PROJECT DELIVERABLE REPORT

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Advanced personalised, multi-scale computer models preventing osteoarthritis

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Table of Abbreviations

AR	Augmented Reality
BMI	Body Mass Index
CFD	Computational Fluid Dynamics
CGM	Continuous Glucose Monitoring
CNNs	Convolutional Neural Networks
EC	European Commission
EU	European Union
EURs	End User Requirements
FCNs	Fully Connected Neural Networks
KAM	Knee Adduction Moment
OA	Osteoarthritis
RNNs	Recurrent Neural Networks
WP	Work Package

1 EXECUTIVE SUMMARY

The main objective of this deliverable is to elaborate the user requirements for the proposed OACTIVE framework. By concluding that understanding the end users is the key to success, 'D2.1 User requirements analysis report ' appears to be very important topic of the OACTIVE project. It will have a deep impact on the proposed activities and research strategies during the runtime of the project. In order to ensure clinical relevance and foster clinical acceptance of multi-scale computer models in the future, the whole endeavor is driven by the clinical partners of the consortium and compatibility with in silico systems is guaranteed.

The OACTIVE project intents to make a significant leap forward adopting a multi-scale holistic analysis where patient-specific information from various levels, including molecular (e.g. biochemical/inflammatory biomarkers), cell, tissue and whole body, will be integrated and combined with information from other sources such as, environmental, behavioural and social risk factors to generate robust predictors for new personalised interventions for delaying onset and/or slowing down progression of OA. OACTIVE targets patient-specific OA prediction and interventions by using a combination of mechanistic computational models, simulations and big data analytics. Once constructed, these models will be used to simulate and predict optimal treatments, better diagnostics and improved patient outcomes. Developing robust, producible, interoperable and collaborative personalized multi-scale computer model for predicting Osteoarthritis is a sine qua non necessity if rational, coherent and comprehensive exploitation of the invaluable information hidden within human multiscale biological data is envisaged.

The proposed/envisaged OACTIVE holistic framework consisting primarily of:

- Mechanistic modelling framework of the musculoskeletal system
- Systemic health and inflammation modelling framework
- Behaviour, social and environmental modelling framework
- Hypermodelling framework empowered by big data
- Ontology-based framework for data /models reusability and sharing
- Personalised interventions using Augmented Reality (AR)
- Technology Validation

The OACTIVE tools and repositories will provide the community with a collaborative interface for exchanging knowledge and sharing work in an effective and standardized way. A number of open source features and tools will enhance usability and accessibility. State-of-the-art security and data protection are regarded as a sine qua non.

Perspectives on user requirements

The OACTIVE framework has different and complex user requirements and in order to overcome the complexity of the proposed project's goals. All scenario based user requirements have been aligned according to three main pillars:

- A technological perspective;
- An end users' perspective;
- A clinical/medical perspective.

The technological perspective on user requirements will have an important impact on the requirements of the OACTIVE project. Nevertheless, it needs to be flexible enough to deal with the 'End users requirements' perspective as well as the 'Clinical/Medical' perspective.

This deliverable will focus exclusively on the perspectives of End Users and the Clinical/Medical perspective. The linkage to the Technological perspectives is underlined and described whenever needed.

2 INTRODUCTION

The scope of this document is the first deliverable of WP2 "System Architecture Requirements and Use cases" and represents part of the results of task "T2.2: Design of the Data Collection Protocol and user requirements" which runs the first five months of the project (M1-5). In this deliverable, according to DoW:

"This deliverable will pro-vide a reference set of user requirements. It should constitute a reference guide for the development of different functions of OACTIVE. One chapter of this report will be dedicated to the analysis of the state-of-the-art technology."

The deliverable report contains the following sections:

• The first main section, provides an overview of the adopted methodology, including the identification of the users and systems' stakeholders, description of the expert panel that was used to collect requirements and final the questionnaire that was structured to gather the requirements are attached.

• Next the Experts' feedback is reported and there is performed an analytical evaluation and assessment of the end users requirements. Users' requirements are then analysed. Finally, the adopted approach for the system based on all the above factors along with the related benefits and impacts are presented.Analytical system specification will be presented in D2.3 System Specification Report.

3 PROBLEM DEFINITION: IMPROVE HEALTHCARE BY TRANSFORMING AND ACCELERATING THE OSTEOARTHRITIS (OA) DIAGNOSIS AND PREDICTION

3.1 Introduction to OsteoArthritis Disease

Osteoarthritis (OA) is a degenerative disease of the joints and the most common form of arthritis that causes pain and mobility limitation and, thus, reduces independence and overall quality of life [1]. Osteoarthritis is a complex disease in which biochemical and biomechanical factors are involved and occurs mostly in the weight-bearing joints of the lower limbs, such as the hip and in particular the knee [2] in addition to the hands and spine, although, almost any joint can be affected. Structurally, the whole joint is usually involved including diffuse and progressive loss of articular cartilage with concomitant changes in underlying bone (osteophyte growth and increased thickening or sclerosis) and soft tissue structures in and around the joint (synovitis, meniscal degeneration, ligamentous laxity and muscle weakness [3]). These changes affect musculoskeletal function and body movement in general, reducing general mobility and increasing disability with age. It is, therefore, of particular concern that OA is one of the most common diseases affecting old age and the single most important cause of disability in older people [4,5]. The prevalence of the disease in people over 65 years old ranges from 12- 30% [6]

and the knee is the most commonly affected joint [2]. Around 10% of people over 55 years of age have knee OA, and some of them are severely disabled [7]. Although the usual population associated with the condition is the elderly, who are mostly inactive, athletes and younger individuals are also susceptible. A great cause of concern is the large percentage of knee injured athletes that develop OA later in life, in their 40s or 50s, following successful operative repair of knee ligaments when they are young. These are particularly serious problems when there are multiple structures affected in the knee such as meniscus damage during anterior cruciate ligament rupture. The development of the disease in such a relatively young age leads to a long period of living with the consequences of OA. Depending on the population, the aetiology may differ; injuries, occupational activities, and obesity appear to be the most common causes of OA in young and athletic populations. Diagnosing OA in athletes and young individuals is sometimes challenging because of their increased pain tolerance [8]. In young and athletic individuals, the more time they spend engaging in occupational and recreational activities, their higher predisposition to injuries contribute to their higher likelihood of developing OA. Obesity and a history of traumatic knee injury (e.g., anterior cruciate ligament rupture and/or meniscal tear) are key risk factors for the accelerated development of knee OA, while structural hip deformities (including those contributing to femoroacetabular impingement syndrome) are strong predictors of early-onset hip OA. In view of these associations, rising rates of obesity and sports injuries are concerning, and may signal a future surge in OA incidence among younger people [9]. There is also a confirmed an association between type 2 diabetes and osteoarthritis and between cardiovascular diseases and osteoarthritis [10].

OA is not easy to define, predict or treat. Despite extensive research costing many billions of Euros, no drugs have been proven to modify the biological progression of OA, and only a few treatments are proven to relieve symptoms beyond the placebo effect. Given this failure to find an effective post-diagnosis treatment, attention should turn to preventing or delaying the onset of cartilage degeneration. Identification of the risk factors for developing arthritis has been limited by a lack of longitudinal data, as well as an absence of reproducible, non-invasive methods to measure changes in joint morphology and function. As a result, the disease processes governing osteoarthritis progression are still poorly understood. Although most of the existing research has focused on factors associated with the disease, the lack of longitudinal data examining the factors associated with disease onset and progression has resulted in a lack of prevention and treatment interventions that aim to target the most appropriate modifiable risk factors and, therefore, prevent or delay the onset and/or progression of the disease. Medical risk factors known to influence development of the disease include advanced age, gender, hormonal status, body weight or size, usually quantified using body mass index (BMI), and a family history of disease [11]. Additionally, there is now evidence supporting a strong genetic association [12,13]. Other known risk factors for the onset and progression of OA include joint loading during occupational or physical activity and sports participation, muscle weakness, a past history of knee injury and joint operations (ACL injury and reconstruction, meniscal damage and partial meniscus removal) and depression. Although many of the above factors are fixed, other risk factors such as body weight, physical activity and occupation are modifiable. For many people occupational activities involving physically-demanding jobs, such as manual handling of heavy loads or prolonged kneeling may be associated with the disease [14].

3.2 Cost Analysis of Osteoarthritis

OA is associated with an extremely high economic burden attributed to the effects of disability, comorbid disease, and the expense of treatment. While direct and indirect per capita costs for OA have stabilized in recent years, the escalating prevalence of the disease has led to much higher overall spending for OA. Considering the vast socioeconomic costs that represent the ageing population in the western societies directly linked to hospital admissions, emergency treatments, nursing home care, rehabilitation, community-based services, use of medical equipment, prescription drugs, changes made to the home, and insurance processing – the economic impact of OACTIVE is directly connected to the slowing down of the ageing process leading to functional decline, falls accidents, frailty, mental decline, loss of autonomy and many more, which in turn represents an economic benefit for the health and social care systems.OACTIVE will offer early diagnosis and prediction of OA benefitting this way the implementation of early and appropriate treatment before the disease becomes really painful for the patient. By delaying the presence of the disease even by few years the benefits for the society and economy will be remarkable. More specifically, direct savings for the EU health system will be generated by reducing expenses for medications (currently one-third of direct OA expenditures, much of which goes toward pain-related agents) and hospitalization and surgeries (currently 50% of direct costs, patients who undergo knee or hip replacement surgery).

Indirect savings for the EU economy by reduction of work-related losses due to sick-leave days and home-care costs:

OACTIVE will reduce indirect costs incurred as a result of losses such as lost wages, lost productivity, and expenditures resulting from the need for home care and child care, as days of medical care will be reduced. An analysis of costs related to OA compared with patients without OA or rheumatoid arthritis, but who might have other illnesses, found that patients with OA required 3 more days of medical care per year than controls and experienced significantly greater costs for issues such as home care, child care, medical equipment, and home remodelling necessary to address disability. By decreasing the disease's prevalence, indirect savings will be also generated by the reduction of costs related to OA patients' inability to find a job (9.4% of OA patients were unable to acquire jobs as a result of their illness compared with 5.2% of nonarthritic patients).

4 STATE-OF-THE-ART

4.1 Vision of OACTIVE

The vision of OACTIVE project is the development of a holistic framework that envisages to consider individual/patient-specific information in a multi-scale approach. Computer modelling will be combined with simulations aggregating various information sets and inputs from models such as full body, organ and tissue level mechanistic models along with behaviour, lifestyle, environmental and other biochemical biomarkers of systemic health. The ultimate objective is to make a significant leap forward in ***developing patient-specific predictive and preventive computer-based models*** of the physiological systems at various scales combined with data on population statistical variability and simulation tools for understanding the development and progression of OA. Applying these models at the individual patient level and thus being able to

predict outcomes more accurately at different stages of the disease would help clinicians make informed decisions regarding the potential necessity of appropriate treatment at each stage and through time and will lead to the development of individually tailored preventative measures or treatments to maximize the efficacy of the intervention.

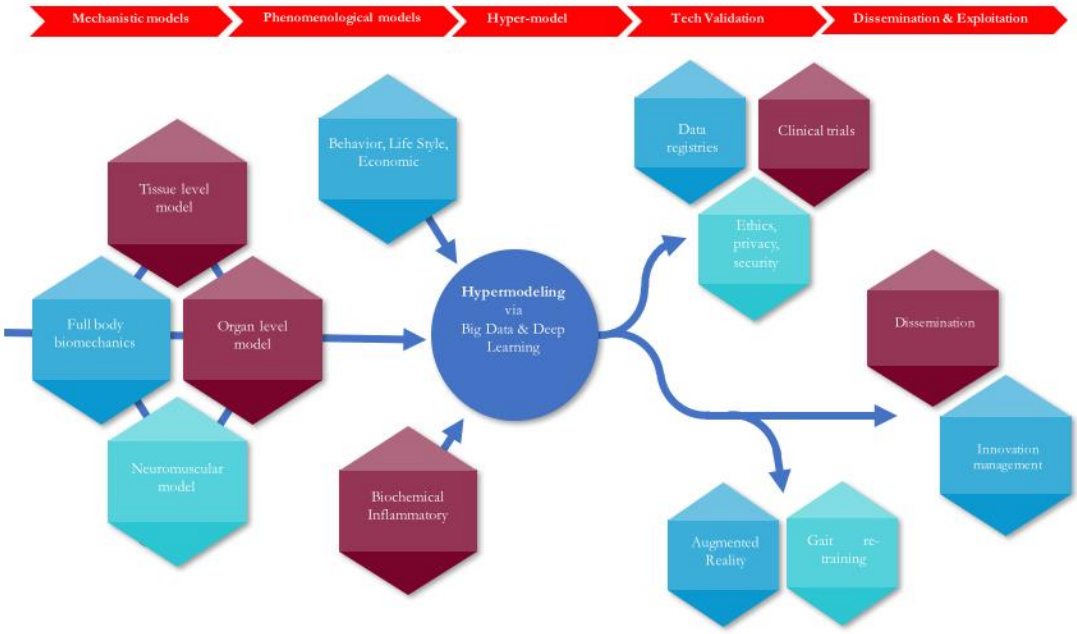

Figure1. OACTIVE Vision

Multi-scale modelling framework empowered by big data.

Currently, there are numerous efforts underway in the design and development of the 'Digital Patient', a framework of methods and technologies that would enable the investigation of the human body as a single complex system. The idea behind the vision of such an approach is to reduce the increased body complexity by decomposing living organisms into parts (at the cell, tissue, and organs level), use computer modelling separately to obtain knowledge from each level and finally investigate how these parts interact with each other across space and time. This widely-adopted approach poses tremendous challenges in terms of (i) the development of the required mathematical predictive models, (ii) the generation of mechanistic models that would capture the essential aspects of the mechanisms involved and (iii) modelling the complex interactions between the numerous models either mechanistic or phenomenological (or statistical). Different approaches have been proposed to cope with the aforementioned challenges from the field of medical imaging and sensing technologies (to produce quantitative data about the patient's anatomy and physiology) [15-17], data processing to extract from such data information that in some cases is not immediately available [18-20], biomedical modelling to capture the available knowledge into predictive simulations [21,22] and multi-scale modelling using computational science and engineering to run huge hypermodels (orchestrations of multiple models) under the operational conditions imposed by clinical usage [23-25].A number of relevant EU projects have reached the clinical assessment stage such as the VPHOP project

[26] where multi-scale modelling technology was employed for patients affected by osteoporosis and the ARCH project [27] that aims to develop patient-specific computational models for vascular surgeries. Computational Fluid Dynamics (CFD) models were created into clinical tools for physicians to use across the spectrum of coronary, valvular, congenital, myocardial and peripheral vascular diseases [28]. CFD is an in-silico model used for minimally-invasive patient assessment [28]. Continuous Glucose Monitoring (CGM) is another computer simulation which is capable of providing invaluable information about the safety and the limitations of closed-loop control algorithms, guiding clinical studies, and out-ruling ineffective control scenarios in a cost-effective manner [29]. Another in silico experimental modelling is the one that Trisilowati et al. created for cancer which combines findings from biological literature with computer-based models of biological systems in order to conduct investigations of hypotheses entirely in the computer laboratory [30]. In terms of OA, numerous projects of mechanistic models were found such GUIDES [31] that aims to improve the impact of computerised decision support system through better content wise development and optimised implementation. Regarding relevant studies Cox et al. created a bone adaptation model, which simulated various conditions associated with OA without altering the articular cartilage and evaluated if mechanoregulated bone remodelling by itself could lead to OA-like bone structural changes [32].

Despite the fact that some of the aforementioned research approaches have reached pre-clinical or clinical assessment stages, the great majority of them have been proved to be insufficient to capture mechanistic knowledge that would allow the development of reliable clinically relevant models. In some cases, simplistic mechanistic models have been considered resulting to poor high-risk predictions, whereas the use of phenomenological modelling may be useful in some applications but typically leave a sense of fragility and mistrust lacking any interpretation. Big data technologies will be developed in OACTIVE to bridge mechanistic with epidemiologybased knowledge along with exogenous parameters / biomarkers increasing the acceptance of the already-established models in clinical practice. The employed big data will allow the analysis of large number of patients, the determination of patterns/correlations and the development of predictive individualised modes using advanced analytics and modern machine learning algorithms.

OACTIVE Beyond the State of the Art

Although sometimes overhyped, big data technologies do have great potential in the domain of computational biomedicine, but their development should take place in combination with other modelling strategies, and not in competition. Big data and deep learning will play key role in OACTIVE since they will enable the analysis of a large collection of data from hundreds to thousands of patients and thus will allow the development of personalized predictive models. GPU-accelerated deep learning will be employed to process diverse medical data over time whereas knowledge obtained from huge phenomenological data and the outputs of multiple single-scale mechanistic models will be combined with other exogenous risk factors e.g. biological, social, environmental, lifestyle, occupational and economic factors related to OA.

To accomplish this ambitious aim, an advanced 4-step data processing methodology is proposed as given below:

- *Gather:* This step involves the collection of data streams – structured and unstructured – from the different information sources (mechanistic, phenomenological and other). Emphasis will be

given to capture, store and organise data so that it can be manipulated/analysed for useful information and potentially re-used. Challenge: data confidentially (see below).

- *Analyse:* A number of advanced data analytics will be employed here to pre-process the collected data, extract useful information/parameters and combine/convert varieties of data including automating conversion from unstructured to structured data. Challenge: Data heterogeneity (refer to the relevant section below).

- *Identify*: GPU-accelerated deep learning will be integrated to discover associations and understand interaction patterns and trends within the data. Computational efficient data mining algorithms and feature/data selection tools will be used to assess the data capacity in predictive medicine in both individual and population levels. Challenge: data complexity (see below).

- *Predict:* The step involves the development of personalized predictive models using complexity-efficient machine learning models. The models will be based on the associated parameters as selected in the previous step. Challenge: data interpretation (refer to the relevant section below).

Data confidentiality

The majority of big data applications deal with data that do not refer to an individual person. This does not exclude the possibility that their aggregated information content might not be socially sensitive, but very rarely is it possible to reconnect such content to the identity of an individual. In the cases where sensitive data are involved, it is usually possible to collect and analyse the data at a single location, so this becomes a problem of computer security; within the secure box, the treatment of the data is identical to that of non-sensitive data. Healthcare poses some peculiar problems in this area. First, all medical data are highly sensitive, and in most developed countries are legally considered owned by the patient, and the healthcare provider is required to respect patient confidentiality. The European parliament is currently involved in a complex debate about data protection legislation, where the need for individual confidentiality can be in conflict with the needs of society. Secondly, in order to be useful for diagnosis, prognosis or treatment planning purposes the data analytics results must in most cases be re-linked to the identity of the patient. This implies that the clinical data cannot be fully and irreversibly anonymised before leaving the hospital but requires complex pseudo-anonymization procedures.

OACTIVE Beyond the State of the Art

In OACTIVE the clinical data will be pseudo-anonymised so as to ensure a certain k-anonymity, which is considered legally and ethically acceptable. Specific algorithms will be developed that prevent data aggregation when the k-anonymity drops below the required level. Given person-specific field-structured data, a release of the data will be produced with scientific guarantees that the individuals who are the subjects of the data cannot be re-identified while the data remain practically useful. Patient-centred authorisation mechanisms will be also developed that will allow automatic requests for secondary use of clinical data after collection and anonymization.

Data heterogeneity

In recent years, there has been a tremendous increase in the volume and complexity of data available to the medical research community. To enable the use of this knowledge in clinical

studies, users generally require an integrated view of medical data across a number of data sources. Clinicians, the end users of medical data analysis systems, are normally unaware of the storage structure and access mechanisms of the underlying data sources. Consequently, they require simplified mechanisms for integrating diverse heterogeneous data sources to derive knowledge about those data in order to have a holistic view of patient information and thereby to deliver personalized healthcare. The heterogeneity of the various data types associated to OACTIVE projects is indicatively given in the table below. It becomes clear that data must be formatted in a predefined standardised and certified way in order to make it available for later sharing (provided patient consent about the level usage is embedded) for research purposes.

Table 1. Indicative dataset associated with a patient

Type	***Description***	***Quantity***
textual information items	*Narrative, textual data e.g. from anamnesis and textual recordings of physical examinations and functional tests*	*>100 per patient*
Medical imaging	*2D/3D imaging data from the knee using various imaging technologies*	*>10 images patient*
Numerical data	*Numerical data/ parameters stored in predefined data-base formats e.g. sequences of data exported from the developed mechanistic models*	*>100 per scale per patient*
Data from wearable sensors	*Data (time series) exported from Vicon or other wearable sensors made by Smartex*	*>500 per patient*
Biomarker data	*Data from prognostic biomarkers of bone and cartilage degradation and synthesis or other inflammatory biomarkers*	*>10 per patient*
Organ-level model	*FEA model with the estimation of forces, pressures applied in multiple locations*	*5*
Neuro-muscular model	*Detailed and scalable musculoskeletal model of the knee joint capable of predicting joint forces and loading*	*5*
Tissue-level model	*Detailed cartilage and bone models that can be incorporated in the musculoskeletal model and use the force predictions as input to estimate tissue loading responses*	*5*

OACTIVE Beyond the State of the Art

OACTIVE will develop model and data encoding and exchange standards for multiscale modelling to ensure model reproducibility and sharing. Emphasis will be given in the development of modular approaches to ensure that self-contained models could be developed and validated independently before being incorporated into the big data hierarchy of imported models. The OACTIVE project relies on a separation of encoded information into data, metadata and semantics. The employed data model will ensure that all the information recorded

can be stored and reused. The metadata model will ensure the abstraction required to integrate pieces of data into a coherent whole and to define sufficient description of data elements so that they can be properly interpreted and compared. The model will be enhanced with a semantic layer to facilitate the semantic coherence of the integrated data and to allow linking and reuse of the external medical knowledge. The metadata will reveal the structure of the underlying heterogeneous medical data allowing consistent queries across populations of patients and disease types. The semantic layer will add knowledge to this metadata thereby facilitating the resolution of queries that bridge between related concepts. It is this combination of descriptive metadata with system semantics that will allow the OACTIVE data model with the ability to be both reactive in terms of the queries generated by user applications and to have the richness to enable integration across heterogeneous data sources. The format used to temporarily analyse the collected data might be different from the final format used for storage in open-access repositories. However, one-to-one two-way exchange mechanisms without data loss will be employed.

Data complexity

There are a lot of challenges in signal processing of the multi-scale data, given their current state and the non-standardized structure. But there are opportunities in each step of the process towards providing systemic improvements. Despite the need for further research in the area of data wrangling, aggregating, and harmonizing continuous and discrete medical data formats, there is also a similar need for the development of novel signal processing techniques specialized towards physiological signals. Research relevant to biomarkers and clandestine patterns within biosignals to understand and predict disease cases have shown potential ability in providing actionable information. However, there are opportunities for developing algorithms to address data filtering, interpolation, transformation, feature extraction and feature selection. Furthermore, with the notoriety and improvement of machine learning algorithms, there are opportunities in improving and developing robust Clinical Decision Support Systems for clinical prediction, prescription, and diagnostics [33,34].

Deep Learning algorithms are one promising avenue of research into the automated extraction of complex data representations (features) at high levels of abstraction. In the past decade, deep learning techniques currently achieve state of the art performance in a multitude of problem domains (vision, audio, robotics, natural language processing, to name a few). Recent advances in Deep Learning also incorporate ideas from statistical learning [87, 88], reinforcement learning (RL) [89], numerical optimization, and broader fields [90, 91]. The success of deep learning is attributed to its high representational ability of input data, by using various layers of artificial neurals [35]. GPUs have played a key role in the success of deep learning by significantly reducing the training time [36]. In order to increase the efficiency in developing deep learning methods, there are a number of open-source deep learning toolkits including Caffe from UC Berkeley [37], CNTK from Microsoft [38], TensorFlow from Google [39], Torch [40], and many other tools like Theano [41], MXNet [42], etc. All these tools support multi-core CPUs and many-core GPUs. One of the main tasks of deep learning is to learn a number of weights in each layer of network, which can be implemented by vector or matrix operations. TensorFlow uses Eigen as accelerated matrix operation library, while Caffe, CNTK, Torch employ OpenBLAS [43] or cuBLAS, to speed up matrix related calculations. All the mentioned tools import cuDNN

[44], which is a GPU-accelerated deep learning library, for their neural network computing. However, because of the difference of optimization methods by vendors, these tools exhibit different running performance even when training the same neural network on the same hardware platform. Furthermore, the performance of a tool also changes a lot when training different types of networks or using different types of hardware. Given the diversity of deep learning tools and hardware platforms, it becomes difficult to choose an appropriate tool to carry out their deep learning tasks.

OACTIVE Beyond the State of the Art

To cope with the data complexity issue, a number of computational efficient machine learning algorithms will be employed making use of the latest technological advancements in ICT. In terms of deep learning three major types of deep neural networks will be considered (i.e., fully connected neural networks (FCNs) [45], convolutional neural networks (CNNs) [46-48] and recurrent neural networks (RNNs) [46, 49,50] on state-of-the-art GPU-accelerated tools (i.e., Caffe, CNTK, TensorFlow and Torch). The algorithms' advantages and disadvantages will be analysed on both CPUs and GPUs, in terms of running time performance. For each type of networks, a small-size network and a large-size network will be used for more robust evaluation of the results.

Data interpretation

There is an intrinsic dichotomy in classification problems in the health domain in general. It could be argued that the only goal of a study should be to develop a system that is able to attribute correctly cases to classes, and in this case we assume a "black-box" model of the system being developed (Artificial Neural Networks or Support Vector Machines, for example). Similar kinds of algorithms take some inputs and return some outputs; they can reach a quite high level of accuracy but they will not enrich the human knowledge of the disease process under investigation. This is a key point in the biomedical context: clinicians often want to understand the way the classifier is behaving to judge its performance. This is a quite interesting perspective: underlying their interest there is the desire of gaining a deeper knowledge of the biological disease processes by interpreting the results returned by the system. This is a peculiar aspect of the biomedical field in which a percent point in the classifier accuracy can decide the heath and treatment implications of a patient. Another model is then needed to address these requirements. A second set of approaches provides a deeper insight into the problem adding a clear description of how the system arrived at the prediction. Such clear descriptions can be represented by IF-THEN classification rules and the process of rule extraction from a dataset is called rule induction. Several algorithms have been proposed for accomplishing the rule induction task, with C4.5, probably, being the most famous [51].

Although rule-based knowledge discovery has been utilized in the various clinical applications, just few techniques have been developed in the challenging clinical problem of OA prediction. A methodological difficulty in deriving relevant criteria is choosing the most appropriate statistical techniques to maximize the potential of the data generated by a prospective cohort design and presenting the results in a practical way that makes clinical sense. Predictive models were classically developed through logistic regression models and, later, through CART analysis. CART analysis is useful mainly because it allows for the presentation of results in the form of understandable decision trees. The clinical classification criteria developed by the American

College of Rheumatology (ACR) [52] was the first time that clinical and objective data generated from prospective studies have been used to classify knee osteoarthritis using CART analysis. More recently, two studies [53,54] have been reported dealing with the extraction of explicit clinical criteria for the indication of OA-related diseases utilizing CART analysis. However, caution is needed when applying classification criteria in circumstances different from those in which they were derived and doubts have been expressed about the validity of these clinical criteria in the general population and primary care.

OACTIVE Beyond the State of the Art

The challenge of managing the wealth of such a complex biomedical problem like osteoarthritis invites us to go one step further than traditional statistics and resort to knowledge discovery and data mining. Although existing methods could produce reasonable predictions, they were not capable of capturing physio-genetic principles behind the predictions. In many situations, however, these hidden principles were of more importance because they could uncover how medical, biological and environmental factors interact to each other and why some of them would result in disease. In order to explore these principles, novel designed rule induction methods will be developed in combination with the identification of important risk factors per OA development stage to automatically extract interpretable rules for the OA occurrence and progression. The induced rules will be either consistent with current biological knowledge or providing new insights for the understanding of the risk factors for the development and progression of OA.

Early detection using personalised predictive OA models.

In recent years, generation and analysis of patient-specific models displays great interest. Progress has been made in the integration of image processing and engineering analysis, with many applications in healthcare from orthopaedics to cardiovascular systems and in cases of multiscale models of disease processes, including cancer. Very efficient methods, and associated workflows, have been developed in order to support the generation of patient-specific anatomical models based on exquisite three and four- dimensional medical images [55,56]. The greater challenge now is to use these models to predict acute and longer-term physiological and biological changes that will occur under the progression of disease and under candidate interventions. There is a wealth of data in the clinical record that could support this, but its transformation into relevant information is enormously difficult.

In terms of osteoarthritis, it's a disease not easy to define, predict or treat. Despite extensive research, no treatments/ interventions have been proven to modify the biological progression of OA, and only a few treatments are proven to relieve symptoms. The KNEEMO [57]training programme combined existing best practices from consortium members and was designed to equip researchers with skills and knowledge specific to the research field (KOA anatomy, pathology and disease mechanisms, musculoskeletal modelling, functional assessment, KOA interventions), generic research skills (epidemiology, methodology, statistics, clinimetrics, ethics), and complementary training (entrepreneurship, project management, product development, intellectual property issues).In an another research effort, CarBon [58] project aimed to understand cartilage to bone transition, to identify targets to develop novel functionalised biomaterials and to discover therapeutic drugs that either prevent or stimulate cartilage to bone transitions.

Another limitation of the current risk prediction models is that they are based on logistic regression which includes some controversial assumptions about the relation of the probability of developing the disease and the associated risk factors. The number of related risk factors that have to be included is also limited given the computational limitations associated with these statistical techniques and large datasets. The large number of medical, biological and environmental factors that need to be included, so that the risk prediction model is based on a comprehensive map of all the known risk factors and their interactions, requires a beyond the state of the art model and computational approach to the problem. The review and evaluation of the state-of-the-art in this area has shown that, perhaps surprisingly given the epidemiological evidence in OA and the advanced risk prediction models in other diseases, there are only a few valid existing OA risk prediction models but they suffer from some major limitations that include:

- Inability to harness and explore the large amount of information present in extensive epidemiological work on OA risk factors and their predictive power.
- Limitations in model development for disease classification and prediction of risk.
- Limitations in modelling appropriately and accurately even some of the main known risk factors.
- Inefficient computational techniques given the high dimensionality problems and the requirements to model a very complex array of risk factors.

OACTIVE Beyond the State of the Art

The development of computer-based, patient-specific predictive models of the occurrence and progression of OA forms the main objective of the OACTIVE project. This valuable medical tool could be used in preventive medicine, to predict occurrence or worsening of the OA disease in people at risk. The proposed hybrid approach will take advantage of the knowledge (models) extracted for OA multi-scale modelling and will further be extended to patient-specific modelling and prediction by applying advanced post-processing techniques (meta-analysis). OACTIVE aims at breaking through the area of the existing processing techniques applied in the OA problem. The great majority of the current computer-based models just provide crisp clinical decisions (OA diagnosis) and cannot identify/qualify (i) the tendency of a healthy subject to show signs of the disease and (ii) the disease progression based on patients' outcomes. By improving the means to measure and predict the OA process and its clinical consequences, OACTIVE targets: (i) to screen individuals for high-risk factors, combining medical clinical factors with information from imaging and other biomarkers and biological, social and environmental factors and (ii) to make a significant impact in this high-risk condition by preventing or delaying OA onset and slowing down progression both structurally and symptomatically.

Adopting an Open Platform philosophy

The heterogeneity of the information to be shared poses a grand challenge in the area of data sharing and data modelling infrastructure. One of the main issues that still remain in multi-scale modelling is the adoption of data encoding and exchange standards to ensure model reproducibility and sharing. The first modelling standard developed by the Physiome Project was CellML10 245 [18,20]. This standard covers models that use ordinary differential equations and algebraic expressions (both of which can be nonlinear). The 'ML' refers to 'Markup Language' and in particular the 'eXtensible Markup Language' or XML, which is the Web2.0 standard for exchanging information on the web. Another modelling standard developed under the VPH/Physiome Project, dealing with spatially varying structure and processes, is called FieldML. The most common format for these models uses finite element basis functions that interpolate nodal parameters that are themselves the value of the field (and sometimes its spatial derivatives) at that material point. The whole field is made up of many such finite element patches, chosen with the spatial resolution needed to achieve any desired level of accuracy for either fitting measured data or representing the field solution of partial differential equations that characterize the physical processes being modelled. A model repository and open source tools based on the FieldML standard are also available [59,60]. CellML and FieldML together provide the means to encode any biophysical model in a standardized and reproducible format. Data encoding standards are less well defined, although DICOM [61] is a well-established standard for clinical images and BioSignalML [62] is a standard developed by the VPH-Physiome community for time varying signal data. OpenCOR incorporates the BioSignalML API in order to import or export signal data in this format. To standardize the way CellML or SBML models are run and compared with experimental data, a standard called SED-ML has been developed by the VPH/Physiome and Systems Biology communities. The SED-ML API has been incorporated into OpenCOR so that the simulation parameters can be read in from a file or defined in OpenCOR and exported to a SED-ML file. A tutorial on the use of CellML, OpenCOR and PMR is available on the VPH-Institute website [63]. Another VPH initiative that facilitates the development of computational models for the clinics VPH-Share [64]. This major project, led by the University of Sheffield, has created a cloud-based IT infrastructure and universal clinical workflow development system capable of supporting the construction and operation of complete software systems to extract novel and possibly complex biomarkers from raw clinical information, and so to provide clinicians with decision support for diagnosis, stratification, therapy selection and treatment planning.

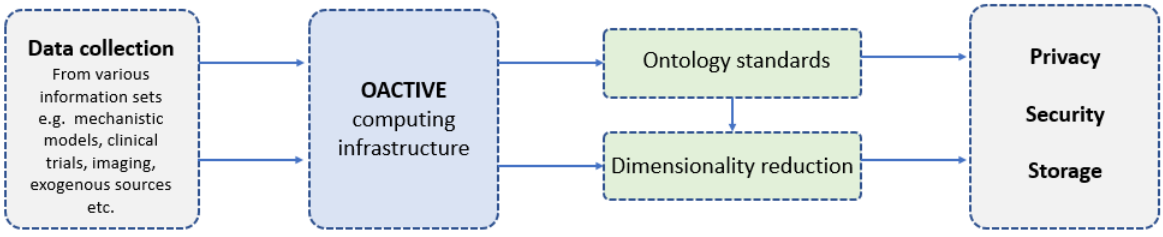

Figure 2.OACTIVEreproducibility and sharing architecture

OACTIVE Beyond the State of the Art

Our approach prioritizes the standardization of data collection using an ontology-based framework including the development and establishment of tools to align existing ontologies cultivating a concept of unified ontology. In light of this semi-automatic ontology mediation methodologies will be adopted. Open source data and modelling standards will be used including CellML and FieldML for the modelling tasks, DICOM and BioSignalML for data, whereas VPH-Share and Apache Hadoop [65] will be considered for cloud-based storage. Dimensionality reduction techniques will be employed to deal efficiently with the heterogeneity and the complex structure of available data, and with differences in origin, quality and ontologies. Security and privacy frameworks will be also established to insure data protection, safety, cautious usage and exchange, anonymity during exchange, retrieval and in storage. The project will adapt an open development approach where access to ongoing work by the research team, the biomechanics community, and public will be available, not only for viewing but also for active contributions. Any interested party will be able to freely download release versions of the models and also have access to the developing source code. For those who wanted to contribute actively, mechanisms will be implemented, where a request to be added as a team member need to be submitted with a brief description on the reason of their interest in the project and their planned contributions. This approach successfully enables a volunteer investigator to upgrade model development scripts, which will be provided as a result of their appreciation for being able to use OACTIVE freely for their research. A necessity of open model development is that any computational tool used for relevant work need to be accessible. All supporting model development and analysis scripts will be written in free programming language. Musculoskeletal modelling and Finite element analysis will be conducted by using the open source programmes Opensim [1] and FEBio [6]. The project will include many subprojects: analysis of experimental data for model development, individual components of model generation, and simulations for verification and validation. Many of these subprojects will be incorporated into a community projects program similar to the Google Summer of Code [26]. Each of these projects will be designed by the research team to fit into a work load equivalent of the traditional summer student research. The projects will be summarized and listed at the project. Applications from the members of the research community (students, post-docs, any interested party) to complete such projects will be accepted by the research team. Review of applications will be conducted by the research team and the Advisory Board. Selected members will become part of the development team and they will be rewarded through a fee-for-service mechanism, in concert with the review of their work.

Personalised interventions through augmented reality.

Personalized OA management can be thought of as the broad application of approaches that allow decision making to be based on the individual's specific test results and clinical factors rather than being based on global recommendations. Risks and benefits should be considered for each patient and therapy should be individualised wherever possible. Although established OA is currently an irreversible, chronic, disabling and painful condition that is not curable with existing treatments, research on the epidemiology of OA over recent decades has identified several risk factors that include biological, medical, environmental and social characteristics and influences. Most importantly, however, they include both non-modifiable and modifiable risk factors and this opens up the possibility of disease prevention before it is developed into an established

incurable condition or slowing its progression and debilitating consequences once developed through appropriate interventions to modify the relevant risk factors [66,67]. This is currently the most promising approach to tackle OA, but **personalised disease prevention or treatment through modification of appropriate risk factors requires accurate and comprehensive risk prediction models**. These must include all the main known risk factors for the development and progression of knee OA, but most importantly, the models must also capture the complex interactions between environmental, social and biological/medical factors. With such complete and accurate risk prediction models, it is possible to estimate the risk reduction by targeting one or several modifiable risk factors through patient-specific and effective treatments or interventions that can prevent the disease or slow down its progression and therefore have a major public health impact. Although such conventional risk prediction models and prevention strategies have been developed for other major diseases such as cardiovascular disease and cancer, there are only a few and quite limited models in OA such as the Nottingham knee OA risk prediction models [66], the OA Policy model (OAPol) [68] or a limited factor joint replacement prediction model [69]. Although there are some other OA prediction models reported in previous studies [70], the main criticism is that they are actually classification models of the disease rather than conventional risk prediction models that can be used for prevention [66]. The most comprehensive and extensive risk prediction models by far are the Nottingham knee OA risk prediction models [66]. These authors developed risk prediction models for incidence of radiographic and symptomatic knee OA and progression using conventional risk factors such as age, gender, BMI, family history of OA, occupational and sports participation risks, knee joint injury, and number of knee joint compartments affected by OA. Although the prediction outcomes are normally robust in various sensitivity analyses for these models, the range of risk factors included is very limited and future research should be performed to extend the efficiency of the modelling method in utilizing more information from the range of risk factors relevant to OA.

The OACTIVE project aims to revolutionize current practices for managing OA. These practices include non-pharmacological treatments such as providing patient education and self-management strategies, advising weight loss, strengthening programs, and addressing biomechanical issues. Oral analgesics and anti-inflammatories are pharmacological approaches that are commonly used and the literature overall supports that some of these medications can be helpful for managing OA in the short-term but are less effective for long-term management. Additionally, more prolonged use significantly increases the risk of serious associated side effects that are not too uncommon. Disease modifying OA drugs are being researched as a treatment modality to potentially halt or slow disease progression. Intra-articular injections are also implemented to manage OA ranging from corticosteroids to hyaluronans to more recently platelet rich plasma and even stem cells while several other injection therapies are presently being studied. The goal of developing new treatment strategies for OA, through the OACTIVE model is to prolong the need for total arthroplasty which should be utilized only if other strategies have failed. Arthroscopy has been commonly used for many years to treat OA to address degenerative articular cartilage, however, several high-quality studies have shown that it is not a very effective treatment for the majority of cases and should generally not be considered when managing OA. Improving the management of OA requires a multi-faceted treatment approach along with continuing to broaden our understanding of this complex disease so that therapeutic

advancements can continue to be developed with the goal of preventing further disease progression and even potentially reversing the degenerative process.

Table 2. State of the Art in Osteoarthritis treatments

Acronym	***Objectives***
ADIPOA2 *[71] (H2020-PHC-2014)*	*Clinical trial of autologous adipose-derived mesenchymal stromal cells (ASC) in the treatment of mild to moderate osteoarthritis.*
Hy2Care *[72](H2020-SMEINST-1-2016-2017)*	*Injectable hydrogels made out of advanced nanomaterials that integrate the repair tissue.*
REGHA *[73](H2020-SMEINST-1-2014)*	*This therapeutic approach is applied by local injection into the joint of a pharmacological active patented molecule stimulating chondrocytes proliferation, the only cells producing and maintaining the cartilage matrix.*

In our approach for OA treatment all factors are taken under consideration and only when needed, in the proper stage of the condition, the suitable suggestion will be given. It is evident that in OA management not all treatments are suitable in all cases, patients have different phenotype, symptoms and progress. For that important reason our OACTIVE for personalised, predictive and preventive management of OA is innovative and beyond the state of the art.

Augmented Reality (AR) superimposes a computer-generated image on a user's view of the real world. It not only preserves some benefits of leveraging VR such as fully controlled setting and measurable feedbacks, but also needs less computation time to model the 3D environment [74]. Moreover, to interact with a non-immersive VR setting (which is widely used in motor and cognitive rehabilitation), the subject needs to perform at least one extra transformation to translate the virtual world's coordinate to the body-centered coordinate, which could be challenging to elderly patients with cognitive difficulties. This is not needed in an AR setting. In AR, patients experience a more engaging and natural interaction since virtual objects can be manipulated in an intuitive and natural way to maximize learning activities of daily living (ADL's) [75]. The haptic feeling [76] of the real objects could bring on a more natural interaction. There is consensus amongst therapists that as the interaction of patients with the physical environment is reduced, their DL's recovery starts to deteriorate [77]. Thus, an essential factor to successful recovery is to increase the patient's level of interaction with their environment. With the advances of AR interaction technology, AR games combine traditional digital games and physical activities providing alternative leisure opportunities for older adults. Different from traditional digital games that rely on joysticks or related controllers to receive players' feedback and signals, AR games are obviously more enjoyable by providing instant, positive feedback on current actions as well as a clear picture on long-term performance. Given their widespread availability and (relatively) inexpensive price tags, handheld gaming devices and mobile phones are now capable of supporting AR. An AR gamer environment motivates the individual and makes him/her train more often and for a longer period of time without getting tired. The continuous feedback provided by the AR therapeutic programs builds and strengthens the user's motivation.

OACTIVE Beyond the State of the Art

OACTIVE will thus rely on the AR gaming concept offering both clinical assessment and rehabilitation options, usually not available with traditional rehabilitation methods. It aims at exploiting haptic and vision technologies to provide patients with assistive visual and contact feedback while performing games/rehabilitation as well as medical staff with biomechanical indicators for assessment and diagnosis support. It will go beyond the existing AR rehabilitation programs by:

- expanding & improving the currently limited opportunities for rehabilitation scenarios,
- enhancing primitive spatial and temporal training scenarios,
- addressing staff and facility limitations as well as human factors,
- creating user friendly interfaces and integrating interactive environment,
- accurately implementing crucial stimuli (force sensing, visual information) together to have a real impact on the game task completion performance.

More specifically the AR games will be used for the treatment of OA by using the gait retraining method. In OA gait retraining is proving to be an effective treatment for correcting gait alterations. Current gait retraining methods for knee OA rely on the use of simple biomechanical models for calculating the external knee adduction moment (KAM) as a target variable to control during the gait retraining interventions [78]. Decreasing the early stance peak KAM has been reported to also decrease pain, disease progression, and disease severity in OA patients [79-81]. Recent studies have explored real-time visual and vibrotactile feedback to enable subjects to relearn their gait with reductions in KAM that ranged from 7% to 48% [78, 81,82]. Similar procedures are currently being developed and tested for treating hip OA [83].Retrained gaits with minimal *in vivo* tibiofemoral contact forces may be more effective than gaits with minimal KAM peaks to the treatment of OA condition [84] because OA progression is directly related to tibiofemoral contact forces and only indirectly to KAM peaks [84]. The availability of EMG-driven models that can predict accurate estimates of tibiofemoral forces [84] in real time [85,86] will offer the possibility of performing joint contact force-based gait retraining to any subject through AR games. Inertial sensors (IMU's) will be placed on lower limb segments to provide estimates of joint kinematics. Together with electromyography (EMG), these data will be used within a surrogate contact model that includes muscle force estimates using an EMG-driven musculoskeletal model. Estimates of peak contact force or pressure are then used in a data-driven gait prediction model to provide a stimulus to the subject in real-time via AR game to alter their gait.

4.2 Overall advancements over the OA-related EU funded projects

Table 3 cites all the OA-related EU-funded projects in comparison with OACTIVE with respect to the expected impact of the SC1-PM-17-2017 call. At the moment, there is no other *In Silico* model addressing the challenges of a holistic approach of predictive, preventive and "time scale"

management model of OA. The combination of the computer hyper-model with the proposed AR intervention forms a truly novel OA diagnosis and management methodology.

Table 3. OA-related EU funded projects and their relation with OACTIVE

Acronym	*New personalised interventions for increasing resilience and recovery.*	*Advancements in medical computer-modelling and simulation that takes into account time scale.*	*Supporting predictive and preventive approaches.*	*Improving knowledge about well-being and association with life circumstances.*	*Multi-scale analysis*
APPROACH	×	✓	×	✓	×
KNEEMO	✓	×	×	✓	✓
INpaCT	×	✓	×	✓	×
OA AM	×	✓	✓	×	✓
GUIDES	×	×	✓	✓	✓
GAIT-2-OA	×	✓	✓	×	×
MAMBO	×	✓	✓	×	✓
OAPROGRESS	×	×	✓	✓	×
MODELLING_JOINT_DEV	✓	×	✓	×	×
OACTIVE	✓	✓	✓	✓	✓

In the OACTIVE project, one of the main objectives is to connect multi-scale mechanistic modelling outputs with biological (including microbiome), social, environmental, lifestyle, occupational and economic factors on human physiology in an In Silico machine intelligence-inspired hyper-model. The unique, holistic approach to patient-specific predictive model development incorporates various scientific fields such as clinical research, modelling at various scales and advanced computer and mathematical/statistical modelling technologies. Being able to predict disease outcomes more accurately and suggest suitable predictive actions would help clinicians make more informed decisions regarding the potential of treatment appropriate for the patient-specific risk factors and has the potential to lead to the development of individually tailored interventions to maximize the efficacy of treatment. Consequently, the project will open up fundamentally new opportunities for preventing or managing OA efficiently, contributing ultimately to a reduction in overall health care cost and a significant improvement in the patients' quality of life.

5 OVERALL PROCESS FOR THE IDENTIFICATION OF USER REQUIREMENTS

Even though some basic principles and methodologies (such as questionnaireσ, focus groups, interviews) can be applied for eliciting user requirements from an application such as the one designed and developed as part of OACTIVE project, in truth a combination of methods is needed for fully understanding users' expectations and build an application that will be really useful.

In OACTIVE a questionnaire for defining the basic principles of the final OACTIVE outcomes was prepared. The questionnaire was in practice used as a basis for an open exchange of views, a brainstorming procedure, through which the user needs were acquired and further analyzed. In fact, in the following this feedback that was received from clinical and biomedical experts is presented.

The OACTIVE project intents to make a significant leap forward adopting a multi-scale holistic approach where patient-specific information from various levels, including cell,tissue, organ and whole body will be integrated and combined with information from other sources such as biochemical/inflammatory biomarkers, behaviour modeling and social/environmental risk factors to generate robust predictors for new personalised interventions for delaying onset and slowing down progression of OA. OACTIVE targets to patient-specific OA prediction and interventions by using a combination of mechanistic, phenomenological computational models, simulations and big data analytics. Once constructed, these models will be used to simulate and predict optimal treatments, better diagnostics, and improved patient outcomes. Overcoming the limitation of the current treatment interventions, Augmented Reality empowered interventions will be developed in a personalised framework allowing patients experience the treatment as more enjoyable, resulting in greater motivation, engagement, and training adherence. OACTIVE's mission is to improve healthcare by transforming and accelerating the OA diagnosis and prediction based on a more comprehensive understanding of disease pathophysiology, dynamics, and patient outcomes.

A crucial phase is the requirements elicitation in order to identify the experts' needs for such a system and define the usage scenarios that will set the directions for the analysis of functional and non-functional specifications. In order to efficiently record the experts' requirements, we conducted an anonymous survey.

5.1 The User Requirements Methodology

The methodology of identifying the user requirements can be divided in the following Steps, as illustrated in the following **Figure 3**:

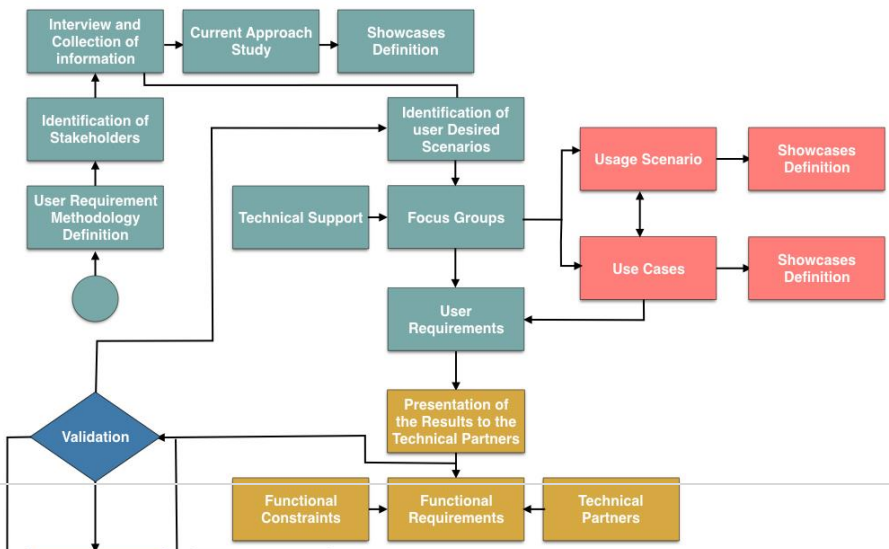

Figure 3. The steps of the identification of the OACTIVE User Requirements

Users' requirements were captured through:

• analysis of the state of the art (previous Section);

• interviews with experts and questionnaires; As already mentioned above the adopted methodology is a combination of user requirements acquisition and analysis methodologies (questionnaire, interview, and brainstorming) and follows a two steps approach:

-Discussion in order to identify the basic principles the application should have (such as the type of knowledge, skill, attitudes, or behaviour addressed, the clinical procedures, the kind of feedback for the user etc.)

-Analysis of the feedback received through the abovementioned discussion, determination of requirements along with a feasibility study taking into consideration limitations such as budget, time, technology and any other resources in order to determine the approach to be followed for the implementation of OACTIVE system.

In this deliverable the aim is to define the approach adopted for the application and not the definition of the technologies, specifications and architecture (details for these will be provided in D2.3). For this aim the "orange" tasks are not included in this deliverable. Moreover, for the "red" tasks there will be presented in this deliverable an overview of the analysis but the details use cases and system scenarios will be included in the D2.3.

As it is evident from the diagram, the user requirements analysis defines the approach. Once the approach is defined and agreed there is no way back concerning the basic principles of the application. The development and the evaluation is a more dynamic procedure, but the approach to be adopted is a much more straightforward decision.

The main steps of the User Requirements gathering methodology that was followed can be summarized in the following:

• User requirement methodology definition

• Identification of stakeholders

• Interviews and collection of information

• Current approach study and Showcases definition

• Identification of user desired scenarios

• Focus groups to identify the Use Cases

• Presentation of the results to the technical partners

• Functional and non-functional requirements and Functional constraints of the system

• Validation by the Pilot partners / Consortium and finalization of analysis

There was formed a questionnaire in order to better analyse the responses and collect valuable information on the system design and functionality:

5.2 Users and Stakeholders Identification

The definition of stakeholders involves all different categories of individuals, groups or organizations directly or indirectly involved in the planning and decision making process. The important issue to be determined for each stakeholder is to which extent their involvement will take place and at which phase of the project.

In order to identify the project's stakeholders it is needed to be considered which individuals and organizations are primarily involved in the project. There is also a section of stakeholders that relates to those that may be affected by the outcome of the project. These may be separated into individuals, groups or organizations. Therefore, the stakeholders may be identified in the following categories.

1. Project outcome stakeholders

These can be identified as the project team that provides the execution of the project. Therefore, it can be deduced that the main areas of interest are universities, university hospitals, research teams and private or public companies with specific R&D interest.

2. Product Usage stakeholders

This is the most important category of stakeholders. It refers to the end users of the system that will be produced. A further separation may be done at this point. There can be identified as the business end of the users and the customer end. At the business end category there are hospitals, private clinics, private clinicians and research laboratories. The customer end involves a much broader spectrum and it is difficult to assume all descriptions. The main areas involve patients and research scientists, who may directly use the product.

3. Funding stakeholders

This category is directly related to category 1. The only addition to that part is the European commission in the sense that major funding comes from their resources. Since they approve the release of funding and provide major part of the resources, they are also accountable for the results of the project.

4. Contributors stakeholders

This category refers to the level of commitment of groups or individuals. Their contribution is not directly associated with the success of the project. Such individuals may be identified as clinicians and research scientists with this specific field of expertise.

5. Review stakeholders

In this category we refer primarily to the individuals assigned by the European commission to review or audit the project. Their main interest is to ensure the success of the outcome of the project. This is done through the review of the quality of the deliverables (reviewers), the general management of the project that involves guidelines and intra- and post- project reviews (project officer) and the review of the project's expenditures (auditors). It is clear that there is overlapping of stakeholders in different categories. The issue of consideration though is the level of commitment of each stakeholder. This may vary greatly between different individuals, groups or organizations. In that way the stakeholders may be identified in four categories depending on the level of commitment.

5.3 Expert Panel Description

On the 27th and 28th of November 2017, the kick-off meeting for OACTIVE was held in Nicosia, Cyprus. During that event, stakeholders in the knee Osteoarthritis and Infostructure sub-groups met separately and simultaneously to discuss the next steps in their respective areas of the project in detail. A comprehensive initial list of user requirements was drawn from the content of these discussions.

A questionnaire was prepared based on the initial list (shown in Appendix A). Henceforth, it will be referred to as Questionnaire A. Its objective was two-fold. First, it would allow the grading of the identified user requirements in order of perceived importance such that the most desired functionalities of the infostructure are identified and potentially implemented first. It also provided the opportunity for stakeholders to add and grade requirements that were not yet identified. To gather responses for the questionnaire, a head-to-head stakeholder interview session was organized between technological and clinical partners involved in OACTIVE.

In this deliverable, a brief overview of the technical assets at the disposal of the Infostructure group is first presented. The order in which the assets will be integrated into the OACTIVE framework depends on the demands of the primary users of the system. To determine the functionalities most in demand, we then proceed to analyze the responses to Questionnaire A.

5.4 Determining priority domains

To make best use of limited resources and to set up a working system as soon as possible, prioritising the implementation of the varying needs of stakeholders is necessary. This section deals with the analysis of the responses of stakeholders to Questionnaire A.

For each user requirement identified in the Questionnaire A, choosing one of the four options between highest and lowest priority adds 4, 3, 2 or 1 respectively to the its score. If the requirement is unrated, it means that it is seen as not a priority and, therefore, receives a score of zero. A normalized score varying from zero to one is then derived from the previous score and that is used to quantify the level of priority of each requirement. A normalized score of one would represent the case where all respondents rate a requirement as being of the highest level of priority.

Normalized priority score, $S = \frac{4 \cdot a + 3 \cdot b + 2 \cdot c + 1 \cdot d + 0 \cdot e}{4 \cdot (a + b + c + d + e)}$.

Having found a measure for the level of priority of a given requirement, we proceed to the assessment of the priority score for each user requirement identified prior to the May 2nd meeting and present in Questionnaire A.

5.5 Analysis of User Requirements

Questionnaire A

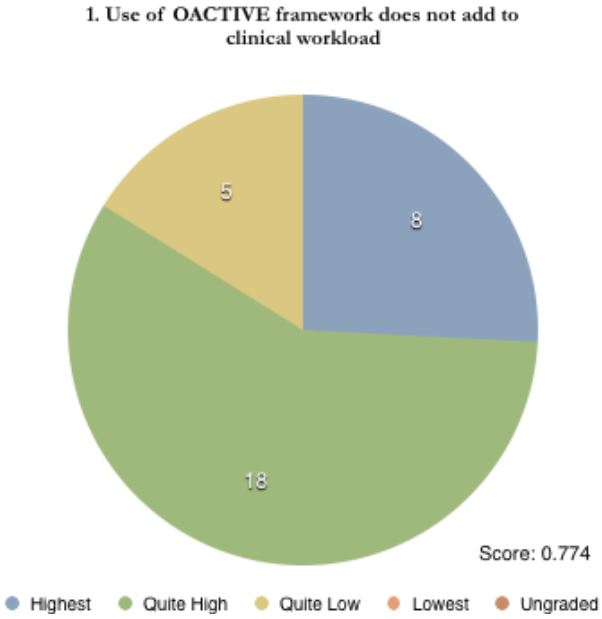

Figure 4. Data and calculated score for workload-related requirement

If the future use of OACTIVE considerably increases the amount of time and or effort that a clinician spends from initial contact with the patient to final diagnosis, it will not be deemed useful and will never come into widespread use. User-friendliness of OACTIVE will aid in reducing the extra workload brought upon by the use of the proposed system and will, therefore, increase its appeal among clinicians. As can be seen from figure, that requirement has a high priority rating.

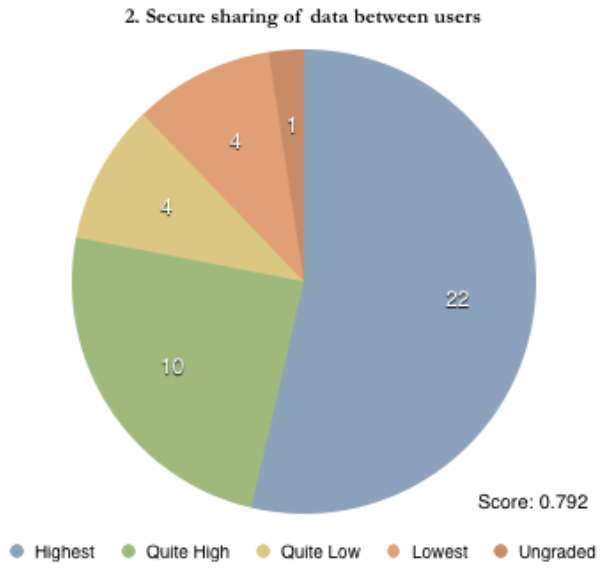

Figure 5. Data and calculated score for security-related requirement

Security is a high-priority requirement as figure demonstrates. During the requirement-gathering interview, it became apparent that it is also a very delicate issue and is tough to implement. The less anonymous the data is, the more the OACTIVE system needs to protect the data from unauthorized access. The discussions surrounding security also tended to focus on the exact type of consent that patients need to provide when making their data available for research. In line with the concept of 'enhanced privacy', giving feedback (if wanted) to the patients at the end of studies that used their data was also considered.

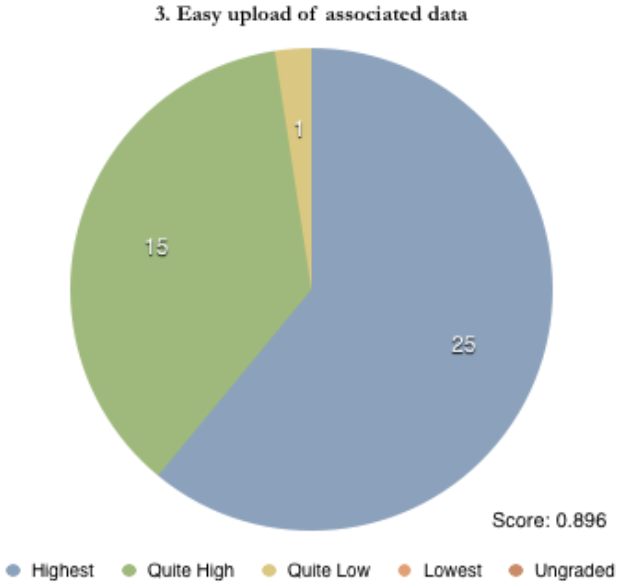

Figure 6. Data and calculated score for the easy uploading of associated metadata

In line with the notion of minimizing the impact on clinical workflow of using OACTIVE, the ease of uploading data to the repository would be very important. It has been identified as a high-priority requirement, as figure demonstrates.

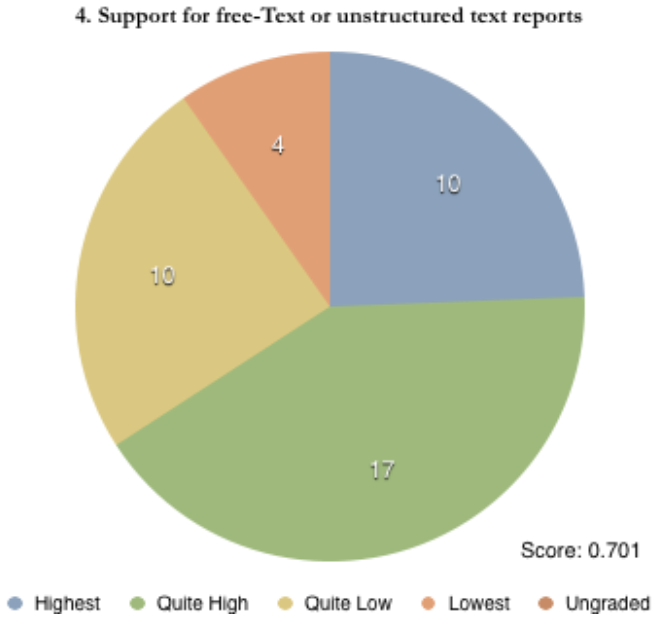

Figure 7. Data and calculated score for support of free-text and unstructured text reports

Numerical and image data is often accompanied by complementary unstructured text reports, the availability of which would be very useful for later study. OACTIVE should, therefore, be able to handle such text inputs. The questionnaire participants, accordingly, assigned a quite high priority to such a feature.

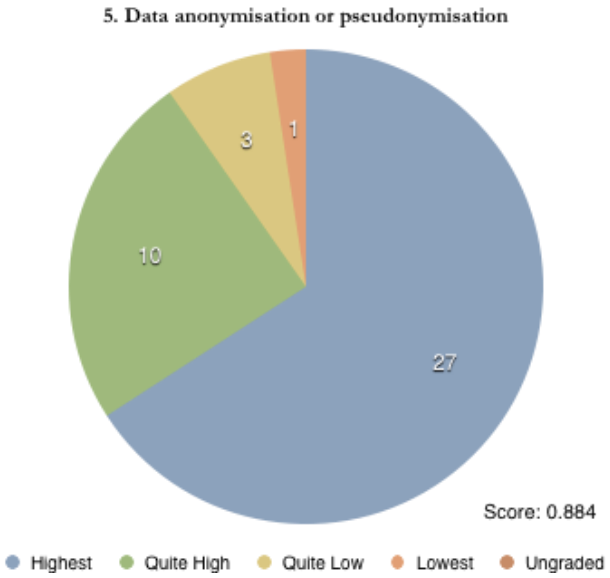

Figure 8. Data and calculated score for automatic anonymisation and pseudonymisation

Removing identifying information from patient data may be non-trivial and time-consuming. If OACTIVE had an in-built automatic depersonalisation or pseudonymisation tool, clinicians would just need to upload complete datasets to the system without spending any time on removing personal details of patients. The clinicians have indicated that the development of such a tool within the system is of high priority, as can be observed in Figure.

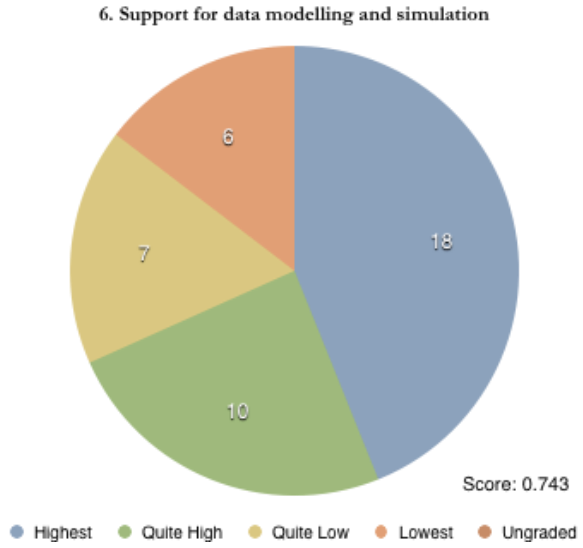

Figure 9. Data and priority score for implementing data for modelling and simulation

Enabling data modelling and musculoskeletal simulation would allow clinical researchers to manipulate patient data the within OACTIVE repository. In that way, they could make even

better use of the available information and be in a better position to make calls on the treatment of the patient. Figure X shows that this requirement has a fairly high priority.

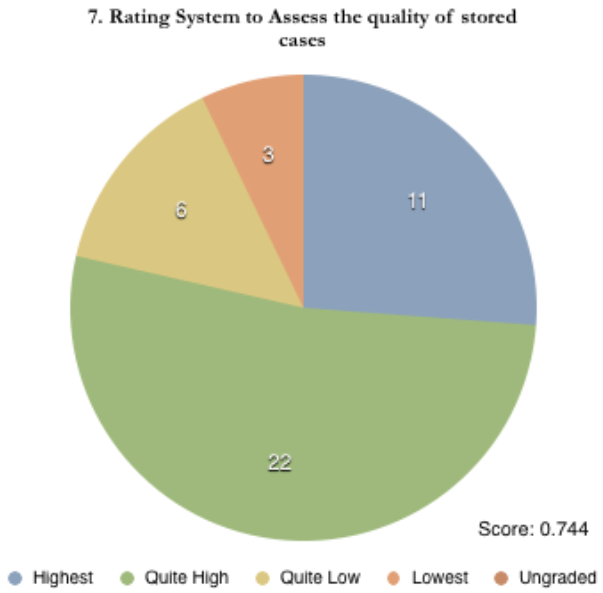

Figure 10. Data and priority score for implementing a rating system to assess the quality of stored cases

A rating feature would allow users of the repository to flag cases of interest such that they become more prominent in the future. Such a feature would ensure that clinicians get alerted to the existence of highly interesting cases that they can learn from and that can influence their choice of treatment for their patients. Figure points to the fact that clinicians assigned a high priority to its inclusion in the system.

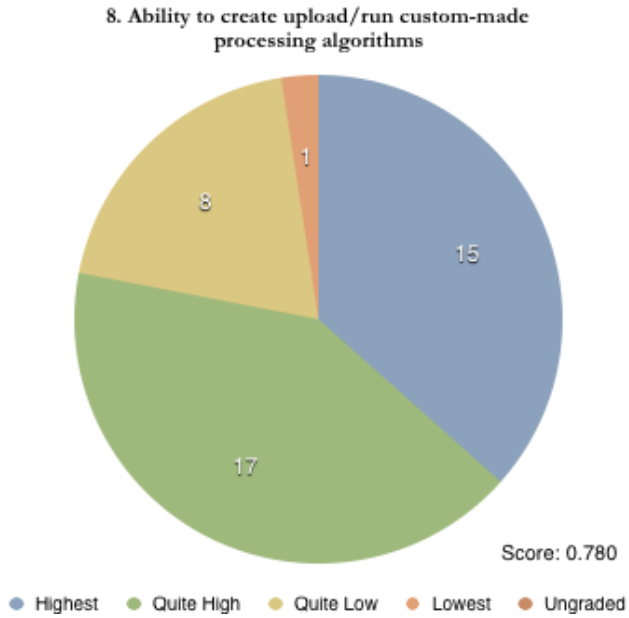

Figure 11. Data and priority score for implementing an ability to upload/run custom-made processing algorithms

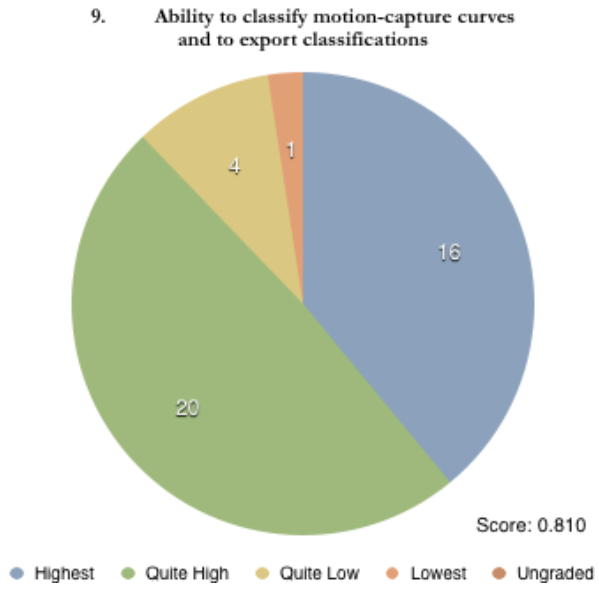

Figure 12. Data and priority score for implementing the ability to classify motion capture curves and to export classifications

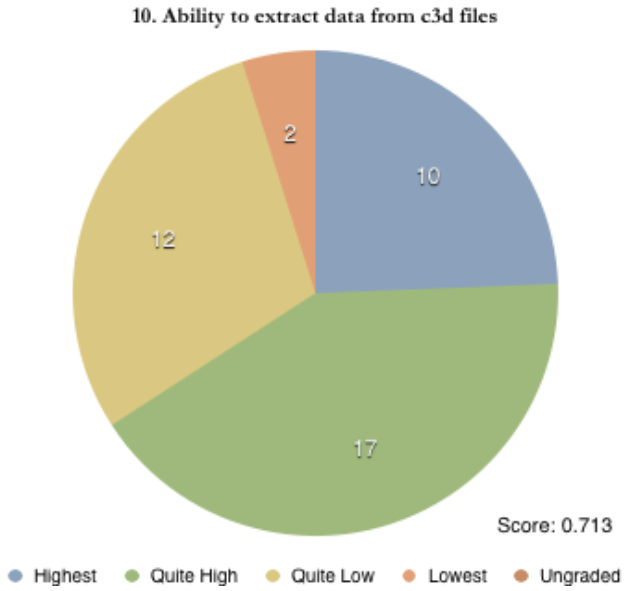

Figure 13. Data and priority score for implementing the ability to extract data from c3d files

As a summary, the answers to the questionnaire are considered as both reliable and helpful for users requirement determination. All experts categories were proportionally represented and information was gathered by different points of view. Answers to specific technical questions and correct approaches to prediction of parameters used and outcomes expected regarding to limitations and restrictions of the project show that the choice of the experts user panel was correct. Experts, who answers showed a deep knowledge of the field and an understanding of the project structure.

OACTIVE framework should incorporate highly rated requirements from the outset while the less popular ones should be added incrementally over time in order of priority or based on dependencies of functionalities. In this way, the end users will immediately be able to put the digital repository to good use and, over time, will embed it in their daily clinical and/or research workflow. An important use and acceptance by the clinicians is one of the major objectives of OACTIVE. The requirements analysis will be continuing throughout the first years of the project and it is thus a living document that will be updated with requirements coming up when data acquisition has started and clinical workflows have gained experiences with using the first versions of the framework.

5.6 Use cases

A. Clinical Studies

For the validation for the tool that will be developed (based on users requirements) during the lifespan of OACTIVE project 320 subjects will be recruited. For the validation dataset size, we focus on sensitivity and specificity, as defined by the Buderer's formula. Specifically, for a target value of sensitivity of 0.95 and specificity of 0.75, with a confidence interval half-width equal to 0.1, 310 subjects have to be recruited at a 5% significance level, given that the prevalence is 0.25. Allowing for an attrition rate of 4% the planned number of subjects will be increased to 320.

The process involves data collection in 3 different countries (Spain-HULAFE, Greece-ANIMUS and Cyprus-Apollonion Private Hospital) involving patients that may develop OA, athletes and elderly people with developed OA. The aim of the clinical studies will be to collect data, examine the relationship between the various risk factors generated by the different information sources and the clinical diagnosis (physical examination of clinicians).

- HULAFE (Spain): targeted population: subjects entering OA being at high risk of developing OA. Desired population size: >100
- ANIMUS (Greece): targeted population: athletes in post-traumatic OA. Desired population size: >90
- NIC (Cyprus): targeted population: elderly people with developing OA. Desired population size: >130

Clinical studies will last more than 2 years so as to allow the collection over a long period of time covering potentially different periods of well-being and periods of illness within a patient-specific framework. The date collected from each patient will be divided in different data subsets: (i) training data: data collected at the first 3 months that will be used for building the personalised models, (ii) fine-tuning data: the ones collected in the next 12 months that will be used for further optimising the models and (iii) validation data: data collected during the last 12 months of the project that will be utilised for testing the efficiency of the trained and fine-tuned patient-specific models. In addition, the proposed AR-based treatments will be evaluated towards the goal of personalized medicine in the cases of athletes and elderly people by modifying the gait pattern and/or proposing carefully selected exercises.

Table 4.OACTIVE clinical studies

Partner responsible	**HULAFE**	**ANIMUS**	**NIC**
Targeted patients	Healthy ones in high risk of developing OA	Post-traumatic evaluation of athletes	Elderly people
Population size	More than 100 patients	More than 90 patients	More than 130 patients
Information sets	Behaviour, imaging, Biochemical, Socio-economic. *Target*: data collection, examination of the relationship between various collected biomarkers for OA and clinical diagnosis (physical examination of clinicians).		
Duration	27 months. Starting from month 10 of the project and will last until the end of the project		
Outcomes	These results will be used for the development of advanced computer modelling and simulation tools in order to be used in early diagnosis or prognosis of OA.	These results will be used for the development of advanced computer modelling and simulation tools in order to be used in post-traumatic OA prediction	These results will be used for the development of advanced computer modelling/simulation tools in order to be used in OA prediction in elderly people
Intervention	-	Testing the efficiency of gait re-training and exercise intervention using AR.	

B. Big data registries

The integrated OACTIVE hyper-model will be validated using two big data registries, namely the OAI and the UK BIOBANK. These initiatives have collected substantial amounts of imaging, lifestyle, and biochemical data and other complementary data streams on the healthy subjects, and patients affected by OA. In OACTIVE, we will combine all of this information allowing for the first time the simultaneous exploration of multiple risk factors in big human populations involving thousands of patients. The knowledge (data) extracted here will then serve as input for the integrated computer hyper- models that will be constructed in work package 6. In task, the big data methodology, developed in WP6, will search through massive amounts of information, analysing it to predict outcomes for individual patients. That information will include data from past treatment outcomes with the outcome not only to predict but also to reveal surprising associations in data that our human brains would never suspect. In terms of the validation, patient-specific data with follow-ups of more than 100 months will be used as follows: the personalised models will be built using data from the first months and the efficiency of OACTIVE will be tested using the latest data available against the following criteria: prediction accuracy and maximum prediction timeframe. The personalised models will be finally

progressively updated incorporating more information from subsequent months and the predictive performance of the models will be estimated per case.

6 CONCLUSIONS

The main goals of this deliverable were to identify, to elaborate and to specify the end-user requirements for the proposed OACTIVE project framework. This document, would serve as a 'guideline' for further project activities.

The process of identification the end user requirements was the most challenging activity of this deliverable. It required full use of the abilities, resources and professionalism of our partners. We could conclude it as being an "ambitious task", but as result of the analysis of the active/continuous scientific literature review we had concluded that it was impossible to present from the very beginning an advanced and"complete" description of "all" End User Requirements (EURs). As a solution we proposed versioning control of the identified EURs.

Moreover, there are linkages to other Work Packages, where the identified and presented EURs will serve as an approved and mutually agreed "starting point" for developments and research activities.

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APPENDIX A

Questionnaire

Questionnaire- OACTIVE Requirements

To help the OACTIVE project consortium draw a list of requirements for the OACTIVEframework and prioritize the development of the most useful features, please fill in the following questionnaire. The project team thanks you in advance for your participation.

Full name

E-mail address

Institution

Age

Sex

Existing Requirements

Please rate the following requirements in terms of the level of priority to be assigned to them. They were identified at the kick-off event in Nicosia, Cyprus. There are four levels of priority per requirement ranging from highest priority (leftmost boxes) to lowest priority (rightmost boxes). Please mark your choice of level of priority with a tick mark (✓).

1. Use of OACTIVE does not add to the workload of users.

Highest	Quite High	Quite Low	Lowest

2. Secure data sharing between users.

Highest	Quite High	Quite Low	Lowest

3. Easy upload of associated data.

Highest	Quite High	Quite Low	Lowest

4. Support for free-text or unstructured text reports.

Highest	Quite High	Quite Low	Lowest

5. Data anonymisation or pseudonymisation

Highest Quite High Quite Low Lowest

6. Support for data modelling and simulation

Highest Quite High Quite Low Lowest

7. Rating System to Assess the quality of stored cases

Highest Quite High Quite Low Lowest

8. Ability to create upload/run custom-made processing algorithms

Highest Quite High Quite Low Lowest

9. Ability to classify motion capture curves and to export classifications

Highest Quite High Quite Low Lowest

10. Ability to extract data from c3d files

Highest Quite High Quite Low Lowest

Open-ended questions

Please answer the following questions in a clear and concise manner.

11. Please describe your usual clinical and/or research work-flow especially with regards to the use of image and associated non-image data for the treatment of knee OA patients.

12. Please list the difficult decisions that need to be made in the clinical workflow and state the type of information that can aid the decision-making process.

13. Please state the modality and, if known, the file format/extension for each type of image and non-image data that you would like to upload to the OACTIVE framework.

14. Please list the methods you employ to gather complementary information about cases at hand e.g. asking colleagues, searching on google or pubmed and so on.

Other required or desired features in OACTIVE

Please use this section to add and rate further requirements that have not been covered so far in this questionnaire.

15.

Highest Quite High Quite Low Lowest

16.

Highest Quite High Quite Low Lowest

17.

Highest Quite High Quite Low Lowest

18.

Highest Quite High Quite Low Lowest

19.

Highest Quite High Quite Low Lowest

20.

Highest Quite High Quite Low Lowest

21.

Highest Quite High Quite Low Lowest

22.

Highest Quite High Quite Low Lowest

23.

Highest Quite High Quite Low Lowest

24.

Highest Quite High Quite Low Lowest

Comments

25. Please add any further comments here.