SUBMISSION FORM OF PROPOSALS FOR DOCTORAL RESEARCH PROJECTS

Objective of the Doctoral Programme in Health Sciences and Technologies

The objective of the new interdepartmental Doctoral Programme in Health Sciences and Technologies is to train the next generation of leaders in industrial, clinical, and academic research. Our goal is to develop an organic research programme at the interface between engineering and medicine, which is inspired by the quantitative and integrative approach of physical sciences, and by the latest development in biomedical research, drive the development and clinical translation of disruptive health technologies.
The doctoral training programme will prepare students in conducting research which:

- *Extend the comprehension of how human physiology and pathology work in term of physical and chemical mechanisms, and how these mechanisms respond when perturbed by external factors such as therapies, changes in life style, and environmental factors;*
- *Develop new technologies that by leveraging on this mechanistic understanding pursue a wide spectrum of applications relevant to human health, including prevention, diagnosis, prognosis, treatment, and rehabilitation.*

Procedural aspects on the submission of proposals for doctoral research projects

Every year the PhD process will start with the submission of proposals for doctoral research projects. Each proposal must be submitted jointly by two supervisors, one providing the clinical expertise, the other the technological expertise. The Project Selection Committee will select a number of projects that is three times the number of available scholarships and should be distributed in similar proportion between medical-led or technology-led proposals. The resulting list of projects will be included in the call for student applications that the Executive Committee will compile soon after. Each student, depending on their degree, will be able to apply only for a sub-set of projects; among them each student will be allowed to select three projects, and name them in order of preference; however, in some cases it might not be possible to satisfy all requests, and some students might be offered a research project different from those they selected.

Doctoral training program

In order to be admitted to the selection, a student needs a five-year higher education degree, which includes at least one module for each of the following disciplines: mathematics, physics, computer science, biology, physiology, and anatomy.

Max number of proposals for each member of the Academic Board: 3 (three)
Max number of selected projects for each member of the Academic Board: 2 (two)
Max number of selected projects for 2019: 12 (twelve)

Title of the project

Patient-Specific Spinal Surgery for Severe Scoliosis (PS5)

Student's degree (you can choose more than one, if needed)

Yes/Not	Cultural area
NO	Medicine, biology, or related disciplines
YES	Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines. **Degree in Mechanical Engineering or Biomedical Engineering or Computer science**

Student's skills (you can fill more than one field, if needed)

Cultural area	Skills
Medicine, biology, or related disciplines	Desirable (but not mandatory) experience: • In the field of orthopaedics • Spinal surgery • In the area of medical imaging
Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines	Mandatory: • Background in biomechanics • Some background in numerical modelling (multi body dynamics, finite element modelling) Desirable: • Mechanical testing • Musculoskeletal biomechanics

Tutors (2, from different cultural areas and with at least 1 from the Academic Board)

Cultural area	Name & Surname	Department
Medicine, biology, or related disciplines	Dr Tiziana Greggi	Head Rachis Deformation Surgery Rizzoli Orthopaedic Institute
Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines	Prof. Luca Cristofolini Prof. Marco Viceconti	Dept. Industrial Engineering (DIN) Dept. Industrial Engineering (DIN), and Medical Technology Lab, Rizzoli Orthopaedic Institute

Research project

	Synthetic description
Summary (max 1000 chars)	Scoliosis can be extremely threatening: pain, disability, compression of internal organs, breathing problems are just some of the consequences. In the most severe cases, corrective spinal surgery is the only viable option. In young and growing patients, adjustable devices must be used, that are mobilized over the months to correct the spine and follow the patient's growth. One main challenge for the clinical specialist is to choose the optimal treatment for each patient, for example how to plan the right amount of adjustment over time, so as to achieve the desired correction while avoiding complications and adverse effects. Currently, surgeons are guided only by intuition and experience. The aim of this PhD project is to develop and validate a modelling technology capable of generating patient-specific predictive models of the spine biomechanics that can be used as a treatment planning tools, by simulating different treatment options and predict the occurrence of adverse effects including spinal cord compression, facets impingement, excessive strain of the intervertebral discs, excessive stretch of the muscles.

<table>
<tr><td>Objectives
(max 1000 chars + max 5 relevant references)</td><td>The project aims to develop a treatment simulation environment to optimise the treatment of scoliosis patients. The research will articulate in the following phases:
• Collection of dedicated biomechanical information (stiffness of discs and ligaments, range of motion) through ex vivo testing of spine specimens.
• Development of the protocol to build patient-specific computer models of the spine biomechanics from medical imaging data (CT, MRI and X-ray).
• Use of the ex vivo experimental data to quantify the model predictive accuracy.
• Develop a treatment simulation environment, where the most common interventions are properly simulated, and adverse effects (if any) predicted.
• Use retrospective clinical data to establish the clinical accuracy of treatment simulation environment when compared with the actual outcome of a specific treatment in a given patient.
Through these activities, the PhD student will gain skills in the area of biomechanics, in silico modelling, and orthopaedics (spine)that will make him/her employable in the academia, but also in device manufacturers and developer of medical software.</td></tr>
<tr><td>Rationale and scientific background y
(max 2000 chars+ max 5 relevant references)</td><td>Congenital and idiopathic scoliosis can be extremely threatening when causing severe deformity. Pain, disability, compression of internal organs, breathing and cardiac problems are just some of the consequences. Corrective surgery is the only option in extreme cases: this consists in the implantation of screws (or hooks) and rods that restore alignment in the frontal and sagittal planes. The surgeon must find a compromise between extreme correction (ideally restoring “perfect” anatomy) and avoiding damage due to compression or stretching of the spinal cord or nerves. In young patients, an additional challenge derives from the changes over time due to growth. In these cases, the surgeon can use Magnetically Controlled Growing Rods that must be mobilized at time intervals to induce progressive correction and allow natural lengthening. Currently, no evidence-based tool is available to help the surgeon plan the optimal compromise. Surgeons can only follow their experience and, to some extent, a trial-and-correct approach [1]. This clearly exposes the patient to the risk of unnecessary pain, organ damage, and sub-optimal correction.

References:
1. A Gonzalez Alvarez, KD. Dearn, BM. Lawless, C Lavecchia, , T Greggi, DET Shepherd Design and mechanical evaluation of a novel dynamic growing rod to improve the surgical treatment of Early Onset Scoliosis. Material and Design 2018;155:334-45</td></tr>
<tr><td>Preliminary results if existing
(max 1000 chars+ max 5 relevant references)</td><td>Prof Cristofolini has extensive experience in testing ex vivo preparation to evaluate the biomechanical properties of human spine tissues. His group developed and validated internationally acknowledged protocols for measuring the displacements and deformations in the human spine (Ref. #1).
Prof Viceconti has already developed a similar simulation environment to predict the soft tissue balance and the functional outcome of total knee replacement (Ref. #2). He also has developed patient-specific models for treatment evaluation in paediatric diseases (Ref. #3).
Dr Greggi has a massive clinical experience on the subject, and her department was one of the testing centres for Magnetically Controlled Growing Rods (Ref. #4).
Although with a more limited scope patient-specific simulators of spine biomechanics already exist (ie. Ref. #5), confirming the feasibility, in principle, of this project.

References:
1. Palanca M, Ruspi M, Cristofolini L. Full-field strain distribution in multi-vertebra spine segments: in vitro application of digital image correlation. Med Eng Phys 2018;52:76-83
2. Viceconti M, Ascani Dm Mazzà C. Pre-operative prediction of soft tissue balancing in knee arthoplasty part 1: effect of surgical parameters. J Orthop Res 2019, in press.
3. Modenese L, Montefiori E, Wang A, Wesarg S, Viceconti M, Mazzà C. Investigation of the dependence of joint contact forces on musculotendon parameters using a codified workflow for image-based modelling. J Biomech. 2018 May 17;73:108-118.
4. Choi E, Yaszay B, Mundis G, Hosseini P, Pawelek J, Alanay A, Berk H, Cheung K, Ferguson J, Greggi T. Complications after magnetically controlled growing rods for early onset scoliosis: multicenter retrospective review. J Pediatr Orthop. 2017;37:588-92
5. Musapoor A, Nikkho M, Haghpanahi M. Finite element study on intra-op corrective forces and evaluation of screw density in scoliosis surgery. Proc Inst Mech Eng 2018;232:1245-54</td></tr>
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Research project including methodology (max 5000 chars)	The focus of the activities will be on developing a numerical model of the growing spine while undergoing correction. This PhD candidate will spend 60-70% of his/her time in the biomechanical laboratory developing *in vitro* tests (supervisor L. Cristofolini) and numerical models (supervisor M. Viceconti), 30-40% of the time in the clinical settlement (Rizzoli Orthopaedic Institute) collecting and analysing retrospective patient cases. Furthermore, an international secondment of 4-5 months at a foreign clinical institution (for example, the Buda National Center for Spinal Disorders led by Prof Peter Paul Varga, in Budapest), preliminary step to develop a full scale multicentric clinical trial for the new technology after the end of the PhD project. **WP1** – BASIC CLINICAL TRAINING. Building the understanding of spinal deformity, surgical corrections, short-and long-term outcomes and complications. This WP will be particularly intense during the 1st year, to acquire new clinical understanding. However, during the entire duration of development and validation activities will be closely connected to the clinical environment. . Task 1.1: Basic knowledge: In this phase the candidate will be trained to comprehensively understand the indications and consequences for spine surgery. . Task 1.2: Specific training: in this phase the candidate will become familiar with the different surgical techniques, complications and failure scenarios of spinal corrective surgery. Furthermore, he/she will participate on the outpatient, hospital department to get involved and aware about the real clinical problems. Through this activity, he/she will develop a first concept of what is needed to assist spine surgeons to plan interventions and correction. **WP2** – COLLECTION OF *EX VIVO* DATA. Within this WP the candidate will collect a set of biomechanical data from cadaveric spines from young donors. This will serve to initialize the models and identify the relevant parameters (WP3 and 3) . Task 2.1: *Development of dedicated* in vitro *tests*. The candidate will get familiar with a multiaxial spine simulator available at the Biomechanical lab (DIN) and of the displacement and strain measurement techniques dedicated for spine testing developed at DIN. . Task 2.2: *Ex vivo characterization of cadaveric spines*. At least six spine specimens will be assessed. First, high-quality calibrated CT scans will be acquired which will be used for the numerical models (WP2). The spines will then be subjected to non-destructive tests with different types of loading and kinematics, replicating the physiological range **WP3** – PROTOCOL FOR PATIENT-SPECIFIC MODELLING . Task 3.1: *Development of the modelling protocol on retrospective data*. Initially the candidate will access retrospective imaging data of patients treated by Dr Greggi; the Rizzoli Institute default informed consent includes the permission of secondary use of clinical data in anonymised form for research. Using these data, he/she will develop the image-based modelling protocol. . Task 3.2: *Development of ad hoc imaging protocols*: if the results obtained with retrospective data are considered insufficient, the candidate will refine the current protocols for CT and MRI so that they provide the information required to properly initialise the model. To the purpose, a few new patients, for which the imaging has been requested for clinical reasons, will be examined with this new sequences, which in any case need to involve similar effective radiation doses, and continue to provide the diagnostic information required by the standard clinical protocol.

WP4 – EX VIVO VALIDATION OF PREDICTIVE MODELS. The candidate will use the experimental data collected in WP2, and the modelling protocol developed in WP3, to develop predictive models of the ex vivo experiments form CT data of the specimens and validate the modelling protocol by comparing the model predictions to the experimental measurements.

. Task 4.1: *Imaging and modelling of cadaver specimens*: before they are tested the specimens will be CT scanned with a protocol similar to that to be used *in vivo*; water-equivalent materials will be used to obtain images comparable the clinical ones. With these data the candidate will develop a complete model for each specimen.

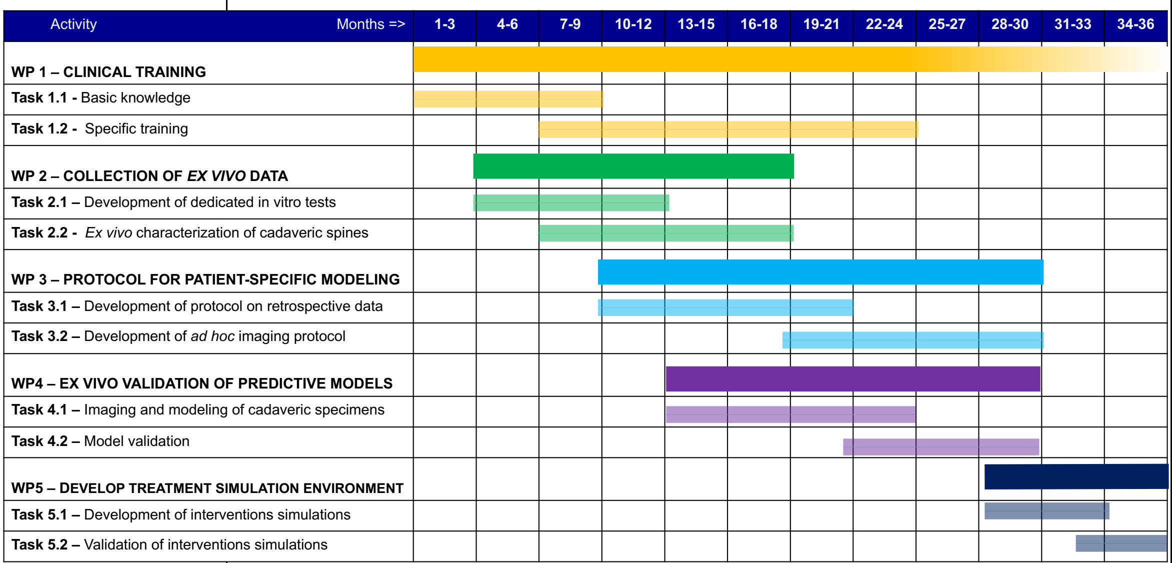
. Task 4.1: *Model validation*. The candidate will simulate for each specimen the experimental conditions and predict biomechanical quantities (displacements, forces, deformations) which are also measured during the experiment. If the comparison yields the expected predictive accuracy, the candidate will move to the next step. If not, he/she will revise the modelling protocol, the modelling assumptions, etc. Eventually it might be even necessary to revise the experimental design, and conduct new experiments, if the experimental conditions cannot be sufficiently controlled or accurately modelled.

WP5 – DEVELOP TREATMENT SIMULATION ENVIRONMENT. Once the model is fully validated *ex vivo*, the candidate will develop the simulation of the various interventions available.

. Task 5.1: *Development of interventions simulation*: in close collaboration with the clinical specialists the candidate will develop a modelling simulation for each of the interventions that are considered for these patients, or at least for the most commonly used, and/or the most complex to use optimally.

. Task 5.2 *Validation of the intervention simulations*. In a few cases it might be possible to validate the intervention simulation again *ex vivo*, but in most cases we will use retrospective data relative to patients already treated by Dr Greggi team.

Gantt chart



Innovation potential (scientific and/or technological) (max 1000 chars)	There is an acute unmet need for proper planning tools in the treatment of sever scoliosis. While the biomechanics of the scoliotic spine is complex, in the last 20 years a massive amount of experimental and modelling work has been done, which can be capitalised here. We thus believe there is a significant innovation potential in this project. If reasonable predictive accuracies are achieved, after the end of the project we will explore the possibility to hand over the technology to a company, or to establish an exploitation team without our group. In both cases, a multicentric clinical trial will be required to demonstrate the efficacy of this new technology when compared to the current standard of care. Meanwhile we will work to establish a planning service for Dr Greggi clinic, and for any other spine surgeon at the Rizzoli Institute, who is interested in using this technology to plan their interventions.
Expected results and applications to human pathology and therapy (max 1000 chars)	In this case, the clinical impact is self-explanatory: if the technology works as expected, and provide sufficient accuracy to be clinically informative, this could radically change the standard of care for the handling of sever scoliosis cases.

Available resources for the project

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<tr><th></th><th>Synthetic description</th></tr>
<tr><td>Research environment
(labs involved, background, and location)</td><td>This candidate will have an engineering background. While this will facilitate him/her in grasping the technical part of the project, some time and effort must be dedicated at the beginning to improve his/her understanding of the clinical problem. This project is rooted between different and complementary expertise:
- The group of Prof. Cristofolini (Department of Industrial Engineering) will provide “training through research” in the area of biomechanics and material characterization.
- The group of Prof. Viceconti (Department of Industrial Engineering) will provide “training through research” in the area of computational biomechanics and patient-specific modelling.
- The group of Dr. Greggi will provide training and supervision on the surgical procedures for the spine and on complications, and will supervise the design of the modelling strategy, and the retrospective validation.

This PhD candidate will enjoy this extremely stimulating interdisciplinary environment and will share his/her research time between clinics (in tight collaboration with Rizzoli Orthopaedic Institute) and biomechanics lab.

The Department of Industrial Engineering includes a large Biomechanics lab that is extremely active in the field of orthopaedic biomechanics. The focus of the biomechanics group directed by prof. Cristofolini within DIN is on the multi-scale biomechanical characterization of skeletal structures and orthopaedic devices, and on the integration of in vitro tests and numerical modelling. Furthermore, this group is acknowledged internationally for the applications of DIC to biomechanics.

The Head Rachis Deformation Surgery of the Rizzoli Orthopaedic Institute is nationally recognized for the treatment of severe deformity in adult and young patients. The group directed by dr Greggi is constantly developing new surgical protocols to improve treatment of young and growing patients. Comparison between different procedures and cases are routinely performed in order to continuously improve the patient’s provision of care.</td></tr>
<tr><td>Main equipment
(facilities and location)</td><td>The Labs of the Department of Industrial Engineering (Via Terracini 24-28, Bologna) are equipped with the testing facilities required for this project, including:
- Five universal testing machines
- Under construction: a proprietary multiaxial simulator for biomechanical testing
- State-of-the-art digital image correlation (DIC) system.
- Equipment and procedures for safe storage, preparation, testing and disposal of biological tissue specimens (both human and animal)

The Medical Technology Lab at the Rizzoli Institute has a long history of computational orthopaedic biomechanics research, under the supervision of Prof Viceconti. A set of workstations, simulation servers, and access to HPC resources through various local and international schemes, provide all the necessary computational power. The team has a vast library of specialised software, including 25 full licenses of the Ansys suite for finite element simulation.</td></tr>
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Additional funding (title, amount, start date, duration)	No significant costs are expected on behalf of Rizzoli Institute, most of the research and training costs will be covered within the Department of Industrial Engineering. However, the Medical Technology Lab of Rizzoli will make available the existing hardware and software computational resources. Funding already available at DIN will cover the cost for laboratory testing (synthetic and biological specimens, access to testing machines, lab consumables, dedicated testing fixtures): • Industrial funding on related activities (static and dynamic testing of orthopaedic implantable components): 130'000 Euro • PON 2017 "Bone++" on innovative orthopaedic devices (2019-2021): 320'000 Euro • UniBo "Proof of Concept" on a related patent: under evaluation: 40'000 • Ongoing MSCA ITN "SPINNER" (2018-2022) project: the ESRs involved in this project are developing experimental methods to investigate spinal treatments such as discoplasty, and failure mechanisms such as proximal junctional kyphosis. Great synergies are therefore possible. • Additional funding will be sought with an orthopaedic manufacturer that has approached us for the exploitation of this idea. • The CompBioMEd 2 project, which is currently under negotiation and is expected to start in Ocotober with Prof Viceconti as UNIBO principal investigator, offers an European HPC centre of excellent for computational biomedicine. This will provide to our student extraordinary opportunities for training and for access to wolrd-class computational resources.

International collaborations for the project (also in view of the Student's secondment)

	Project	**Location and team**
#1	CompBioMed Centre of Competence	EU project; coordination at UCL, London.
#2	Access to post-operative follow up statistical analysis for corrective spinal surgery	Buda National Center for Spinal Disorders, Budapest (Prof Peter Paul Varga and dr Aron Lazary)
#3	Mariano Vasquez	Barcelona Supercomputing Centre