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

Innovative technique to repair osteoporotic fractures with bone substitutes

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 Material 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 • in the field of bone biology
Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines	Mandatory: some background in polymer biomechanics Desirable: • material testing • handling and preparation of biological tissue specimens

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	1) Dr Enrico Guerra 2) Prof Cesare Faldini	1) Division for Shoulder and Elbow Rizzoli Orthopaedic Institute 2) Dip. Scienze Biomediche e Neuro-Motorie (DIBINEM) and I Clinic of Orthopaedic and Trauma Surgery of the Rizzoli Orthopaedic Institute
Engineering, physics, mathematics, computer science, chemistry, materials science or related disciplines	Prof. Luca Cristofolini	Department of Industrial Engineering (DIN), UniBo

Research project

	Synthetic description
Summary (max 1000 chars)	The second most common site for traumatic fracture in the elderly is the upper limb (proximal humerus and distal radius). Reconstruction of these fractures is currently performed with plates and screws. In both cases, healing failures (mainly pseudo-arthrosis) derive from lack of stabilization of the bone fragments, which is particularly frequent in case of poor bone quality and osteoporotic defects. As the current technique is dissatisfactory (adding more screws would not solve the problem) we will explore a different approach. A bone substitute will be used in combination or in replacement of plates and screws. This PhD project consists of three main actions: (i) biomechanical testing of different reconstruction techniques to identify the optimal ones; (ii) definition of surgical guidelines based on *ex vivo* fluoroscopic imaging (similar to the foreseen surgical protocol), in relation to biomechanical performance; (iii) definition and following of clinical trial on selected fracture cases. This project originated from the clinical problem encountered by orthopaedic surgeons, will require significant input from the technical area, and will rely on collaboration with a biomedical company.

Objectives (max 1000 chars + max 5 relevant references)	This PhD project addresses a clinical objective: developing and validating an alternative technique for the treatment of osteoporotic fractures of the upper limb. This project will start from preclinical *in vitro* testing, and will finally reach the first stages of clinical trial. The following specific aims will be targeted: • Adapting the surgical technique through *in vitro* tests and biomechanical simulations. This will allow to define the biomechanical criteria for the use of the bone substitute, and will confirm which of the traditional osteosynthesis components can be avoided. • Definition of the surgical guidelines to indicate the surgeon the optimal amount of bone substitute to be delivered in each patient under safe conditions. This part will integrate imaging techniques with biomechanical testing, so as to confirm the conditions to be achieved during surgery to grant optimal strength of the reconstruction. • Testing the concept through a first clinical trial so as to provide clinical evidence about the safety and efficacy of this technique.
Rationale and scientific background (max 2000 chars+ max 5 relevant references)	Proximal humeral and distal radial fractures account for about 25% of all fractures in the elderly and affecting approximately 142 out of 10,000 persons per year [1]. Locking plate fixation is considered the optimal treatment for these fractures, when possible. Incidence of complications increases according to patient's age, number of fragments, fracture pattern and dislocation [2]. Intra-operative risks of this technique include articular cartilage damage while drilling or inserting the screws [3]. This risk is increased as the surgeon may need to use multiple screws to stabilize the different fragments, since in osteoporotic setting the screws must be long enough to achieve fixation in the subchondral bone. The most common post-operative failure mechanism of plated proximal humeral fractures is a secondary loss of reduction [3]. Low bone mineral density (BMD) is the primary cause of this complication. In fact, one of the most common mechanisms of failure is a sliding of the fragment: osteoporotic bone has a weak mechanical structure, and repetitive loading damages the cancellous bone because of the high stress at the tips and threads of the screws. In these fractures it is important to obtain immediate post-operative fixation strength, to early mobilize the shoulder and prevent post-operative stiffness. To reduce the incidence of mechanical failure, several augmentation techniques have been developed. While augmentation provides some improvements, it also has different specific drawbacks [3]. Recently some innovative products have been released, with the aim of conjugating the positive aspects of the different augmenting materials. In particular the biomaterial used for this study is a combination of beta-TCP (beta-tricalcium phosphate) and polymethylmethacrylate (PMMA), aiming to provide good initial mechanical property, and bone ingrowth with partial substitution over time [4]. Therefore, to improve the reconstruction technique for such fractures, alternative techniques are being sought. Rather than increasing the number of screws, the focus is shifting towards bone substitutes as means of initial fixation, and to promote bone healing [5]. The trauma surgeons in Rizzoli area are among the pioneers in this field. ***References*** [1] WHO, 2007. Assessment of fracture risk and its application for postmenopausal osteoporosis. Report of WHO study group, World Health Organization, Geneva. [2] Gavaskar AS, Karthik B, Tummala N Second generation locked plating for complex proximal humerus fractures in very elderly patients. Injury 2016; 47(11): 2534–38 [3] Thanasas C, Kontakis G, Angoules A. Treatment of proximal humerus fractures with locking plates: systematic review. J. shoulder Elb. Surg. 2009;18(6):837–44. [4] Dall'Oca C, Maluta T, Micheloni GM, et al. The biocompatibility of bone cements: progress in methodological approach. Eur. J. Histochem. 2017;61(2):2673. [5] Kammerlander C, Neuerburg C, Verlaan J-J, et al. The use of augmentation techniques in osteoporotic fracture fixation. Injury. 2016;47:S36–S43.

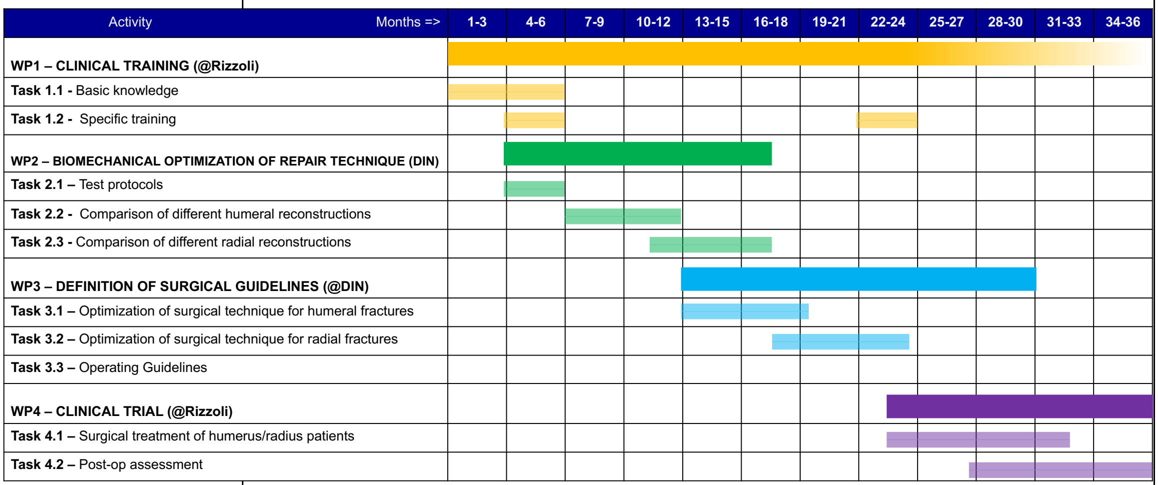
Preliminary results if existing (max 1000 chars+ max 5 relevant references)	The Shoulder and Elbow surgery of Rizzoli Institute is exploring new and dedicated surgical techniques to improve the treatment of fractures in the elderly. Options such as bone grafts are often considered [1]. The main limitation of this approach is the limited availability of heterologous graft. Alternative techniques consisting in optimal placing of the screws have been developed [2] with debatable results. Smart or bioactive cement augmentation is an option for osteoporotic bone. Bioactive cements and substitutes are being developed. It has been shown that such beta-TCB additivated cements can fill bone defects, promote blood infiltration and are osteoconductive [3]. The collaboration of prof Cristofolini and dr Guerra recently led to an innovative concept where the screws are partly or completely replaced with a bioactive bone substitute. This concept was first explored using composite bone models [4]. We recently extended our pilot study with cadaveric humeri [5]. This confirmed the excellent biomechanical potential of this surgical technique. Dr Guerra already submitted a request for a first clinical trial for approval to the ethical committee and to the health advisory board. The first stage of approval has been granted, further details have already been submitted. ***References*** [1] Bellato E, Rotini R, Marinelli A, Guerra E, O'Driscoll SW "Coronoid reconstruction with an osteochondral graft." Shoulder Elbow Surg. 2016;25(12):2071-77. [2] Marinelli A, Guerra E, Ritali A, Cavallo M, Rotini R. "Radial head prosthesis: surgical tips and tricks." Musculoskelet Surg. 2017;101(Suppl 2):187-196. [5] Dall'Oca C, Maluta T, Micheloni GM, et al. The biocompatibility of bone cements: progress in methodological approach. Eur. J. Histochem. 2017;61(2):2673. [3] Cristofolini L., Morellato K., Soffiatti R., Rotini R., Guerra E., 2018, "Reconstruction of fractures of the proximal humerus with a reduced number of screws and a reinforced bone substitute," J Bone Joint Surgery (Br) Orthop Proc, 100-B(Supp 3) [4] Cristofolini L., Morellato K., Cavallo M., Guerra E., IN PRESS, "Reconstruction of proximal humeral fractures with a reduced number of screws and a reinforced bone substitute: a biomechanical study," J Shoulder Elbow Surgery.
Research project including methodology (max 5000 chars)	This project aims at bringing towards the clinical trial a treatment solution that currently has been exploratively tested *in vitro*. This PhD project will start with training of the candidate (which must have a technical background) on the clinical problem (WP1). The candidate will then spend 60-70% of his/her time in the biomechanical laboratory of prof. Cristofolini developing and testing the treatments solutions (WP2 and 3). Finally, he/she will spend the remaining time in the Rizzoli Orthopaedic Institute, analysing the results from the clinical trial. **WP1** – CLINICAL TRAINING. The candidate first will need to get familiar with the types of fracture, treatment options, and failure scenarios. This activity 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.* The student will receive materials and specific training in order to comprehensively understand the epidemiology and the causes of upper limb fractures, the treatment options for the different groups of patients, the standard imaging protocols. . Task 1.2: *Specific training.* the candidate will focus on the different options for fracture treatment, and on the different post-operative failure scenarios. To do so, he/she will participate on the outpatient, hospital department and first aid activities so as to get involved and aware about the actual clinical problems. **WP2** – BIOMECHANICAL OPTIMIZATION OF REPAIR TECHNIQUE. This part of the project will explore different treatment options aiming to

	reduce/avoid the use of screws and plates in osteoporotic fractures of the upper limb, and to assess the biomechanical influence of using a bone substitute. The core of this WP is a series of biomechanical *in vitro* tests on cadaveric bone specimens. . Task 2.1: *Test protocols*. The PhD student will develop dedicated biomechanical *in vitro* tests to assess the strength of reconstructions of the proximal humerus and distal radius. The focus will be on: (i) eliciting common failure scenarios; (ii) high test repeatability. Bone and implant deformations will be measured with digital image correlation (DIC). The protocol will be able to quantify the strength of the different reconstructions under cyclic loading. The PhD student will be able to exploit other similar tests previously developed in the group of prof Cristofolini. . Task 2.2: *Comparison of different humeral reconstructions*. A protocol for replicating relevant fractures of the proximal humerus will be agreed upon with the surgeons. 2-3 different innovative reconstruction techniques will be defined, where fewer screws than the standard are used, and a bone substitute is injected. Pair of cadaveric humeri will undergo simulated fracture. One humerus of each pair will be treated with the currently standard technique, the contralateral one with one of the innovative techniques. The strength of the reconstructions will be assessed using the protocols from Task 2.1. . Task 2.3: *Comparison of different radial reconstructions*. This task is quite similar to Task 2.2., except that the focus will be on radial fractures, and on different reconstruction techniques. **WP3** – DEFINITION OF SURGICAL GUIDELINES. While WP2 concentrates on biomechanical optimization, this WP aims to identify the optimal indications for actual clinical implementation. The optimal types of reconstruction for the humerus and radius (not necessarily the same) will be addressed. Reconstructions will again be performed on cadaveric specimens, but using instrumentation and imaging as in real surgery, to define the ideal protocol. Task 3.1: *Optimization of the surgical technique for humeral fractures*. The most effective technique from Task 2.2 will be adopted. Reconstruction under fluoroscopy will be performed to monitor the amount of bone substitute delivered. Biomechanical testing will be performed again on the new reconstruction, with the same protocol as in WP2. Task 3.2: *Optimization of the surgical technique for radial fractures*. The same strategy as in Task 3.1 will be applied to the optimal technique chosen from Task 2.3. Task 3.3: *Operating guidelines*. The optimal surgical protocol for the humeral and radial fractures will be defined based on the results from Tasks 3.1 and 3.2. The focus is on minimize the risk of leakage of the bone substitute, while achieving the required biomechanical strength. **WP4** – CLINICAL TRIAL. The best solutions (from WP2) will be applied to fracture patients following the guidelines (from WP3). Preliminary approval by the ethical committee and the relevant authorities has already been submitted for an initial clinical trial. . . Task 4.1: *Surgical treatment of humerus/radius patients*. At least 10 patients with each type of fracture will be enrolled during this project to receive the innovative treatment. A matched group of control patients receiving gold standard treatment (plates and screws) will be recruited. Information about intra-op complications

will be collected (e.g. cement leakage, difficulty in recomposing the fragments).

. Task 4.2: *Post-op assessment*. The PhD candidate will analyze the immediate post-op bi-planar images with a 2D to 3D reconstruction software. This way it will be possible to (i) assess the shape of the bone substitute delivered; (ii) measure cement leakage (if any). Furthermore, follow-up during the 3 post-op months will allow collecting information about success and mid-term complications (fragment sliding, loss of articular mobility, pain etc) following standardized metrics currently adopted at Rizzoli.

Gantt chart



Innovation potential (scientific and/or technological) (max 1000 chars)

This PhD student, in collaboration with the orthopaedic surgeons involved and the biomechanical group, will develop and assess a new solution for treating osteoporotic fractures. The combined use of an osteoconductive injectable bone substitute and classic screws, and the use of such bone substitute are a new concept for the treatment of this type of fractures. This project will therefore lead to technological innovation in the delivery and use of such cement (possibly requiring further development of the bone substitute itself, in collaboration with the Manufacturer).

Expected results and applications to human pathology and therapy (max 1000 chars)

This project will develop and validate better treatments for osteoporotic fractures of the upper limb, that are currently difficult to treat, and have unacceptably high failure rate. It is expected that the innovative solutions proposed will improve fracture treatment in different ways:

- Lower incidence of articular damage due to intra-op cartilage drill-in
- Lower incidence of short- and mid-term failures (pseudarthrosis, malunions)
- Better bone healing thanks to the osteoconductive bone substitute.

Available resources for the project

	Synthetic description
Research environment (labs involved, background, and location)	This candidate will have a technical 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 between a technical and a clinical environment: - The group of Prof. Cristofolini (Department of Industrial Engineering) will provide "training through research" in the area of biomechanics and material characterization. - Rizzoli Institute (dr Guerra and prof. Faldini) will provide training and supervision on the most frequent bone fractures, on the current techniques for osteosynthesis, and on the need for improvement; dr Guerra will contribute to the design of the reconstruction techniques, and on laying down the specifications for biomechanical testing. Prof. Cristofolini has been intensively collaborating for years on research projects at the intersection between orthopaedic clinical application and biomechanics research together with dr Guerra and with prof Faldini. A strong integration of the two research groups has been achieved by involving the clinical staff in lab activity, and the lab staff in clinical research. The success of collaboration is documented by a number of joint publications. 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 modeling. Their main activities focus on preclinical testing of orthopaedic implantable devices, and validation of innovative surgical techniques. Furthermore, this group is acknowledged internationally for the applications of DIC to biomechanics. The **Dept. of Shoulder and Elbow surgery** of the Rizzoli Orthopaedic Institute continuously performs teaching and research activity. It participates to several national and international clinical studies, for example for the ultrasound guided treatment of calcific tendinopathy, the development of new materials for osteosynthesis of shoulder and elbow fractures. Several patents have been ideated and registered, such as a titanium mini-plate for surgical repair of the rotator cuff, a special postoperative brace for the shoulder, a self-threading titanium screw for a plastic plate. The Unit has a constant partnership with scientific laboratories to improve arthroscopic suture techniques in rotator cuff repair, for shoulder prosthesis design improvement, and in the field of regenerative medicine for poor quality or massive tears of rotator cuff tendons, for the study and treatment of osteoporosis. The **I Clinic of Orthopaedic and Trauma Surgery** of the Rizzoli Orthopaedic Institute is nationally recognized for the treatment of severe orthopaedic conditions including joints diseases which require both primary and revision surgery. Its activity is mainly focused on surgical treatment of complex cases, analysis and data collection of multiple type of joint replacement surgery through different surgical approach and procedures. Comparison between different procedures and cases are routinely performed in order to continuously improve the patient's provision of care.

Main equipment (facilities and location)	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)
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. 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): • PON 2017 "Bone++" on innovative orthopaedic devices (2019-2021): 320'000 Euro • Partnership with company producing bone cements and bone substitutes (Tecres SpA) for mechanical testing of materials, and exploration of applications for fracture treatment: currently granted for 2018-2020: 85'000 Euro + supply of cadaveric tissue specimens • Industrial funding on related activities (static and dynamic testing of orthopaedic implantable components): 130'000 Euro

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

	Project	Location and team
#1	Collaboration on innovative bone substitutes stimulating faster bone healing	Uppsala University, Department of Technology and Science, Sweden (dr Cecilia Persson and dr Caroline Öhman)
#2	Ongoing collaboration on consensus agreement about classification and treatment protocols	Orthopädische Chirurgie und Traumatologie des Bewegungsapparates, Lindenhof, Bern, Ch (Prof. Ralf Hertel)
#3		