Deliverable No. 2.4

Requirements for enhancing VPH models for clinical decision support

Grant Agreement No.:	270089
Deliverable No.:	**2.4**
Deliverable Name:	**Requirements for enhancing VPH models for clinical decision support**
Contractual Submission Date:	January 31st, 2012
Actual Submission Date:	February 10th , 2012

Dissemination Level		
PU	Public	**X**
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

COVER AND CONTROL PAGE OF DOCUMENT	
Project Acronym:	***p-medicine***
Project Full Name:	From data sharing and integration via VPH models to personalized medicine
Deliverable No.:	D2.4
Document name:	**Requirements for enhancing VPH models for clinical decision support**
Nature (R, P, D, O)[1]	**R**
Dissemination Level (PU, PP, RE, CO)[2]	**PU**
Version:	**FINAL**
Actual Submission Date:	10/02/2012
Editor: Institution: E-Mail:	Eftychia Lekka BIOVISTA e.elekka@biovista.com

ABSTRACT: Deliverable 2.4 aims to specifically address decision supporting tools and VPH models from a clinical and biomedical perspective. Questions that were further elaborated were related to the requirements and/or challenges (biomedical, ICT, healthcare) needed so as to facilitate VPH models, validation and certification tools and requirements needed for clinical decision support. Ultimately these tools will be use in Good Clinical Practice (GCP) conform and evaluated in the context of the clinical trials in p-medicine.

KEYWORD LIST: Virtual Physiological Human (VPH), p-medicine, cancer, clinical trials

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 270089.

The author is solely responsible for its content, it does not represent the opinion of the European Community and the Community is not responsible for any use that might be made of data appearing therein.

[1] **R**=Report, **P**=Prototype, **D**=Demonstrator, **O**=Other

[2] **PU**=Public, **PP**=Restricted to other programme participants (including the Commission Services), **RE**=Restricted to a group specified by the consortium (including the Commission Services), **CO**=Confidential, only for members of the consortium (including the Commission Services)

MODIFICATION CONTROL			
Version	**Date**	**Status**	**Author**
1.0	05/01/2012	Draft	EL, ED, AS, AP
2.0	13/01/2012	Draft	EL, ED, AS, AP, RD
3.0	26/01/2012	Draft	EL, ED, AS, AP, RD
4.0	31/01/2012	Pre-final	EL, ED, AS, AP, AB, DB
4.1	10/02/2012	Final	EL, ED, AS, AP

List of contributors

- Eftychia Lekka (EL), BIOVISTA
- Evi Dodou (ED), BIOVISTA
- Anuj Sharma (AS), BIOVISTA
- Andreas Persidis, BIOVISTA
- Ruslan David (RD), USAAR
- Holger Stenzhorn (HS), USAAR
- Anca Bucur (AB), Philips
- Danny Burke (DB), ecancer

CONTENTS

1 EXECUTIVE SUMMARY

WP2 of the p-medicine project aims at addressing the needs and requirements for the proposed technological and clinical research infrastructure to develop an environment that is able to run tools for clinical decision support and Virtual Physiological Human (VPH) by different end-users with the ultimate gaol to drive common clinical practice to personalized medicine. This deliverable report (D2.4) entitled *"Requirements for enhancing VPH models for clinical decision support"*, as part of this WP, aims at identifying the requirements that are needed to facilitate VPH models for clinical decision support and review the current guidelines for the validation and certification of tools and software to make these GCP conform for usage in the clinical trials and in daily clinical practice.

Virtual Physiological Human (VPH) is a methodological and technological framework within which it is possible to represent the human body as a single, coherent and dynamical system. It reaches down to the level of the human genome, and up to the whole human (and beyond, into population studies)". The VPH initiative (VPH-I) was developed as an approach to support the development of patient-specific computer models and their application in personalized and predictive healthcare. VPH is a methodological and technological framework that aims to be descriptive, integrative and predictive. By attempting to overcome existing challenges in the biomedical, healthcare, IT and legal setting, P-medicine will try to develop and utilize VPH cancer models pointing towards better integration and management of patient data and decision support tools to help the clinician, ultimately aiming to reduce mortality from malignant neoplasms by personalizing treatment and individualizing care needs. The scope of this report is an attempt to address these requirements and how these will be developed and tackled for the purposes of p-medicine.

2 INTRODUCTION

Purpose of the document

The report provides, first of all, a brief introduction to the VPH initiative, an approach developed in order to support the development of patient-specific computer models and their application in personalized and predictive healthcare. Moreover, VPH-oriented projects and their interconnections with p-medicine are being outlined. The main focus of this report is the possible biomedical, healthcare, IT and legal impediments accompanying the development of VPH cancer models for p-medicine. Finally, the remaining part of this report focuses on the attempt to highlight how these specific needs and requirements will be tackled in p-medicine.

Introduction to the VPH framework and VPH-I

One of the most ambitious goals of systems biology is to model human physiology. "Virtual Physiological Human (VPH) is systems biology written on the largest of scales, as a methodological and technological framework within which it is possible to represent the human body as a single, coherent and dynamical system. It reaches down to the level of the human genome, and up to the whole human (and beyond, into population studies)". [3]

The VPH initiative (VPH-I) was developed as an approach to support the development of patient-specific computer models and their application in personalized and predictive healthcare. VPH is a methodological and technological framework that aims to be descriptive, integrative and predictive. [4,5]

Descriptive: the framework should allow observations made in laboratories, in hospitals, and in the field, at a variety of locations situated anywhere in the world, to be collected, catalogued, organized, shared and combined in any possible way.

Integrative: the framework should enable experts to analyze observations collaboratively and to develop systemic hypotheses that incorporate the knowledge of multiple scientific disciplines.

[3] Coveney PV, Diaz V, Hunter P, Kohl P and Viceconti M. The Virtual Physiological Human. Interface Focus. June 6, 2011 (1): 281-285.

[4] Clapworthy G, Viceconti M, Coveney PV, and Kohl P. Theme issue: "The virtual physiological human: building a framework for computational biomedicine I". Editorial. Phil. Trans. R. Soc. A September 13, 2008 (366): 2975-2978.

[5] Viceconti M, Clapworthy G, Van Sint Jan S. The virtual physiological human-A European Initiative for In Silico Human Modelling. J.Physiol.Sci 2008 (58): 441-446.

Predictive: the framework should facilitate the interconnection of predictive models defined at different scales, with different methods, and with different levels of detail, producing systemic networks that breathe life into systemic hypotheses; simultaneously, the framework should enable their validity to be verified by comparison with other clinical or laboratory observations.

VPH-I constitutes an integral part of the international Physiome Project [6], and is a core target of the European Commission's Seventh Framework Programme. It was launched in 2008 with a 72 M€ call funding 12 research projects, two coordination and support actions, and one Network of Excellence (VPH-NoE). Alongside the p-medicine project, these include: euHeart, VPHOP, ARTreat , Synergy, preDiCT, ContraCancrum, ARCH, PASSPORT, PredictAD, NeoMARK, VPH2, IMPPACT, HAMAM, Action-Grid , RADICAL.

The VPH-NoE and the VPH-Toolkit standards, tools and services

The VPH-NoE initiative[7] aims to facilitate the interaction between the various VPH-oriented projects and address challenges of common concern.[8] Writing the Application Programming Interfaces (APIs) for the markup languages is a key task of VPH-NoE, thereby allowing the application software packages to read models and data from the repositories. The markup languages provide the syntax (the grammar) for encoding models and data. Equally important are the semantic 'metadata' that give biological and biophysical meaning to the models and data via biological and biophysical ontologies (structured vocabularies). Moreover, standards developed by VPH NoE need to be suitable for, adopted by, and adhered to not only within the European VPH initiative, but also on a global basis, for example via interaction with the international Physiome Project. The VPH Toolkit, a key VPH-NoE deliverable, provides a means to ensure that all VPH-funded projects are able to work towards this aim. VPH Toolkit provides the technical and methodological framework that will support and enable VPH research through the creation, accumulation and curation of VPH research-related 'capacities'.[9] The VPH Toolkit is considered as a 'toolbox' of relevant technologies, interacting around a common set of standards. The latter apply to the information used by tools, including any data and the VPH models themselves, and also to the naming and categorizing of entities and concepts involved. [8]

Currently the VPH Toolkit encompasses the following components

[6] Bassingthwaighte, J. B. Strategies for the Physiome Project. Ann. Biomed. Eng. 2000 (28): 1043–1058.

[7] http://www.vph-noe.eu/

[8] Cooper J, Cervenansky F, De Fabritiis G, Fenner J, Friboulet D, Giorgino T, Manos S, Martelli Y, Villà-Freixa J, Zasada S, Lloyd S, McCormack K, Coveney PV. The Virtual Physiological Human ToolKit. Philos Transact A Math Phys Eng Sci. 2010 Aug 28;368(1925):3925-36.

[9] http://toolkit.vph-noe.eu/

- Standards in terms of ontology, data modelling, infrastructure interoperability
- Imaging tools
- High performance computing
- VPH-Toolkit portal website. The aim of this website is to provide a knowledge base of the "capacities" available, whether these are specific tools, methods for conducting VPH research in an integrative fashion, or services available to researchers. It thus enables researchers to find technologies easily that may be of relevance to them, rather than re-inventing the wheel. It also provides a structure that can help to place individual activities in their correct context within the VPH initiative as a whole.

Guideline documents have become available (http://toolkit.vph-noe.eu/toolkit-guidelines) to assist groups preparing content for submission to the ToolKit in ensuring that their submissions are of the highest quality.

Summary of VPH Projects

This chapter provides a short overview of the set of VPH research projects funded under the 6th and 7th (FP6-FP7) framework Programme for Research and Development.

13 projects of Sixth framework programme (FP6) call 4 have been pioneering the Virtual Physiological Human, which afterwards has become one of the three objectives of Challenge 51 "Towards sustainable and personalized healthcare" of the Seventh framework Programme.

13 projects of FP6 call 4:

- **@Neurist**-Integrated Biomedical Informatics for the Management of Cerebral Aneurysms. @neurIST aim was to transform the management of cerebral aneurysms by providing new insight, personalized risk assessment and methods for the design of improved medical devices and treatment protocols.

- **ACGT** -Advancing Clinico-Genomic Clinical Trials on Cancer. ACGT aimed to present the 'next-step' in cancer research and fill-in the technological gaps of clinical trials targeting two forms of cancer: breast cancer and paediatric nephroblastoma. The programme aimed to develop a Biomedical GRID infrastructure supporting seamless mediation services for sharing clinical and genomic expertise, so as to help identify quicker and more efficiently the characteristics that determine what form of treatment best suits which patient.

- **ASSIST**-Association Studies Assisted by Inference and Semantic Technologies. ASSIST's scope was to provide medical researchers of cervical cancer with an integrated environment that would virtually unify multiple patient record repositories, physically located at different laboratories, clinics and/or hospitals. Thus, the goal was for researchers to be able to combine phenotypic and genotypic data and perform association studies on larger sets of patient records from several clinics.

- **EuResist.** EuResist referred to the integration of viral genomics with clinical data to predict response to anti-HIV treatment. The EuResist project aim was to

develop a European integrated system for the clinical management of antiretroviral drug resistance, so that the system would predict patient reactions to antiretroviral treatments for HIV, thus helping clinicians to select the most appropriate drugs and drug combinations for any given HIV genetic variant. The aim of the project was to create a huge European integrated data set, linking three of the largest existing resistance databases: ARCA, AREVIR and Karolinska.

- **Heath-e-Child.** The Health-e-Child project aimed at developing an integrated healthcare platform for European paediatrics, providing seamless integration of traditional and emerging sources of biomedical information. Disease modelling and decision support in cardiology, and knowledge discovery in rheumatology and brain tumours were the main focus areas of the project.

- **I-Know**-Integrating information from Molecule to Man: Knowledge Discovery Accelerates Drug Development and Personalized Treatment in Acute Stroke. I-Know involved a knowledge discovery IT -based tool designed to aid early stroke diagnosis, stroke treatment, drug development and identification of risk factors as targets in disease prevention for the benefit of European industry and citizens.

- **ImmunoGrid**-The European Virtual Human Immune System Project**.** The project focus was the on establishment of an infrastructure for the simulation of the immune system that integrated processes at molecular, cellular, and organ levels. This would be designed for applications that support clinical outcomes such as design of vaccines and immunotherapies and optimization of immunization protocols.

- **LHDL**. The Living Human Project (LHP) was a grass-roots initiative aimed at developing an *in silico* model of the human musculo-skeletal apparatus that could predict how mechanical forces are exchanged internally and externally, from the whole body down to the protein level, consistently with the scope of the Physiome project.

- **MULTI-KNOWLEDGE** The MULTI-KNOWLEDGE project aimed to integrate different biomedical information from heterogeneous sources (clinical, laboratory and metabolic) with data on gene and protein expression provided by new high throughput technologies in a system committed to cardiovascular risk profiling.

- **Sealife.** Sealife involved a semantic grid browser for the life sciences applied to the study of infectious diseases.

- **Share**-Supporting and structuring HealthGrid Activities and Research in Europe: developing a roadmap. SHARE goal was to ensure the successful take up of HealthGrids in the next 10 years by creating a roadmap for essential technology development years.

- **STEP**-A Strategy for the EuroPhysiome. STEP was a Coordination Action that sought to coordinate European activity relating to the physiome-a description of human physiology that will span multiple levels from the whole body down through the organs to the cells and beneath in an integrated manner.

- **VIROLAB**-A Virtual Laboratory for Decision Support in Viral Disease Treatment. ViroLab sought to enable easy access to distributed resources as well as the sharing, processing, and analysis of virological, immunological, clinical and experimental data.

A total of €72 million was allocated to VPH in the FP7 Call 2, which resulted in a portfolio of 15 projects.

15 projects of FP7 Call 2:

- **Action-Grid-**International Cooperative Action on Grid Computing and Biomedical Informatics between the European Union, Latin America, the Western Balkans and North Africa. The project aims were to exchange research results and foster collaborations in Nanoinformatics, Grid technologies and Biomedical Informatics among Latin America, the Western Balkans, North Africa and the European Union (EU). One of its main aims was to deliver a White Paper that will provide input to the European Commission in developing a future agenda in R&D in these areas.

- **ARCH.** Patient specific image-based computational modelling for improvement of short- and long-term outcome of vascular access in patients on haemodialysis therapy. The ARCH project aimed at developing image-based computational modelling tools for surgical planning and management of vascular access, the surgical arterio-venous shunt used to connect patient circulation to artificial kidney, a critical component of renal replacement therapy. The modelling tools would be validated in real-world clinical settings and provided to clinical end-users through a distributed ICT infrastructure.

- **ARTreat.** Multi-level patient-specific artery and atherogenesis model for outcome prediction, decision support treatment and virtual hand-on training. ARTreat aimed at developing a patient-specific computational model of the cardiovascular system, which would be used to improve the quality of prediction for the atherosclerosis progression and propagation into life-threatening events that need to be treated accordingly.

- **CONTRACANCRUM-** Clinically Oriented Translational Cancer Multilevel Modelling. The ContraCancrum project aimed at developing a composite multilevel platform for simulating malignant tumour development and tumour and normal tissue response to therapeutic modalities and treatment schedules in order to optimise the disease treatment procedure in the patient's individualized context.

- **EuHeart**-Personalized and Integrated Cardiac Care: Patient-specific Cardiovascular Modelling and Simulation for In Silico Disease Understanding & Management and for Medical Device Evaluation & Optimization. The euHeart project aimed to use patient-specific cardiovascular modelling as biophysically-based integration framework to improve the diagnosis, planning, and treatment of cardiovascular disease and to reduce the allied healthcare costs.

- **HAMAM**-Highly Accurate Breast Cancer Diagnosis through Integration of Biological Knowledge, Novel Imaging Modalities, and Modelling Improving breast cancer diagnosis. HAMAM's aim was to tackle the challenge of early detection and accurate diagnosis of breast cancer by integrating available multi-modal images and patient information on a single clinical workstation. Based on knowledge gained from a large multi-disciplinary database, populated within the scope of this project, suspicious breast tissue would be characterised and classified.

- **IMPPACT**-Image-based Multi-scale Physiological Planning for Ablation Cancer Treatment. IMPPACT developed an intervention planning system for Radiofrequency Ablation of malignant liver tumours accounting for patient-specific physiological factors. Validation was performed at multiple levels through comparison of simulation and treatment results gathered in animal studies and during patient treatment.

- **NeoMark**-ICT Enabled Prediction of Cancer Reoccurrence. Improve management of highly invasive and recurring cancers through a computer-assisted risk stratification and disease evolution prediction system. The aim was for the NeoMark Virtual Physiological Human (VPH) approach to integrate heterogeneous data collected with different techniques and *in-silico* representation, to model and predict biological phenomena linked to the disease evolution, so as to improve significantly the management of oral cancers.

- **PASSPORT.** PASSPORT aimed at developing a dynamic liver modelling, which through a preoperative surgical planning simulator, would allow prediction of a surgery's feasibility and thus increase the rate of surgical treatment so as to save patients suffering from liver pathologies.

- **PreDICT-(**Computational Prediction of Drug Cardiac Toxicity) Predicting Drug Interactions. The preDiCT project aimed to model and ultimately predict the impact of pharmaceutical compounds on the heart's rhythm using computer simulation. Using this information, the project sought to identify new biomarkers which would provide more reliable indication of harmful drug side effects.

- **PrecitAD**-From Patient Data to Personalized Healthcare in Alzheimer's Disease. PREDICTAD aimed to develop an objective tool for enabling earlier diagnosis of Alzheimer's disease. Biomarkers derived from various data sources of patient monitoring, such as neuropsychological tests, medical imaging, electrical brain activity measurements and blood samples were studied and combined.

- **RADICAL**-Road mapping technology for enhancing security to protect medical and genetic data. RADICAL coordination action aimed at approaching coherently, studying in depth and revealing scientifically, the beyond the state-of the art research and policy roadmap for security and privacy enhancement in Virtual Physiological Human, taking into consideration technology advancements, business and societal needs, ethics and challenges that should be addressed and answered.

- **VPH-NoE**-Virtual Physiological Human Network of Excellence. As previously mentioned, VPH NoE has been designed with 'service to the community' of VPH researchers as its primary purpose. The aims of the network range from the continued development of a VPH ToolKit and associated infrastructural resources, to integration of models and data across the various relevant levels of physiological structure and functional organisation, through to VPH community building, training activities and support.

- **VPH2.** Virtual Pathological Heart of the Virtual Physiological Human. VPH2 (Virtual Pathological Heart of the Virtual Physiological Human) aims to develop a patient-specific computational modelling of the heart to assist cardiologists/cardiac surgeons in defining the severity and extent of disease in patients with post-ischemic

Left Ventricular Dysfunction (LVD), with or without ischemic mitral regurgitation (IMR).

- **VPHOP**-the Osteoporotic Virtual Physiological Human. The VPHOP research project will develop, validate and deploy to pilot clinical studies the next generation of technology for predicting the risk of fracture in patients with low bone mass and assisting clinicians in prognosis and treatment planning (both pharmacological and interventional). The most advanced multiscale modelling technologies will be used to predict the patient-specific risk of fracture, and how it would change as a result of the various potential treatment options.

€5 million was allocated to VPH in the FP7 Call 4, which resulted in a portfolio of 5 projects

5 STREPs of the FP7Call 4:

- **NMS-Physiome**-VPHOP-SIMBIOS co-operation: Tools to develop the Neuro-Musculo-Skeletal Physiome. With the NMS Physiome project, the SIMBIOS and VPHOP consortia intend to establish a more organic co-operation, structured around three objectives: integrate the project communities, integrate the projects' tools, and work collaboratively on grand challenges.

- **MSV**-Multiscale Spatiotemporal Visualisation: development of an open-source software library for the interactive visualisation of multiscale biomedical data.

- **Sim-e-Child**-A grid-enabled pan-Atlantic platform for large scale simulations in paediatric cardiology. The Sim-e-Child project proposes to develop a grid-enabled platform for large scale simulations in paediatric cardiology, providing a collaborative environment for constructing and validating multi-scale and personalized models of a growing heart and vessels.

- **Tumour**-Transatlantic TUmour MOdel Repositories. The project aims at developing a European clinically oriented semantic-layered cancer digital model repository from existing EU projects that will be interoperable with the US grid enabled semantic-layered digital model repository platform at CViT.org (Center for the Development of a Virtual Tumor, Massachusetts General Hospital (MGH), Boston, USA) which is NIH/NCI-caGRID compatible. This interoperable, CViT interfaced, environment will offer a range of services to international cancer modelers, bio- researchers and eventually clinicians aimed at supporting both basic cancer quantitative research and individualized optimization of cancer treatment

- **RICORDO**-Researching Interoperability using Core Reference Datasets and Ontologies for the Virtual Physiological Human.

€62 million was allocated to VPH in the FP7 Call 6, which resulted in a portfolio of 12 projects that started early 2011.

15 projects of FP7 Call 6:

- **AirPROM**-Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling. AirPROM brings together the existing clinical consortia

(EvA FP7, U-BIOPRED IMI and BTS Severe Asthma), and expertise in physiology, radiology, image analysis, bioengineering, data harmonization, data security and ethics, computational modelling and systems biology. The project will aim to develop an integrated multi-scale model building upon existing models. This airway model will be comprised of an integrated 'micro-scale' and 'macro-scale' airway model informed and validated by 'omic data and ex vivo models at the genome-transcriptome-cell tissue scale and by CT and functional MRI imaging coupled to detailed physiology at the tissue-organ scale utilising Europe's largest airway disease cohort.

- **GRANATUM**-A social collaborative working space semantically interlinking biomedical researchers, knowledge and data for the design and execution of in-silico models and experiments in cancer chemoprevention. The vision of the GRANATUM project is to bridge the information, knowledge and collaboration gap among biomedical researchers in Europe (at least) ensuring that the biomedical scientific community has homogenized, integrated access to the globally available information and data resources needed to perform complex cancer chemoprevention experiments and conduct studies on large-scale datasets.

- **FUSIMO**-Patient specific modelling and simulation of focused ultrasound in moving organs.

- **MySPINE**-Functional prognosis simulation of patient-specific spinal treatment for clinical use. The objective of My SPINE is to adapt and integrate existing generic finite element (FE) models and use them as ICT tools in a clinical setting. The project will impact e-health by bringing new engineering rationale in the clinical decision-process. Impact is thus directly linked to ICT companies for clinical software development and hospital for the development of new clinical protocols.

- **SYNERGY**-Supporting Highly Adaptive Network Enterprise Collaboration Through semantically enabled knowledge services. SYNERGY aims to (a) provide semantic ontology-based modelling of knowledge structures on collaborative working; (b) develop the service-oriented self-adaptive SYNERGY holistic solution for knowledge-based collaboration services; and (c) facilitate the testing and evaluation of the efficiency and effectiveness of the SYNERGY solution in concrete case studies.

- **TBIcare**-Evidence based Diagnostic and Treatment Planning Solution for Traumatic Brain Injuries (TBI). TBI care transfers the scientific Virtual Physiological Human (VPH) concepts to clinical practice. TBIcare has impacts for healthcare professionals by improving the healthcare process and increasing medical knowledge; for the patients and their nearest by increased quality adjusted life years; for society it brings reduction in healthcare costs and losses due to working disability, and for the European industry it brings an impetus to increased global competitiveness by providing immediately exploitable innovative methods.

THROMBUS-A quantitative model of thrombosis in intracranial aneurysms. THROMBUS will study through numerical simulation the effect of stent configuration in patient specific geometry and will help explain why some stents produce good thrombus while others don’t. The project will develop a multiscale computational modelling and simulation framework based on the triptyc*h In Vitro - In Vivo - In Silico* - rule of three for the thrombosis. The associated technological aim of

the project is to deliver software with an interactive end-user interface, providing virtual simulation of the thrombosis leading to the optimal stent for a specific patient's aneurysm. This goal will be achieved by integrating some of the leading open source software and VPH toolkit software in the area of computational bioengineering.

- **VIGOR**++- Virtual GastrOintestinal tRact. The VIGOR++ project aims to create a multiscale, personalized GI tract model, which facilitates improved detection of Crohn's disease and drives an accurate index of Crohn's disease severity. VIGOR++ will acquire laboratory, MRI, colonoscopy and microscopy (histopathology) data in order to develop the targeted ICT tools. A novel integration of existing models is employed to predict features on the molecular to cellular scale (microscopy/colonoscopy) from descriptive properties at the organ to patient scales (MRI/laboratory).

- **INTEGRATE**-Driving Excellence in Integrative Cancer Research through Innovative Biomedical Infrastructures. INTEGRATE aims to build solutions that support a large and multidisciplinary biomedical community ranging from basic, translational and clinical researchers to the pharmaceutical industry to collaborate, share data and knowledge, and build and share predictive models for response to therapies, with the end goal of improving patient outcome. Moving away from empirical medicine, towards evidence-based personalized care has the potential to both dramatically improve patient outcome and to reduce costs. INTEGRATE will deliver reconfigurable infrastructure components; tools for sharing and collaboration; standards-based data models; and repositories of data, models and knowledge.

- **VPH-Share**-Virtual Physiological Human: Sharing for Healthcare - A Research Environment. VPH-Share will develop the organizational fabric (the infostructure) and integrate the optimized services to (1) expose and share data and knowledge, (2) jointly develop multiscale models for the composition of new VPH workflows, (3) facilitate collaborations within the VPH community. Four flagship workflows (from @neurIST, euHeart, VPHOP, Virolab) provide existing data, tools and models, engage with the services developed by VPH-Share to drive the development of the infostructure, and pilot its applications.

- **p-medicine**- From data sharing and integration via VPH models to personalized medicine. P-medicine brings together international leaders in their fields with an aim to create an infrastructure that will facilitate this translation from current practice to personalized medicine. In achieving this objective, p-medicine has formulated a coherent, integrated workplan for the design, development, integration and validation of technologically challenging areas of today. The project emphasizes on formulating an open, modular framework of tools and services, so that p- medicine can be adopted gradually, including efficient secure sharing and handling of large personalized data sets, enabling demanding VPH multiscale simulations (*in silico* oncology), building standards-compliant tools and models for VPH research, drawing on the VPH Toolkit and providing tools for large-scale, privacy-preserving data and literature mining, a key component of VPH research.

- **INBIOMED vision**- Promoting and Monitoring Biomedical Informatics in Europe. INBIOMEDvision aims to become a European-wide initiative intended to monitor the evolution of the Biomedical Informatics field and address its scientific challenges by means of collaborative efforts performed by a broad group of experts

with complementary perspectives on the field. These efforts will certainly contribute to the strength and expansion of the Biomedical Informatics scientific community, particularly in Europe. INBIOMEDvision will develop a series of services and activities to serve the aforementioned purposes (inventory of resources and initiatives, state of the art reviews, prospective analyses, community-building actions and dissemination and training activities).

At the core of the above VPH projects is the idea of translating all functions of the human body into a coherent set of multi-scale computer models. The scales of modelling span spatially from the whole body down to the cells and the proteins they synthesise, and temporally from years to microseconds. The VPH framework provides ICT tools for developing patient-specific computer based models and simulations using specific patient data allowing for personalized and predictive healthcare. These multi-scale models are widely explored in the frames of the above projects.

Interactions Between p-medicine and the VPH NoE

The p-medicine project will draw capacity from the VPH-NoE achievements and realisations by targeting the implementation, exploitation and integration of these. The overall aim of p-medicine will be to make tools from the VPH Toolkit available to clinicians so as to enhance clinical decision support.

As described in the p-medicine deliverable *D2.1 – "State of the art review of the p-medicine environment"* (submitted 09/2011), the present deliverable (D2.4) is amongst those describing the interaction between p-medicine and the VPH Toolkit and VPH-Share. Other relevant deliverables in p-medicine include the following:

- Data Warehouse stores ontologically annotated clinical, patient and simulation data, sharing cloud-based solutions with VPH-Share (report 9/2011, integration 9/2014)
- Workbench contributes tools to and use tools from the VPH Toolkit and set a collaboration exchange mechanism (Specification 1/2012)
- Clinical Trials uses and validates VPH tools and adapt them for clinical use (9/2013)
- VPH Modelling and Integrated Oncosimulator models which satisfy major VPH compatibility requirements (9/2014)
- Patient empowerment tool to monitor and implement donors' wishes (1/2013) and an interactive tool to support empowerment (7/2013)
- Education/training tutorials and eLearning tools submitted to the VPH Toolkit (1/2013)

P-medicine may draw heavily upon the models developed in the NoE, and aims to make them available to clinicians. P-medicine will also share strategies for use of cloud technologies with other VPH projects, most notably VPH-Share. Tools developed during the p-medicine project should aim to adhere to guidelines set by the

NoE, and they should be made available to the community through the VPH toolkit website, where appropriate.

Structure of the document

The remainder of this document is organized as follows:

- Chapters 3-5 deal with the biomedical, ICT and healthcare challenges for the VPH, respectively.

- Chapter 6 outlines validation and certification issues behind the VPH vision and how these are applied to the clinical setting.

- Chapter 7 presents the requirements for clinical decision support and chapter 8 provides an overview of the p-medicine environment and architecture in terms of meeting the afore-mentioned challenges.

- Finally, the last section of this report, chapter 9, summarizes all relevant comments and points described in all previous chapters.

3 Biomedical challenges for the VPH

Diseases are represented by variations of physiological parameters leading to reduction of organ(s) functionality or their mutual control, both accompanied with a significant negative impact on the functionality of the overall system, in extreme cases with fatal consequences. Creating and implementing tools for the simulation and modelling of living systems is considered a very promising approach in the context of offering solutions for the diagnosis, prognosis and treatment of a disease, particularly cancer. This is also a long-term goal which needs realistically assessed resources. Cancer is a complex disease characterized by multiple types of biological interactions across diverse physical, temporal, and biological scales. This complexity presents substantial challenges for the characterization of cancer biology, and motivates the study of cancer in the context of molecular, cellular, and physiological systems.[10]

Modelling cancer also requires a precise simulation of tumour growth and tumour/normal tissue response to a variety of drugs and therapeutic regimens, i.e. chemotherapy, radiotherapy and their combinations. Optimal simulation of the disease and therapy response, therefore, would translate into better clinical decision making. Because of the complex and heterogeneous nature of the disease, simulating cancer behaviour creates a multitude of challenges in the biomedical setting. Technically, the design and *in silico* implementation of a cancer simulator is a monumental task that has been extensively pursued for the past few decades.

Modelling the interplay between genetics/proteomics/metabolomics and physiological disease models

Genetic, proteomic and metabolic modifications influence healthy state and affect physiological parameters resulting in disease. Disease modelling requires careful consideration of the interplay between these parameters, parameter shifts and threshold values above which disease can develop. For instance, a genetic mutation which usually results in the overexpression or suppression of a protein or the reduced enzymatic activity of an enzyme can be compensated by the expression of other proteins or result in a shift of a physiological parameter. Therefore, the sensitivity of physiological model parameters which are influenced by genetic/proteomic/metabolic inter-related shifts needs to be quantified with good accuracy.

Moreover, multiscale modelling is a huge challenge. Modelling approaches need to be multiscale so as to quantify the impact of disease-related shift on these parameter levels to human physiology macroscopically and down to the cell level. Existing models in the context of cancer typically focus on a single spatial scale, thus being unable to assess the interaction

[10] Edelman LB, Eddy JA, Price ND. In silico models of cancer. Wiley Interdiscip Rev Syst Biol Med. 2010 Jul-Aug;2(4):438-59.

SEVENTH FRAMEWORK PROGRAMME

of phenomena at different scales or to combine, in a systematic manner, data from the various scales. [11,12,13]

- Since cancer is a multiscalar disease, scales of resolution must be carefully chosen and unnecessary detail needs to be omitted. This must be performed on every level. At the gene/protein level, one could encounter duplications of pathways, or one pathway could converge with a particular phenotypic result (influencing disease outcome or response to therapy).
- Reduce complexity/ maintain accuracy

Genetic variation also influences the sensitivity of physiological parameters in response to disease and/or treatment outcomes, as this is the case with a number of susceptibility genes in cancer. Modelling frameworks which enable the simulation and analysis of the effects of population heterogeneity need to be established in the context of cancer modelling. These advanced multiscale physiological models, such as those envisioned by the VPH initiative will describe how genetic variation manifests in phenotypic variation at various systemic levels up to the tissue, organ and whole-organism level. [14]

Finally, defining homeostasis and how this influences physiological parameter models is another crucial challenge. As mechanistic models do not enable the understanding of the quantitative biomedical mechanisms underlying disease, identification tools are required so as to allow the discrimination between sub-clinical and disease-related physiological states.

Model-based identification of specific biomarkers

Biomarkers are used to identify patients at risk for disease and to predict potential response to treatment, adverse event occurrences and favourable clinical outcomes, particularly in cancer, thus allowing earlier, more robust drug safety and efficacy measurements. “Validated biomarkers with acceptable sensitivity and specificity are urgently needed to help guide the selection of the most beneficial treatments for patients with cancer”.[15] Cancer biomarker research has seen an important increase in recent years. Large-scale molecular biomarker analysis facilitated by the technological/bio-computing outbreak has enabled researchers to capture and assess complex molecular information from biological samples. The biomarker

11 Alarcon T, Byrne H.M, Maini P.K Towards whole organ modelling of tumour growth. Prog. Biophys. Mol. Biol. 85, 2004a 451–472.

12 Arakelyan L, Merbl Y, Agur Z. Vessel maturation effects on tumour growth: validation of a computer model in implanted human ovarian carcinoma spheroids. Eur J Cancer. 2005 Jan;41(1):159-67.

13 Byrne HM, Alarcon T, Owen MR, Webb SD, Maini PK. Modelling aspects of cancer dynamics: a review. Philos Transact A Math Phys Eng Sci. 2006 Jun 15;364(1843):1563-78.

14 Hunter P, Coveney PV, de Bono B, Diaz V, Fenner J, Frangi AF, Harris P, Hose R, Kohl P, Lawford P, McCormack K, Mendes M, Omholt S, Quarteroni A, Skår J, Tegner J, Randall Thomas S, Tollis I, Tsamardinos I, van Beek JH, Viceconti M. A vision and strategy for the virtual physiological human in 2010 and beyond. Philos Transact A Math Phys Eng Sci. 2010 Jun 13;368(1920):2595-614.

15 Wistuba II, Gelovani JG, Jacoby JJ, Davis SE, Herbst RS. Methodological and practical challenges for personalized cancer therapies. Nat Rev Clin Oncol. 2011 Mar;8(3):135-41.

knowledge has been integrated into drug discovery and thus drugs which rely upon biomarkers for their activity are being developed for cancer therapy.[16] The analysis of complex sets of biomarkers in large biospecimens collected from clinical studies, such as in the case of the p-medicine trials, and stored in biorepositories contribute to the significant progress made in current biomarker research. Identification of cancer-relevant biomarkers, particularly in the early stages of the disease so as to guide prevention, is one of the challenges in successfully modelling cancer. However, early biomarker identification as opposed to later-stage disease identification of biomarkers requires a characterization of the physiological parameter range which is associated with the "healthy" state.

Modelling the effects of co-morbidities

Co-morbidities play a significant role in cancer and constitute a challenge in the case of cancer modelling. Complex disorders like cancer are not simply associated with a single gene, but rather with large sets of genes. Aside from the genotype-physiology interaction, other relevant biological mechanisms such as epigenetics, transcriptomics, post-translational modifications or protein phosphorylation may be neglected. Moreover, the disease-gene relations are not one-to-one. The majority of causative genes or gene sets often show an overlap with other disorders, showing interconnections between complex disorders. Using these overlaps, both on the disease and genome level, one can establish a relationship network either between two diseases and the causative gene(s) or between two different genes both related to the same disease. In the case of human cancers, the concept of network can be used so as to infer knowledge regarding risk genes. As this is a complex disorder, network-based description of cancer needs to be in the form of layers; i.e. one layer could represent the interaction between humans/patients, a second layer related to comorbidities and causal relationships, while other layers could be applied in the context of molecular (for example protein) interactions and co-expression patterns or common pathways. On the molecular level, disease related abnormalities could either arise from single biochemical systems as reflected in alterations of only few molecules, however, cancer complexity is usually reflected in abnormalities involving large sets of genes, molecules and thus symptoms. Similarities in the underlying molecular pathologies between different diseases enable the identification of relationships among these diseases. Therefore, disease and molecular networks are closely interlinked so as for disease networks to be seen as a collection of disease-specific clusters that interact with each other depending on the molecular similarities or discrepancies.

16 Hainaut P, Plymoth A. Biomarkers in cancer research and treatment: promises and challenges. Curr Opin Oncol. 2011 Jan;23(1):61.

Modelling cancer dynamics and overcoming various other challenges

- Tumor growth. Because of the versatile nature of cancer, sophisticated, nonlinear mathematical models are required in order to capture more realistic growth dynamics and morphologies.
- From avascular tumor to tumor-induced angiogenesis. Tumor-induced angiogenesis is the process by which cancers recruit blood supply to provide oxygen and nutrients that are commonly considered necessary to support growth into larger, more invasive tumor masses. This process needs to receive significant attention when dealing with cancer modelling and is, thus considered an important challenge. An example of a model of tumor-induced angiogenesis was described in Anderson and Chaplain, which developed a relevant model with the ability to follow the motion of endothelial cells at the capillary tips and control important processes, such as proliferation, branching and anastomosis. This model used a hybrid approach, both continuum and discrete modelling, and focuses on three significant variables related to angiogenesis: endothelial cell density, pro-angiogenic proteins and fibronectin concentrations.[17] This model appears to capture the irregularity of tumor vasculature through appropriate adjustment of the governing mathematical parameters. However, it merely only describes the physical structure of the capillary network. Direct extensions of this early model were performed by others. [18,19] First generation multi-dimensional tumor simulator, produced by Zheng and colleagues[20], involved the first coupling of models of growth and angiogenesis and enabled the simulation from the avascular stage to the development of in situ carcinoma. [21]
- Tumour escape mechanisms, whereby tumour cells efficiently hide from immune attack, are also a barrier in cancer modelling.

Cancer is a multifaceted disease with complex governing processes occurring at a wide range of temporal and spatial scales. Because of its obscure nature, it has been made difficult to identify unique molecular and pathophysiological signatures for each variant of cancer, thus impeding the development of effective therapies and providing a great challenge for the VPH vision. Mathematical modelling and computer simulation are tools which help understand the complex and constantly evolving nature of cancer towards achieving this.

---

[17] Anderson ARA, Chaplain MAJ. Continuous and discrete mathematical models of tumor-induced angiogenesis. Bull. Math. Biol. (1998) 60:857-899.

[18] McDougall SR, Anderson ARA, Chaplain MAJ, Sherratt JA. Mathematical modelling of flow through vascular networks: implications for tumor-induced angiogenesis and chemotherapy strategies. Bull. Math. Biol. (2002): 64: 673-702.

[19] Stephanou A, McDougall SR, Anderson AR, Chaplain MA. Mathematical model of flow in 2D and 3D vascular networks: applications to anti-angiogenic and chemotherapeutic drug strategies. Math. Comp. Model. (200) 41: 1137-1156.

[20] Zheng X, Wise SM, Cristini V. Nonlinear simulation of tumor necrosis, neo-vascularization and tissue invasion via an adaptive finite-element/level-set method.Bull Math Biol. 2005 Mar;67(2):211-59.

[21] Sanga S, Sinek JP, Frieboes HB, Ferrari M, Fruehauf JP, Cristini V. Mathematical modelling of cancer progression and response to chemotherapy. Expert Rev Anticancer Ther. 2006 Oct;6(10):1361-76.

4 ICT challenges for the VPH

Information and communications technology (ICT), is a term that highlights the importance of integration of telecommunications technologies (telephone lines and wireless signals), computers, software, storage- and multimedia systems, to enable a user to perform common tasks on data and information. The hypothesis behind the growing induction of ICT in a variety of domains is that better information and communication furthers the development of its field of application.

The main issue with ICT, that is also very pertinent to VPH, is security. In the last two decades a myriad of electronic attacks, malware, vulnerabilities and intrusions in the domain of ICT have been observed. There are several problem areas where security related issues impact ICT negatively. Some of these areas, particularly of interest in large VPH related projects, are: security awareness and training, design complexity and multiple layer approach.

Training of network administrators and technical staff, who are in charge of ICT infrastructure and security, is one of the most basic yet marginalised aspects, of setting up a secure ICT infrastructure, that result in poor security standards. Due to lack of funding and /or support from the top management underqualified staff fail deal adequately with security issues. In large VPH related projects, where several partners are engaged in developing, deployment and maintenance of the ICT infrastructure, training to impart a common understanding of the security standards and methods of implementing them becomes highly critical.

In large consortiums the infrastructure that must be supported as part of the overall ICT infrastructure is very diverse. This applies not only to the backend, or server side, resources shared by the consortium but also the user machines which act as client terminals for the services. Further, diverse user needs result in diverse software which require equally divert and complex backend and middleware support. All this complexity must be effectively and efficiently managed in a successful project. The design complexity, of ICT infrastructure for VPH related projects, is due to the sophisticated products and hardware involved as well as due to the diversity of user needs that must be met. While ICT infrastructure is already very complex the trend for the future only indicated even more complexity as more specialized hardware and software become available. Thus ICT based VPH projects are likely to suffer in the future because of complex designs and difficulty in troubleshooting or supporting systems. Care must therefore be taken to simplify designs in the infrastructure as much as possible to keep the future expectations manageable.

A closely related issue to the one raised by design complexity, for ICT infrastructure, is that of the very prevalent multiple layer approach in which modern software operates. Consider for example a user accessing a service using the browser. The communication between the users machine and the remote machine involves several layers of software – OS, Network, Application etc – in order for the communication to complete. This multiple layer approach naturally deteriorates the security of ICT systems and increases the complexity of the design. The ICT infrastructure management teams must therefore constantly evolve the software and hardware to meet challenges posed by unforeseen interactions between applications, which lead to vulnerabilities in the system.

SEVENTH FRAMEWORK PROGRAMME

Yet another major challenge faced by ICT for VPH related projects is conforming to the legal and ethical standards. The soft requirements introduced by the legal and ethical standards can translate into extremely challenging technological requirements. An effective legal framework would account for: (i) the scope with which personal data is used; (ii) the introduction of a complex delivery system into a direct doctor-patient consulting healthcare setup, involving multiple users and communication methods. These can result in multiple levels of design complexity to be introduced in order to meet the requirements introduced. Key areas, which ICT challenges are introduced due to legal aspects of a VPH project are – managing informed consent, reidentification attacks and annonymisation of patient data.

Patient consent, in a VPH, is very complex, more so than traditional healthcare solutions, since a VPH employs new technologies to provide sophisticated patient data sharing and use abilities. Consent is a fundamental element in the relationship between patients and healthcare professionals and informed consent implies shared responsibilities. Often this results in very stringent requirements on confidentiality, integrity of software and individual practices from the staff. Developing ICT solutions that provide a quantifiable support for these requirements is challenging and often results in large systems that are difficult to maintain.

In VPH, there is the need to protect patient privacy, taking care not to share any identifiable information, while providing sufficient data for the data sharing to be useable. Typically this is achieved through the use of Pseudonymisation and Deidentification steps in an ICT system. Sophisticated implementations of achieving these two very important tasks exist and must be used in order to provider the required privacy. However, the requirements of different VPH related projects vary and therefore tailored solutions must be developed within the ICT infrastructure to ensure appropriate level of support is available for the users of the system to freely share, use and reuse data. A solution would be to develop and adopt Codes of Conduct specific to the requirements of the VPH. However, defining such guidelines is difficult and translating them into appropriate technological solutions is complex.

ICT systems are always at a risk of being attacked with malicious intent. Such attacks can be particularly harmful if they are targeted knowingly or unknowingly at database / servers which are engaged in deidentification of patient records. Attacks such as these, known as Re-identification attacks (databases), can allow the attacker to compromise the ICT infrastructure of VPH project and its implementation instance by violating privacy of the user data. Since patient data privacy is extremely critical these attacks are particularly high priority and an ICT system must provide enough security measures to meet this challenge.

5 Healthcare challenges for the VPH

One of the major challenges for the VPH vision in the diagnosis and treatment of cancer is the complex nature of the disease; environmental, life style, ageing and genetic components all contributing to its pathogenesis. Knowledge gained from these different components needs to be translated into robust and fully reliable computer models and *"in silico"* environments that will help the development and testing of new therapies and better disease prediction and prevention tools in healthcare. Advances in computing power and associated information helps towards delivering custom-made clinical decisions/treatments based on simulation studies of the genetic profile of the individual patient.

What are the healthcare challenges and needs

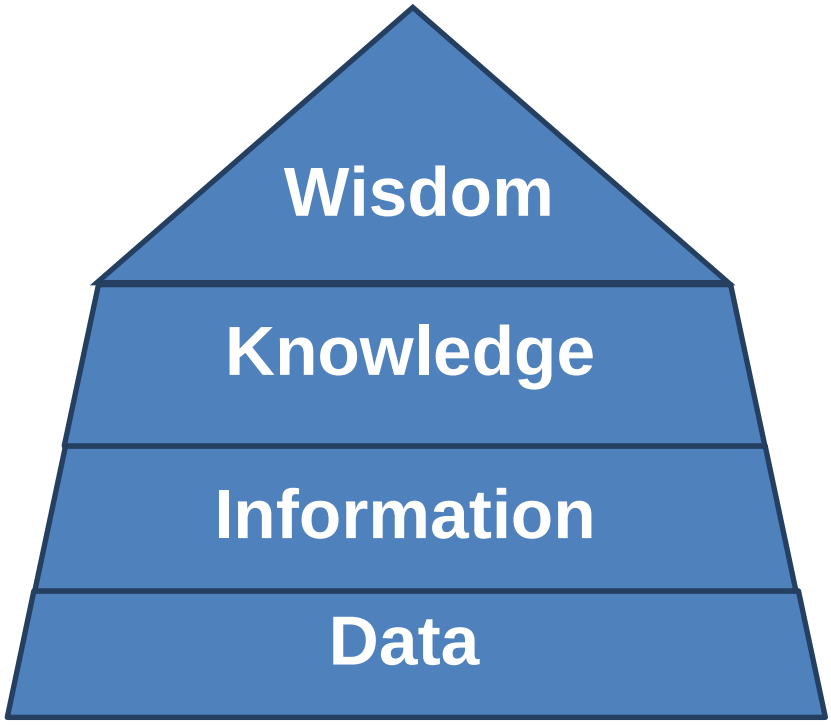
- Digital health information needs to be shared on a global scale. Data coming from the same patient will need to be integrated in different hospitals/partners in different member states or in clinical research databases.
- The information related to various parts and processes of the human body need to be integrated into a uniform way so as to provide systemic knowledge of the patient's pathophysiology.
- This knowledge has to be digitally captured into metadata, ontologies and models in order to keep up with the combinatorial explosion of cognitive complexity.
- The need to integrate scientific knowledge coming from research/clinical practice and formalize this in guidelines, standards and protocols, ultimately translating basic science and integrative models into healthcare benefits.
- Personalised, predictive, and integrative healthcare. There is need for a more personalized diagnosis, prognosis, treatment planning, and monitoring. There is need to develop "tailored" drugs/therapies as well as medical devices and diagnostic technologies for specific groups of patient subgroups, as in the case of cancer patients that are refractory to treatment, or patients with different co-morbidities.
- Expenditure of biomedical research needs to be maximized
- Clinical decision needs to be reliable and reproducible.
- Privacy of health data

However, it is of emerging importance to collect input from different medical organizations and hospitals, so as to provide a coherent, fully justified and detailed description of the healthcare needs.

The Digital me/patient vision

The "*digital patient"* is a powerful vision of future healthcare provision that aims to contain all personal/population healthcare (e.g lifestyle, genotype, clinical, therapy outcome, epidemiological) information safely managed for access by the various biomedical professionals with the approval of the patient, communicated with all wearable and implanted technology to constantly monitor patient's health status and informing the patient, its family and friends, or healthcare providers of alarming events, supporting the collaboration of various specialists around complex systemic diseases, and used with all patient data to predict the future development of patient's health in order to facilitate disease prevention and a fully self-aware lifestyle. VPH provides the supporting infrastructure towards achieving this, although it is not the model itself. Alongside of The Physiome, Systems Biology , Personal Health Systems, Biomedical Informatics, Life Science e-Infrastructures, Systems Pharmacology, VPH is one of the domains that share one common issue; the need for integration. The implementation of biomedical research outputs into clinical practice and healthcare industries requires data integration, information, knowledge and wisdom, as pointed out by Byrne et al (reference no 13).

.



The vision of a "digital me" that contains all personal healthcare information, safely managed for access from the various biomedical professionals, communicated with wearable and implanted technology to constantly monitor the health status and informing the individuals, peers, or the related healthcare providers, supporting the collaboration of various specialists around complex systemic diseases, and used with all patient data to predict the future development of the health in order to facilitate disease prevention and a fully self-aware lifestyle, is a powerful and ambitious vision, but the challenges are huge.

In order to approach the "digital me" challenge all VPH projects need to integrate data, information, knowledge and wisdom. We need to integrate data of the same patient stored in different hospitals in different member states or in clinical research databases; we need to integrate the information related to various parts and processes of the human body into a systemic understanding of pathophysiology; we need to integrate the knowledge digitally captured into metadata, ontologies and models in order to fight the combinatory explosion of cognitive complexity integrative research is producing; and we need to integrate the wisdom produced in the research laboratories and in the clinical practice, so that it can be formalised in guidelines, standards, and protocols.

Some of the major VPH achievements related to the above needs and challenges were:

- the creation of a European Virtual Physiological Human (VPH) Institute for Biomedical Integrative Research, incorporated as a non-profit, non-governmental international organisation, and
- the first joint meeting of the FP7 projects p-medicine and VPH-Share

The projects p-medicine and VPH-Share[22] explore the common VPH topics and were expressly asked by the European Commission to work closely together in this area. Within the scope of this first meeting, which took place in July 2011 in Amsterdam, a joint strategy was adopted between p-medicine and VPH-Share to exchange information and technical knowledge regarding both projects. Regular six-monthly meetings between p-medicine and VPH-Share will take place to plan project interactions and to ensure a productive cooperation.

[22] Virtual Physiological Human: Sharing for Healthcare - A Research Environment, www.vph-share.eu (January, 2012)

6 Regulatory challenges for the VPH

Validation in Clinical trials

Validation of the tools and models defined by p-medicine would be in the context of the three cancer trials: nephroblastoma, breast cancer and Acute Lymphoblastic Leukemia (ALL). The integration of VPH in clinical practice requires standards for model validation. Methods are needed to ensure that models are consistent with their claims, accompanied by explicit statements concerning assumptions and limitations along with care in the acquisition of validation data and acknowledgement of errors and limitations. [23]

First of all the validation of software tools and/or clinical research computer systems is required by regulatory guidelines on Good Clinical Practice (GCP) (see section 6.1.1 of this report). The rationale for validation has a complex background but close to its complexity it makes as well a good business sense by ensuring quality, timeliness and efficiency.

The published results of a survey[24] of the European Clinical Research Infrastructures Network (ECRIN)[25] CENTERS suggests that although quality management systems for data management are in place in most European clinical research CENTERS, there exist some deficits in the area of system validation. The survey shows that about 90% of CENTERS have a Clinical Data Management Systems (CDMS) in routine use. Of these CDMS nearly 50% are commercial systems; Open Source solutions don't play a major role. In general, solutions used for clinical data management are very heterogeneous: 20 different commercial CDMS products (7 Open Source solutions) in addition to 17/18 proprietary systems are in use. The most widely employed CDMS products are MACRO and Capture System, followed by solutions that are used in at least 3 CENTERS: eResearch Network, CleanWeb, GCP Base and SAS. Although quality management systems for data management are in place in most CENTERS/units, there exist some deficits in the area of system validation. As result the researchers suggest that standards like CDISC (Clinical Data Interchange Standard Consortium) should be implemented more widely. Additionally, ECRIN if promoting the strategy of establishing certified data CENTERS to support electronic data management and associated compliance needs of clinical trial CENTERS in Europe.

One of the prominent last achievements is that ECRIN proposed the standard[26] intended to provide an open and widely used set of requirements for GCP-compliant data management, particularly in academic trial units which is of high relevance to p-medicine project related

[23] Clapworthy GJ, Kohl P, Gregerson H, Thomas SR, Viceconti MD, Hose R, Pinney D, Fenner J, McCormack K and Lawford P, et al. Digital Human Modelling: A Global Vision and a European Perspective. Lecture Notes in Computer Science, 2007 (4561): 549-558.

[24] Kuchinke W, Ohmann C, Yang Q, Salas N, Lauritsen J, Gueyffier F, Leizorovicz A, Schade-Brittinger C, Wittenberg M, Voko Z, Gaynor S, Cooney M, Doran P, Maggioni A, Lorimer A, Torres F, McPherson G, Charwill J, Hellström M, Lejeune S. Heterogeneity prevails: the state of clinical trial data management in Europe - results of a survey of ECRIN CENTERS. Trials. 2010 Jul 21;11:79.

[25] ECRIN, http://www.ecrin.org (January, 2012)

[26] Ohmann C, Kuchinke W, Canham S, Lauritsen J, Salas N, Schade-Brittinger C, Wittenberg M, McPherson G, McCourt J, Gueyffier F, Lorimer A, Torres F; ECRIN Working Group on Data CENTERS. Standard requirements for GCP-compliant data management in multinational clinical trials. Trials. 2011 Mar 22;12:85.

clinical trials. The standard includes 115 IT requirements, split into 15 separate sections, 107 DM requirements (in 12 sections) and 13 other requirements (2 sections). Sections IT01 to IT05 deal with the basic IT infrastructure while IT06 and IT07 cover validation and local software development. IT08 to IT015 concern the aspects of IT systems that directly support clinical trial management. Sections DM01 to DM03 cover the implementation of a specific clinical data management application, i.e. for a specific trial, whilst DM04 to DM12 address the data management of trials across the unit. Section IN01 is dedicated to international aspects and ST01 to the competence of a trials unit's staff.

The presented ECRIN standard close to other available model validation requirements have been already covered in the frames of previous WP2 deliverables. All will serve as a background for further p-medicine deliverables and activities related to p-medicine platform development, evaluation, certification and validation.

Certification challenges and compliance with EU legislation

According to the European Medicines Agency (EMA) and the World Health Organization (WHO), Good Clinical Practice (GCP) is a process which incorporates international ethical and scientific quality standards for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that: 1) the rights, safety and wellbeing of trial subjects are protected; 2) the clinical trial data collected during the trial is credible.

The protection of clinical trial subjects is consistent with the principles set out in the Declaration of Helsinki with adoptions.[27] This is a statement of ethical principles developed by the World Medical Association.[28] Requirements for the conduct of clinical trials in the European Union (EU), including GCP and good manufacturing practice (GMP) and GCP or GMP inspections, are implemented in:

• the Clinical Trial Directive (Directive 2001/20/EC)[29]

• the GCP Directive (Directive 2005/28/EC).[30]

All p-medicine clinical trial-related activities, tools, software and services will be in strict conformance with the above EC directives.

Taking into consideration both the guidelines from the WHO and EMA, following are the basic principles of GCP [31,32]:

[27] http://www.wma.net/en/30publications/10policies/b3/ July 2011

[28] http://www.wma.net/e/ July 2011

[29] DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001, Official Journal of the European Communities, 2001

[30] COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005, Official Journal of the European Union, 2005

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Within GCP, clinical trials should be described in a clear, detailed protocol. The sponsor, often in consultation with one or more clinical investigators, generally designs the study protocol; clinical investigators may also design and initiate clinical studies, as sponsor-investigators. Integral to protocol development are the concepts of risk identification, study design and control groups, and statistical methodology. The sponsor and clinical investigator(s) should be aware of any national/ local laws or regulations pertaining to designing, initiating, and conducting the study.
6. A trial should be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s). Clinical investigators must be qualified and have sufficient resources and appropriately trained staff to conduct the investigation and be knowledgeable of the national setting and circumstances of the site and study population(s). Sponsors should review the requirements of the study protocol to determine the type(s) of expertise required and identify clinical investigators who have the particular medical expertise necessary to conduct the study and who have knowledge, training and experience in the conduct of clinical trials and human subject protection.
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation. The clinical investigator has primary responsibility for recruiting subjects, ensuring that only eligible subjects are enrolled in the study, and obtaining and documenting the informed consent of each subject. Within GCP, informed consent must be obtained from each study subject prior to enrolment in the study or performing any specific study procedures.

[31] ICH Topic E 6 (R1) Guideline for Good Clinical Practice, Note for guidance on clinical practice, EMA, July 2002, CPMP/ICH/135/95

[32] WHO-Handbook for good clinical research practice (GCP): guidance for Implementation; Clinical trials-methods. World Health Organization. ISBN 92 4 159392 X (NLM classification: W 20.5)

SEVENTH FRAMEWORK PROGRAMME

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable GMP. They should be used in accordance with the approved protocol. GCP requires that sponsors control access to the investigational product and also document the quantity(ies) produced, to whom the product is shipped, and disposition (e.g. return or destruction) of any unused supplies. GCP also requires investigators to control receipt, administration, and disposition of the investigational product.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented. Appropriate support systems and tools facilitate the conduct of the study and collection of data required by the protocol. Support systems and tools include, but are not limited to, trial-related information documents (e.g. investigator's brochure, case report forms [CRFs], checklists, study flow sheets, drug accountability logs, computer hardware and software, electronic patient diaries, and other specialized equipment. The sponsor is generally responsible for developing, maintaining, modifying, and ensuring the availability of support systems and tools for conducting the trial and collecting and reporting required data.

Need for GCP-Compliant Clinical Data Management Solutions

CDMS are required in clinical research so as to manage the increasing amount of data that must be collected, processed and analysed in clinical research, whether that data is initially captured remotely and directly from clinical sites using Remote Data Capture (RDC), or using more traditional paper based methods.[33]

In general, trial data are collected at investigator sites with appropriate CRF forms, queried, cleaned, stored and analysed with the CDMS. To reduce the possibility of errors, a CDMS employs means to verify the correctness and plausibility of entered data. Another function of CDMS is to code data or to generate reports. The collection of clinical data by means of electronic forms is called Electronic Data Capture (EDC) or Remote Data Entry (RDE).

The recent paper by Ohmann et al[26] (Heinrich-Heine-University Düsseldorf-UDUS) addresses the need for GCP-compliant CDMS, so as not only to protect patients but also to ensure that the collected data are correct. As the authors stress, the development and maintenance of an appropriate data management environment is a tough challenge for academic clinical trials units. Moreover, input from a recent survey has outlined several problems with data management systems in clinical trials conducted at academic centers.[24] This survey addressed the following issues:

[33] Kuchinke W, Ohmann C. A technical introduction to the basic requirements of clinical trials. EJHPP 2009/5. pp. 20–22.

a) First of all, there is a significant heterogeneity in the use of different software products for data management. Often proprietary solutions are in place rather than open source or industry supported commercial products.

b) There are deficits in the quality of data management, including in computer system validation.

c) Most centers are constrained by limited human and financial resources in providing adequate levels of data management.

d) The complexities of running a local IT/data management center, especially for international clinical trials, are underestimated.

e) There exists no widely recognised, specific, practicable and open standard for GCP-compliant data management and the underlying IT infrastructure, which is both generally applicable and practical, as well as being open and available free of charge.

Establishing a consensus for GCP-compliant data management, the underlying IT infrastructure and the relevant indicators of good GCP practice has been the driving force behind the European Clinical Research Infrastructures Network (ECRIN) Working Group on Data Centers. ECRIN is an ongoing EU-FP7 project which aims to provide a not-for-profit platform for the support of pan-European clinical research projects. It does this by connecting national networks of clinical research centers (CRCs) and clinical trial units (CTUs), working across all disease areas. ECRIN aims at developing a sustainable infrastructure able to support the set-up, conduct, and analysis of multinational trials in Europe.

One limitation/challenge is the extent to which clinics or clinical data management centers have reached levels of GCP compliance, as these may vary in size, available resources and the extent of quality management. System validation is an important component in ensuring GCP-compliance of a computer system, but it can be problematic. "Academic units do not, in general, have the resources available in the pharma industry to conduct or outsource a 'full' validation for every system component, including the vendor audit, and to maintain complete change management".[29] In addition, there is no simple way to know how much system validation is necessary or sufficient[34] and the extent and depth of validation required may depend on the interpretation of a particular auditor and whether a commercial software or an in-house developed software is used.

As the survey by Kuchinke et al outlines, using CDMS in clinical trials is characterized by the impact of regulations on data management (e.g. 21 CRF Part 11, EU GMP Guideline Vol. 4, Annex 11 Computerized Systems, GCP, data protection laws, e-signature requirements). It is necessary for clinical centers employing CDMS to implement best practices for CRF design, query resolution, and study start-up in an EDC environment, including user acceptance testing, system validation, creation of a data management plan and training of investigators in the use of the application. These requirements may cause considerable pressure on the data management resources of a data center.

[34] Mullendore B. Computer Validation Master Planning - Technical Guide. IVT. 2002.

SEVENTH FRAMEWORK PROGRAMME

In the case of IT requirements, academic clinical trial units usually rely upon the IT infrastructure services provided by the parent organization, or a commercial host, or another collaborating trials unit. In that case, data centers require formal written agreements, e.g. in the form of contracts or service level agreements (SLAs), that ensure that the relevant requirements of the standard will be met by the organization(s) that provides them. As stressed out by Ohmann et al, this attempt to introduce a new standard into the field of computer systems in clinical trials must deal with two related questions: *a) What is the justification for a new requirements standard for trials units?* and *b) how does this new standard fit in with existing requirements for IT systems, validation, data management etc?*

To summarize, heterogeneity of DM software solutions may be a barrier to co-operation based on trial data exchange, therefore standards, like CDISC should be implemented more widely. In such a heterogeneous environment, the use of data standards can simplify the exchange of data (for instance clinical, genomic, etc.) and increase their quality for the benefit of the patient, as well as to enable centers for future developments. Because DM and the use of EDC systems in clinical trials are characterized by the impact of regulations and guidelines, ethical concerns are also a factor. In this context, quality management becomes an important part of compliant data management.

P-medicine deliverable D9.1 (“Report of regulatory and international aspects of clinical trials”) due on 01/2012 will address and outline in detail the regulatory issues in the context of the clinical trials in p-medicine.

7 Requirements for Clinical decision support

Clinical Decision Support (CDS) is a critical component for organizations seeking to improve the health of the healthcare delivery system. Hospitals, health systems and medical groups already realize that increased patient volume requires more than simply adding staff. It means leveraging technology to improve care quality, access, effectiveness, efficiency and safety, the result of which is better care at lower costs. CDS Systems (CDSSs) are "active knowledge systems which use two or more items of patient data to generate case-specific advice".[35] CDSSs form a significant part of the field of clinical knowledge management technologies through their capacity to support the clinical process and use of knowledge, from diagnosis and investigation through treatment and long-term care. Many healthcare organizations have implemented CPOE (Computerized Physician Order Entry) systems and EHR (Electronic Health record) Systems. However, challenges remain in system selection, adoption, implementation and use:

- Aim is to develop clinically-friendly user interfaces in close collaboration with end-users
- Simulations must be performed on a routine basis in the clinical setting

Four key functions of electronic CDSSs are outlined in (Perreault and Metzger, 1999)[36]:

- *"Administrative:* Supporting clinical coding and documentation, authorization of procedures, and referrals.
- *"Managing clinical complexity and details:* Keeping patients on research and chemotherapy protocols; tracking orders, referrals follow-up, and preventive care.
- *"Cost control:* Monitoring medication orders; avoiding duplicate or unnecessary tests.
- *"Decision support:* Supporting clinical diagnosis and treatment plan processes; and promoting use of best practices, condition-specific guidelines, and population-based management."

Major challenges towards successful CDS

This section is relevant to Section 10.4 of the D2.1 deliverable (*"State of the art review of the p-medicine environment"*) (30/09/2011).

Successful implementations of CDSS have not been widely repeated due to the major challenges that exist in design, development and implementation of CDSS. Some of these

[35] Wyatt J, Spiegelhalter D. Field trials of medical decision-aids: potential problems and solutions. In Clayton P (ed). Proc. 15th Symposium on Computer Applications in Medical Care, Washington 1991. New York: McGraw Hill Inc. 1991: 3-7

[36] Perreault L, Metzger J. A pragmatic framework for understanding clinical decision support. Journal of Healthcare Information Management. 1999;13(2):5-21.

challenges have their root in the inherent complexity of the task of decision making while others originate from the integration to the clinical workflow, the technical aspects needed for CDS implementation, the knowledge maintenance, and so much more. Of particular interest is the work by Sittig et al [37], who have identified 10 major challenges and classified those into 3 categories, so as to: a) improve the effectiveness of CDS interventions, b) create new CDS interventions and c) disseminate existing CDS knowledge interventions. These 10 challenges identified are as follows:

1. Improve the human-computer interface (HCI): CDS should unobtrusively, but effectively, remind clinicians of things they have truly overlooked and support corrections, or better yet, put key pieces of data and knowledge seamlessly into the context of the workflow or clinical decision-making process, so the right decisions are made in the first place.[38,39] According to Sittig et al, the need for new HCIs is required so as to facilitate the process by which CDS is made available to clinicians to help them prevent both errors of omission and commission.

2. Summarize patient-level information: The CDS challenge is to intelligently and automatically summarize all of a patient's electronically available clinical data, both free text and coded, and to create brief synopses of the patient's pertinent past medical history, current condition(s), physiologic parameters, and current treatment(s). Ultimately, vast amounts of data may be reduced to a summary set of indicators allowing 'at a glance' assessment of patient status.

3. Prioritize and filter recommendations to the user: The challenge here is to create a robust, reliable, evidence-based CDS value model, particularly for intrusive CDS interventions. Such a system could automatically prioritize recommendations according to a multi-attribute utility model by combining patient- and provider-specific data. I could, for instance, take into account factors such as expected mortality or morbidity reduction, patient preferences and life style, cost to the individual or organization, effectiveness of the test or therapy, how the patient might tolerate the recommended intervention, location in the clinician's workflow, insurance coverage, genetic and genomic considerations, clinician's past performance, etc. The main challenge here is to appropriately account for competing influences and values impacting clinical decision making, and thus clinical decision support. The second challenge is to rank in priority order, and reduce the number of computer-generated recommendations that a clinician or patient has to deal with to a manageable number based upon an explicit value model, thus reducing the ''alert fatigue'' that is a frequent cause of user dissatisfaction.

4. Combine recommendations for patients with co-morbidities: Most of the current clinical care guidelines currently ignore co-morbidities found in many patients, so that these are addressed by their patient care team. One of several reasons why clinical guidelines are underutilized in practice is because they do not adequately address these co-morbidity issues. Addressing this challenge may require new combinatorial, logical, or semantic approaches to combining and cross-checking recommendations from two or more guidelines.

---

[37] Sittig D, Wright A, Osheroff J, Middleton B, Teich J, Ash J, Campbell E, Bates D. Grand challenges in clinical decision support. J Biomed Inform. (2008) 41 (2): 387-92.

[38] Berner ES, Moss J. Informatics challenges for the impending patient information explosion. J Am Med Inform Assoc 2005;12(6):614–7.

[39] Miller RA, Waitman LR, Chen S, Rosenbloom ST. The anatomy of decision support during inpatient care provider order entry (CPOE): empirical observations from a decade of CPOE experience at Vanderbilt. J Biomed Inform 2005;38(6):469–85.

5. Use free-text information to drive clinical decision support: this is a very significant point made, considering the fact that at least 50% of the clinical information describing a patient's current condition and stage of therapy resides in the free-text portions of the EHR. Automatically extracting information from free-text documents and structuring it appropriately for the use of CDS is a challenging task that should be addressed in order to fully benefit from the CDS.

6. Prioritize CDS content development and implementation: As Sittig et al suggest, "*the development and implementation of clinical decision support content required to help clinicians and organizations deliver the highest quality, yet still reasonably priced health care, will take many years.*" Deciding which content to develop or implement first (e.g. interventions to improve patient safety, chronic disease management, or preventive health interventions) according to pertinent factors like value to patients, cost to the health care system, availability of reliable data, difficulty of implementation, acceptability to clinicians and patients, and national interests and overall health care value is another challenge of CDS development.

7. Mine large clinical databases to create new CDS: There is always a large amount of new guidelines, CDS interventions and knowledge that are produced but not yet compiled and made ready for the use of CDSS. One needs to develop and test new algorithms and techniques to allow researchers to mine large clinical data repositories so as to expand the global fund of clinical knowledge, thus promoting improved clinical decision outcomes. However, this development requires the consideration of legal issues for accessing the databases as well as privacy issues.

8. Disseminate best practices in CDS design, development, and implementation: More robust methods are required so as to identify, describe, evaluate, collect, catalogue, synthesize and disseminate best practices for CDS design, development, implementation, maintenance, and evaluation. Specifically, measurement tools are necessary to help identify the most usable, economical and effective methods of implementing these CDS-related initiatives. Common success factors can be derived from the best practices of CDSS. This kind of knowledge is frequently not readily available to other organizations seeking to develop CDS programs. To accomplish this, a consensus on a standard taxonomy of clinical decision support interventions and outcomes that would allow us accurately describe the best practices is needed as well as comparison of outcomes between implementations of different systems and across organizations.

9. Create an architecture for sharing executable CDS modules and services: The goal is to create a set of standards-based interfaces to externally maintained clinical decision support services that any EHR could "subscribe to", in such a way that healthcare organizations and practices can implement new state of the art clinical decision support interventions with little or no extra effort on their part. These knowledge modules can be loaded into a clinical information system, or to execute as a remote service, with the local clinical system invoking them over a network according to a standardized interface.

10. Create internet-accessible clinical decision support repositories: The challenge here is to build one or more internet-accessible repositories of high quality, evidence-based, tested, clinical decision support knowledge modules. Using the architecture described in challenge 9, these interventions and services could then be easily accessed and/or modified on any Certification Commission for Healthcare Information Technology (CCHIT)-certified EHR

product.[40] To accomplish this, standards for accessibility, sponsorship, and trust levels, and appropriate business models to ensure sustainability are needed.

To summarize, it is noteworthy that there are other challenges in CDS which are important, but the above-mentioned clearly represent a pivotal set. As Sittig et al stresses: *"It will take some time to address these and the answers will likely vary somewhat, but proceeding down this path will move things forward"*.

Requirements for the use of VPH models and knowledge by the clinical decision support tools

In order to be able to provide recommendations in the context of a clinical decision, a CDS system first needs to extract the needed clinical knowledge with semantics. Therefore, the following challenges need to be overcome:

- Representation and elicitation of medical knowledge: Medical knowledge needs to be extracted from literature, clinical trials and guidelines.

- Linkage to machine-processable semantics. To automatically combine data from multiple sources the understanding of the semantics is essential.

- Linkage to patient data. The knowledge extracted needs to be semantically linked to patient data from multiple sources. Therefore, shared semantics is required to enable machine-processability.

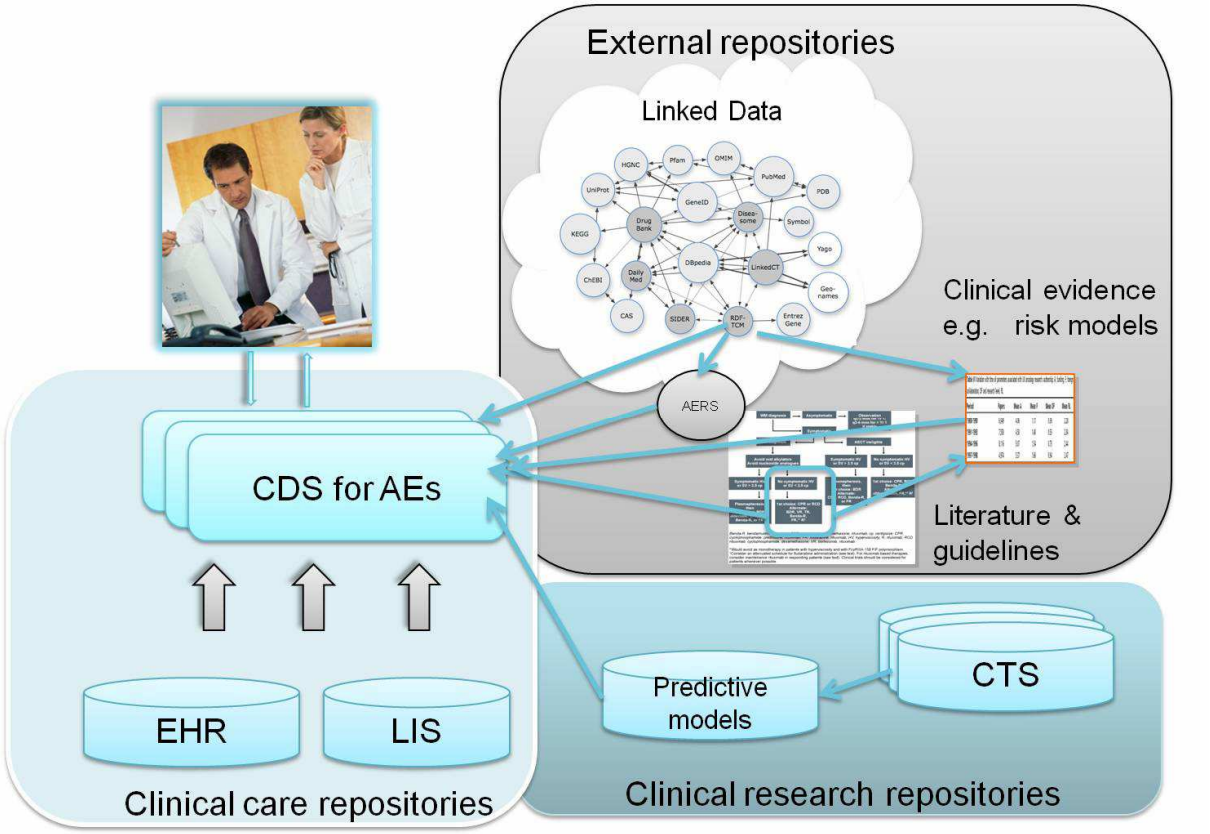
- Additionally, seamless integration within the care workflow is a key success factor. This also means that only clinically validated VPH models can be used as input to decision support.

The figure below describes the context of a CDS tool. There are various sources of knowledge that are relevant for such a tool. Some of that knowledge is external and can be stored in public repositories or in proprietary sources of knowledge (e.g. publishers accumulate large amounts of clinical knowledge in the form of scientific articles, published guidelines, etc.). The format and the representation of the available knowledge are also essential for the use in a decision support tool, with the use of standards and of shared semantics always a plus. The significant and steadily growing cloud of Linked Data (RDF-based), built through a community effort, is a very valuable source that can be easily integrated and freely used in a CDS tool.

[40] Certification Commission for Healthcare Information Technology Certified Ambulatory Electronic Health Record (EHR) Products – Available at: http://www.cchit.org/certified/products.htm

SEVENTH FRAMEWORK PROGRAMME

However, there are other sources of relevant knowledge that are public but not in a format that can be automatically processed and understood. To use such content in a CDS tool, one needs to clean and structure it and add well defined semantics. It would be meaningful in our project to follow the Linked Data standard for all new knowledge we restructure and to contribute it back to the public domain.



Additionally, P-Medicine will generate new knowledge based on clinical trial data and part of the VPH modelling effort. These predictive models will be highly relevant input for the CDS tools. Prerequisites to use those models in the CDS context are proper clinical validation and semantic representation. The P-Medicine model repository should also include comprehensive metadata that will fully describe the models and their use. Next to helping users understand the models, this descriptive data will be used by the CDS tools to show the clinical user the origin of the model, the validation, the data based on which it was generated, the applicability, versioning, related models, etc.

It is of key importance for any recommendation used to support a clinical decision that the clinical user has full access to all the background of the recommendation to be able to make an informed decision of whether the recommendation is sound and applicable to the concrete patient case. This requirement is therefore also applicable to recommendations generated based on VPH or predictive models in general.

Finally, shared standardized semantics (in terms of standards for data models, ontologies, terminologies) with the other sources of knowledge and data used in the CDS tools are an important argument to promote the use of the VPH models for CDS.

8 VPH in the P-medicine environment

VPH models are considered as a means to accomplish personalized medicine, aiming towards better clinical decision. Individual healthcare practitioners and institutes need to be able to access and share a large volume of patient-specific information. The VPH integration in p-medicine would aim to develop patient-specific computer models for personalized and predictive healthcare and ICT-based tools for modelling and simulating human physiology and disease-related processes. As outlined earlier, there are several requirements for tools, methods and services for VPH research regarding:

- The interaction between p-medicine environment and the VPH toolkit
- The secure and safe storage of data
- The seamless integration of clinical care data, trial data, hospital information system data and research data
- The process of evaluation and verification of tools, methods and services
- The process for the certification of GCP compliant tools

Moreover, WP13 (Task 13.3) will be dealing with the requirements for enhancing VPH models addressed in this report. Data from the breast cancer trial will be used for the validation of decision making tools and data acquisition, sharing, joining and analyzing and the breast cancer neoadjuvant pharmacodynamic phase II trial will be used to extend the VPH tools.

Meeting the biomedical challenges in p-medicine

VPH Modelling and the Integrated Oncosimulator

The Oncosimulator is a concept of multilevel integrative cancer biology, a complex algorithmic construct, a biomedical engineering system and eventually a clinical tool which primarily aims at supporting the clinician in the process of optimizing cancer treatment in the patient individualized context through conducting experiments *in silico*. Additionally it is a platform for simulating, investigating, better understanding and exploring the natural phenomenon of cancer, supporting the design and interpretation of clinicogenomic trials and finally training doctors, researchers and interested patients alike [41,42,43,44,45,46,47,48]. In the

[41] Stamatakos, G. S. and Uzunoglu, N. Computer Simulation of Tumour Response to Therapy. Cancer Bioinformatics: from therapy design to treatment Edited by Sylvia Nagl , John Wiley & Sons, Ltd., Chichester,UK,2006

[42] Stamatakos G.S., D.D. Dionysiou, N.M. Graf, N.A. Sofra, C. Desmedt, A. Hoppe, N. Uzunoglu and M.Tsiknakis. The Oncosimulator: a multilevel, clinically oriented simulation system of tumor growth and organism response to therapeutic schemes. Towards the clinical evaluation of in silico oncology. Proc 29th Annual Intern Conf IEEE EMBS. Cite Internationale, Lyon, France Aug 2326. SuB07.1: 66286631, 2007

[43] D.D. Dionysiou, G.S. Stamatakos, D. Gintides, N. Uzunoglu, K. Kyriaki Critical Parameters Determining Standard Radiotherapy Treatment Outcome for Glioblastoma Multiforme: A Computer Simulation The Open Biomedical Engineering Journal 2, 43-51, 2008

context of p-medicine, three multiscale simulation models corresponding to the three tumour types to be addressed i.e.nephroblastoma, breast cancer and acute lymphoblastic leukaemia are being developed. The models make use of multiscale (imaging, histological, molecular, clinical, treatment) data of the patient and focus on tumour response to treatment (chemotherapy, targeted therapy, radiotherapy and combinations). Discrete mathematics serves as the main mathematical tool whereas continuous mathematics is recruited in order to address special facets of cancer treatment and response. The modelling core developed by the *In Silico* Oncology Group, Institute of Communication and Computer Systems - National Technical University of Athens (ICCS-NTUA)[49]and extended within the framework of the EC funded ACGT and ContraCancrum projects serves as the development basis of the models. For each solid tumour case a discretization mesh is superimposed upon the anatomic region of interest and the most critical biological and biophysical rules (or "laws") are applied on each geometrical cell of the mesh at each virtual scan of the region to take place at intervals of one time unit (e.g. 1 h). In the case of leukaemia a non-spatial compartmental model of cells distributed over the various proliferative potential cell categories serves as the basis of the corresponding Oncosimulator model. Cell cycling, symmetric and asymmetric cell division, metabolism, molecular profile, key molecular interactions and survival fraction following treatment represent some of the key rules of the models. The treatment limits imposed by normal tissues will also be taken into account. The development of all models is strictly driven by the corresponding clinical trial protocols. These three models constitute the simulation basis of the p-medicine Oncosimulator and will be clinically adapted/validated using one clinical trial per model.

The p-medicine Oncosimulator models will be quantitatively adapted to clinical reality by exploiting sets of real multiscale biodata including imaging (where applicable), histological, molecular, clinical, and treatment data produced by the clinical trials of the project. Clinical trial data will also be used in order to optimize and validate the simulation codes. To this end the following clinical trials will be used:

i) For the nephroblastoma model: the nephroblastoma SIOP 2001/GPOH clinical trial including the antigen scenario (ACGT version).

ii) For the breast cancer model: the breast cancer bevacizumab-1 and -2 trials

iii) For the acute lymphoblastic leukaemia model: the ALL BFM 2000 clinical trial.

---

[44] G.S.Stamatakos, D.D. Dionysiou Introduction of Hypermatrix and Operator Notation into a Discrete Mathematics Simulation Model of Malignant Tumour Response to Therapeutic Schemes In Vivo. Some Operator Properties Cancer Informatics 7, 239 - 251, 2009

[45] Graf, N., A. Hoppe , E. Georgiadi, R. Belleman, C. Desmedt, D. Dionysiou, M. Erdt , J. Jacques, E. Kolokotroni, A. Lunzer, M. Tsiknakis and G. Stamatakos. 2009. "In silico oncology" for clinical decision making in the context of nephroblastoma. Klin Paediatr 221: 141149

[46] G. S . Stamatakos, In Silico Oncology Part I: Clinically Oriented Cancer Multilevel Modeling Based on Discrete Event Simulation in *Multiscale Cancer Modeling* Edited by Tomas Deisboeck and Georgios S . Stamatakos, CRC Press 2011, Pages 407–436, Print ISBN: 978-1-4398-1440-6, eBook ISBN: 978-1-4398-1442-0, DOI: 10.1201/b10407-19, http://www.crcnetbase.com/doi/abs/10.1201/b10407-19

[47] N. Graf, Chapter 19. In Silico Oncology Part II: Clinical Requirements Regarding In Silico Oncology, in Multiscale Cancer Modeling, Edited by Tomas Deisboeck and Georgios S . Stamatakos, CRC Press 2011, Pages 437–446, Print ISBN: 978-1-4398-1440-6, eBook ISBN: 978-1-4398-1442-0, DOI: 10.1201/b10407-20 http://www.crcnetbase.com/doi/abs/10.1201/b10407-20

[48]G.S.Stamatakos, E.Ch.Georgiadi, N.Graf, E.A.Kolokotroni, and D.D.Dionysiou, "Exploiting Clinical Trial Data Drastically Narrows the Window of Possible Solutions to the Problem of Clinical Adaptation of a Multiscale Cancer Model", PLOS ONE 6(3), e17594, 2011

[49] www.in-silico-oncology.iccs.ntua.gr

SEVENTH FRAMEWORK PROGRAMME

Meeting the ICT and regulatory challenges in p-medicine

Implementation of the information system in p-medicine in order to meet the ICT and Regulatory challenges can be found detailed in deliverable D3.2 (Initial System Architecture). Several aspects such as security, pseudonymisation & anonymization are critical in p-medicine in order to meet various standards and these have been elaborated and discussed in the aforementioned document.

Meeting the CDS challenges in the context of the clinical trials in p-medicine

CDS is the most important goal of p-medicine-developed tools. Clinicians need to efficiently access all relevant data and infer knowledge necessary to reach the most accurate diagnosis and prescribe the most suitable treatment. By making use of the latest medical evidence, CDS solutions will support clinicians to provide personalized treatment and improve patient outcomes. As discussed in chapter 7 *"Requirements for clinical decision support"* of this report, overcoming the challenge of reducing errors, requires proper implementation and use of CDS systems. A second main goal is to enable the prevention and early identification of potential adverse events to a treatment/drug, and identifying those patients most susceptible to develop serious adverse effects, overall aiming towards optimizing clinical trial design.

Based on the clinical scenarios proposed in D2.2 (*"Definition on scenarios and use cases and report on scenario based user needs and requirements"*) (30/09/2011), CDS-related requirements were identified as part of D13.1 (*"CDS scenarios and requirements for the clinical decision support tools"*) (31/10/2011).

Requirements for CDS in Breast Cancer, Nephroblastoma and ALL

In the case of breast cancer, the aim would be to find suitable biomarkers predictive of response to metronomic chemotherapy. Tools need to be domain-independent for usage in other cancer domains. Moreover, there is need to find predictive biomarkers that will help clinicians to identify potential patient subgroups that will benefit the most from metronomic chemotherapy.

Requirements for CDS tools in Oncosimulator scenario

- To predict the likely response of a given patient's breast cancer to one or more candidate treatment schemes while toxicological limitations are taken into account.
- To clinically adapt and validate the breast cancer Oncosimulator in such an extent so as to allow its clinical translation.
- Personalization of treatment, optimization of treatment outcome, increase of life expectancy and improvement of the quality of life.

Requirements for CDS tools in Biobank scenario

A biobank, also known as a bio-repository, is a place that collects, stores, processes and distributes biological materials and the data associated with those materials. These may include human bio-specimens such as tissue or blood and related clinical information

pertaining to the donor of that bio-specimen. Patients will be able to access the biobank data stored on them with the data "translated" into a patient friendly format and language. Some of the requirements for CDS tools identified involve giving appropriate meaning to the biobank data for patients, displaying the information in a way that is suitable for all patients with differing levels of understanding and education. Access to each of the biobank repositories is also a requirement.

Requirements for CDS in Patient empowerment scenario

Although patients are typically seen as the recipients of care, personalized medicine aims at better enabling patients themselves to be participants and guides in their own health care. .Patient empowerment pervades clinical practice, teaching and research: patients are expected to take control over their illnesses or treatments where possible, and doctors are expected to encourage or 'empower' them to do so. Thus, the role of patients will be strengthened in p-medicine by allowing them to decide at any time what kind of research is allowed to be done with their data and their own biomaterial. Patient empowerment is based on information coming from research. Only by using this information to educate patients shared decision support is possible. This will enhance transparency for patients in the healthcare system and will convince patients to use their data for research purposes.

The relationship between a physician and his/her patient is crucial to quality care. The acceptance of decision support systems depends on their ability to cater to this need. Systems have to make the physician feel more equipped to provide better care while instilling trust and confidence in the patient that the technology is not a replacement of the physician, but a tool that enhances the treatment process. Towards achieving this, the following needs/requirements have been identified:

- The need to help physicians to better understand the psychological and cognitive aspects of the patients so that they can find the best therapeutic approach giving them information and treatments personalized on their needs and values finding.
- The need to increase the power of patients during the therapeutic process.
- To create a fast, easy-to-use tool to collect data from patients that can be easily interpreted by physicians.
- The need to give patients the possibility to monitor their feelings and quality of life through the use of internet-based questionnaires.
- The need to obtaining a personal patient's profile which will help physicians to better understand the patients and their needs.
- The need to ask patients to answer the questionnaires will help increase their participation and their level of empowerment. The need to provide information to patients in a language and style that they comprehend
- The need to provide information to patients in a language and style that they comprehend

9 Conclusions

One of the most ambitious goals of systems biology is to model human physiology. VPH is systems biology written on the largest of scales, as a methodological and technological framework within which it is possible to represent the human body as a single, coherent and dynamical system. It reaches down to the level of the human genome, and up to the whole human (and beyond, into population studies)". Moreover, cancer is a complex disease characterized by multiple types of biological interactions across diverse physical, temporal, and biological scales. This complexity presents substantial challenges for the characterization of cancer biology, and motivates the study of cancer in the context of molecular, cellular, and physiological systems. Modelling cancer also requires a precise simulation of tumour growth and tumour/normal tissue response to a variety of drugs and therapeutic regimens, i.e. chemotherapy, radiotherapy and their combinations. Optimal simulation of the disease and therapy response, therefore, would translate into better clinical decision making. Because of the complex and heterogeneous nature of the disease, simulating cancer behaviour creates a multitude of challenges in the biomedical setting. Technically, the design and *in silico* implementation of a cancer simulator is a monumental task that has been extensively pursued for the past few decades. One of the key endeavours of p-medicine is to develop and utilize advanced VPH cancer models in order to both integrate multiscale information available through the patient's heterogeneous data and provide a rational decision support tool to the clinician based on the virtual reproduction of multidimensional cancer dynamics. Tools and services developed for this purpose in p-medicine will be evaluated and validated before they will be integrated in clinical daily practise or prospective clinical trials for decision-making. This report has focused on addressing the various challenges or hurdles (biomedical, healthcare, IT, legal) accompanying the development of VPH cancer models and their usage in the scope of personalized medicine, as well as how these will be surmounted in p-medicine.

Relevant Publications

The following p-medicine reports are relevant to D2.4:

D2.1 “State of the art review of the p-medicine environment” (30/09/2011)

D2.2 “Definition on scenarios and use cases and report on scenario based user needs and requirements” (30/09/2011)

D3.1 “State-of-the-Art report on Standards” (31/08/2011)

D3.2 “Initial system architecture” (31/01/2012)

D7.1 “Report on overall system design including VPH-Share D2.2 and indicating its impact” (30/09/2011)

D9.1 “Report on regulatory and international aspects of the clinical trials” (contractual deadline 01/2012)

D13.1 “CDS scenarios and requirements for the clinical decision support tools” (31/10/2011)

Appendix - Abbreviations and Acronyms

ALL	Acute Lymphoblastic Leukemia
CDISC	Clinical Data Interchange Standard Consortium
CDMS	Clinical Data Management Systems
CDS	Clinical Decision Support
CDSS	CDS Systems
CPOE	Computerized Physician Order Entry
CRC	Clinical Research Centers
CTU	Clinical Trial Units
CRF	Case Report Forms
DM	Data Management
ECRIN	European Clinical Research Infrastructures Network
EDC	Electronic Data Capture
EHR	Electronic Health record
EMA	European Medicines Agency
GCP	Good Clinical Practice
HCI	Human Computer Interface
CCHIT	Certification Commission for Healthcare Information Technology

ICT	Information and Communications Technology
RDC	Remote Data Capture
RDE	Remote Data Entry
SLA	Service Level Agreements
VPH	Virtual Physiological Human