Model Driven Paediatric European Digital Repository

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List of Contributors

Name	**Affiliation**
Marcello Chinali	OPBG
Gabriele Rinelli	OPBG
Alexander Jones	UCL
Alberto Martini	IGG
Jaap Harlaar	VUmc

List of reviewers

Name	**Affiliation**
Giacomo Pongiglione	OPBG
Edwin Morley-Fletcher	LYNKEUS
Bruno Dallapiccola	OPBG

Abbreviations

CUR	Clinical User Requirements
PM	Project Management
DoW	Description of Work
WP	Work Package
CVD	Cardiovascular Disease
JIA	Juvenile Idiopathic Arthritis

NND	Neurological and Neuromuscular Diseases

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1 Introduction

1.1 Purpose

This document is designed to obtain a list of variables and requirements for the disease modelling for each area of the MD-Paedigree clinical project – these being cardiomyopathies, obesity related cardiovascular risk, juvenile idiopathic arthritis and neurological and neuromuscular diseases. Although the four areas are all focused on chronic medical conditions occurring in children, the requirements for each field are in many respects different given the significant differences in the pathophysiology, evolution and outcome of the four disease areas.

The MD-Paedigree is a clinically driven project, thus the main objective of WP-2 is to guarantee that the features and capabilities of the disease models merge the clinical needs and answer clinically relevant medical questions. In order to achieve this aim, it ensures that the models incorporates features and variables that are analyzed by the clinicians in their routine activity. The ultimate goal is to provide computational models that can be personalized by adapting the parameters to the integrated data of a specific patient and to improve the current knowledge and understanding of the disease by simulating different aspects on the evolution of a disease. In addition it also aims at providing insights on the effect of a specific therapeutic intervention; being this either pharmacological, behavioral or surgical. Based on the targeted clinical needs, requirements are defined for all disease areas to ensure that MD-Paedigree models have the highest possible impact on medical knowledge and clinical care.

Indeed, to obtain an effective modelling a number of different variables and features of the diseases (cardiomyopathy, obesity, neuro-muscular, and rheumatology) must be taken into account and merged to obtain a stable and effective model of the diseases.

The main purposes of this work package are:

- To elaborate the user needs and requirements for the proposed models for clinical decision support with the goal to drive common clinical practice to personalized medicine.
- To provide for activities to assure that the project will meet its specified requirements and will be fit-for-use

1.2 Scope

This document is applicable to the MD-Paedigree project until the next programmed document release (D2-2: "Revised Requirements Analysis Document")

1.3 Project Overview

MD – PAEDIGREE *Model-Driven European Paediatric Repository* is a research project funded by the European Commission under the Virtual Physiological and Human Area (VPH) of the ICT Theme of the Seventh Framework Programme.

MD-Paedigree aims at finalizing patient-specific computer-based predictive models of various paediatric diseases (cardiomyopathy, risk of cardiovascular disease in obese children and adolescents, Juvenile Idiopathic Arthritis (JIA) and neurological and neuro-muscular diseases (NND), in order to increase the potential acceptance in the clinical practice not only in the form of usable and reliable models and simulations, but also to define new workflows for personalized predictive medicine in clinical care.

MD-Paedigree's goal is to integrate highly heterogeneous biomedical information, using adaptable and composable multi-scale VPH workflow models and to support evidence-based translational medicine at the point of care practices. Thus it represents a major step towards personalised paediatric medicine, based on data-driven models, patient-specific simulations and a sustainable data and model repository.

From the Clinical User Requirements standpoint, it is important to note that the main focus within the MD-Paedigree project can be divided into:

- Identifying the core clinical aim of the four disease areas (JIA, CVD risk in obese children, NND, Cardiomyopathies).
- Identifying the clinical user expectation on the developed models (computational models and disease simulations) in order to improve and support clinical management of the different disease (including prediction of disease development and prediction of treatment impact).

As a priority for implementation, it also aims on initial identification of the technical needs in order to provide the requested model. In details, starting to establish the key data acquired in clinical setting needed to build and verify the models (i.e. reverse user requirements).

2 User Requirements

2.1 General Considerations and Approach

Understanding and correctly defining clinical user requirements is a crucial step in the development of useful and usable patient-specific models. However assuming that that user requirements are established and delivered from the clinical partner to the technical developer at the beginning of a development project may lead to the development of models not fully meeting the requirements, as these may change over the time of the clinical study and the ongoing process of testing and verifying the model prototypes. Accordingly another approach may be preferred, in which specifications and interpretations of user requirements, will change over time as they evolve with experience. This aspect is especially true for the MD-Paedigree project where the development and detailed definition of the specific clinical workflows has changed the original clinical protocols during this first year.

Evidently during the study, clinical user requirements may evolve or become more detailed on specific and more clinically relevant aspects of the four specific diseases on which the project is focused.

Accordingly, this document represents the first step in an ongoing and evolving understanding of user requirements under consideration by system designers and developers as they face the "real" requirements of adapting function to the constraints of clinical needs, computer platforms, project cost, and delivery schedule.

2.2 MD-Paedigree Requirements Work Package

The project recognizes the importance of requirements analysis and documentation in successful software development and end-user satisfaction. Accordingly, other work packages are also dedicated to the analysis and documentation of users' requirements as well as semantic interoperability:

- WP13 - Requirements and Compliance for the MD-Paedigree Infostructure. Separate tasks will assure compliance with two major initiatives in the field, (i.e. VPH Share and OpenAIRE).

- WP15 - Semantic Data Representation and Information access – deals with the Semantic interoperability, ensuring that the project uses wherever possible standard terminological resources (such as ICD-10, LOINC, WHO-ATC, SNOMED, FMA, or RadLex) and appropriate representation languages (e.g. OWL, RDF) for encoding all data items.

The requirement gathering efforts have started in the first phase of the project and will continue throughout the clinical protocol data collection in order to assure that clinical and technical requirements are met.

2.3 Data Acquisition

The MD-Paedigree project involves both the enrollment of new patients and the use of existing data that have already been acquired in the context of other projects and clinical studies (SeC, HeC, etc).

Dedicated clinical protocols and informed consent forms for the different areas of clinical studies have been prepared according to current National, EU and USA laws and regulations, and approval sought from each clinical partner's local Ethical Committee.

2.3.1 Data collection – general principles

- The diagnoses of enrolled patients must strictly adhere to the diagnosis chosen for the project.
- Define what data will be used for the creation of the disease models.
- Data must be collected according to agreed protocols and forms.
- Incomplete data may be collected for specific and previously agreed purposes (i.e. legacy data).

3. Merging Models with Clinical Needs

As stated in the general project description the goal of the MD-Paedigree is to find efficient ways to optimise and combine multiple statistical and/or specialized VPH simulation models in prediction tasks supporting the creation and validation of model-driven clinical workflows; as illustrated in the Figure below.

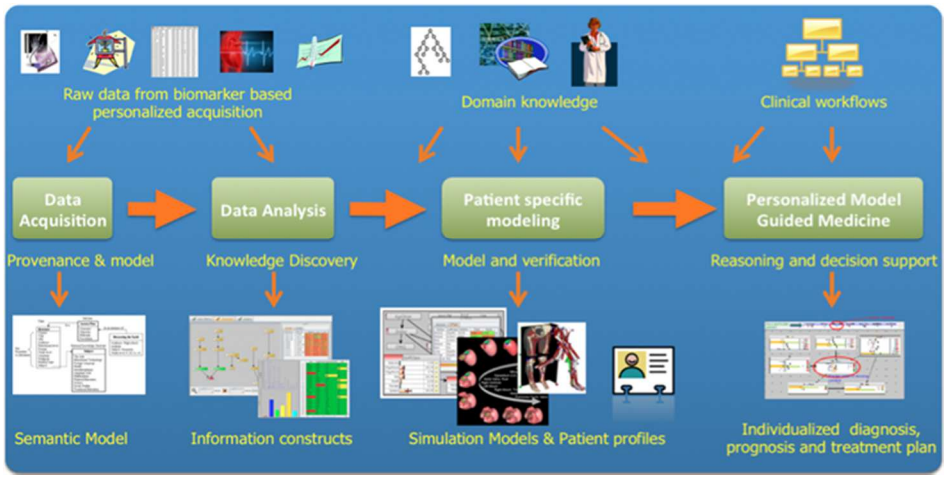

Figure 1: Illustration of Model Guided Personalized Medicine Process

3.1 Clinical Questions of the Disease Areas

The purpose of the current section is to identify the core clinical aim of the four different disease areas. Clearly identifying the main clinical question of the study is a key feature for the understanding of the user requirement. Usually to correctly understand clinical questions, 4 components should be taken into account. The PICO model is a helpful tool in organizing and focusing foreground question into a searchable query. The PICO model can be so defined: P = Problem (What are the most important characteristics of the patient?); I = Intervention (What main intervention are you considering?); C = Comparison (What is the main alternative to compare with the intervention?); O= Outcome (What are you trying to accomplish?).

However, this traditional approach has limited applicability in the setting of the current project, as MD-Paedigree is focused on the identification of patient specific modelling rather than on identifying the average, common features of patients sharing a similar medical condition. Given these assumptions, and the nature of the different diseases in the MD-Paedigree, its clinical protocols focus on either 'background questions' (i.e. knowledge about the illness), 'foreground questions' (specific knowledge to inform clinical decisions) or both. Given the heterogeneity of the different clinical focuses of the MD-Paedigree project, user requirements have been analyzed separately for each clinical workpackage.

3.2 Interviews With Clinical Partners

In order to properly understand the clinical user requirements for the MD-Paedigree project for each clinical area, a number of individual interviews were undertaken with clinical partners to answer questions on the expected support from the mechanical or statistical models on clinical issues.

Obviously, a critical step in obtaining this aim is to clearly identify the clinical need and relevant clinical questions raised in the different disease areas. Focusing on the most critical and complex aspects of the different diseases. Accordingly, a fist interview with all clinical partners was undertaken in order to establish the primary clinical user requirements for the success of the MD-PAEDIGREE project.

Clinical partners were interviewed on both general and specific requirements regarding their disease areas. A first interview was performed to identify the most pressing clinical questions for the different disease areas, identifying the aspects in which current medical knowledge is still limited due to a traditional research approach.

Table 1. Reported current limiting factors in medical practice of the four disease areas.

Limitations in knowledge of the disease	Limited data on factors influencing the progression of the disease
	Difficulties in merging different features of the disease
	Individual features affecting the development of the disease
Limitations on the effect of treatment	Limited data on the effect of changes due to: • medical therapy • surgical therapy
	Individual features affecting the response to intervention.

Accordingly a general questionnaire was carried out to establish, for each clinical WP, which aspect of the disease modelling represented the highest priority (detailed explanation are reported below):

TABLE 2. Specific level of priorities for each aspect of the clinical question on the clinical work-packages

Support in improving the understanding of complex pathological features of the disease	Highest priority for WP-4
	High priority for WP-6 and WP-3
	Medium priority for WP-5
Support in predicting the evolution of the disease	Highest priority for WP-5 and WP-6
	High priority for WP-3 and WP-4
Support in predicting the potential effect of treatment/intervention	Highest priority for WP-6 and WP-3
	High priority for WP-5
	Medium priority for WP-4

4. User requirements separated by clinical work package

Then a detailed interview was undertaken in order to obtain a specific list of user requirements form each single clinical work package.

4.1 WP3. Cardiomyopathies

Cardiomyopathy is a rare life-threatening disease leading to chronic cardio-active therapy, or even to mechanical support (artificial heart), heart transplantation or death. However, it is very difficult to predict which group any patient will end up in. Thus the main user requirements for modelling in patients for cardiomyopathy regard both the understanding of the complex interactions between hart size, geometry and shape, cardiac workload, heart rate and heart pump function as well as the ability to provide better insight into prognosis of cardiomyopathies, which will help in patient management and in telling families how their child will progress. The mechanical model is expected to integrate and merge information from different diagnostic and clinical tools in order to uncover number pf both backward questions on and forward questions.

CLINICAL USER REQUIREMENTS FOR WP-3.

Backward questions: (Unfold complex interactions)

- Establishing the interaction between the different components of the heart and cardiac performance in dilated cardiomyopathy (mechanical modeling, hemodynamic modelling, fluid-structure interaction).
- Impact of heart rate on cardiac performance
- Relation between cardiac performance and clinical functional class

Foreword questions: (Identifying possible effect of time and intervention)

- Predicting evolution of the disease and identifying possible predictors of outcome
- Impact of changes in cardiac performance by changing heart rate and cardiac load using specific medications

A list of the expected information from the computer models is provided below.

In details, modelling change in the input variable is expected to provide quantitative information on the impact in outcome variables and thus to provide information on a number of aspects of the disease including progression and impact of intervention.

TABLE 3. DETAILED USER REQUIREMENT LIST FOR WP-3

INPUT VARIABLE	OUTCOME VARIABLE	
Time lapse (2 years)	Left ventricular systolic/diastolic diameters Left ventricular mass Left ventricular volume Left ventricular sphericity index Left ventricular ejection fraction Left ventricular stroke volume Left ventricular mitral valve dimension Mitral valve regurgitant fraction Mitral inflow early and late velocities	Mitral tissue Doppler velocities Right ventricular tricuspid plane excursion Right ventricular ejection fraction Right ventricular systolic pressure Intra-ventricular systolic synchronicity Inter-ventricular systolic synchronicity Inter-ventricular interaction index Percent regional systolic myocardial deformation
Change in heart rate (bpm')	Left ventricular stroke volume Left ventricular cardiac output Left ventricular systolic/diastolic diameters Left ventricular sphericity index Left ventricular ejection fraction Left ventricular stroke volume Inferior vena cava dimensions Inferior vena cava respiratory variation Left ventricular mitral valve dimension Mitral valve regurgitant fraction	Mitral inflow early and late velocities Mitral tissue Doppler velocities Right ventricular tricuspid plane excursion Right ventricular ejection fraction Right ventricular systolic pressure Intraventricular systolic synchronicity Interventricular systolic synchronicity Interventricular interaction index Percent regional systolic myocardial deformation
Change in volume load	Inferior vena cava dimensions Inferior vena cava respiratory variation Left atrial diameter Left atrial volume Heart rate	Left ventricular stroke volume Left ventricular cardiac output Left ventricular mitral valve dimension Mitral valve regurgitant fraction

	Left ventricular systolic/diastolic diameters Left ventricular mass Left ventricular volume Left ventricular sphericity index Left ventricular ejection fraction	Mitral inflow early and late velocities Mitral tissue Doppler velocities Right ventricular tricuspid plane excursion Right ventricular ejection fraction Right ventricular systolic pressure

4.2 WP4. Cardiovascular disease risk in obese children

Support in identifying pathological features of the disease was defined as the highest priority for WP-4 (i.e. focusing on cardiovascular risk in pediatric obesity). Reason for this priority was derived from the specific nature of this work package's clinical aim and scope. As stated by clinical partners, obesity in childhood should not be considered as a clear cut disease, but rather as a threatening risk factors which might lead to overt cardiovascular disease. However time of overt disease development from exposure varies between many years to decades, thus resulting in the obvious difficulty of the current project (4 years) in verifying the ability of the predictive models (either statistical of mechanical) in predicting the development of clear cut disease of in the effect of an hypothetical treatment. Nonetheless, from the medical knowledge standpoint the development of a disease model for childhood obesity represents an unprecedented tool to answer both backward and forward clinical questions:

DETAILED CLINICAL USER REQUIREMENTS FOR WP-4.

Backward questions: (Unfold complex interactions)

- Building a complete risk profile geno/phenotyping (food intake habits, physicological, excercise, gut microbiome, inflammatory sytatus, diagnostic testing, etc.)
- Establishing the interaction between the different components of fat (amount and distribution), and cardiovascular system (at both rest and under meal stress)
- Identification of different pathophysiological patterns in obesity (as not always a strict association between amount of obesity and risk)

Forward questions (Identifying possible effect of time and intervention):

- Identify individuals at higher risk of developing overt cardiovascular disease
- identifying possible predictors of the development of early markers of disease (the so-called preclinical markers of cardiovascular disease)

A list of the expected information from the computer models is provided below.

In details, modelling change in the input variable is expected to provide quantitative information on the impact in outcome variables and thus to provide information on a number of aspects of the disease including pathophysiology and insights into the progression of the disease.

TABLE 4. DETAILED USER REQUIREMENT LIST FOR WP-4

INPUT VARIABLE	OUTCOME VARIABLE	
Body Fat Content (%)	Anthropometrics (BMI, BSA) Blood lipid profile (triglycerids, LDL, HDL etc) Glucose level (baseline and at tolerance test) Glycated haemoglobin Liver function tests (alanine-aminotransferase, aspartate amino transferase, γ-glutamyl transferase) Heart rate Systolic, diastolic and mean blood pressure Leptin, adiponectin, CRP, Tumor-Necrosis Factor-alpha, TNF-alpha; Interleukin 6, IL6, E-Selectin, Intercellular Adhesion Molecule 1, ICAM-1 Gut microbiota taxa distribution	CARDIAC: • Left ventricular mass • Right ventricular volume • Right ventricular systolic pressure • Left ventricular stroke volume • Left ventricular cardiac output • Mitral inflow early and late velocities • Mitral tissue Doppler velocities • Left atrial volume • Total peripheral resistance Ancillary (impact of meal): • Hormonal response • Stroke volume • Arterial compliance
Change in body weight (BMI)	Blood lipid profile (triglycerids, LDL, HDL etc) Glucose tolerance test Liver function tests (alanine-aminotransferase, aspartate amino transferase, γ-glutamyl transferase) Heart rate Systolic, diastolic and mean blood pressure Leptin, adiponectin, CRP, Tumor-Necrosis Factor-alpha, TNF-alpha; Interleukin 6, IL6, E-Selectin, Intercellular Adhesion Molecule 1, ICAM-1	CARDIAC: • Left ventricular mass • Right ventricular volume • Right ventricular systolic pressure • Left ventricular stroke volume • Left ventricular cardiac output • Mitral inflow early and late velocities • Mitral tissue Doppler velocities

	Gut microbiota taxa distribution	• Left atrial volume • Total peripheral resistance Ancillary (impact of meal): • Stroke volume • Arterial compliance

4.3 WP5. Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is a clinically heterogeneous group of arthritis of unknown origin. The cause and pathogenesis of JIA are still poorly understood and disease heterogeneity implies that different factors probably contribute to its pathogenesis and development. Personalized joint biomechanical modeling allows critical evaluation of the forces within the joint under physiologic and pathological loading conditions, and evaluation of the impact of joint mechanical abnormalities on disease progression are needed for an accurate outcome prediction. The main differences compared to controls lay in reduced hip extension, reduced knee extension, and reduced plantar flexion with a passive and decelerated push off of the ankle. Joint restriction goes along with a hypertonic flexor muscle loop and a hypotonic extensor muscle loop. The expected role of the multi-scale modeling is to make the exploration of complex systemic interactions between the neuromuscular control, the musculoskeletal functional anatomy, and the local biomechanical determinants acting in the joint space at the tissue level possible, and to improve early diagnosis and therapeutic intervention.

DETAILED CLINICAL USER REQUIREMENTS FOR WP-5.

Backward questions: (Unfold complex interactions)

- interaction between the different components the ankle region – containing bones, cartilage and ligaments- in defining functional impairment
- complex relationship between inflammation and movement ability

Forward questions:

- identify features of patients at higher risk of disease progression
- Be able to personalize risk stratification in order to start therapy more aggressively and or earlier

A list of the expected information from the computer models is provided below.

In details, modelling change in the input variable is expected to provide quantitative information on the impact in outcome variables and thus to provide information on a number of aspects of the disease progression.

TABLE 5. DETAILED USER REQUIREMENT LIST FOR WP-5

INPUT VARIABLE	OUTCOME VARIABLE	
Time lapse (2 years)	Anatomic features:	GAIT: Pelvic Tilt-Average Pelvic Obliquity (ROM (P1-P2))

	• Limb length (from anterior iliac spine to apex of medial malleolus); • Distance between the two anterior iliac spines; • Distance from posterior iliac spine to trochanter; • Distance between the two epicondyles of the femur; • Distance between the lateral and medial malleoli Walking functional parameters: • Foot Off • Step Length • Dimensionless Step Length • Walking Speed • Dimensionless Walking Speed • Step Width	Pelvic Obliquity ROM Hip Flex/Ext-max. extension Hip Flex/Ext-max. flexion Hip Flex/Ext-ROM Hip Abd/Add-max.Abd Hip Abd/Add-max.Add Hip Abd/Add-ROM Knee Flex/Ext-K1 Knee Flex/Ext-K2 Knee Flex/Ext-K3 Knee Flex/Ext-K4 Knee Flex/Ext (ROM (K1-K2)) Knee Flex/Ext (ROM (K2-K3)) Knee Flex/Ext (ROM (K3-K4)) Ankle Dorsi/Plan-A1 Ankle Dorsi/Plan-A2 Ankle Dorsi/Plan-A3 Ankle Dorsi/Plan-A4 Ankle Dorsi/Plan-(ROM (A1-A2)) Ankle Dorsi/Plan-(ROM (A2-A3)) Ankle Dorsi/Plan-(ROM (A3-A4)) Plantar Angle-Initial Contact Plantar Angle-max (swing phase) Foot-Flat (±2°)
Inflammatory state - **erithrociyte sedimentation rate** - **C-reactive protein** - **plasma viscosity**	Walking functional parameters: • Foot Off • Step Length • Dimensionless Step Length • Walking Speed • Dimensionless Walking Speed • Step Width	**Ground rotational force** GRF(Z) P1 GRF(Z) P2 GRF(Z) P3 GRF(Y) P1 GRF(Y) P2 Ankle (max-Dorsi-moment) Ankle (max-Power generation)

4.4 WP6. Neurological and neuromuscular disease

In Neurological and Neuromuscular Diseases (NND) as well as in certain chronic diseases of the musculoskeletal system in children, treatments are strongly guided by maximizing the walking function of the human movement system, which is considered as highly valued by the patients. Although walking is a common task executed by a healthy individual in a seemingly effortless manner, it implies a complex involvement of inputs from several senses (visual, vestibular, proprioceptive, somatosensory). The clinical study focuses on the walking ability of three different disease groups: Duchenne's muscular dystrophy, cerebral palsy and Charcot-Marie-Tooth disease. Its main clinical aim is to monitor disease course. However, in the CP group a specific interest on modelling relies on the possibility to predict the effect on walking of different therapeutic approaches, including surgical intervention. Accordingly, a number of specific backward and forward clinical questions are required to be answered by the models for each specific disease:

DETAILED CLINICAL USER REQUIREMENTS FOR WP-6.

DMD & CMT:

- Obtain a detailed muscle/bone structural/functional interaction model (reproducing muscle length, weight, insertion points)
- Evaluate the impact of this interaction in defining walking functionality.
- Predict evolution of the disease (identify features of patients at higher risk of disease progression)

CP:

- Obtain insight on treatment (virtual 'correction' of joint deformities and muscle lengthening)

A list of the expected information from the computer models is provided below.

In details, modelling change in the input variable is expected to provide quantitative information on the impact in outcome variables and thus to provide information on a number of aspects of the disease including progression and impact of intervention.

TABLE 6. DETAILED USER REQUIREMENT LIST FOR WP-6

INPUT VARIABLE	OUTCOME VARIABLE	
Time lapse (2 years)	Muscular weakness (MRC values): • Ileopsoas • Rectus Femoris • Gluteus Maximus	GAIT: Stance time (% gait cycle)

	• Tibialis Anterior • Gastrocnemius Walking functional parameters: • Foot Off • Step Length • Dimensionless Step Length • Walking Speed • Dimensionless Walking Speed Anatomic features: • Limb length (from anterior iliac spine to apex of medial malleolus); • Distance between the two anterior iliac spines; • Distance from posterior iliac spine to trochanter; • Distance between the two epicondyles of the femur; • Distance between the lateral and medial malleoli	Cadence (steps/min) Velocity (m/(s H)) Stride length (m/H) Step width (m/H) Stride time (ms) Pelvic obliquity (°) Pelvic tilt (°) Pelvic rotation (°) Hip Ab-adduction (°) Hip rotation (°) Hip flex-extension (°) Knee flex-extension (°) Knee Hyperextension (% gait cycle) Ankle plantar-flexion (°) Foot progression (°) H3 peak of hip power (W/kg) Maximum of ankle power (W/kg)
Virtual intervention: **-Ankle plantar flexor lengthening** **-Rectus femoris transfers** **-Hamstring lengthenings** **- Femoral derotation osteotomies** **- Psoas lengthenings**	Walking functional parameters: • Foot Off • Step Length • Dimensionless Step Length • Walking Speed • Dimensionless Walking Speed • Step Width	Gait Pelvic obliquity (°) Pelvic tilt (°) Pelvic rotation (°) Hip Ab-adduction (°) Hip rotation (°) Hip flex-extension (°) Knee flex-extension (°) Knee Hyperextension (% gait cycle) Ankle plantar-flexion (°) Foot progression (°) H3 peak of hip power (W/kg) Maximum of ankle power (W/kg)

5. Priorities for implementation

5.1 Bringing clinical requirements to technical partners

After having acquired from clinical partners the initial clinical user requirements it is of great importance to stimulate and support the interaction between the clinical and the technical arm of the project. In this view a crucial step is to provide technical partners with a clear insight of the expectation of clinical partners regarding the disease models. This is relevant also to provide technical partners with the needed data for adequate disease modeling or, in contrast to inform the clinical partners which and how specific clinical requirements can be satisfied with the data provided from the point of care. In this view it has to be underlined that clinical protocols of the MD-Paedigree have been designed to obtain data from 'routine' clinical examination, thus it is reasonable (expected) that not all variables will be available in all patients.

Thus it becomes crucial for technical partners to provide clinical partners with a tentative list of required data to perform modelling.

Accordingly interviews with technical partners were performed, presenting for each WP the resulted clinical user requirements. This initial interaction with the technical partners will be object for the definition of a more detailed user requirements document once the clinical studies have started active enrollment of clinical subjects and data will start to flow in a consistent manner, providing a sufficient amount of data to the technical partners in order to clearly identify the needs to fulfill clinical user requirements.

A preliminary list of technical needs (so-called reverse user requirements) are here reported:

–MRI: all WP

- WP Specific:
  - –Structure hepatic and distribution of fat (WP4)
  - –Cardiac intraventricular blood flows (WP3)

–Detailed gait analysis

- WP 5 (highest, no model possible if any missing information)
- WP 6

–US (WP4, WP3 - 3D Scan acquisition)

- EKG: for times and axis (WP 3 highest)
- Arterial BP (WP 3, WP4)

6. Conclusion

Having found what the most pressing needs of the clinical users of MD-PAEDIGREE are, the technical group can now focus on specific questions for the construction of the models. Feedback from the technical partners in now essential to identify specific reverse user requirements and provide adequate amount and type of data from the clinical centers.

Significant use and acceptance by the clinicians is one of the major objectives of MD-PAEDIGREE, thus the requirements analysis will be continuing throughout the years of the project and needs therefore to be considered as a living document, that will be updated with the upcoming requirements in parallel with progress in data acquisition and with accrued experience in the relevant clinical workflows.