Consiglio Nazionale delle Ricerche

La Fabbrica del Futuro

Progetto Bandiera
"La Fabbrica del Futuro
Piattaforma Manifatturiera Nazionale"

Sottoprogetto 2
Annex B
Format for Project Proposals

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1. General Information

1.1. Cover Page

Proposal full title:
Hospital Factory for Manufacturing Customized, Patient Specific 3D Anatomo-Functional Model and Prostheses

Proposal acronym:
Fab@Hospital

Title of the *Call Topic* the proposal aims to answer:
Methodologies for the joint design of customized products, processes and production systems (metodologie per la progettazione congiunta di prodotti personalizzati, processi e sistemi produttivi).

Code of the *Call Topic* the proposal aims to answer:
1.1

ERC sectors of reference:
PE8_10 Production technology, process engineering
SH1_9 Organization studies, strategy
LS7_1 Medical engineering and technology
PE8_14Industrial bioengineering

Name of the coordinating Institute:
Istituto di Matematica Applicata e Tecnologie Informatiche "Enrico Magenes" (IMATI), Consiglio Nazionale delle Ricerche (CNR)

Director of the coordinating Institute:
Annalisa Buffa

Address of the coordinating Institute:
CNR IMATI (Milan Department)
Via Bassini 15
20133 Milan, Italy

E-mail address of the Director of the coordinating Institute (PEC-Posta Elettronica Certificata)[1]:
protocollo.imati@pec.cnr.it

Name of the scientific project coordinator:
Ettore Lanzarone

E-mail address of the scientific project coordinator:
ettore@mi.imati.cnr.it

[1] This e-mail address will be used for all official communications related to the project.

1.2. List of partners

No.	Name of the Partner	Typology of the Partner	Postal address	Name of the scientific responsible	E-mail address of the scientific responsible
P1	CNR-IMATI	CNR	Via Bassini 15, 20133 Milan, Italy	Ettore Lanzarone	ettore@mi.imati.cnr.it
P2	CNR-ITIA	CNR	Via Bassini 15, 20133 Milan, Italy	Giacomo Copani	giacomo.copani@itia.cnr.it
P3	UNIPV	University	Via Ferrata 3, 27100 Pavia, Italy	Ferdinando Auricchio	auricchio@unipv.it

The typology of the Partner can be “CNR”, “University”, “Other public research institutions”.

1.3. Industrial interest group

Besides the list of research institutes proposers must list the composition of the industrial group interested in the project. Each company will have to submit a letter of intent signed by the company responsible person.

No.	Name of the industrial interest group member	Postal address	Name of contact person	E-mail address of contact person
I1	OVERMACH SpA	Via Giuseppe Righi 12, z.i. Moletolo, 43122 Parma, Italy	Giacomo Cacciani	giacomo.cacciani@overmach.it
I2	Sarix SA	Via Ai Molini 22, C.P.621 CH 6616 Losone	Franck Leleu	franck.leleu@sarix.com
I3	I.R.C.C.S. Policlinico San Donato	Via Morandi 30, San Donato Milanese (MI), Italy	Santi Trimarchi	santi.trimarchi@grupposandonato.it
I4	I.R.C.C.S. Policlinico San Matteo	V.le Camillo Golgi 19, 27100 Pavia, Italy	Andrea Pietrabissa	a.pietrabissa@smatteo.pv.it
I5	Azienda USL della Valle d'Aosta	Via Guido Rey 1, 11100 Aosta, Italy	Raffaella Pagano	rpagano@ausl.vda.it

1.4. Project abstract (maximum 1000 characters including spaces)

The fabrication of personalized prostheses tailored on each patient is one of the major needs and key issues for the future of the several surgical specialities. Moreover, the production of patient specific anatomo-functional models for pre-operative planning is an important requirement in the presence of such tailored prostheses, as also the surgical treatment has to be optimized for each patient.
The presence of a prototyping service internal to the hospital would be an added value for the clinical activity, and its location inside the hospital allows closer interactions with clinicians, leading to significant time and costs reduction.
At present, no such services are active in Italy and are extremely rare worldwide.
The Project investigates enhanced methods and technologies required for implementing such service. Moreover, the Project analyses the sustainability of the service and, thanks to a demonstration activity, shows the real applicability of the idea and the results.

2. Project description

2.1. Concept and objectives

The "Grand Challenges", defined by the European Commission and the "Europe 2020 strategy" proposed in order to meet them, require breakthrough multi-disciplinary innovation in several societal and industrial domains. This is particularly true for the European system of the healthcare structures and of all the companies producing products and services that allow the accomplishment of their mission.

Ageing population is one of the "Grand Challenges" that Europe must face. The significant increase of life time expectation that was possible in the last decades due to the progress of medical sciences (Geriatric Healthcare Statistics: Demography of Aging www.americangeriatrics.org/press/reporter_resources/statistics) generated, as a counterpart, the need for a higher service demand to the healthcare systems, since elderly people generally need more intensive medical assistance. In addition, the modern possibilities to save patients' life in many severe type of diseases, such as for example cardiovascular and neurological pathologies, generated a new class of customers, not necessarily of advanced age, that need specific and highly qualified treatments to be able to be included in the social system, for example being part of the active employed population (the need of social inclusion is one of the priorities of "Europe 2020 strategy").

This new demand of more intensive and advanced healthcare services is clearly in contrast with the general pressure to reduce the cost of healthcare systems in the European countries, due to national financial sustainability reasons. Consequently, Europe must find new innovative models to solve this paradox in order to continue guaranteeing the growth of social and health conditions of its citizens. These models should break the usual boundaries of the existing healthcare eco-systems and should leverage on the strengths of European capabilities, not only in terms of medical services and healthcare excellence, but also in the field of technology and industry, which is a fundamental enabler of the value provided to customers in healthcare services. The involvement of industry as a necessary party to meet this challenge should also represent a new opportunity to increase European industrial and technological competitiveness, coherently with the target of "Industrial Leadership" stated by the new Horizon2020 program.

This Project aims at proposing *an innovative paradigm for heath care systems and medical product manufacturers: the production of personalized medical products and devices through new design approaches and technologies, in an environment closely integrated with the hospital which guarantees the direct contact between the patients, medical personnel and devices manufacturers*. Such a paradigm has the potential to drastically improve the quality of life of people, the performance of health care services and the competitiveness of medical products manufacturers.

In the current medical practice, devices to be implanted are produced in standard sizes and shapes and are stocked in the hospitals (for example mini- and macro-fixation systems, namely fixation devices like screws and mini-plates for hand reconstruction and screws with interconnected channels for bone integrable macro-fixation in orthopaedics, etc.) (Figure 1).

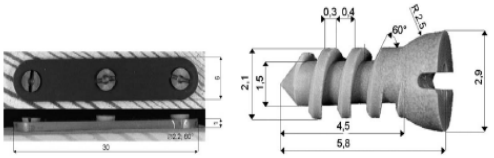

Figure 1: mini-plates and screws for mini-fixation

The device to be implanted is chosen between the available versions (if provided) as the one closest to the anatomy of the patient, typically assessed with imaging techniques of common

clinical use. Frequently, there is the need to adapt manually the devices to the anatomic characteristics of patients, with the possibility of damaging them or not to reach the right size or shape that would be optimal for the patient. This can also be the cause of long surgery times, with increased occupation of operating theatres and higher cost per patient.
In the new paradigm:

- advanced mathematical and modelling technologies will be applied to build the anatomical model of patient through the combination and analysis of bio-images;
- the model is sent to a "hospital factory", which can be located inside the hospital or closely integrated with it by the adoption of real-time connection tools;
- the hospital factory is able to produce the personalized product in a very short time (1-2 days), thanks to the combination of a set of innovative technologies (such as additive manufacturing, micro-EDM, micro-extrusion, etc.) and processes to manufacture personalized products;
- the personalized product is implanted to the patient with the guarantee of optimal size, fitting and comfort, and with minimum time and complexity of surgery.

Besides products, the hospital factory will produce also personalized anatomical models (for example cardiovascular models) that can help surgeons to study patients' pathologies treatment in advance, in order to simulate different surgery strategies (Figure 2).

Figure 2: silicon mock carotid artery with the implantation of a stent

In order to contribute reaching these goals, the Project has the following scientific and technological objectives:

I) Propose new viable business models for personalized medical products implying new business processes for hospitals, products manufacturers and technology providers, compliant with health care systems safety, certification requirements and ethical regulations.
II) Define new statistical methods and approaches to elaborate an accurate anatomical model from bio-images in order to design personalized products.
III) Define improvements to the existing technologies for personalized products, mainly additive manufacturing and micro-EDM, in order to lower production costs, thus allowing the wide diffusion of personalized medical products.
IV) Propose innovative process combinations and manufacturing approaches, mainly considering additive manufacturing and micro-EDM technologies, in order to lower production costs, thus allowing the wide diffusion of personalized medical products.
V) Demonstrate the new technological approaches in real products and medical scenarios, provided by hospitals and companies of the Industrial Interest Group.

The following table outlines how the Project proposal meets the Topic Call objectives.

Topic Call Objective **(*also in Italian as reported in the Call*)**	**Scientific Objective responding to the Topic Call Objective**
It is required to develop innovative approaches of design, management and dynamic cooperation for supply chains, business networks or individual companies, to support the design of personalized products. *Si richiede di sviluppare approcci innovativi di progettazione, gestione e cooperazione dinamica per filiere produttive, reti di imprese o singole aziende a supporto della progettazione di prodotti personalizzati.*	I, II
The research may focus on the development of some relevant contributions to the innovation of these approaches, such as methodologies for collection processes and analysis of the personalized needs for the design of custom-made products and /or the related design of production processes, methodologies for design and management of production systems able to produce customized products. *La ricerca potrà focalizzarsi sullo sviluppo di alcuni contributi rilevanti all'innovazione di tali approcci, quali ad esempio metodologie per i processi di collezione ed analisi dei bisogni personalizzati per la progettazione di prodotti su misura e/o per la relativa progettazione dei processi di produzione, metodologie per la progettazione e la gestione di sistemi produttivi in grado di realizzare prodotti personalizzati*	II, III, IV
For this topic, it will be particularly relevant the definition of a significative industrial interest group that refers to the sectors of Made-in-Italy. This interest group will provide feedback on the feasibility of the solutions developed during the project. *Per questo topic sarà particolarmente rilevante la definizione di un gruppo di interesse industriale significativo che faccia riferimento ai settori del Made-In-Italy. Tale gruppo di interesse dovrà fornire dei feedback sulla percorribilità delle soluzioni sviluppate durante il progetto*	V

2.2. Progress beyond the state-of-the-art

The possibility of fabricating personalized prostheses tailored on each specific patient is one of the major needs and key issues for the future of the several surgical specialities. In addition, the possibility of producing patient specific anatomical models for the pre-operative planning is an essential requirement in the presence of prostheses tailored on the specific patient, where also the surgical treatment requires to be optimized on each specific patient. For these purposes, the presence of a prototyping service internal to the hospital would be a great support and an added value for the clinical activity. The location of the service inside the hospital will allow a closer interaction with clinicians during the model development, leading to a significant time and costs reduction, and to a better efficiency of the service with respect to an external one. At the present state, no such services are active in the Italian territory, and are extremely rare worldwide. On the other hand, thanks to the great diffusion of rapid-prototyping technologies and in particular of the 3D printing, we can notice a significant growth of rapid prototyping services dedicated to the medical field, aimed to answer the increasing demand of instruments for personalized medicine. These services are becoming worldwide spread, while they are still sporadic although increasing, on Italian territory.

In the last few years, the medical field has started to benefit from the potential of rapid prototyping, especially for pre-operative planning purposes [1]: despite the evolution of imaging systems and 3D rendering tools, which provide very accurate and easy to navigate virtual models of patient-specific anatomy, nothing can come closer to clinical reality than a real model of the patient. Maxillofacial surgery and orthopaedics are the two medical fields that are starting to use rapid prototyping services in the clinical practice. In these cases, the surgeon uses physical models to test different surgical solutions, such as the implant of screws or bone plates, on the specific anatomy. However, physical models for the pre-operative planning have across the board usage in the different medical specialties, given the higher informational value of a physical object respect to a virtual one. The educational value of these models is also another fundamental aspect.

Unlike other specialties, vascular surgery has seen the development of a dedicated rapid prototyping sector: in this case, the utility of the anatomical model for the pre-operative planning for stents or vascular prostheses apposition, is not linked only to the morphological characteristics, but also to the mechanical properties of the vascular district. For a good and comprehensive planning, the surgeon must be able to test the placement, the prosthesis release and should evaluate the interaction between the prosthesis and the vessel. To do so, the vessel is required to have a behaviour as consistent as possible to real pathophysiology.

Currently, there are very few companies full or partially devoted to the prototyping of patient-specific silicon vascular models: in particular, it is highlighted the absence of these companies in the Italian territory. The state of the art on these services stands on the replica of the patient's geometry and its functional characteristics, such as compliance or wall thickness: functional characteristics have to be defined by the user. The availability of models endowed with these features it is of great usefulness and interest for clinicians, as they allow to highlight complications arising during the prosthesis apposition process, such as an excessive stress of the vascular walls or a poor adaptation of the prosthesis to the patient's anatomy.

The main disadvantages of the current state of the art regarding the prototyping services for anatomical models and in particular for vascular compliant models concern:

- Costs: as regard anatomical models just for visualization purpose, prices are a little lowering thanks to the progressive spread of prototyping technology, while for vascular compliant model prices are still prohibitive (thousands of euros even for very small vascular districts).

- Functional features: as said before, functional characteristics have to be defined by the customer, in this case the clinician, but typically he doesn't have proper instruments and the know how to extract functional information from medical images (compliance, wall thickness , etc.).

These problems prevent such services from being introduced into the clinical practice and restrict the use of these anatomical models only to scientific research purposes. The Project aims to overcome the highlighted problems and to provide all the instruments to make prototyping services available for the clinical practice. Moreover, the Project aims at investigating the methodologies for the joint design of customized, patient specific 3D anatomo-functional models and prostheses, together with the related processes and production systems. Thus, we will also highlight possible new solutions to make even more affordable the proposed service. On the other side, patient specific fixation plates and screws has not been widely introduced yet due to the difficulties in small scale production of 3D complex components made of hard, brittle materials (such as ceramics, or hard metals as titanium) and micro sized features without defects and at acceptable cost.

Micro-EDM is a promising technology for high precision manufacturing of complex 3D shaped mini/micro devices made of hard, brittle materials, featuring micro-sized tool diameters, extremely low energy entity and high energy density, high temperatures and absence of contact between work piece and tool. However, it still displays some challenges to the scientific community. The variability of the machining performance dependent on the materials and on the stochastic nature of the sparking process, as well as the more and more urgent constrictions imposed by the micro-component designs, call for novel approaches to manage and control the machining process and to go beyond structural and geometrical limits (surface roughness <0.1μm and geometrical accuracy ≤1μm).

Indeed, conventional machining processes do not seem to provide the required surface integrity [2]. Electrical discharge machining (EDM) can be used to manufacture conductive materials regardless to their hardness and strength, and so, complex shapes can be realized. This technology is based on a material removal mechanism accomplished by melting and evaporation induced by sequences of electrical sparks and discharges occurring between the tool and work piece electrodes. In case of titanium and its alloys, the thermal effect intrinsic to the erosion process causes the deposition of the so-called white layer, which is an oxidized recast layer due to the not effective flushing of debris from the working zone. The final surface structure consists typically of debris, cracks and drops of solidified material. Hence, EDM affects the surface quality, surface roughness and promotes the creation of subsurface layers [3]. These effects are detrimental for the feature machining precision and consequent operating life of the machining parts. Moreover, EDM process parameters, in particular, pulse current and pulse width, influence the surface roughness [4]. Experiments [5] demonstrate that the material removal rate increases at higher content of TiN, i.e. higher electrical conductivity. When micro-EDM is considered to machine Si3N4-TiN composites [6, 7], voltage and current increase is generally recommended in order to have acceptable values of Material Removal Rate and Tool Wear Rate, along with the choice of hydrocarbon oil for the dielectric flushing to obtain a better performance in terms of surface roughness. Some authors [8] have tested different techniques aimed to the realization of textures featuring sizes ideally ranging from 5 to 100 μm on ceramic materials such as alumina, zirconia, silica and hydroxyapatite. The evaluation of the performance, in terms of surface roughness, verticality of sidewalls, precision and accuracy for each ceramic material, reveals that when aqueous ceramic suspensions-based techniques are used, the micro geometries (sizes down to 30 μm) have highly accurate shapes with vertical sidewalls, but the surfaces generally suffer of cracks and

are affected by the presence of molten material (especially caused by sintering and drying phases).

1. S. Singare, Q. Lian, W. P. Wang, J. Wang, Y. Liu, D. Li and B. Lu, 2009, Rapid prototyping assisted surgery planning and custom implant design. Rapid Prototyping Journal, Vol. 15 Iss: 1, 19 – 23.
2. C.H.C. Haron, A. Jawaid, 2005, The effect of machining on surface integrity of titanium alloy Ti–6Al–4V, J. Mater. Process. Technol. 166, 188–192.
3. L. Reissig, R. Volkl, M.J. Mills, U. Glatzel, 2004, Investigation of near surface structure in order to determine process-temperatures during different machining process of Ti–6Al–4V. Scripta Mater. 50, 121–126.
4. Y.C. Lin, B.H. Yan, F.Y. Huang, 2001, Surface improvement using a combination of electrical discharge machining with ball burnish machining based on the Taguchi method, Int. J. Adv. Manuf. Technol. 18, 673–682.
5. Liu C.-C., Huang J.-L. Effect of the electrical discharge machining on strength and reliability of TiN/Si3N4 composites. Ceramics International 29, 2003, pp. 679–687.
6. Liu K., Paris J., Ferraris E., Lauwers B. and Reynaerts D., Process investigation of precision Micro-Machining of Si3N4-TiN ceramic composites by electrical discharge machining (EDM), Proceedings of the 15th International Symposium on Electromachining (ISEM), 23-27 April, 2007, Pittsburgh, PA, USA, pp 221-226.
7. Liu K., Lauwers B. and Reynaerts D. Process capabilities of micro-EDM and its applications, Int. J. Adv. Manuf. Technol. (2010), 47:11–19.
8. Holthaus M. G., Treccani L., Rezwan K., Comparison of micropatterning methods for ceramic surfaces, Journal of the European Ceramic Society 31 (2011) 2809–2817.

2.3. S/T methodology and associated work plan

The Project is composed by seven workpackages (WPs): six of them are related to the year 1 of the Project, whereas the seventh one is the additional WP.
Three are focused on the industrial business models (WP1) and on the technical aspects that have to be faced (WP2 deals with the CAE modelling and WP3 with the fabrication technologies). In addition, WPs related to Project management (WP0) and dissemination (WP5) are also included in order to implement procedures for quality management, respect of the ethics issues (privacy), risk management and Project integration as well as to disseminate the developed technologies, models and recommendations both to the scientific community and to the industrial world.
Work Packages and their interconnections are illustrated in Figure 3.
WP0 and WP5 are transversely connected to all of the other WPs. WP0 coordinates and receives information from all other WPs and WP5 disseminates their results. Among the others, WP2 and WP3 are strongly related as the outcomes of WP2 determine the starting point of WP3 and a feedback is also present, as the technologies influence the CAE modelling. In addition WP1, which analyses the business models, gives the general framework to WP2 and WP3. Finally, WP1, WP2 and WP3 together determine the demonstration activities of WP4.

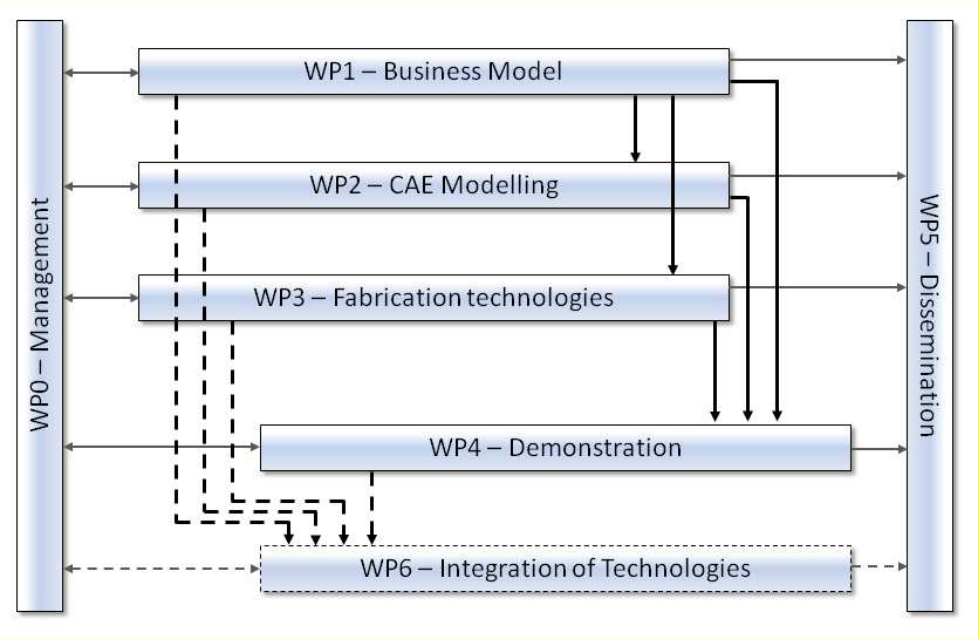

Figure 3: Work packages and their interconnections

In case the additional WP6 will be implemented (dashed lines), WP2 and WP3 will be the basis for the study of the integration of technologies, WP1 gives information about the possible impact of the different alternatives and also the result of the demonstration (WP4) will be the starting point for optimising and integrating the technologies on real already implemented cases.
The timeline of the WPs also respects these connections, as shown in the GANTT reported below.

WP No	WP leader	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M12
0	IMATI												
1	ITIA												
2	IMATI												
3	UNIPV												
4	UNIPV												
5	IMATI												
6	ITIA												

3. Partnership

3.1. Individual partners

CNR-IMATI

The Research Unit is within the Milan Department of the "Istituto di Matematica Applicata e Tecnologie Informatiche Enrico Magenes" (IMATI) of the "Consiglio Nazionale delle Ricerche" (CNR). The Institute carries out research activities in several fields of Mathematics, Information Technology and their applications, which can be mainly classified as follows:

- Mathematical Statistics and Probability: development and study of methodologies and models for the description of random phenomena with applications to several fields (e.g., image analysis, medical procedures, pharmacological and clinical data analysis, operations research under uncertain parameters).
- Modelling of Biomedical Phenomena: design and development of methods for supporting the *in vitro* replication of patho-physiological systems (e.g., cardiovascular system), and for identifying biological and physical systems.
- Geometric Modelling and Computer Graphics: development of methods of shape analysis and synthesis applied to CAD, GIS systems, health, cultural heritage and virtual reality techniques, as well as methods for curve and surface reconstruction.
- Differential Modelling from theoretical, numerical and computational points of view; results of these research programs are widely used to deal with applied problems.
- Computing Architectures and High Performance Computing: development of methodologies, algorithms, models and tools for an efficient and effective use of computing architectures.

Two researchers of IMATI will be involved in the Project:

- Ettore Lanzarone (coordinator): he has been Researcher at IMATI since 2011. Previously, he was Research Fellow at the Department of Mechanics, Politecnico di Milano, Milan, Italy, and Ph.D. student at the Laboratory of Biological Structure Mechanics, Politecnico di Milano, Milan, Italy. His major research interests are: *in vitro* replication of the cardiovascular system for supporting clinical and theoretical studies; cardiovascular prostheses and extracorporeal circulation; stochastic modelling and parameter estimation of dynamic systems; stochastic models for estimating the demand in industry and healthcare facilities; mathematical programming and metaheuristics for optimizing activity planning in industry and healthcare facilities. He is co-author of more than 25 papers in international journals and conference proceedings (www.mi.imati.cnr.it/ettore).
- Raffaele Argiento: he has been Researcher at IMATI since 2011. He received his BSc in Mathematics at the Federico II University, Naples, Italy, his Master in Applications of Mathematics in Industry and Services at the University of Milan Bicocca, Milan, Italy, and his Ph.D. degree in Statistics at the Bocconi University, Milan, Italy. He spent part of his Ph.D. studies at University of Pennsylvania, Philadelphia, USA. His research interests include Bayesian nonparametric methods, system reliability and probability and statistics in the electrical power industry. Since 2010 he is in the organization committee of the applied Bayesian summer school (ABS). Since 2013 he is executive director of ABS. He as been elected Treasurer of the Industrial Statistics section at the International Society for Bayesian Analysis (IS-ISBA) (www.mi.imati.cnr.it/raffaele).

Moreover, a Research Fellow (Assegnista di Ricerca) will be recruited for the Project.

The scientific activity of IMATI in the Project will mainly involve the modelling aspect of the prostheses and the artefact for the in vitro simulation of surgical treatments. Indeed, the activity will involve the definition of their geometrical and mechanical properties (anatomo-functional artefacts) starting from acquired medical images. In other words, given the specifications from the surgeons and the acquired medical images, the activities will be devoted to the CAE for the production of the prosthesis/artefact.

CNR-ITIA

CNR-ITIA, as a promoter of industrial innovation, performs strategic activities of Scientific Research and Technological Development for the Competitiveness and Sustainability of Italian and European Manufacturing Industries. ITIA contributes and supports the European initiative Manufuture, which is finalized to the development of added high value manufacturing based on research and innovation. ITIA works on the development of production systems and elements for knowledge-based factories, business models and related enabling technologies in tight collaboration with research centres, universities and enterprises at national, European and international level. ITIA has currently focused its competences on the following areas: microsystems, mechatronic, knowledge-based systems, robotics, multi-layer adaptive control systems, virtual prototyping and integrated simulation of mechatronic manufacturing systems and methods and new organizational, management and business paradigms. ITIA is a founding member of the European Technology Platform for Micro- and NanoManufacturing (MINAM) and member of the satellite group of MINAM 2.0.
ITIA Scientific and Technological background and excellence on the topics of its main tasks in the Fab@Hospital Project can be testified by past and present involvement in a number of research projects funded by the EC and European industrial partners. ITIA has participated in several relevant European (Cooperation: LEADERSHIP, NEXT, SMERobot, EUMECHA-PRO, microSAPIENT, IPPMAN DEMAT, Robofoot, DOROTHY, LICOPRO, ENEplan, People: Net4m) and national (FLEXProd, REMS, BackOP) projects, which deal with machinery and production systems innovation, data monitoring, environmental issues and energy efficiency of processing, high precision manufacturing, robotics and microrobotics. Within the current Project, ITIA participate with two research groups, namely: MBM (Manufacturing Business Models) and MEDIS (Micro Enabled Devices and Systems).
Three researchers of ITIA will be involved in the Project:

- Dr. Ing. G. Copani, PhD, MSc degree in industrial management engineering from Politecnico di Milano. After the professional experience as management consultant, he joined CNR-ITIA in 2005 and he is currently responsible for the research group MBM. He is currently the project manager for ITIA of the WP4 of the "DEMAT-Dematerialised Manufacturing Systems" FP7 EU project, of the "FoodManufuture" FP7 EU project, of the "KTRM-Knowledge Transfer of Rapid Manufacturing" LdV EU project and he is the responsible for Italy of the "European Manufacturing Survey, a permanent international survey investigating manufacturing innovation. He participated to European and national projects in the field of business model innovation, business networking and process reengineering in the sector of machine tools, textile and healthcare. He is reviewer for international journals and conferences and author of more than 30 scientific papers to international peer reviewed conferences, journals, scientific reports and book chapters. He is research affiliate of the CIRP academy ("The International Academy for Production Engineering").
- Dr. Ing. Irene Fassi, Ph.D. (2001), MSc in Mechanical Engineering (1997) from Politecnico of Milano. Since 1998 she is full time researcher at CNR-ITIA, where she is currently responsible of the MEDIS research group, performing research activities in the field of micro engineering and robotics, within a variety of regional, national and European

projects. She is member of the ASME/DAD TC on Micro Nano Systems and member of the executive board of SIRI (Italian Robotics and Automation Association). She is author of more than 100 scientific papers submitted to international journals, books and conference proceedings.

- Eng. Francesco Modica received the MSc degree in Aeronautical Engineering (1999) from University of Palermo, Italy. Since 2000 he is full-time researcher at ITIA-CNR, where his research activity focuses on micro-manufacturing of micro features via micro-EDM and micro-engineering. He has been involved in various national and European projects. From 2000 to 2009, his research activity focused on machine tool mechatronic analysis and simulation. From 2005 to 2009, he has been involved as researcher and project manager in Sintesi s.c.p.a. developing mechatronic solutions for machine tools.

Moreover, a Research Fellow (Assegnista di Ricerca) will be recruited for the Project.

UNIPV

The UNIPV research unit belongs to the Department of Civil Engineering and Architecture (DICAr) of the University of Pavia, Pavia, Italy. At DICAr, the central research field is the Mechanics of Structures and Materials. Other areas of interests cover Civil and Industrial Engineering, Biomechanics and, in general, all those technical and scientific fields where structures play a relevant role. The UNIPV Research Unit belongs to the Computational Mechanics and Advanced Materials group (http://www.unipv.it/compmech) that have interests in computational theoretical issues and in several applications (e.g. numerical simulation of minimally-invasive cardiovascular devices, development of informatics tools for medical imaging analysis, see www.unipv.it/compmech/publications.html). The group has also established the ß-laboratory (www-2.unipv.it/compmech/beta-lab.html) in collaboration with CNR-IMATI of Milan and San Donato Hospital. The mission of the laboratory is to increase the clinical effectiveness of vascular surgical techniques, and its activities are aimed at: studying the cardiovascular fluid-dynamics with in vitro models; supporting the clinical practice of vascular surgery; validating computational models. The lab activity focuses on the development of the facilities required for *in vitro* studying the cardiovascular fluid-dynamics and their application to real clinical cases. Specific features are: pulse-duplicator meant to reproduce the cardiac output or the pressure/flow characteristic in specific district of the vasculature; differential and stochastic mathematical methods to support the experimental activity and the design of the facilities; experimental testing of vascular prostheses such as endografs or stents. Other facilities available for the Project are:

1. MTS insight 10 tensile machine, at disposal for the mechanical characterization of material samples and device (www-2.unipv.it/compmech/mate-lab.html).
2. Objet 30Pro 3D printer, able to print models in 7 different materials (4 rigid opaque materials, transparent, high-temperature and polypropylene-like materials). For more details please refer to www.unipv.it/compmech/proto-lab.html.

The members of UNIPV Unit that will take part in the Project are:

- Ferdinando Auricchio (coordinator): he is Full Professor of Mechanics of Solids at the Department of Civil Engineering and Architecture of the University of Pavia (where he is also the Department Chair), Research Associate at the IMATI-CNR, Scientific Committee member of the CeSNA-IUSS, and Adjunct Professor of the Faculty of Engineering and of the Faculty of Graduate Studies at the Dalhouise University (Canada). He has interests in computational issues; in particular, he focuses on research topics like: development and analysis of constitutive models for advanced materials and development and use of

computational methods for the simulation of biomechanical problems, both considering classical finite element techniques as well as innovative isogeometric approaches. He has published more than 110 papers in international journals (www-2.unipv.it/auricchio)

- Michele Conti: from 2012 to 2015 he has an assistant Professor position at the University of Pavia, Pavia, Italy. In 2011, he received a joint Ph.D. degree in Bioengineering and Bioinformatics between Pavia University and Ghent University, Belgium. His Ph.D. thesis was selected as the Italian candidate for the ECCOMAS (European Community on Computational Methods in Applied Sciences) Award for the Best PhD Theses 2010. From September 2013, he is president of Italian Chapter of European Society of Biomechanics (www.esb-ita.it). Among the others, his research interests include computational biomechanics for simulation of minimally invasive cardiovascular surgery and medical analysis and elaboration. He has author and coauthor of 20 papers in peer-reviewed journals (www.unipv.it/compmech/members/micheleconti.html).

Moreover, a Research Fellow (Assegnista di Ricerca) will be recruited for the project.

3.2. Partnership as a whole

The three partners belong to complementary research sectors that are all required to achieve the goals of the Project.
Moreover, collaborations among the Research Units have been activated for some time and documented. Indeed, the coordinating Research Unit IMATI already collaborates with both the other two Research Units. IMATI and UNIPV established the BetaLab laboratory (www-2.unipv.it/compmech/beta-lab.html) at the beginning of 2012 for the study of the cardiovascular fluid-dynamics with *in vitro* models, aiming at supporting the clinical practice of vascular surgery and validating computational models. IMATI and ITIA are collaborating in two Projects of the Factory of the Future series within the Subproject 1, i.e., the Project NanoTWICE (www.fabbricadelfuturo-fdf.it/progetti/sottoprogetto-1/progetto-nanotwice) and the Project ZeroWastePCBs (www.fabbricadelfuturo-fdf.it/progetti/sottoprogetto-1/progetto-zero-wastepcbs).
Each partner will participate to the activities of the Project making available its actual specific expertise to the consortium, as detailed in the work plan description.
The know-how of the partners in their specific sectors is well-balanced for the activities and the objectives of the Project. Each partner is in charge of one or more specific competencies that are useful for achieving the goals and these competencies can be easily integrated, as documented by the already active collaborations. Competencies can be mainly classified as follows:

- Technological competencies: ITIA
- Business model competencies: ITIA
- Bioengineering competencies: UNIPV
- 3D printing: UNIPV
- Data analysis: IMATI
- Stochastic modelling: IMATI

Moreover, the coordinator of the leading IMATI Research Unit has previous documented working experience at the Department of Mechanics, Politecnico di Milano (Milan, Italy) and at the Bioengineering Department, Politecnico di Milano (Milan, Italy). The first Department carries out parallel research activities with respect to ITIA (with strict collaboration in several fields), whereas the latter carries out the same activities of UNIPV in the bioengineering field. This guarantees enough competencies to coordinate the activities of the Units.

3.3. Resources to be committed

The total value of the Project is 249.437,5€ (with a further value of 65.312,5€ for the additional WP), divided among the different cost items as reported in Figure 4.
Since project partnership is already active in the fields of research of the proposed Project, they can count on laboratories that already offer the majority of instruments and equipments necessary to carry out the research activities and the demonstration.
In particular UNIPV owns a 3D printer (Objet 30Pro 3D printer) and ITIA owns ITIA will make available the equipment of the Micromanufacturing lab and specifically: a micro-EDM machine (SARIX SX 200), a Labtech twin screw corotating micro extruder, a Zeiss confocal microscopy and a Shimadsu tensile testing machine for geometrical and mechanical characterization of the samples.
IMATI owns several computation facilities and software licenses for supporting its activities.
This explains the relatively limited budget in materials and equipments. Thus, the partnership and their infrastructures allow developing new research results in the most efficient conditions.
The distribution of Project costs among the Research Units is shown in Figure 5. The highest cost is for ITIA, due to the additional equipment required to upgrade the micro-extruder machine for the preparation of nano-enhanced materials, followed by UNIPV. Additional interpolated indexing and tilting axes will be acquired to upgrade the micro-EDM machine.

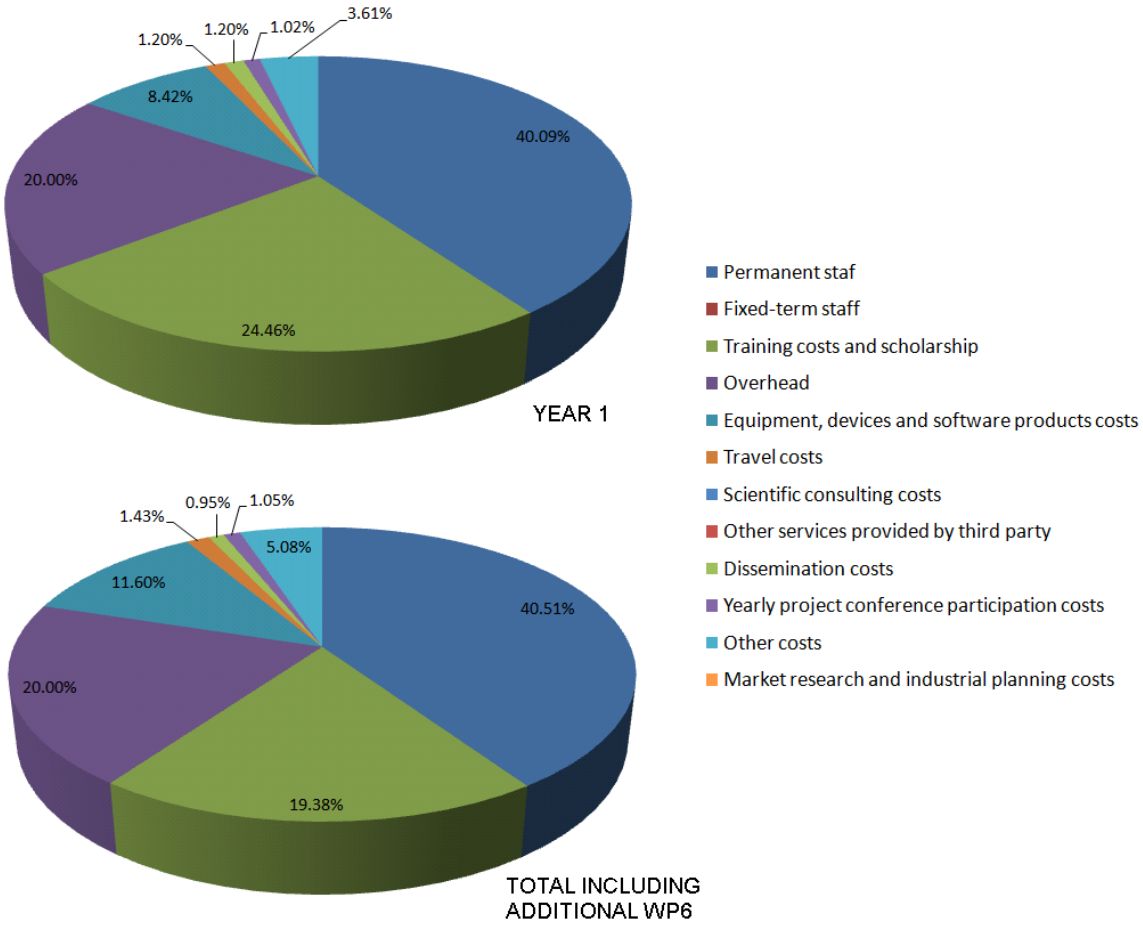

Figure 4: Project costs per item (both year 1 and including the additional WP)

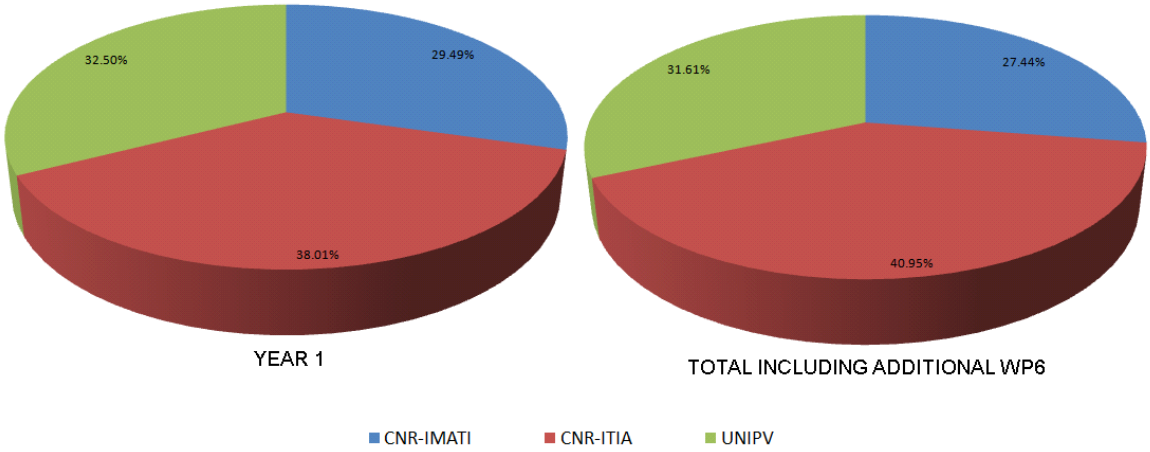

Figure 5: Efforts per Research Unit (both year 1 and including the additional WP)

Items of expenditure		Limits on total project costs[2]	Budget for the "main project" (for each partner)			Total costs per item	Percentage on total project cost
			CNR IMATI	CNR ITIA	UNIPV		
Staff costs[3]	Permanent staff[4]	min 40%	32000,0	37000,0	31000,0	100000,0	40,09 %
	Fixed-term staff[5]	max 10%	0,0	0,0	0,0	0,0	0,00 %
Training costs and scholarship[6]			19000,0	23000,0	19000,0	61000,0	24,46 %
Overhead[7]		max 20%	14712,5	18962,5	16212,5	49887,5	20,00 %
Equipment, devices and software products costs[8]			2000,0	12000,0	7000,0	21000,0	8,42 %
Travel costs[9]			1000,0	1000,0	1000,0	3000,0	1,20 %
Scientific consulting costs[10]			0,0	0,0	0,0	0,0	0,00 %
Other services provided by third party[11]			0,0	0,0	0,0	0,0	0,00 %
Dissemination costs[12]			1000,0	1000,0	1000,0	3000,0	1,20 %
Yearly project conference participation costs[13]		min 1%	850,0	850,0	850,0	2550,0	1,02 %
Other costs[14]			3000,0	1000,0	5000,0	9000,0	3,61 %
Market research and industrial planning costs[15]			0,0	0,0	0,0	0,0	0,00 %
TOTAL COSTS			73562,5	94812,5	81062,5	249437,5	100.00 %

2 Please see Section 10 of document "Bando di invito a presentare progetti di ricerca industriale e sviluppo sperimentale nell'ambito del Sottoprogetto 1".

3 Spese di personale.

4 Personale dipendente a tempo indeterminato.

5 Personale dipendente a tempo determinato.

6 Spese di formazione tra cui i costi di assegni di ricerca, dottorati di ricerca e borse di studio.

7 Spese generali.

8 Attrezzature, strumentazioni e prodotti software.

9 Stage e missioni in Italia e all'estero.

10 Consulenze scientifiche

11 Altre prestazioni di terzi.

12 Spese di pubblicizzazione.

13 Spese per la partecipazione alle tre conferenze annuali del Progetto Bandiera "La Fabbrica del Futuro".

14 Altri costi funzionali al progetto.

15 Studi di mercato, piani industriali, piani di sviluppo e/o potenziamento.

Items of expenditure		Limits on total project costs[16]	Budget for "additional WP" (for each partner)			Total costs per item	Percentage on total project cost
			CNR IMATI	CNR ITIA	UNIPV		
Staff costs[17]	Permanent staff[18]	min 40%	8500,0	10000,0	9000,0	27500,0	42,11 %
	Fixed-term staff[19]	max 10%	0,0	0,0	0,0	0,0	0,00 %
Training costs and scholarship[20]			0,0	0,0	0,0	0,0	0,00 %
Overhead[21]		max 20%	2562,5	5812,5	4687,5	13062,5	20,00 %
Equipment, devices and software products costs[22]			500,0	12000,0	3000,0	15500,0	23,73 %
Travel costs[23]			500,0	500,0	500,0	1500,0	2,30 %
Scientific consulting costs[24]			0,0	0,0	0,0	0,0	0,00 %
Other services provided by third party[25]			0,0	0,0	0,0	0,0	0,00 %
Dissemination costs[26]			0,0	0,0	0,0	0,0	0,00 %
Yearly project conference participation costs[27]		min 1%	250,0	250,0	250,0	750,0	1,15 %
Other costs[28]			500,0	4500,0	2000,0	7000,0	10,72 %
Market research and industrial planning costs[29]			0,0	0,0	0,0	0,0	0,00 %
TOTAL COSTS			12812,5	34062,5	18437,5	65312,5	100.00 %

16 Please see Section 10 of document "Bando di invito a presentare progetti di ricerca industriale e sviluppo sperimentale nell'ambito del Sottoprogetto 1".

17 Spese di personale.

18 Personale dipendente a tempo indeterminato.

19 Personale dipendente a tempo determinato.

20 Spese di formazione tra cui i costi di assegni di ricerca, dottorati di ricerca e borse di studio.

21 Spese generali.

22 Attrezzature, strumentazioni e prodotti software.

23 Stage e missioni in Italia e all'estero.

24 Consulenze scientifiche

25 Altre prestazioni di terzi.

26 Spese di pubblicizzazione.

27 Spese per la partecipazione alle tre conferenze annuali del Progetto Bandiera "La Fabbrica del Futuro".

28 Altri costi funzionali al progetto.

29 Studi di mercato, piani industriali, piani di sviluppo e/o potenziamento.

4. Impact

4.1. Expected impacts listed in the work programme

The impact that the project aims to achieve includes an improvement of clinical procedures and a consequent outcome of the treatment. The instruments that will be made available through the prototyping service will allow clinicians to get a clearer view of the anatomy and the specific: this will allow them to include a greater number of variables in the choice of the most suitable treatment. On this point, we will have an initial assessment of the project expected outcome during its final phase, in which we have included a demonstrator. The demonstrator is designed precisely to investigate the impact of the service on the clinical practice: applying the methodologies developed to the clinical reality, we will face a direct evaluation of the end users, i.e., the doctors. A direct consequence of an improved treatment planning will be an improvement of the outcome of the treatment itself. A better therapy brings advantages in terms of patient time of recovery and thus of hospitalization. This will also result in money saving for the hospital structure.

One of the major factors that can determine the success of the project is that it responds to a need of clear evidence within the public opinion, not only at a national level. Actually, at European level the public opinion interest on the issues addressed in the project, in particular relating to the personalization of medical treatments, is emphasized by the presence of similar issues in the objectives listed in the Horizon 2020 Work Programme 2014-2015: the programme includes a specific section entitled "Personalising Health and Care" with an actual indicative budget of EUR 549.30 million from the 2014 budget and EUR 537.00 million from the 2015 budget. In particular, one of the 34 themes of the section is entitled "Development of new diagnostic tools and technologies: in vitro devices, assays and platforms" which highlight the great coherency of our work with thematics of European interest. Moreover, within the area "Call for Factories of the Future", is listed a specific call entitled "Manufacturing of custom made parts for personalised products" with an actual assigned budget of EUR 145 million: the call topic regards the development of new strategies integrating design with manufacturing and incorporating appropriate control methodologies for the manufacturing of customised products (e.g. consumer goods and medical devices), in order to ensure small or large lot quantities which meet the specifications. Also in this case, it is highlighted the strong connection with the issues that this Project aims to answer.

Another important factor in the success of the project is the ability to make the service accessible for different kind of hospitals, regardless of the size of the structure or the envelope of technology. In fact, where possible, thanks to the availability of space and facilities, the service can be internalized in the hospital, otherwise it will be committed to local businesses. In both cases, the service could be very easy to implement thanks to the limited investment needed in terms of technology and knowhow. The spread of the proposed service will be boosted by the presence of a market demand which is in a phase of strong growth. To give an example, the global orthopedic implant market is projected to reach US$19.4 billion by the year 2015 and has been growing during the last 40 years following a technology-pushed model imposed by available manufacturing processes (casting, forging and machining) that present a strong economy of scale and a poor cost-efficiency in front of design changes. These few considerations strongly marked the orthopedic market evolution. The novel approach proposed in the Fab@Hospital production chain framework can constitute a breakthrough for the successful manufacturing of highly customised implantable devices, adopting new materials and a versatile manufacturing process. This approach will positively impact also on

the maxillofacial market and will evolve in benefit for patients and local economies, as soon as the foreign standard products will be progressively converted in local personalized services.

4.2. Dissemination and/or exploitation of project results and management of intellectual property

Dissemination is considered an important action of the Project, as one of the main goals of Project is to show the possibility of a real implementation of the Fab@Hospital idea and the t hospitals interest in applying it for supporting the clinical practice.
Moreover, the dissemination at the industrial level, showing the interest of the hospitals in personalized prostheses and anatomo-functional models, is another key point for a future real implementation of the idea and the results. Hence, the dissemination will be conducted at two levels: the industrial level and the scientific level.
As for the industrial level, we will show the benefits and the remarks related to the creation of a Fab@Hospital structure. First, we will share the results and the potential impact of our Project with the industrial interest group. Then, we will contact other companies operating in the same sector. For this purpose, we will prepare informative material and a conference website will be published. From the scientific point of view, we will disseminate the results to both the industrial research community and the clinical community. This activity will main involve papers on international peer reviewed journal and participations to international scientific conferences and meetings.
Finally, dissemination activities will also include a Project website and the participation to the Annual Conference of Project Fabbrica del Futuro. A dedicated website on the institutional portal of the leading partner (IMATI) will produce an extensive record of all publications and contributions originated during the course of the Project. The web pages will contain general information on the Project, links to the related literature, a download area for downloading Project brochures, videos, demos, and other material (e.g., news for communication of events, workshops, conferences related to the topic of the Project), and contacts to allow the visitors to have a direct link to the Project partners.

With regard to the innovation dimension, verification, testing, and prototyping will be considered. For this purpose an entire WP is devoted to applying the methodologies of the Project to answer specific case studies that the clinical members of the Project interest group will propose. The application of the work to such cases will be a key validation of the entire Project.

In order to protect the intellectual property, all information pertaining to the Project that is passed within the Partnership is deemed to be confidential and, therefore, shall not be disclosed outside the Project Fab@Hospital (or, in case, the Project Fabbrica del Futuro) without the written permission of the partners. In this sense, publications will be authorized by all partners before being made public. Exploitation of the results will be coordinated by the partnership in agreement with the interest group, which will be continuously informed about the Project work progress and the results. Finally, partners will be entitled to use their results for further researches; if this involves the use of information supplied or generated by other Partners, consent should not be unreasonably withheld, subject to the agreement that the results of such further research will be made available to the other partners.

5. Ethics Issues

Describe any ethics issues that may arise in the project (if applicable).

(Maximum length for the whole of Section 5 – 1 page)

Ethics issues arise in the Project due to the connection with clinics and hospitals, and two main aspects can be individuated: issues related to the use of patient data (e.g. acquired medical images and clinical information) and issues related to the implementation of the Fab@Hospital in real hospitals. The first one is strictly related to the Project activities (and Task 0.4 is also devoted to the control the respect of patient privacy), whereas the second one is not immediately involved in the Project but it has to be dealt with in perspective for a real application of Project results.
As for patient data, all participants will be aware of the possible use of their data, and will have to sign a written informed consent form before inclusion into experiments. All collected data will be handled and stored under conditions of the highest possible confidentiality and used exclusively for the purposes of this research Project. Indeed, all the acquired data will be treated in accordance with relevant national and international codes of conduct, such as:

- European Science Foundation's briefing on Good Scientific Practice in Research.
- 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.
- Council Decision 1513/2002/EC of 27 June 2002 concerning the FP6 programme of the European Community for research, technological development and demonstration activities, contributing to the creation of the European Research Area and innovation.
- Council Decision 2002/835/EC of 30 September 2002 adopting a specific programme for research, technological development and demonstration.
- The Charter of Fundamental Rights of the EU.

The Project does not foresee any gender-related issues as it is targeted equally towards members of both sexes. Special care will be taken during the data acquisition phase to ensure that both male and female volunteers are equally represented.
As for the implementation of the Fab@Hospital in real hospitals, ethics issues will arise for the utilisation of the patient specific prostheses and for the application of the anatomo-functional models to get suggestions for the surgical treatments. As example, non patient specific prostheses are certified considering the product, whereas for patient specific prostheses the certification has to involve the production process rather than the product.
Even these aspects are not directly related to the actual activities of the Project, they are fundamental for the future application of our idea and, for this purpose, they are investigated together with the business model.
Finally, we report the Ethical Issues Table taken from FP7 (tp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-issues-table-annex4.pdf), in order to check that all the issues are addressed or not involved in this Project.

	YES/NO
Informed Consent	
• Does the proposal involve children?	NO
• Does the proposal involve patients or persons not able to give consent?	NO
• Does the proposal involve adult healthy volunteers?	NO
• Does the proposal involve Human Genetic Material?	NO
• Does the proposal involve Human biological samples?	NO
• Does the proposal involve Human data collection?	YES
Research on Human embryo/foetus	
• Does the proposal involve Human Embryos?	NO
• Does the proposal involve Human Foetal Tissue / Cells?	NO
• Does the proposal involve Human Embryonic Stem Cells?	NO
Privacy	
• Does the proposal involve processing of genetic information or personal data (e.g. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	YES
• Does the proposal involve tracking the location or observation of people?	NO
Research on Animals	
• Does the proposal involve research on animals?	NO
• Are those animals transgenic small laboratory animals?	NO
• Are those animals transgenic farm animals?	NO
• Are those animals cloned farm animals?	NO
• Are those animals non-human primates?	NO
Research Involving Developing Countries	
• Use of local resources (genetic, animal, plant etc)	NO
• Benefit to local community (capacity building i.e. access to healthcare, education etc)	NO
Dual Use	
• Research having direct military application	NO
• Research having the potential for terrorist abuse	NO
ICT Implants	
• Does the proposal involve clinical trials of ICT implants?	NO

Table 2.3a: Deliverables List

Del. No[1]	Deliverable Name	WP No.	Nature[2]	Dissemination level[3]	Delivery date[4]
D.0.1	Project presentation	0	R	PU	M 1
D.0.2	Report of the all the management and coordination activities, and respect of ethical issues	0	R	PP	M 12
D.1.1	New business models for personalized medical products	1	R	PP	M 8
D.1.2	Standardization, certification and ethical implication of new business models for personalized medical products	1	R	PP	M 9
D.2.1	Stochastic procedure to estimate mechanical properties	2	R	PU	M 3
D.2.2	Design process	2	R	PU	M 8
D.3.1	Report on enhanced 3D printing technologies and methods for model fabrication	3	R	CO	M 11
D.3.2	Report on enhanced microEDM technologies and methods for model fabrication	3	R	CO	M 11
D.4.1	Assessment of time and production costs, in the case of a small local company	4	R	CO	M 12
D.5.1	List of the activities for dissemination at industrial level	5	O	PU	M 12
D.5.2	List of papers and presentations at international conferences	5	O	PU	M 12
D.6.1	Technical Report on compounding of nano-enhanced polymeric materials	6	R	CO	M 12
D.6.2	Anatomo-functional model - Demonstrator	6	D	PU	M 12

1 Deliverable number in order of delivery dates. Please use the numbering convention <WP number>.<number of deliverable within that WP>. For example, deliverable 4.2 would be the second deliverable from work package 4.

2 Please indicate the nature of the deliverable using one of the following codes:
R = Report
P = Prototype
D = Demonstrator
O = Other.

3 Please indicate the dissemination level using one of the following codes:
PU = Public
PP = Restricted to partners of the projects belonging to "La Fabbrica del Futuro"
RE = Restricted to a group specified by the partnership
CO = Confidential, only for members of the partnership.

4 Measured in months from the project start date (month 1). Project proposals should foresee separate WPs for the first and second year, leading to tangible and identifiable results at the end of the year. Delivery for the first year should take place within month 11.

Table 2.3b: Work package description

Work package number	WP 0		Start month	1		End month	12				
Project year 1 or additional WP[1]	year 1										
Activity type[2]	MGT										
Work package title	Management										
Work package leader	IMATI										
Partner number	1	2	3								
Partner short name	IMATI	ITIA	UNIPV								

Objectives:

WP0 is devoted to the activities for coordinating the Project, regulating the Project progress, and sharing information among the Research Units and between the Units and the industrial and clinical interest group. WP0 also ensure a quality control to all deliverables as well as the right harmonisation among the WPs and the contained Tasks. Indeed, WP0 will coordinate the production of all reports, organise the management meetings, provide Project reviews, and manage the ethic issues of the Project.

Description of work (possibly broken down into tasks), and role of partners

This WP includes all the management and coordination activities of the Project.
This is divided into four Tasks:

Task 0.1: Administrative and financial management (IMATI-ITIA-UNIPV)
The following discrete regular responsibilities (in the form of subtasks) will be deployed for assuring fluent coordination:

- project coordination and management, ensuring that the overall objectives are met at reasonable times;
- internal reporting though standardised progress report forms;
- financial and administrative management.

Task 0.2: Scientific and technical management (IMATI-ITIA-UNIPV)
This Task refers to the activities related to ensuring technology soundness, scientific and technological quality. This will be implemented by reviewing activities and results, and by technical analysis of the solutions developed during the Project. In addition, this Task deals with the risk analysis, the review and the final check of all deliverables and documents produced during the Project execution.

Task 0.3: Meetings (IMATI-ITIA-UNIPV)
This includes activities related to the organization of Project progress meetings, technical sessions, administrative management board and Project review meetings. A kick off meeting will take place at the beginning of the Project and a closing meeting at the end of the Project; moreover, an overall meeting with all participants will be organised every three months.

Task 0.4: Management of ethical issues (IMATI-ITIA-UNIPV)
This includes activities related to the respect of the ethical issues regarding the Project. In particular, the activities of the Task will guarantee to respect the privacy issues (related to the use of patient data) and all constraints emerging from the interaction with hospitals.

Deliverables (brief description and specification of delivery date)[1]
D.0.1: Project presentation (M1). D.0.2: Report of the all the management and coordination activities, and respect of ethical issues (M12).

Work package number	WP 1		Start month		1		End month				9
Project year 1 or additional WP[1]	year 1										
Activity type[2]	RTD										
Work package title	Business model										
Work package leader	ITIA										
Partner number	3	2	1								
Partner short name	ITIA	UNIPV	IMATI								

Objectives:
WP1 aims at designing and proposing new viable business models for manufacturing personalized medical products in close interaction with industrial and clinical partners.

Description of work (possibly broken down into tasks), and role of partners
WP1 is divided into four Tasks: **Task 1.1: Design of new business models for personalized medical products (ITIA)** New potential business models for manufacturing of personalized products in close interaction with hospitals will be proposed. New business models will define at strategic level aspects such as the production site location (inside the hospital, fence-to-fence, geographically dispersed, etc.), the supply chain configuration in terms of customers-supplier relationships and main business processes, the revenue model, etc. Target performances that the new processes and technologies have to meet for sustainability will be also defined. Different alternatives of business models will be preliminarily generated through a creative approach involving the different stakeholders (surgeons, hospital personnel, technology providers, medical products manufacturers, etc.), based on the state of the art and on the peculiarities of the new technologies and methods developed in the project. The viability and sustainability of alternatives will be than verified, in order to identify the most promising solutions. A quantitative evaluation of the potential benefits of the new business models for the involved stakeholders will be hypothesized. Finally, barriers for new business models implementation will be identified and possible solutions to overcome them will be suggested. **Task2.2: Standardization, certification and ethical implication (ITIA-IMATI-UNIPV)** In this task the implications of new business models identified in Task 1.1 in terms of compliance with existing standards and regulations will be addressed. Eventual criticalities will be outlined and suggestion for evolving normative will be provided.

Deliverables (brief description and specification of delivery date)[1]
D.1.1: New business models for personalized medical products (M 8). D.1.2: Standardization, certification and ethical implication of new business models for personalized medical products (M 9).

Work package number	WP 2		Start month		1		End month				10
Project year 1 or additional WP[1]	year 1										
Activity type[2]	RTD										
Work package title	CAE modelling										
Work package leader	IMATI										
Partner number	1	3									
Partner short name	IMATI	UNIPV									

Objectives:

WP2 deals with the development of the methodologies for designing the prostheses and the artefacts for the *in vitro* simulation of surgical treatments. Indeed, starting from the acquired medical images and the requirements of the surgeon, and taking into account the technological constraints and requirements, the design process has to automatically (or semi-automatically) generate the CAE image of the prosthesis or the artefact. This has to respect anatomical and functional (i.e., mechanical properties) requirements. For example, when a vascular segment is replicated, the internal geometry has to be reproduced together with the vessel compliance. Once the material of the artefact is defined, and its elastic modulus is known, the wall thickness around the internal geometry is defined to obtain the same compliant behaviour of the original vessel. In this sense, we refer to anatomo-functional prostheses and artefacts.

Description of work (possibly broken down into tasks), and role of partners

This objectives of WP2 will be achieved through three Tasks:

Task 2.1: Geometrical reproduction (UNIPV-IMATI)
This Task deals with the acquisition of a single medical image dataset (mainly TAC and MRI images) of a specific district, and with the reconstruction of its geometry based on the acquired image dataset. The reconstructed geometry will be directly reproduced by the artefact intended to mimic the pathophysiological system, or considered as interface for the design of patient specific prostheses. For example, considering a vascular segment, the internal geometry of the vessel will be replicated, whereas for prostheses such as a stent the internal geometry of the vessel represents the boundary condition for design the stent itself.

Task 2.2: Estimation of mechanical properties from medical images (IMATI)
This Task considers the extension from one medical image dataset to sequential datasets for districts with a periodical deformation. This is the typical case of the vascular system, where pressure and flow variations over the cardiac cycle determine a periodic strain in the vessel walls.
In this case, two aspects have to be integrated for the anatomo-functional design. First, in presence of several images, we have to extract the information about the geometrical properties in the absence of external solicitation, as CAE will refer to configuration at rest. Second, starting from this configuration, we have to reproduce the same elastic behaviour of the district when a solicitation is applied. Considering the above

mentioned example about a vascular segment, we have to determine the geometry of the vessel when no pressure is applied (this is the geometry to be fabricated) and to reproduce the compliant behaviour when an internal pressure is applied.

Task 2.3: Automatic or semiautomatic design (IMATI-UNIPV)
This Task refers to the implementation of the methodologies developed in Tasks 2.1 and 2.2 in an automatic or semiautomatic design tool. This tool receives the images and the requirements from the surgeon, together with the technological constraints and requirements, and generates the CAE image to be processed by the fabrication techniques. The final goal is to have an automatic tool (in order to increase efficiency of the process and facilitate the creation of small laboratories in hospitals); however, in this Project a first version of the tool, in which some steps will still require the human intervention, will be implemented. In fact, the automation would require longer time than the Project duration.

Deliverables (brief description and specification of delivery date)[1]
D.2.1: Stochastic procedure to estimate mechanical properties (M5). D.2.2: Design process (M10).

Work package number	WP 3		Start month		2		End month				11
Project year 1 or additional WP[1]	Year 1										
Activity type[2]	RTD										
Work package title	Fabrication technologies										
Work package leader	UNIPV										
Partner number	3	2									
Partner short name	UNIPV	ITIA									

Objectives:

WP3 deals with the manufacturing of the patient specific models starting from the CAE model defined in WP2. Three different technologies will be investigated on the basis of the required functional, mechanical and structural characteristics: moulding, 3D printing, micro-EDM. In order to reproduce the specific pathophysiological behaviour of the vascular and bone districts, the functional characteristics defined during WP2 will be related to specific material mixtures. The machining performances over the quality of the obtained surface and its micro-structure will be assessed toward a cost efficient and sustainable production. Moreover, the development of novel approaches, providing performance improvement for the realization of biocompatible components will be also supported by properly designed experimental machining tests and prototyping.

Description of work (possibly broken down into tasks), and role of partners

WP3 is divided into four Tasks:

Task 3.1 Material and technology selection (UNIPV-ITIA)
This Task will start from the patient specific CAE model, obtained in the previous WP. On the basis of the surgical specifications, the required geometrical and functional (structural and mechanical) properties of the final model will be derived. Afterwards, the most appropriate combination(s) of materials (plastics, ceramics, and metals) and processes will be defined in order to improve the final anatomo-functional model quality. When required, a CAD-CAM procedure will be performed to create the part programs related to the different completed designs. This Task will be strictly linked to the activity of the WP2, because of the possible need of functional parameters refinement, to meet the requirements of the chosen manufacturing process.

Task 3.2: 3D Printing (UNIPV)
This specific Task will focus on the 3D printing of those anatomical models that don't need functional features. The Task will deal with: a) printing material selection, b) virtual anatomical model optimization for 3D printing, c) post-processing of the printed models. A set of guidelines for non-expert users will also be available at the end of the WP, including a report on the covered case studies.

Task 3.3: Moulding (UNIPV-ITIA)
This Task will deal with the fabrication of the mould and the selection of the building materials for mock arteries. In particular, the mechanical properties of the patient-specific vascular segment, identified with the methodology proposed in WP2, will be related to the silicon mixture. Specifically, bi-phase silicones will be considered. Tensile tests will be performed both by UNIPV and ITIA to correlate the mechanical properties of a range of silicon specimen to their composition (ratio between silicon base and activator). In this way, a correlation table between mechanical properties, geometrical features and silicon mixture will be derived. 3D printing technology will be used to fabricate the mould, where the most appropriate strategies will be implemented to reduce fabrication time and costs.

Task 3.4: MicroEDM (ITIA)
Micro-EDM will be exploited to customise hard tissues prostheses and mini-fixation devices. The experimentation will comprise a technological evaluation of the proper micro-EDM technology (milling, wire, sinking, for instance), chosen according to the final design of the components. A design of experiment (DOE) approach will be used to accomplish the optimized parameters combination, properly evaluating the quality indexes (MRR, TWR, surface roughness) and accuracy of the micro-features. Then, a number of micro-features will be fabricated. High demanding specifications, required by the challenging application, will be targeted, such as features down to 5 μm, machining rates up to 0.4 mm3/min at various discharge energy conditions. If required, further optimization in the realization of the elementary features will be scheduled to accomplish and solve problems detected during each machining process. In this Task, also the realization of fixturing parts will be considered if necessary to properly machine the final devices.

Deliverables (brief description and specification of delivery date)[1]
D.3.1: Report on enhanced 3D printing technologies and methods for model fabrication (M11). D 3.2: Report on enhanced microEDM technologies and methods for model fabrication (M11).

Work package number	WP 4		Start month		7		End month				12
Project year 1 or additional WP[1]	year 1										
Activity type[2]	DEM										
Work package title	Demonstrator										
Work package leader	UNIPV										
Partner number	3	1	2								
Partner short name	UNIPV	IMATI	ITIA								

Objectives

In the WP4 we will proof of our work relevance through the set up of a demonstrator. We will apply all the methodologies developed during previous WPs to a real scenario. In particular, we will show the case of the proposed prototyping service implementation in a local small business that serves hospital activities. The reference hospitals will be a) the Vascular Surgery II Unit set in IRCCS Policlinico San Donato (San Donato Milanese, Milan), b) the General Surgery II Unit of IRCCS Policlinico San Matteo (Pavia), c) Orthopaedic Hand Surgery Service of Aosta, Azienda USL of Valle d'Aosta.

Description of work (possibly broken down into tasks), and role of partners

WP4 is divided into two Tasks:

Task 4.1: The case studies (UNIPV-IMATI)
In this phase we will test the effectiveness of the developed productive methodologies. The medical Units involved in the Project will select some cases of particular clinical interest, which they believe could have benefit from a treatment planning aided by the facilities provided by the service. Each case study will be discussed with the medical component mainly in two stages a) at the beginning, for the evaluation of the medical images, b) at the completion of the necessary files for prototyping, to discuss manufacturing proposals, c) at the completion of the required model, to get a feedback from clinicians on the usefulness of the model.

Task 4.2: Time and costs estimation (UNIPV-IMATI-ITIA)
Here we will analyse results coming from the service test on pilot cases. We will analyse the time required for performing each step and we will correlate it with clinical timelines, to ensure its full compatibility. We will consider the operating costs for each step of the manufacturing process. In this way we will be able to estimate the overall cost of a service set in a small local business near the hospital area (in our case the distance can be covered in about 45 minutes).

Deliverables (brief description and specification of delivery date)[1]
D.4.1: Assessment of time and production costs, in the case of a small local company (M12).

Work package number	WP 5		Start month		1		End month				12
Project year 1 or additional WP[1]	year 1										
Activity type[2]	OTHER										
Work package title	Dissemination										
Work package leader	IMATI										
Partner number	1	2	3								
Partner short name	IMATI	ITIA	UNIPV								

Objectives:

The aim of WP5 is to disseminate the ideas and the results of the Project, both at an industrial and a scientific level. With regard to the industrial level, we will first share the results and the potential impact of our Project with the industrial and clinical interest group. Then, through the collaboration of the group, we aim at reaching other hospitals and small companies interested in the outcomes of the Project. From the scientific point of view, we will disseminate the results through papers on international peer reviewed journal and participations to international scientific conferences and meetings.

Description of work (possibly broken down into tasks), and role of partners

The dissemination involves two Tasks:

Task 5.1: Dissemination at industrial level (IMATI-ITIA-UNIPV)
We will first share the results and the potential impact of our Project with the industrial and clinical interest group. Then, through the collaboration of the group, we will reach other hospitals and small companies interested in the outcomes of the Project. For this purpose, we will prepare informative material and a conference website will be published.

Task 5.1: Dissemination at scientific level (IMATI-ITIA-UNIPV)
Each Research Unit will present its proper research results at relative international research conferences. Moreover, some scientific papers on international peer reviewed journals will be prepared (involving at least two of the three Research Units).

Deliverables (brief description and specification of delivery date)[1]

D.5.1: List of the activities for dissemination at industrial level (M12).
D.5.2: List of papers and presentations at international conferences (M12).

Work package number	WP 6		Start month		9		End month				12
Project year 1 or additional WP[1]	additional WP										
Activity type[2]	RTD										
Work package title	Integration of technologies										
Work package leader	ITIA										
Partner number	3	2	1								
Partner short name	ITIA	UNIPV	IMATI								

Objectives:
WP6, on the basis of the preliminary results available from WP1, WP3 and WP4, will assess the process and technologies performance and capabilities to answer to the biomedical field industrial challenges in order to take advantage of its opportunities. Materials with enhanced properties will be prepared and used to overcome the current process limitations and achieve components of better quality.

Description of work (possibly broken down into tasks), and role of partners
The additional WP6 about the integration of technologies involves two Tasks: **Task 6.1 Advanced materials preparation (ITIA)** On the basis of the results of the extensive experimental campaign carried out in WP3, new formulation of polymer composites will be investigated, in terms of plastic matrix (such as PHA, PHB) and nanofillers (such as nanocellulose, CNT, silver nanoparticles), to tackle the scientific and technological challenges of the targeted application: specifically, to reduce adhesion effects between the part and the mould and to enhance the functional behaviour of the final products. The compounding process will be then set up using a twin screws fully intermeshing co-rotating extruder; the screw configuration will be studied taking into account that multiple mixing challenges have to be faced during extrusion, such as the dispersion of primary agglomerations) and homogenous spatial distribution of all the fillers. The obtaining of composites with the proper rheological properties (for the next 3D Printing processing step) is another challenge of the task. **Task 6.2 Integration of product/process/system chain (ITIA, UNIPV, IMATI)** This Task will involve the assessment of the technologies and technology combinations. The materials with enhanced properties will be machined using the technologies identified in WP3 (microEDM only if the material resistivity is < 100Ωcm). The results obtained – in terms of the final product quality (geometrical, surface, mechanical and structural properties) and the overall process chain efficiency and cost effectiveness will be compared to the results previously obtained in WP3.

Deliverables (brief description and specification of delivery date)[1]
D.6.1 Technical Report on compounding of nano-enhanced polymeric materials (M12). D.6.2 Anatomo-functional model - Demonstrator (M12).

1 Project proposals should foresee separate WPs for the first year and the additional activity for the last 4 months, leading to tangible and identifiable results for both.

2 Please indicate one activity per work package:
RTD = Research and technological development
DEM = Demonstration
MGT = Management of the partnership
OTHER = Other specific activities, if applicable (including any activities to prepare for the dissemination and/or exploitation of project results, and coordination activities).

Table 2.3c: Summary of staff effort

A summary of the staff effort is useful for the evaluators. Please indicate in the table the number of person months over the whole duration of the planned work, for each work package, for each partner. Identify the work package leader for each WP by showing the relevant person-month figure in bold.

Staff					
WP No	**WP leader**	**CNR IMATI**	**CNR ITIA**	**UNIPV**	**Total person months**
0	IMATI	2.5	0.5	0.5	***3.5***
1	ITIA	1.0	8.0	1.0	***10.0***
2	IMATI	10.0	0.0	4.0	***14.0***
3	UNIPV	0.0	7.0	8.0	***15.0***
4	UNIPV	3.0	3.0	3.0	***9.0***
5	IMATI	2.5	1.0	1.0	***4.5***
6	ITIA	3.0	4.0	3.0	***10.0***
	TOTAL	**22.0**	**23.5**	**20.5**	**66.0**