedoms of the individual, in particular the confidentiality of data and the reliability of technological systems used;
- the respect for security will be insured in the EVINCI-study by the use of encryption technology where appropriate, anonimization of patient data within the Consortium and the use of closed networks for the transfer of personal health data and organizational measures to support security according to European security standards;
- since medicine is a safety ethical environment, exchange of clinical, biological and imaging data during the EVINCI-study, will be rigorously monitored;

7. participation:

- the EVINCI-study project activity will be carried on in a way that respects the principle that the right to participate in the medical decision-making process is a key part of the notion of the patient as a stakeholder.
- the patient will have access to his/her electronic health record.

8. transparency:

- standardization is inherent in clinical, biological and imaging data acquisition increasingly in the healthcare sector where classification and coding (clinical protocols, diagnostic related code, checklists,…) are in widespread use. As these standards are not neutral, but embody value-related choices, they will be transparent and may be subject to evaluation by independent bodies (for example ethical committees, patients' organizations, professional associations);

9. education and training:

- In order to make the right of self-determination effective, healthcare professionals will inform patients of their rights without a direct request for such information.

Confidentiality

Confidentiality of patient data are preserved, according to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data and to any relevant national regulation. The coordinator will implement the research project in full respect of the legal and ethical national requirements and code of practice.

The participant names and any other information, which might identify them, will not be available to any person or group other than the clinicians of the centre who referred the patients who have direct contact to them and will not appear in any presentation or publication resulting from this study. All clinical information will be kept in secure computer files protected by passwords and accessible only to the researchers involved in the study.

The biological samples obtained from the patients will be coded and deprived of the patient identity and there will be no link, whatsoever, between the patient and the biological sample taken for the research.
The structure of the database will be such that the anonymity of the individual is preserved through the use of number-letter code identifiers. The coded clinical data are stored in a secure data bank at each clinical centre, which is password-protected and is not accessible across the network.
No data is stored that directly identify a respective patient (name, initials, birthdate). Only the personnel involved at each clinical centre can access the decoding sheet. Thus, files used for analysis of data by the partners will not include information that could be used to identify specific individuals. Only the contributing center can identify a specific patient and up-date clinical follow-up with respect to seizure outcome.
There is no commercial exploitation of the samples. In publications, the patient code will be used to label the result source.
All the data generated from the EVINCI-Study and Data-Banks will be preserved for at least ten years.

LOCAL ETHICAL COMMITTEES' OPINIONS AND AUTHORIZATIONS OF COMPETENT BODIES

The partners implement the research project in full respect of the legal and ethical national requirements and codes of practice.
The protocol proposed in the project and any successive modification will be reviewed and approved by the relevant Ethical Committees prior to commencement of the project activities.
As pre-requisite to obtain the Ethical Committees'approval, insurance coverage is assured by the recruiting centres for the participants to the study.
Copies of all relevant authorizations shall be submitted to the Commission prior to commencement of the relevant part of the research project.

The table below provides an overview of the ethical approvals needed for each contractor.

Contractor	Human beings	Human biological samples (including DNA)	Personal data collection	Comments
P1-CNR	Yes	Yes	Yes	Approval should be obtained from the local Ethical Committee. The competent Ethical Committee in Pisa is Comitato Etico Sperimentazione Farmaco (CESF) Azienda Ospedaliero-Universitaria Pisana. Chair: Prof. Romano DANESI **(**Professore Straordinario di Farmacologia Medica). Scientific Secretary: Dr. Diego Carignani. Administrative Secretary: Dr.ssa Franca Cossu. Via Roma 67, Pisa. Phone +39 050 996392 (397-247-287). Telefax: +39 050 996293. Homepage: http://www.ao-pisa.toscana.it/tutela_citt/comit_etico.htm The procedures will follow the rules stated in the "Regolamento del Comitato Etico dell' Azienda Ospedaliero-Universitaria Pisana" (N.492, May, 7th 2004). Submission of the study protocol is ongoing.
P2-U.Turku	Yes	Yes	Yes	The Ethics Committee of Southwest Finland Healthcare District has approved comparable study (Dnro 138/2006 and amendment 150/2008). The approval document of the Southwest Finland Healthcare District Ethics Committee is in Annex A.
P3-UZH	Yes	Yes	Yes	Approval should be obtained from the local Ethical Committee. UZH has a 2-step ethics committee. The first one is from the University Hospital Zurich, where the ethics committees are split according to the discipline. The relevant one is "SPUK ZH Spezialfächer" which

				works on it and after approval sends this to the ethics committee of the Regional authorities; a Region in Switzerland is called "Kanton", and therefore this ethics committee is called "Kantonale EhtikKommission" with the abbreviation "KEK". The KEK gets all applications from the more specialised committees of the different disciplines and takes a final decision. A study can only start when approval is given by this KEK (this OK is called a "nihil obstat") UZH has to apply with a an application form (see attached file "SPUK Basisformular" in Annex A) and add the full protocol on a separate file/printout. A similar protocol is ongoing, included in Annex, where each patient who gets for clinical reasons an invasive cath will also undergo a SPECT and a CT-angiography In Annex an application form for the first step is also provided.
P4 LUMC	Yes	Yes	Yes	Approval should be obtained from the local Ethical Committee.
P6-IR-HSCSP	Not applicable	Not applicable	Yes	Approval should be obtained from the local Ethical Committee (Comité Etico de Investigación Clínica HSCSP). The details on the procedures and requirements for approval provided in a document in Annex A include the timing for receipt of documents; the documents to be presented and number of copies; protocols for post-approval observation studies; changes relevant to the protocol; other clinical investigation projects.
P7-NIC	Yes	Yes	Yes	Approval should be obtained from the local Ethical Committee: Terenowa Komisja Bioetyczna, przy Instytucie Kardiologii, im. Prymasa Tysiaclecia Stefana Kardynala Wyszynskiego ul. Alpejska 42, 04-628 Warszawa, Poland Submission of the study protocol is ongoing. Additional information needed for informed consent is a short and very clear description of each procedure to be performed in the patient. The description of each procedure must contain the following explanation: - how the procedure is performed (how long it lasts, what is invasive, what is unpleasant, what is the preparation of the

				patient before the study, and what are the indications after the study) - what is a radiation dose from each relevant study, how it relates to background radiation per year, and how it influences the probability of the cancer in the future - why the procedure is performed (the goal of the procedure per se and the goal for the EVINCI study) (In case of the center the procedures will be: Blood sample drawing; Stress test; Exercise SPECT; Dobutamine stress ECHO; CTA; CA; FFR; CFR+IVUS). Also, the information about insurance protection of the patient must be given. The procedure to obtain the approval for the study from the ethical committee demands (the most important points): study protocol; flow-chart; CRF (recommended); Information for the patient (comp. 2a above) – in Polish
P8-RBHT	Yes	Yes	Yes	Approval should be obtained from the Brompton Harefield & NHLI Research Ethics Committee. Submission of the study protocol is ongoing. The study is registered with the local R&D office before submittion of the application to the Ethics Committee. Application is made using the new standard application form, available from the National Research Ethics Service (NRES).
P9-AP-HP	Yes	Yes	Yes	Submission of the study protocol to the local ethical committee (Comité de Protection des Personnes Ile-de-France VI, Hôpital Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75013 Paris, France) is ongoing.
P10-UniGE	Yes	Yes	Yes	According to the policy of the Hospital (the unit is part of a larger Research Hospital campus) all procedures that are not justified by clinical need according to the referring physicians have to be approved by the Hospital Ethical Committee. A protocol related to the application of myocardial perfusion imaging and CT coronary angiography is ongoing for patients admitted to the emergency Dept. for chest pain.
P11-SERMAS	Yes	Yes	Yes	The project is being evaluated by the Hospital Ethical Committee and final approval is pending. Informed consent and economic details are needed for the

				final approval.
P12-UniNA	Yes	Yes	Yes	Approval should be obtained from the local Ethical Committee (Comitato Etico, Università Federico II di Napoli, Italia) Submission will be forwarded once a formal and complete protocol is ready.
P13-HUVHEBRON	Yes	Yes	Yes	Approval should be obtained from the local Ethical Committee (Comite Etic Investigació Clínica. Hospital Universitari Vall d'Hebron. Barcelona). Submission of the study protocol is ongoing.
P14-ESC	Not Applicable	Not Applicable	Not Applicable	Not Applicable
P15-INF	Not Applicable	Not Applicable	Not Applicable	Not Applicable
P16-CFc	Not Applicable	Not Applicable	Not Applicable	Not Applicable
P17-FGM	Yes	Yes	Yes	Approval should be obtained from the local Ethical Committee. The competent Ethical Committee in Pisa is Comitato Etico Sperimentazione Farmaco (CESF) Azienda Ospedaliero-Universitaria Pisana. Chair: Prof. Romano DANESI **(**Professore Straordinario di Farmacologia Medica). Scientific Secretary: Dr. Diego Carignani. Administrative Secretary: Dr.ssa Franca Cossu. Via Roma 67, Pisa. Phone +39 050 996392 (397-247-287). Telefax: +39 050 996293. Homepage: http://www.ao-pisa.toscana.it/tutela_citt/comit_etico.htm The procedures will follow the rules stated in the "Regolamento del Comitato Etico dell' Azienda Ospedaliero-Universitaria Pisana" (N.492, May, 7th 2004). Submission of the study protocol is ongoing.
P18-KRITUM	Yes	Yes	Yes	Approval should be obtained from the local Ethical Committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München). Chair: Prof. Dr. Albert Schömig Ismaninger Straße 22 81675 München. Telefon: (089) 4140-4371 Telefax: (089) 4140-4199. Email: info@ek.med.tum.de. Homepage: http://www.ek.med.tum.de
P19-QMUL	Yes	Yes	Yes	Approval should be obtained by the East London REC 1 Room 24 second floor Burdett House, Mile End Hospital, Bancroft Road, London E1 4DG Tel: +44 02089265025

				Fax: +44 2089265009 Contact person: Sandra Burke The documents below needed for submission. The committee members meet and decide. The decision is confirmed via a letter. It usually takes 2 months from submission to the letter. Its is common to receive a letter with questions and clarifications. Again, it takes a while (a couple more months) until you compose your answers and get a reply from REC. Documents: 1) Covering letter on headed paper; 2) REC application; 3)Research protocol (6 copies); 4) Summary CV for Chief Investigator; 5) Research participant information sheet, (PIS); 6) Letters of invitation to participants; 7) GP/Consultant information letters; 8) Statement of indemnity arrangements; 9) Letter from sponsor; 10) Research participant consent form; 11) Letter from funder; 12) Referees or other scientific critique report
P20 AOUC	Yes	Yes	Yes	Approval should be obtained by the Comitato Etico Locale Via delle Oblate 1, 50141 Firenze (Italy)
P21 Ospedale Versilia	Yes	Yes	Yes	Comitato Etico Locale dell'Azineda U.S.L N. 12 di Viareggio Via Aurelia 335, 55041 Lido di Camaiore Phone: +39 0584 605 9418/7121 Lorenzo Bertoli
P22 KAE	Yes	Yes	Yes	Approval should be obtained by the Ethik-Kommission, Landesärztekammer Baden-Württemberg Jahnstr. 40, 70597 Stuttgart Tel.: 0711 / 7 69 89 60 Fax: 0711 / 7 69 89 856 Contact: Patricia Hager patricia.hager@laek-bw.de; Petra.Knupfer@laek-bw.de

The Programme Steering Committee (PSC), in accordance with laws and regulations of the involved countries, overviews that all partners have obtained the relevant authorizations before the start of the relevant project activities, reviews the final protocol and the informed consent form. The Investigators must submit this protocol to the PSC. On the approval/advice sheet, the trial (title, protocol number, acronym, version and date), the document studied (protocol, informed consent material, CRF, SOPs, Investigator Brochure) and the date of the review are clearly stated.
In order to monitor ethical issues, a specific section dedicated to ethical issues will be included in the agenda of each Steering Committee's meetings.

B5. Gender aspects

The Consortium is aware of the fact that sex and gender differences are fundamental features of life and society; recognising these differences has important implications for scientific knowledge.
The Consortium will ensure that gender-related and other differences will be taken into account; the Consortium also aims at improving the understanding of gender issues in science and at sustaining gender equality in science, according to the Commission policies, in particular in line with the (COM (1999) 76)" *Women and Science: mobilising women to enrich European Research*".
It is also important to underline that in some European countries there are still some differences between the career opportunities of women and men. The consortium thinks that women should have the same career opportunities of men. Currently 3 partners have a woman as Principal Investigator.
The policy of the consortium, based on the respect of the gender equality issues, will be followed during the whole project duration.
To achieve this goal, the project will implement an action plan (Gender Action Plan, GAP), which will focus on: the career paths of women and men (including longitudinal analyses), the working culture and existing practices in the recruitment and employment of scientists, the highlighting areas of potential bias, and the establishment of guidelines of good practice.

Our action plan will consist of two main type of action to be undertaken:
1) Actions to encourage women's participation and to promote female occupation in the project management structure. This will be pursued through:

- encouraging women's participation in the proposed project within the consultation, decision and implementation processes, giving equal resources and possibilities at every level. For example, gender balance will be a key point in the composition of the Advisory Board, by having selected a woman candidate.
- special actions to permit the access of a balanced number of women and men in the future implementation of the project.
- encouraging women's participation in mobility actions, applying in the frame of the project;
- ensuring the integration of programmes targeted at women returners to accommodate their re-entry to careers on an equal basis of competitiveness with men after a period at home with childcare responsibilities.

2) Actions to increase awareness of gender issues. This will be pursued through the development of 'best practice' policies in the recruitment and employment of scientists within the project.