

DARE

DIGITAL LIFELONG PREVENTION

CODE NO. PNC0000002

Spoke 3 Deliverable

S3.D2.1 Concept and relevant design of the models

This research is co-funded by the Ministry of University and Research
within the Complementary National Plan PNC-I.1
“Research initiatives for innovative technologies
and pathways in the health and welfare sector”

D.D. 931 of 06/06/2022, PNC0000002 DARE - Digital Lifelong Prevention

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Deliverable information	
Spoke number and title	Spoke 3 - Digitally Enabling Secondary and Tertiary Prevention
WP number and title	WP2 - Personalization and Risk Stratification Tools
Related task(s)	T2.1 - T2.7
Lead beneficiary	IOR
Contributing beneficiaries	UNIROMA2, UNIPR
Dissemination level	Public, fully open
Due date	15/12/2023
Actual date of delivery	20/12/2023
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Document history

Version	Date	Author(s) /Reviewer(s) (Beneficiary)	Description
0.1	1/12/2023	Alberto Leardini (IOR)	First partial draft
0.2	13/12/2023	Alberto Leardini (IOR)	Second partial draft
0.3	20/12/2023	Pilot Leaders (IOR)	First full draft
1.0	27/12/2023	PI co-PI SP3	Final Revision

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Table of contents

Publishable Summary	5
1. Introduction.....	7
1.1. WP2 overview.....	7
1.2. Activities in WP2, and pilots' status at month 12.....	9
1.3. Deliverable outline.....	10
2. Research concept and design	11
2.1. Task 2.1 - A Digital Twin technology to monitor the risk of fragility bone fractures in osteoporotic patients (IOR)	11
2.1.1. Overview.....	11
2.1.2. Objectives.....	11
2.1.3. Study design.....	12
2.1.4. Expected results	12
2.1.5. Project progress.....	12
2.2. Task 2.2 - Predicting the risk of Osteoarthritis and Joint Replacement failure (IOR).....	12
2.2.1. Overview.....	12
2.2.2. Objectives.....	13
2.2.3. Study design.....	13
2.2.4. Expected results	14
2.2.5. Project progress.....	15
2.3. Task 2.3 - Personalized functional models for pre-operative planning of High Tibial Osteotomy (IOR).....	15
2.3.1. Overview.....	15
2.3.2. Objectives.....	16
2.3.3. Study design.....	16
2.3.4. Expected results	17
2.3.5. Project progress.....	17
2.4. Task 2.4 - Predicting the risk of bone fracture in patients with metastatic carcinoma (IOR)	17
2.4.1. Overview.....	17
2.4.2. Objective.....	18
2.4.3. Study design.....	18
2.4.4. Expected results	18
2.4.5. Project progress.....	19

2.5.	Task 2.5 - Cardiovascular radiomics to stratify risks of post-operative adverse events (UNIROMA2).....	19
2.5.1.	Overview.....	19
2.5.2.	Objective.....	20
2.5.3.	Study design.....	20
2.5.4.	Expected results	21
2.5.5.	Project progress.....	21
2.6.	Task 2.6 - Risks of Sleep Disorders in Older Sarcopenic and Physical Frail Patients (UNIPR).....	21
2.6.1.	Overview.....	21
2.6.2.	Objectives.....	24
2.6.3.	Study design.....	25
2.6.4.	Expected results	25
2.6.5.	Project progress.....	26
2.7.	Task 2.7 - Toward a digital twin of postural stability in the elderly (UNIROMA2).....	26
2.7.1.	Overview.....	26
2.7.2.	Objectives.....	27
2.7.3.	Study design.....	27
2.7.4.	Expected results	28
2.7.5.	Project progress.....	28
3.	Conclusion and next steps.....	29

Publishable Summary

Work Package 2 (WP2) of the DARE project is a part of Spoke 3, titled 'Digitally-enabled secondary and tertiary prevention'. The overall scope is to make considerable progresses in current and novel "Personalization and Risk Stratification Tools". WP2 comprises now seven tasks, each with a single pilot study, all focusing in fact on secondary and tertiary prevention interventions supported by ICT infrastructures.

In summary, the targeted scopes and the relevant activities will be the following. In T2.1, the clinical validation of an original digital twin technology is searched to assess more precisely patient-specific risk of hip fracture in patients with primary osteoporosis. In T2.2, digital technologies will be developed to a) assess the risk of disease progression and support clinical management of patients with early osteoarthritis, and b) predict the risk of implant failure in patients with joint prostheses. In T2.3, an available digital tool for a personalized 3D pre-operative planning of knee osteotomy procedures for patient suffering of severe OsteoArthritis will be optimized and made accessible to a large population of hospitals and surgeons; the planning will also be enhanced with a comprehensive biomechanical analysis from instrumented gait-analysis. In T2.4, an artificial intelligence system based on X-ray images will be developed and exploited to assess the risk of pathological fracture in patients affected by metastatic carcinomas, very valuable for both prevention and decision making, i.e. surgical vs non surgical treatments. T2.5 wants to provide a new stroke risk score in patients with coronary artery disease based on specific features at CT imaging, including radiomics data and blood biomarkers, assuming this can enhance the therapeutic diagnostic and stroke prevention pathway. T2.6 wants to detect changes in brain, muscle, bone, cardiovascular system, hormonal milieu and body composition in community-dwelling older frail sarcopenic and healthy active individuals with sleep disorders, to gain a deeper understanding of the impact of sleep health on Mild Cognitive Impairment and cognitive frailty, sarcopenia and physical frailty, dementia and mobility-disability. T2.7 wants to assess the probability of the risk of falling in older persons, based on the reference prior and the individual likelihood estimated from multiple behavioural, anamnestic, anthropometric, and clinico-



haematological parameters; this will inform the generation of digital twins of postural stability from real-time updates on multimodal individual and population data.

These seven pilot studies employ a number of different methodologies, involve diverse groups of patients, take advantage of the most modern instruments and devices, and most of them are based on encouraging preliminary results. The investigators look in fact competent and experienced enough to guarantee a successful completion of all the pilots, eventually providing validated tools in support to secondary and tertiary prevention, in particular to stratify risks and to personalize therapies and treatments.

During the first 12 months of the project, the pilot concepts were defined more clearly and consistently within Spoke 3, also in fruitful collaborations with the Spoke 1 staff, in particular for the formulation of the necessary services and infrastructures, for the statistical analyses, and for the most appropriate indicators to measure the impact of all these new models and tools. All the seven pilots are intended to open new clinical and prevention pathways to improve both the quality of life of these patient populations and the effectiveness of relevant health services. At the time of writing a couple of these pilots have already received approval from the local Ethical Committee, and the other requests are now in preparation; also this process may imply eventually small changes, which however shall improve further the value of the studies.

1. Introduction

1.1. WP2 overview

The Work Package 2 (WP2), “Personalization and Risk Stratification Tools” of the DARE project is part of the Spoke 3 “Digitally-enabled secondary and tertiary prevention” and originally gathered 8 Pilot Studies in 7 Tasks, all focused on secondary and tertiary prevention supported by ICT- infrastructures. One of these Pilots, in Task T2.7 (original Pilot T2.7b) is currently in stand-by waiting for funding of the project from DARE. Thus, eventually WP2 has 7 Pilots, one for each Task. However, a new Task with a single Pilot have emerged in IOR, and in case it will be introduced and described in following reports and deliverables. WP2 is coordinated by Alberto Leardini (IOR), a biomedical engineer from many years working in Biomechanics and Functional Assessments, more recently involved in Personalized Medicine and in the technology for monitoring functional performance in Orthopaedics.

In WP2 we want to address instruments and tools to develop personalized models of single patient conditions, to possibly improve the capacity to identify situations at higher risks, in a way treatments eventually can be planned and performed at the right time, in the right person, with the right technique. In other words, in these pilots we want to stratify the clinical risk in a number of different diseases, selecting more carefully those patients to be analyzed and in case to be treated with higher priority. With this approach we expect less treatments, better clinical results, and thus smaller costs for the National Healthcare System (NHS), in addition to a better quality of life for these patients.

The more specific aim is to deliver digital models of the human body and its function, looking with special care to those mechanistic models, such as those for example called ‘Digital Twins’, i.e. virtual models at the computer designed to accurately reflect a physical object, in our case a part or a system of a human person. Digital twin technology is revolutionizing healthcare systems by leveraging real-time data integration, advanced analytics, and virtual simulations to enhance patient care, enable predictive analytics, optimize clinical operations, and facilitate training and simulation. The Digital Twins addressed in WP2 are those where the biological, physiological and biomechanical laws of human subjects are known, and the expected clinical results are established in the relevant

literature in medicine, biology and bioengineering, or at least are pretty well comprehended.

In vivo models and traditional clinical trials have been the option-of-choice for researchers as they investigate underlying mechanisms of medical conditions, and as they develop effective interventions. The computer model based approach has resulted recently in a number of successful so-called 'in-silico trials' (see clinicaltrials.gov), where the traditional clinical trials, always implying the critical and difficult recruitment of real patients, are somehow replaced by complex computer models, able to replicate digitally the major biological and biomechanical conditions of a large number of clinical cases, and to respond to external solicitations according to the patient-specific situation. Thus, in addition to the traditional in-vivo trials in patients, also in-vitro and animal experimentations shall be overcome by this new generation of models. This is now more and more frequently exploited, to analyze the effect of injuries and diseases, as well as the safety and efficacy of new treatments. In an advanced context, these are used to design customized devices or techniques, according to the specific condition and expectation of the patient, as well as the individual experience of the medical doctor. In addition to the troubles and risks for the patients, conventional clinical trials are also very expensive. Of course after in-silico and in-vitro experimentations, in-vivo trials will be necessary, but likely on more effective and safe treatments, and may be in smaller population sizes. Reliable in-silico models and Digital Twins thus need to be developed further, for the benefit of patients, research and healthcare institutions.

A typical example, somehow inspiring also one of the present Pilots (T2.3), is the surgical treatment of high-tibial-osteotomy for the correction of varus deformity of the knee joint and/or of the lower limb. This at the moment is an established surgical treatment with off-the-shelf instruments able to slow down the progress of the osteoarthritis of the knee, and thus to delay, or to save from, a much more invasive joint replacement. In the recent years, customized procedures are available and are still under validation, for which tools for the stratification of the risk of joint replacement, as well as for personalization of the overall treatment are searched. Recently, in the in-silico trial "Personalised HTO Versus Generic HTO Virtual Clinical Trial" (see also <https://clinicaltrials.gov/study/NCT03419598>) tenths of digital models of the human knee joint were virtually operated and implanted

with two different metal plates for the fixation of the osteotomy, and the relevant risk of fractures was assessed by a validated finite-element model at the computer; this was possible because of the knowledge of the material and mechanics of these plates, and of the biomechanics of the plate- and screw- to-bone interaction, i.e. the boundary conditions for the model. Different bone and plate geometries, different fixation instruments, different material properties, different boundary conditions, different daily living activities, are expected to result in very different outcomes, and these models can easily perform all these simulations and thus return very valuable responses.

With the pilots in WP2 we want to develop, to assess, to improve, and to validate some of these models, and to exploit these in real clinical contexts, according to relevant clinical and surgical questions. As documented in the following of the present Deliverable, the personalization and the risks associated to a large spectrum of human weakness and fragility are addressed, such as those of the bones, the joints, the cardiovascular and motor control systems, as well as those in the emotional / neurological / psychophysical medical area. In addition, musculo-skeletal deformities are analyzed.

These models need to be fed by data, as many as possible and as much accurate as possible, taken from real patients. In WP2, we gather and analyze data from motion capture, medical-imaging, other computer models, available biomechanical repositories, etc. Modern technologies, such as weight-bearing CT, 3T MRI, additive manufacturing, and powerful computers are also available for the creation of original data-sets necessary to run reasonable simulation in realistic conditions. All the relevant details are provided in Section 2, divided for each Pilot.

1.2. Activities in WP2, and pilots' status at month 12

All Pilots and Tasks in Spoke 3 were expected to submit the extensive Pilot Project Form by July 2023. Out of the 8 Pilots, 6 were submitted by May, and 1 in July; the eighth has been recently suspended. In the following months, pilot leaders and colleagues have discussed the content of their projects with experts in WP1 of Spoke 3 and several WPs in Spoke 1. Submission of the final form resulting from these discussions was done by October 2023 by all Pilots. Since that submission, the major work for the majority of the Pilots has been the preparation of all necessary documents for the relevant approval of the corresponding protocol, or protocols, at their Ethical Committee. These activities are

known to be delicate and difficult; also the time for receiving preliminary of final responses is usually long. At the time of writing, only 2 pilots have received this already, while the others expect to receive this at the beginning of 2024. These conditions and plans were discussed in a general meeting of the pilot leaders in WP2 on 20th September 2023.

1.3. Deliverable outline

After the present brief WP2 overview (Section 1), the current 7 pilot reports on the original concepts behind the study and about the design of the relevant models are described (Section 2). The structure of each single pilot report is similar to a standard abstract, with the traditional 5 sub-sections, plus a diagrammatic representation of the study, i.e. a graphical-abstract. Final considerations and conclusion are then made (Section 3).

2. Research concept and design

2.1. Task 2.1 - A Digital Twin technology to monitor the risk of fragility bone fractures in osteoporotic patients (IOR)

2.1.1. Overview

Bologna Biomechanical Computed Tomography (BBCT)-hip is an in-silico methodology which predicts the risk of fracture at the proximal femur for a subject, starting from the subject's femur CT scan, his weight and height. BBCT-hip performs the prediction by orchestrating two different models: one subject-specific finite element model of the femur to predict femur load to failure, and one stochastic model which calculates one million possible forces acting on the femur due to a sideways fall. The risk of fracture is computed by dividing the number of forces which would cause the fracture by the total number of forces considered (one million). Currently, the risk of fracture for the elderly is established starting from the DXA imaging technique, from which an average density, namely the areal bone mineral density (aBMD), is extracted.

2.1.2. Objectives

Clinical evidence is required to establish credibility in BBCT-hip. Hence, clinical studies are required so that its stratification accuracy, i.e., the ability to separate fracture from non-fracture cases, and its predictive accuracy, i.e., its ability to prospectively predict fractures, can be assessed. Main goal of this pilot was to set up a clinical study within Rizzoli Orthopaedic Institute (IOR).

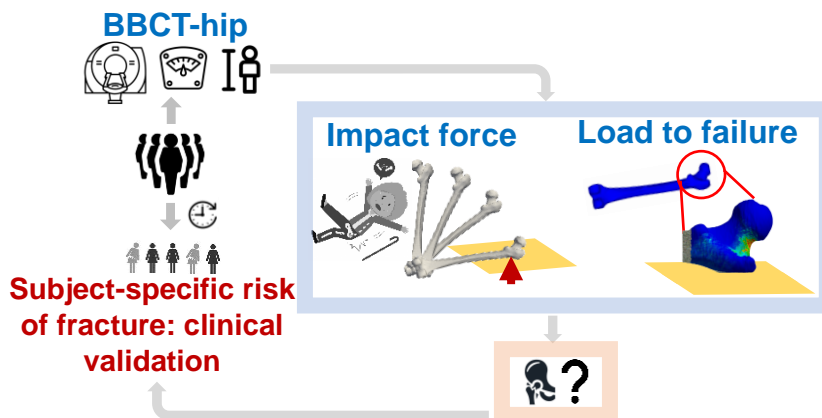


Figure 1. Graphical overview of Task 2.1

2.1.3. Study design

The pilot clinical study aims to enroll 300 subjects in total, 150 control subjects and 150 subjects who are hospitalized because of a proximal femur fracture. The enrolment follows specific inclusion and exclusion criteria. The control subjects are enrolled in IOR while getting a DXA scan. On the other hand, fractured subjects will be included in an already established clinical path which also includes a DXA scan. Hence, both DXA and CT scan will be available for control and fractured subjects to compare the corresponding predictive and stratification accuracy.

2.1.4. Expected results

At the end of the study, we will be able to establish the predictive and the stratification accuracy of BBCT-hip. In addition, thanks to the availability of the DXA scans, we will also be able to extract the gold standard aBMD measurement to assess whether BBCT-hip is able to provide an improved fracture prediction.

2.1.5. Project progress

In October 2023, after the documentation to ask permission for the study was submitted to the Ethical Committee, approval was granted. In November, the enrolment started. So far, around 10 subjects have already been enrolled. CT scans have already been scheduled for the enrolled control subjects.

2.2. Task 2.2 - Predicting the risk of Osteoarthritis and Joint Replacement failure (IOR)

2.2.1. Overview

Among the articulations deploying the stresses developed during locomotion, the knee plays a crucial role. The dynamic remodeling of the knee tissues is crucial to maintain the joint functionality, which can be deregulated by the onset of several chronic and traumatic pathologies.

Osteoarthritis (OA) is a chronic joint disease, whose prevalence depends on age and gender, but also on occupational and traumatic factors. Today, OA affects more than 500 million people worldwide - ~7% of the global population. A survey conducted in Italy in 2019 reported that ~3.9 million individuals are impaired by OA. Approximately 2.5% of

national gross domestic product was attributed to the medical costs of OA, with an yearly mean cost per OA patient of €622 in Italy. Due to both the disabling nature of OA and the absence of effective treatments, a progressive impairment of the joint occurs, ultimately leading to its replacement.

Joint replacement surgery is a common procedure used to relieve pain and restore function in patients with traumatically damaged or diseased joints, i.e., at the ending stage of OA. Despite the positive outcomes achieved a failure of the joint replacement may occur, e.g., due to loosening and instability. The annual report of the Regional Register of Orthopaedic Prosthetic Implantology (RIPO) published in 2022, reported that in 2019 a total of about 650 total knee arthroplasty (TKA) revisions were registered in the Emilia Romagna region (Italy). Compared to primary interventions, revision surgery involves higher average hospital cost. The average surgical fee for knee replacement revisions is about € 11,000 based on the data published in the last report on hospital care services fees in public and private accredited facilities in the Emilia Romagna region.

2.2.2. Objectives

To develop a preliminary digital health technology quantifying the risk of a joint adverse event – i.e., OA or arthroplasty failure of the knee joint – by employing in-silico approaches that integrate clinical imaging, functional evaluations, and experimental findings peculiar to the specific clinical issue.

2.2.3. Study design

Regarding OA, the study will focus on the clinical cases for whom there has already been the onset of OA. In this regard, OA initial stage will be assessed through routinary and quantitative clinical imaging – i.e., Magnetic Resonance Imaging – thus to elucidate the joint pathophysiology according to a standard clinical scoring system, i.e., Kellgren-Lawrence. The risk of disease progression will be assessed by conducting a prospective clinical study, within which information about i) Patient-Reported Outcome measures, ii) gait analysis, and iii) multibody-dynamic analysis will be retrieved. The above-reported investigations will be performed at the beginning of the study, and at a follow-up of 12 months. According to the design of the study, it will be possible to compare an eventual change of the patient-specific OA staging with the findings provided by the developed technological framework, which will integrate the routinary clinical imaging to insights

related to the functionality of the joint. Clinical imaging will be informed by the insights retrieved through an ex-vivo study – performed on specimens retrieved from knee joint arthroplasty – aimed at evaluating the relation between joint pathophysiology and tissues' structural and mechanical features.

Regarding the estimation of the joint replacement failure risk, a first study will be developed to predict total knee replacement contact mechanics using retrospective clinical data. In particular, the relative pose of the tibial and femoral components, extracted during daily living activities in the post-operative phase, will serve as input for a Finite Element (FE) model that will then be employed to predict key parameters such as sliding distance and contact pressure on the tibial insert component. The predicted results will be analyzed and compared to clinical outcomes obtained from questionnaires administered to patients.

Spoke 3 – WP 2 – Task 2.2

S3.D2.1 Concept and relevant design of the models

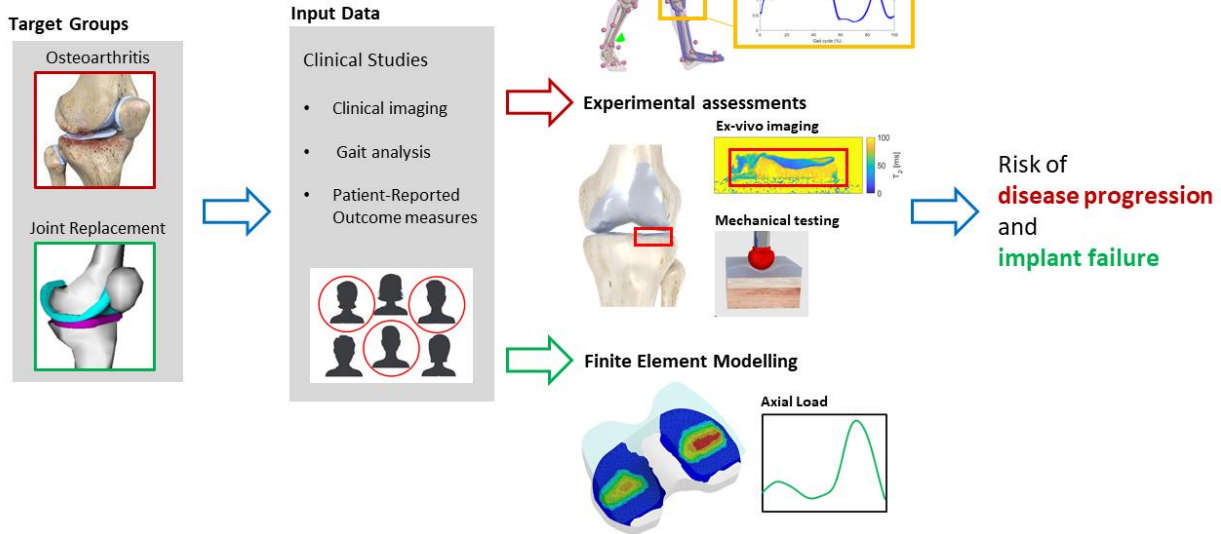


Figure 2. Graphical overview of Task 2.2

2.2.4. Expected results

Through the preliminary implementation of the digital health technology achievable within this pilot it will be possible to suggest the risk of joint adverse events by relying on clinical data. Furthermore, the application of the developed approach could assist clinicians in their decision-making process, by ensuring a consistent selection of currently

available therapies and interventions capable of reducing the risk of occurrence of the events herein investigated.

2.2.5. Project progress

By focusing on the evaluation of OA, it is currently under investigation the definition of the imaging protocols to apply during both the clinical and the ex-vivo studies. Moreover, the protocols mandatory to conduct the relative clinical studies will be presented to the Ethical Committee in the upcoming period.

A first FE model of a Total Knee Replacement has been created using the software Ansys and an open-source CAD model of the implant (Zimmer Natural Knee II Cruciate Retaining). Loading and kinematic conditions defined in the ISO 14243 have been implemented to simulate 10 gait cycles. Results in terms of contact pressures on the polyethylene tibial insert have been compared to experimental data extracted from the literature. Verification studies have been also conducted to estimate possible numerical errors in the implementation of the computational model.

2.3. Task 2.3 - Personalized functional models for pre-operative planning of High Tibial Osteotomy (IOR)

2.3.1. Overview

Open-wedge High Tibial Osteotomy (HTO) aims to treat degenerative processes such as osteoarthritis at the medial compartment of the knee in patients with varus malalignment, and particularly to slow down the progression of osteoarthritis, and thus to delay monocompartmental or total knee replacements which are much more invasive and disabling, at a higher risk of failure, and more expensive for National Health Systems. Comprehensive personalized computer-based pre-operative planning can be performed at IOR by a recently established procedure based on medical imaging and 3D knee joint modelling. However, state-of-the-art gait analysis and other biomechanical techniques, can now be exploited to enhance considerably these planning procedures, also for other even more complex surgical interventions of knee osteotomies, all those for the correction of malalignment of the lower limbs in the frontal plane. These overall improvements are expected to result in a less invasive, more accurate and faster (thus cheaper) surgical

intervention and better clinical outcomes, and thus to enlarge indication and particularly to improve prevention of all those more invasive treatments.

At the moment, these modern procedures are relegated to specialized big health-care providers, where relevant technology and expertise, both in radiologists, surgeons and bioengineers, can be found to be exploited for local patients. Unfortunately, these services are not accessible at the moment to all the many other patients distributed over the country, unless long distance travels and relevant costs are addressed. A major scope of this project is to arrange easy access to these services also to other hospitals, other surgeons and thus to many more patients. The graphical abstract here below shows the general scheme for possibly arranging all that.

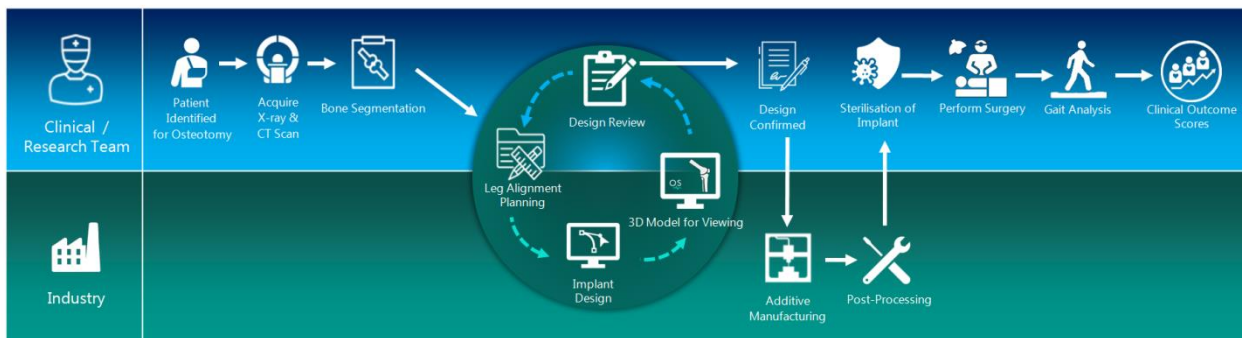


Figure 3. Graphical overview of Task 2.3

2.3.2. Objectives

The major overall objective is to arrange an open access platform for 'smart' planning of knee osteotomies, to be integrated eventually with state-of-the-art biomechanical analyses and to be tested in a distributed group of surgeons. In particular, the following will be performed after initial development. 1. a) To analyze full datasets of personalized HTO already available at IOR; and b) to perform the operability also in new patients suffering of severe knee varus with indication for HTO. 2. To develop advanced pre-operative planning procedures with additional biomechanical analyses. 3. To assess operability also in other different knee alignment correction procedures, i.e. advanced personalized osteotomy at the knee.

2.3.3. Study design

These various developing phases shall advance progressively, in sequence. The image collection procedure, the knee bones modelling, and the relevant personalized planning

for the customized systems (cutting jigs and fixation plates) to be taken in the operating theatre were established and published largely. 1. The operability and accuracy of the new platform will be examined by performing pre-op planning: on the previous series of cases (to be compared with previous surgical plans), and to new cases of HTO. 2. Instrumented gait analyses will be performed pre- and post- operation, respectively to add biomechanical parameters to the planning and to check the expected outcomes. 3. In a final phase, more complex yet feasible knee osteotomies for alignment correction will be performed, among the full spectrum of cases: closing- or open- wedge, at the proximal tibia or at the distal femur, both in medial and lateral side.

2.3.4. Expected results

1. At the end of the project, we shall have tested and validated the operability of the new platform for standard HTO osteotomies, also with successful access by a number of surgeons in remote. 2. A few pre-operative plannings will have introduced biomechanical parameters from advanced gait and imaging analyses. 3. A few planning and operations will be available also for different osteotomies at the knee, for example in closing-wedge at the proximal tibia, or at the distal-femur.

2.3.5. Project progress

The project is still in the overall design phase, for these objectives to be scheduled and arranged carefully. Human and instrumental resources are also under recruitment; not an easy task knowing the limited budget and the administrative constraints.

2.4. Task 2.4 - Predicting the risk of bone fracture in patients with metastatic carcinoma (IOR)

2.4.1. Overview

Bone metastatic cancer management is a growing problem due to the improved prognosis offered by cancer therapies. The risk of under or overtreatment is common, thus raising healthcare system expenses and discomfort to patients.

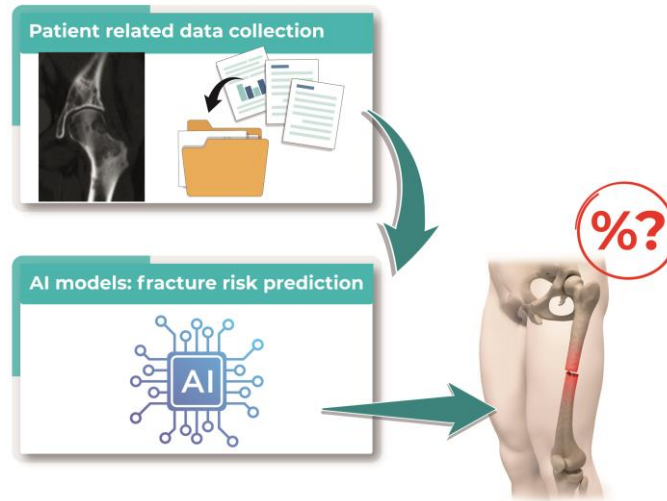


Figure 4. Graphical overview of Task 2.4

2.4.2. Objective

The main aim of this pilot project is to define and evaluate prognosis and fracture risk more efficiently and accurately, aiming to provide personalized treatment in a multidisciplinary care setting for patients with metastatic cancer.

2.4.3. Study design

Due to the complex nature of the task, we will begin by considering patients affected by proximal femoral metastasis and a mechanistic biophysical model. The biophysical model is a digital twin methodology that uses a subject-specific finite element (FE) model to predict femoral bone strength. Quantitative Computed Tomography (QCT) scans of the hip region and patient data (e.g., weight, height) inform a patient-specific computer model capable of predicting the risk of femoral fracture at the time the CT is performed. Different loading scenarios will be considered, such as walking, side-falling, stair climbing, in order to have a comprehensive overview of metastatic femur fracture risk.

2.4.4. Expected results

By using digital methodologies, we expect to better predict the prognosis of bone metastatic patients as well as the risk of fractures. The system should enable a transition from a subjective clinic's single experience to a big-data-based result of a machine learning approach; hence, decisions will be more objectively supported by a Decision Support System (DSS). We also aim to obtain a dataset from a retrospective study to train an AI-

based algorithm supporting healthcare providers in defining the optimal personalized bone metastatic treatment.

2.4.5. Project progress

We started examining the available patient data and drafting the structure of the clinical data collection for the first retrospective study. Additionally, certain medical images were scrutinized to ensure that the region of interest was fully captured, supporting individuals from Spoke 1 who need to adapt the existing biophysical model to our data.

2.5. Task 2.5 - Cardiovascular radiomics to stratify risks of post-operative adverse events (UNIROMA2)

2.5.1. Overview

Coronary artery disease (CAD) and stroke are the leading causes of death and disability in the world. There is a close link between the two diseases; in fact, the prevalence of CAD is consistent in patients with stroke, even in those asymptomatic for coronary artery disease. This is because the two diseases share common risk factors and similar pathophysiological bases, often related to the atherosclerotic process.

Over the past two decades, the angio-CT study has assumed an increasingly prominent role in the early diagnosis of stroke and the evaluation of CAD. There is great interest in the literature in the search for blood biomarkers that can guide clinical decision making in stroke patients. The literature has also drawn attention to several blood biomarkers that appear to be associated with features of coronary plaque instability and vulnerability. It has been shown that cardiac computed tomography angiography (CCTA) is appropriate to perform Texture Analysis (TA). Radiomics has already been shown to improve the performance of CCTA.

CAD and stroke constitute the leading causes of death and disability worldwide. There is a close connection between the two diseases, in fact the prevalence of CAD is consistent in patients with stroke, even in patients asymptomatic for CAD. In a series of autopsy studies for fatal stroke, about 80% of patients had coronary plaques and of these about 37.5% were significant (>50%). Another analysis based on invasive coronarography in patients with recent stroke found an overall prevalence of CAD of 61.9% and obstructive CAD of 25.7.

Studies of coronary analysis by CT in patients with stroke reported a prevalence of obstructive CAD between 20 and 40 %. Therefore, assessment of occult CAD and identification of prognostic factors for adverse cardiac events may change the prognosis of patients with cerebral ischemia.

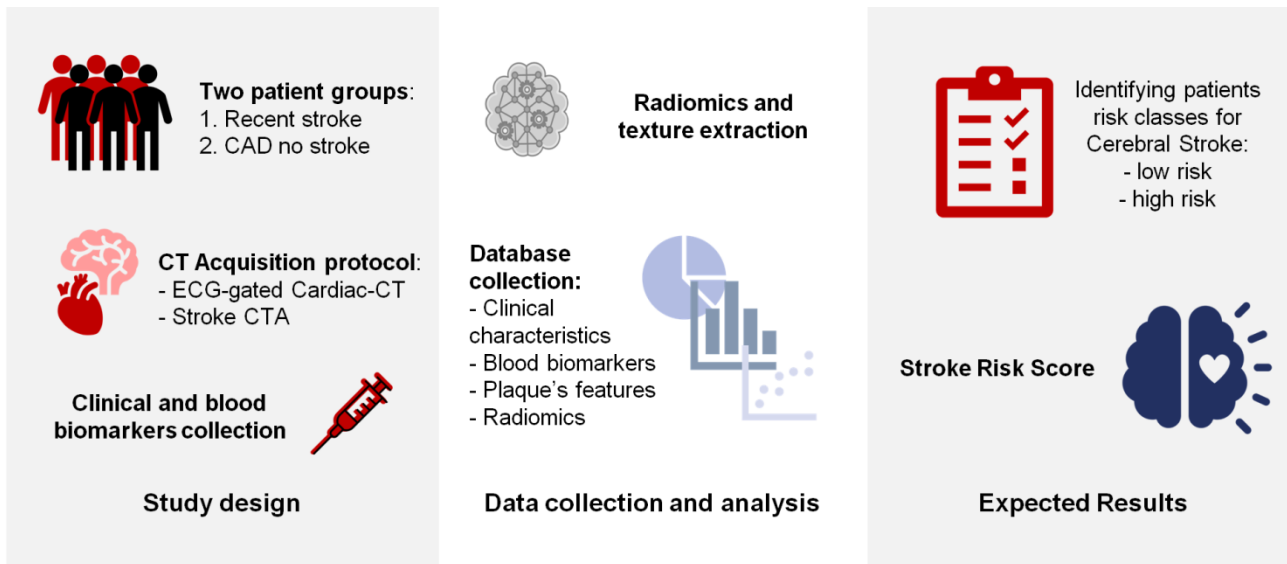


Figure 5. Graphical overview of Task 2.5

2.5.2. Objective

The primary objective of the project is to provide a stroke risk score based on specific features at CT imaging of coronary atheromasic disease, including by radiomics study, and levels of specific blood markers, which may modify the therapeutic diagnostic and stroke prevention pathway in CAD patients.

A secondary objective of the study is to investigate possible associations between stroke risk and the presence of blood biomarkers.

2.5.3. Study design

The study population will consist of two distinct groups of Patients represented by:

- Group 1: Patients admitted to the O.O.S.D.: Stroke Unit of the Tor Vergata Hospital for recent finding of ischemic and/or cardio-embolic cerebral stroke, diagnosed by brain CT scan and supra-aortic trunks Angio-CT.
- Group 2: Coronary artery disease patients with a negative history of cerebral ischemic events.

Both groups of patients will be subjected, after collection of informed consent, to cardiac-CT ECG-gated examination for the study of coronary atheromatic pathology, characteristics of the heart chambers and aortic root, and extraction of features for analysis by Texture Analysis and Radiomics technique.

In patients with cerebral ischemia, coronary-CT examination will be performed during hospitalization. A range of clinical-anamnestic data will be collected such as age, sex, BMI, positive history of previous cerebral and/or cardiac ischemic events, and cardiovascular risk factors (obesity, smoking, diabetes, dyslipidemia, hypertension, hypercholesterolemia, etc.). Patients will undergo blood sampling during hospitalization for analysis of blood, serum and plasma markers including: glucose, triglycerides, cholesterol (HDL, LDL, VLDL), direct and indirect bilirubin, NT-proBNP, markers of inflammation and atherosclerosis (PTX-3, PCR, HbA1c), Lipoprotein A and Apolipoprotein A and Linoleic Acid.

2.5.4. Expected results

We shall identify those CT features, to add to traditional clinical assessments, to identify those patients at high risk for Cerebral Stroke. These will be tested in a relevant number of patients (sample size 100/200 patients).

2.5.5. Project progress

The project has successfully achieved its approval from the institutional Ethical Committee. Patient enrolment is scheduled to begin on 12th December 2023. Concurrently, in line with the project's design, efforts are underway to develop and refine the database that will support the retrospective and prospective patient cohorts.

2.6. Task 2.6 - Risks of Sleep Disorders in Older Sarcopenic and Physical Frail Patients (UNIPR)

2.6.1. Overview

Sleep physiology, skeletal muscle and bone health, body composition, cardiovascular system, cognitive and motoric functions are strictly interconnected. However, how sleep disorders, sarcopenia, impaired bone and systemic metabolism, physical frailty and cognitive decline mutually interact is still far from being clarified. Sleep disorders should

not be considered as normal age-related changes. During aging, brain, cardiovascular physiology, as well as several components of body mass and function (skeletal muscle, adipose tissue and bone) are affected by sleep health. In current clinical practice, sleep disorders are non-routinely screened and monitored. They usually require second level techniques (with higher healthcare systems and patient costs) often not integrated in the comprehensive assessment of older patient. Sarcopenia is one of the most important determinants of physical frailty and is influenced by sleep duration through different mechanisms. According to restorative theory, protein synthesis, muscle repair, the release of anabolic hormones (growth hormone, IGF-1, testosterone and insulin) involved in restoration of muscle structure, strength and function occur during sleep. All these factors have a circadian rhythm, and chronic insomnia may induce the dysregulation of the hypothalamus-pituitary-peripheral glands axes¹. The restoration of favourable sleep patterns could be a promising preventive and therapeutic strategy for attenuating the age-related dysregulation of somatotropic and hypothalamus-pituitary-adrenal axes, stimulating muscle recovery and delaying sarcopenia onset and progression. Epidemiological studies performed in community-dwelling elders have found a U-shape relationship between the risk of sarcopenia and either short or long sleep duration, compared to normal sleep duration. Similarly, usual short (≤ 5 hours per day) and long (≥ 8 hours per day) sleep duration were both associated with lower lean mass and higher fat mass, compared with normal sleep duration. These data suggest that sleep disorders could affect body composition phenotypes in humans; in particular, body adiposity, sarcopenia and physical frailty are fundamental patterns of sarcopenic obesity. The association between sleep disorders and both body composition, specifically sarcopenic obesity, and sarcopenia, has proven to be bidirectional.

Findings from both the EPISONO and ELSA-Brasil studies have shown that obstructive sleep apnoea and nocturnal hypoxia are related to sarcopenic obesity. The risk of obstructive sleep apnoea is greater in older obese adults with low muscle mass and low muscle strength. Since the coexistence of sleep disorders and unfavourable changes in body composition, including sarcopenia, may further worsen the consequences of the individual components, understanding the intertwined pathophysiological mechanisms (Figure 1) shared by these conditions could be crucial to highlight potential targets for

future interventions aimed at preventing and mitigating multimorbidity, physical and cognitive frailty.

The overall world prevalence of sleep disorders in the elderly population is around 50%, while comparable estimates in the Italian population range are about 45%. However, the knowledge on frailty-related sleep disorders and related preventive models for dementia and mobility-disability is still poor. Even less is known on the importance of sleep health perception in healthy middle aged and older citizens. Thus, it is necessary to build-up a prospective observational database of middle aged and elderly individuals unknown to health services but not disabled, not demented, and not institutionalized. This construct is necessary to change the current healthcare system approach from reactive into proactive. The analysis of relevant outcomes for older population needs the comparison between abilities of current and innovative, digital measurements in predicting trajectories of low physical and cognitive function and quality of life. A step forward is required in terms of methodological approach for strategic plans aimed at intercepting physical and cognitive frailty, and to investigate the contribution of the related sleep disorders. These studies are necessary to preventing or slowing their progression into mobility-disability and dementia. There is need of building the rationale for innovative and multi-professional preventive responses, sharing common digital methodologies for sleep characteristics assessment. Future studies are expected to support significant changes in local and national clinical practice and decision-making, highlighting the importance of sleep as a determinant of muscle, brain, and metabolism health. Furthermore, they will support the effectiveness of sleep disorders as early markers of physical and cognitive frailty, speeding up the implementation of clinical and psychosocial interventions aimed to slow down these phenomena, preventing mobility-disability, dementia and improving quality of life.

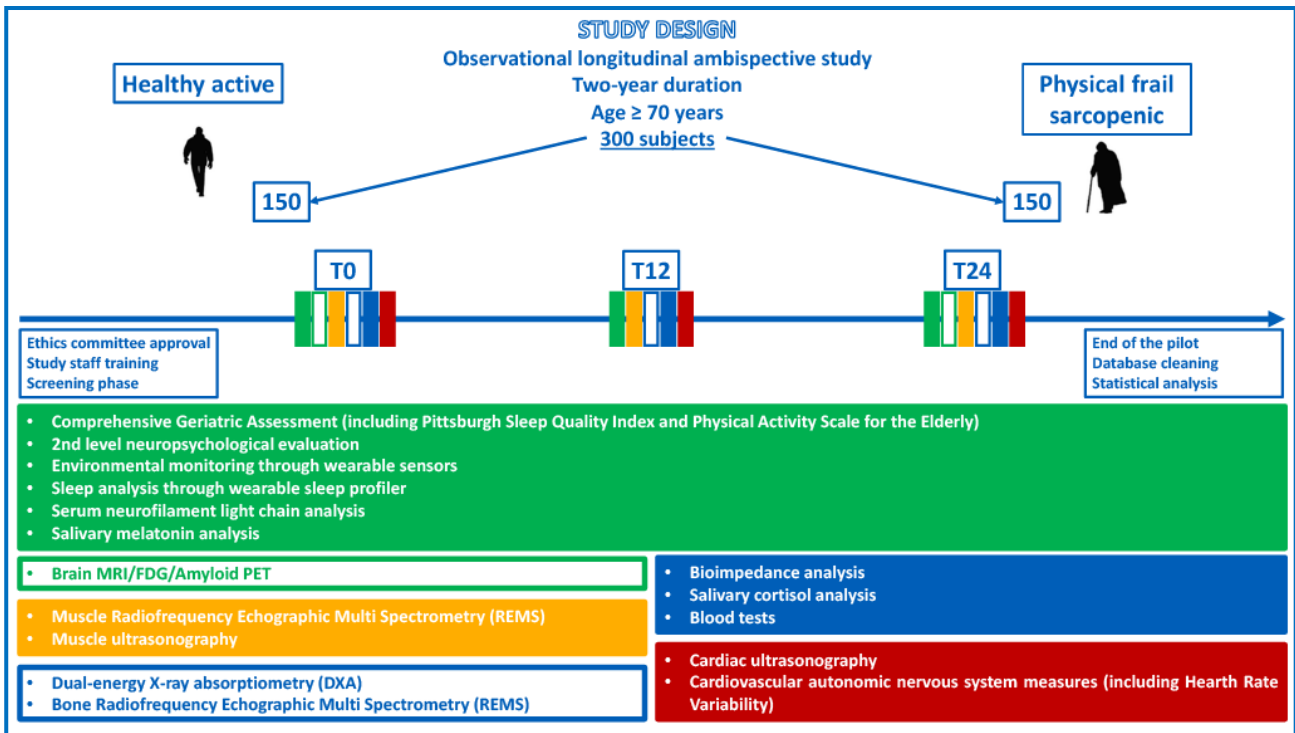


Figure 6. Graphical overview of Task 2.6

2.6.2. Objectives

Detect, in a comprehensive and translational way, changes in brain, muscle, bone, cardiovascular system, hormonal milieu and body composition to gain a deeper understanding of the impact of sleep disorders on Mild Cognitive Impairment (MCI) and cognitive frailty, sarcopenia and physical frailty, dementia and mobility-disability.

Primary objectives are to evaluate the effect of sleep disorders on the incidence of both sarcopenia and physical frailty in healthy active elderly individuals and mobility-disability in physical frail sarcopenic elderly individuals.

Secondary objectives are to evaluate, in healthy active and physical frail sarcopenic elderly individuals with and without sleep disorders, prevalence and incidence of MCI, cognitive frailty, recognized pre-frailty conditions (i.e., motoric cognitive risk syndrome), malnutrition, polypharmacy and multimorbidity; changes in bone, skeletal muscle, and body composition through X-ray, ultrasonography, and bioimpedance; brain volume and function through magnetic resonance and nuclear medicine; cardiovascular system function through cardiac ultrasound; anthropometric parameters and nutritional markers; differences in sun exposure, melatonin and cortisol salivary levels; quality of life, social well-being, and reward level; use of healthcare services and mortality; incidence of

dementia in cognitive frail elderly individuals; criterion validity between Mini Mental State Examination/neuropsychological assessment and brain MRI/FDG/Amyloid PET; characteristics of future clinical trials targeting older persons in order to address the role of recognized pre-frailty conditions in affecting the adherence to a multi-component treatment.

2.6.3. Study design

We will evaluate a well-characterized sex balanced sample of community dwelling physical frail sarcopenic and healthy active elderly people from 70 years of age, not demented and independent in the Basic Activities of Daily Living. Considering the primary objectives to evaluate the effect of sleep disorders on the incidence of sarcopenia and physical frailty as well as mobility-disability in community dwelling healthy active and physical frail sarcopenic elderly individuals respectively, a statistical power calculation will be performed using the relative risk of developing sarcopenia and physical frailty as well as mobility-disability in the two groups above mentioned. Assuming an effect size of 0.3 and α of 0.05, a power of 0.95, the obtained a priori calculation suggests a sample size of 145 subjects per group (healthy active and physical frail sarcopenic). The resulting sample size will be rounded to 150 per group to account for possible drop-outs. The role of sleep disorders on physical, cognitive and cardiovascular function, bone and muscle metabolism and body composition will be evaluated through observational and prospective fashion (Figure 2), at baseline, 12 and 24 months by performing: comprehensive geriatric assessment; sleep analysis and environmental monitoring through wearable sleep profilers and sensors; brain MRI/FDG/Amyloid PET (baseline and 24 months); dual-energy x-ray absorptiometry; radiofrequency echographic multi spectrometry; bioimpedance analysis; cardiac ultrasonography; muscle ultrasonography; serum neurofilament light chain analysis; salivary cortisol and melatonin.

2.6.4. Expected results

Employing some of the most advanced diagnostic and digital health techniques, the project will allow to analyze relevant outcomes for older population, to compare the ability of current and innovative, digital measurements in predicting trajectories of low physical and cognitive function and quality of life.

The expected findings will highlight the importance of sleep as a significant determinant of muscle, brain and metabolism health, as well as sleep disorders as an extremely relevant public health problem for the elderly population. These acquired data will also contribute to the personalization of pharmacological treatment targeting these conditions, where environmental hygiene measures and routine therapeutic expedients have not provided substantial benefits.

2.6.5. Project progress

A number of operational meetings have been done, in particular also with Spoke 1, for this pilot itself and for its twin project, where the following have been addressed:

- Advice on choosing wearable sensors for the pilot;
- Support for data analysis from wearable sensors;
- Identify synergy between this pilot population and that of Spoke 2 - Task 4.3: this synergy may consist of administering additional questionnaires in order to increase the common subset of data;
- Assess whether there is expertise on IoT sensors or other technologies to analyze light exposure.

2.7. Task 2.7 - Toward a digital twin of postural stability in the elderly (UNIROMA2)

2.7.1. Overview

In a prospective clinical study, we aim to assess the individual posterior probability of the risk of falling in older persons, based on a prior and individual likelihood. The prior is taken from a reference population and the likelihood is estimated for each individual using multiple behavioral, anamnestic, anthropometric, and clinico-haematological, parameters. The results of the pilot will inform the generation of digital twins of postural stability in older people from multimodal individual data, population data, and real-time updates on individual and environmental variables. Our approach should be instrumental to design personalized preventive measures tailored on individual responses to simple postural tests.

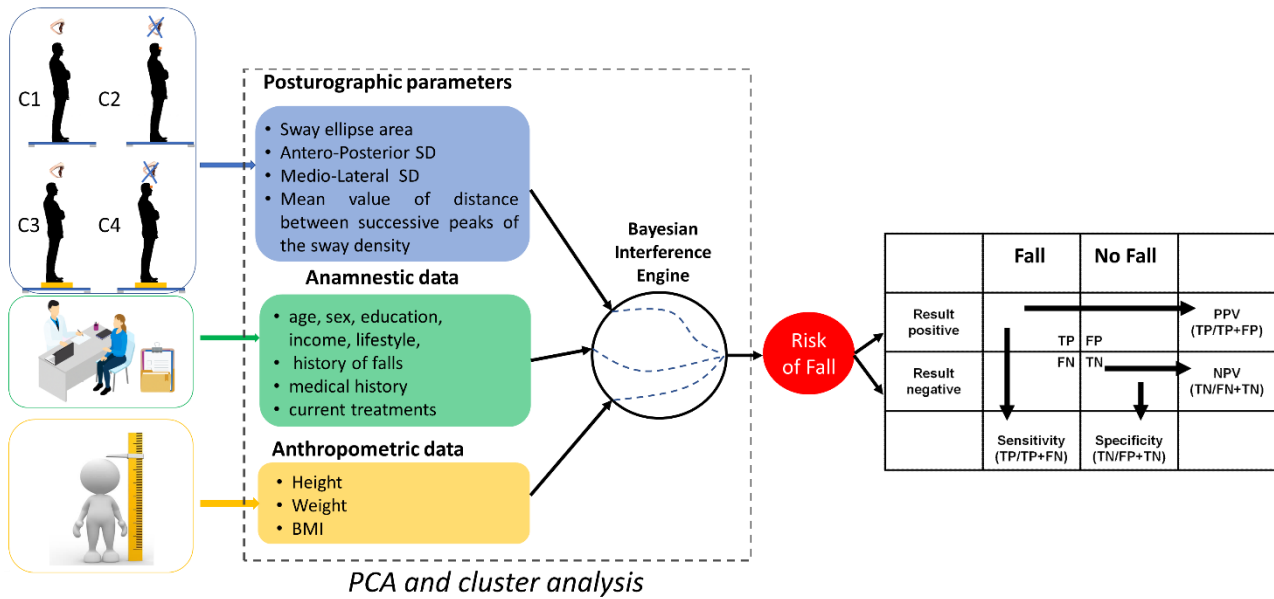


Figure 7. Graphical overview of Task 2.7

2.7.2. Objectives

Development and validation of a quantitative methodology for diagnosis of postural instability in older people. Specifically, we will obtain measurements of posturographic parameters (sway ellipse area, Antero-Posterior SD, Medio-Lateral SD, mean value of the distance between successive peaks of the sway density). We perform correlations of posturographic parameters with anamnestic (age, sex, education, income, lifestyle, history of falls, medical history, current treatments, etc.), anthropometric data (height, weight, BMI, etc), PCA and cluster analysis to identify subgroups of people based on posturography and anamnestic-anthropometric data, calculation of posterior probability of the individual risk of falling based on prior probability and likelihood derived from posturography, falls incidence over 6 months observation, anamnestic-anthropometric plus clinical-haematological parameters

2.7.3. Study design

Power analysis with power=0.80, alpha=0.05 and relative risk increment/reduction for a positive/negative BBS yields an estimate of n=40. We will recruit 100 participants to account for a 30% probability of fallers in the sample (Bergen et al. 2016) and to allow for dropouts. The prevalence of the condition is estimated as follows. According to the Centers for Disease Control and Prevention (CDC), in 2014 about 30% of older adults in the US reported falling at least once in the preceding 12 months (Bergen et al. 2016).

Prevalence of vestibular dysfunction leading to instability in the same category of people is 30-35% (Agrawal et al. 2009; Anson & Jeka 2016).

2.7.4. Expected results

We expect to establish a set of procedures to quantify postural stability, its correlation with clinical-haematological parameters, and to compute the posterior probability of falling. The validity of our methods will be assessed based on their discrimination ability (metric used: ROC and C-statistic). The methods will also be calibrated by adjusting the parameters over the tested population. Outcomes for the expected results are the prediction of instability in older individuals and in the long run the possibility of reducing the risk of falling in older individuals.

2.7.5. Project progress

We obtained the Ethics Committee approval for the project. We worked toward establishing the setup, the protocol, and the main algorithms for collection and first analyses of the data. We have started recruiting the subjects for the study.

3. Conclusion and next steps

The seven pilot projects in WP2 of Spoke 3 look consistent with the general aims and scopes of the overall DARE Project. In addition, six out of seven of these pilots have requested support by Spoke 1, which was again within the spirit and the conceptual management of the entire DARE project.

The adjustments implemented during the preparation of the Pilot Forms and their review have reinforced the scopes, and possibly eventually the value, of these studies. Possibly the EC approvals and the following official start of the study with patient/subject recruitment was expected a bit earlier, but we are also aware of the careful activities which were necessary for this review within DARE, and the summer holidays for most of the actors of the present Pilots and for the human resources in Spoke 1. In conclusion, good progresses have been performed, and we are confident to progress quickly from now on, and to gather preliminary results in line with WP2's schedule, which comprises the next Deliverable at M26.