Digitally · ¶
Integrated · ¶
Scientific · Data · for · ¶
Patients · and · ¶
Populations · in · ¶
User-Specified · ¶
Simulations ¶

DISCIPULUS

DISCIPULUS PROJECT

Deliverable 6.2

First draft of the Digital Patient Roadmap

Based on 1st consultation meeting and early results

Work package 6

SEVENTH FRAMEWORK PROGRAMME

eHealth

DOCUMENT INFORMATION

IST Project Number	FP7-288143	**Acronym**	DISCIPULUS
Full title	Digitally Integrated Scientific Data for Patients and Populations in User-Specific Simulations		
EU Project officer	Joel Bacquet		

Deliverable Number	D6.2	**Title**	First draft of the Digital Patient Roadmap based on 1st consultation meeting and early results
Work package Number	WP6	**Title**	The Digital Patient Roadmap

Date of delivery	**Contractual**	31.05.2012	**Actual**	29.06.2012
Status	Version 1		ongoing ☒	
Nature	Prototype ☐ Report ☒ Other ☐			
Dissemination Level	Public ☒ Consortium ☐			

Authors (Partner)	**All partners**			
Responsible Author	EMPIRICA		**Email**	Veli.Stroetmann@empirica.com
	Partner	EMPIRICA	**Phone**	
Contributors	**All partners**			
Abstract (for dissemination)	This deliverable presents a first draft of the Digital Patient Roadmap. It outlines main issues discussed during the first consultation meeting end of March 2012. The draft roadmap is an evolving document and will be further elaborated & updated on a regular basis to reflect ongoing discussions with key stakeholders including the DISCIPULUS Forum on BiomedTown.			
Keywords	VPH, Digital Patient, clinicians, Roadmap			

Table of contents

1 Objectives of DISCIPULUS

Building on the work of VPH initiatives (32 altogether, with a further 18 new initiatives expected by the end of 2012 from Call 9, 200M€ funding in total), the DISCIPULUS project will create a comprehensive roadmap for the realisation of the Digital Patient (DP) initiative, which will enable clinical decisions to be better informed by the predicted outcomes of different treatment options, and allow patients and clinicians to become more pro-active in instituting lifestyle modifications and clinical surveillance for the prevention of diseases.

The main aims of the DISCIPULUS Project are:

- To consolidate the research and consultation carried out so far on the roles that predictive models might play in healthcare in the future. In particular we will attempt to assess the potential of existing research to make an impact in the clinical decision-making process.
- To capture the needs of relevant stakeholders. To discover the clinical problems that could benefit most from the Digital Patient. What concerns do clinicians have about the incorporation of physiological modelling into their practice, and clinical workflows and what evidence and standards are needed?
- To develop a vision and sound ICT research agenda around the Digital Patient.[1]

In the long-term, computational physiological models will be refined, linked and validated until they are capable of providing essential predictions to clinicians when healthcare decisions need to be made. As the amount of data reinforcing the models grows, predictions will become more and more patient-centred, with models migrating from statistical, average models to physiological and mechanistic models informed by the unique characteristics of the patient[2]. The Digital Patient initiative will propose new ways of combining this rich patient information space in a highly visual, coherent, meaningful way and of generating new clinical information by blending and fusing existing information, ultimately creating a "Patient Avatar" capable of supporting the medical professional by producing new clinical knowledge emerging from the integration of patient- and population-specific information.

The DISCIPULUS project aims to direct the research agenda through consultation and collaboration with the clinical, research and industrial communities.

The Digital Patient is a vision of a coherent digital representation of each patient that is used to provide an integrative framework for Personalised, Predictive, and Integrative Medicine. This vision includes three major challenges (resp. goals):

- To provide medical professionals and biomedical researchers with advanced user-interfaces based on the Digital Patient metaphor that make it easier to access and manage large amounts of information related to different organ systems, different space-time scales, and different diagnostic modalities.
- To provide healthcare providers with an ICT layer capable of retrieving and integrating all health information available for each patient into a coherent whole.
- To provide to biomedical researchers and to clinical research settings, the technology to capture existing knowledge into digital artefacts in the form of

[1] DISCIPULUS newsletter Jan 2012

[2] FP7 factsheet on DISCIPULUS

predictive models, and to compile such digital quanta of knowledge into integrative models of complex systemic mechanisms, thus generating new insight.

The Digital Patient roadmap focuses on problems related to the implementation of the VPH vision, i.e. on problems such as the user interface, information systems interoperability and integrability and generalisation of the integrative model concept.[3]

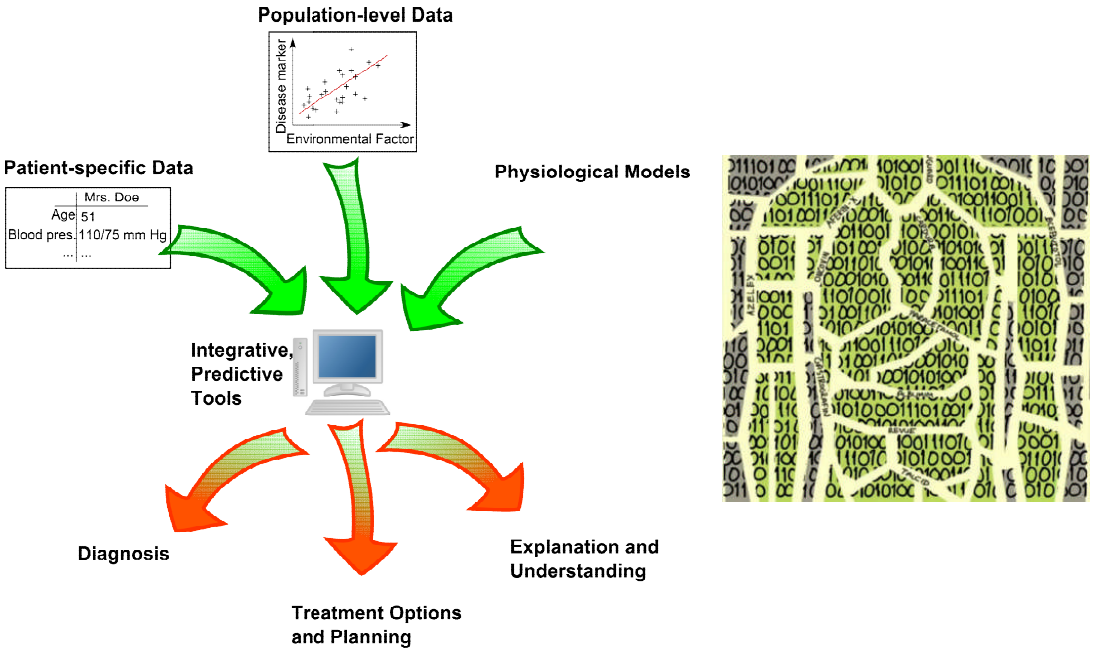
Within Horizon 2020, the "Digital Patient" together with *in silico* clinical trials and Personal Health Forecasting (PHF) form a key research area to be targeted within "ICT for Societal Challenges". It is directed at secondary care, including clinical research & innovation. Key objectives formulated at the consultation meeting on future of eHealth research and innovation organised by the ICT for Health Unit in September 2011 include:

- VPH user-interface development
- Model and knowledge integration and standards
- Intelligent and efficient knowledge extraction (modelling, machine learning, intelligence, decision support, etc.)
- Use of *in silico* models to understand the temporal progression of disease
- Specific tool development
- Management of personal data

For the next Work Programme, in 2013, a focus on clinical validation/trials (with industrial and clinical partners) has been proposed to demonstrate efficacy/proof of concept.[4]

2 The Digital Patient: vision and challenges

Increasing volumes of digital information are collected for each patient but the combinatory potential of these is not exploited fully.



[3] Hunter, P., et al (2012). A Vision and Strategy for the VPH: 2012 update

[4] from consultation meeting document

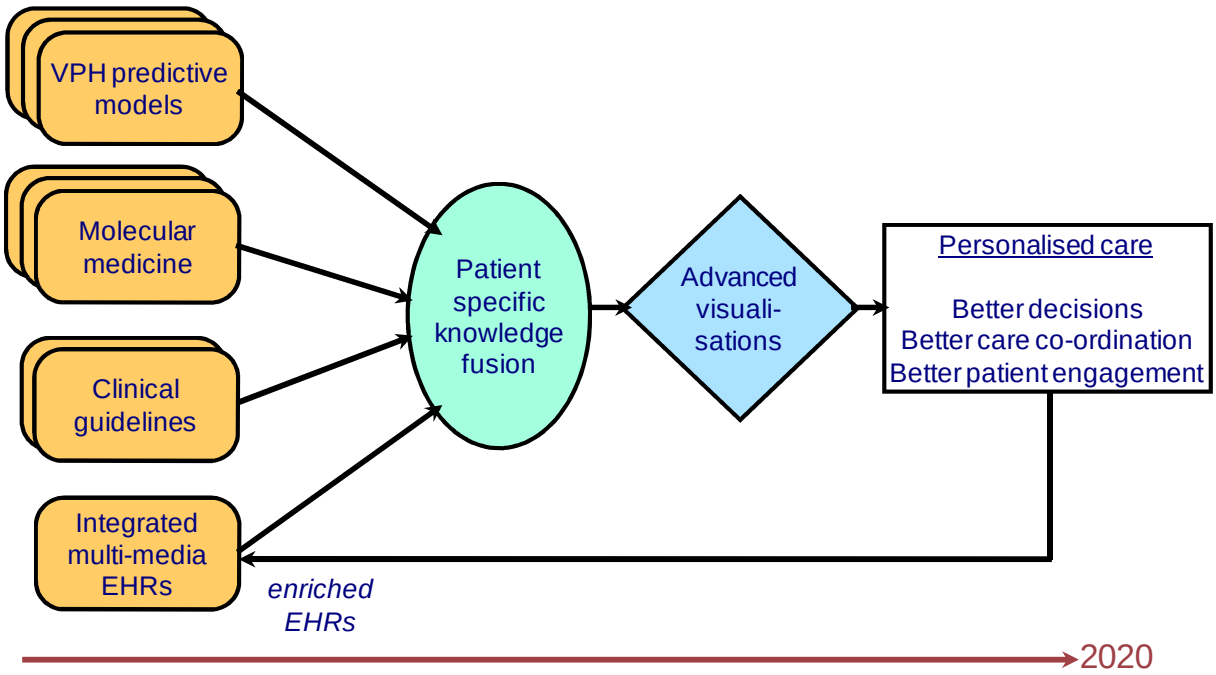
The Digital Patient initiative will propose new ways of combining this rich patient information space into a highly visual, coherent, meaningful way of generating new clinical information. This will be achieved by blending and fusing existing data, and ultimately by creating a "Patient Avatar" capable of supporting the medical professional by producing new clinical knowledge emerging from the integration of patient-specific and population-specific information.

These radically innovative information technologies are expected to have an extremely broad impact, with particular reference to how medical professionals can use simulation of disease progression, treatment, and outcome to support improved diagnosis, prognosis, and choice of treatment; develop evidence-based explanations for complex clinical cases for improving self-understanding, doctor-patient communication, and consensus-reaching within multi-specialist teams; and enhance intervention/treatment planning, especially in the case of complex, multi-professional care.

This is a Grand Challenge, which requires a European-wide coordinated effort both in research and in technology development. Through a consensus process involving all key stakeholders, the DISCIPULUS support action is developing a detailed research roadmap to guide the European Research Area in the pursuit of this ambitious objective.

The DP concept is presented in Figure 1.

FIGURE 1: THE DIGITAL PATIENT CONCEPT



The DP roadmap is investigating two main dimensions related to clinically relevant information and knowledge representation and use:

i. the ***technology dimension*** addressing integration of heterogeneous information and knowledge, its visualisation and representation, knowledge blending and new knowledge generation, and ultimately the development of a "Patient Avatar";

ii. the ***clinical use dimension*** addressing concrete clinical needs, emerging in clinical practice, that could be effectively supported by DP technologies.

From a technological point of view, the DP scenario is extremely broad. It includes, of course, the Virtual Physiological Human technologies for the generation of individualised multi-scale models to predict clinically relevant biomedical and physical processes. It also includes a biomedical information management element. This aspect is even more important than it was in the VPH context, especially in relation to integration and interoperability with the commercial IT systems deployed within European hospitals and includes a completely new element in relation to the user-interface.

These three elements (user-interface, data management, and simulation engines) are not independent from one another. As well as the continuation of core developments in VPH technology, the DP research agenda will also have to drive specific research activities related to the specifications imposed by user-interface research. Table 1 presents an overview of the current consensus in the consortium on the focus, and scope of use, of Digital Patient (DP) technology of different levels of maturity and sophistication.

Many fundamental issues such as standards and security have been/are being explored by the VPH NoE and DISCIPULUS will take full advantage of the results. Various issues related to infrastructure for VPH research, semantic interoperability, data standards, data exchange, privacy, etc. are within the remit of a current Integrated Project; VPH-Share. DISCIPULUS is following VPH-Share closely and will make appropriate use of its outcomes in the Digital Patient roadmap. Same applies also to the P-Medicine Integrated Project: From data sharing and integration via VPH models to personalized medicine.[5]

Similar considerations apply to interoperability issues related to the integration of DP technologies with Electronic Health Record / Personal Health Record systems, Personal Health Systems/Patient Guidance Systems as well as with other clinical decision support applications. Collaboration with projects and initiatives in these areas should be considered.

2.1 The technological dimension: levels of maturity

Three maturity levels of DP technology have been identified[6]. These reflect the level of sophistication of the technology regarding personalisation of information and knowledge, accuracy, predictive power of the (integrated) models, visualisation and representation of knowledge, etc.

2.1.1 Interface to information

The DP provides an interface to information: There is a requirement for a efficient and effective interactive interface to the combined, heterogeneous information based on innovative interactive visualisation technologies. One example of this concept is the driver interface in a car, in order to represent all the complex information received from the extensive electronic monitoring available, driver consoles in modern cars represent the information space visually as … a car. Similarly, we can imagine a *generic human body* as the primary visual element around which to build the interaction between the

[5] http://p-medicine.eu/welcome/

[6] The challenge Global Reference Body. In: VPH-FET Research Roadmap: Advanced Technologies for the Future of the Virtual Physiological Human. Editors: Marco Viceconti, Gordon Clapworthy, September 2011, p. 11. www.biomedtown.org/biomed_town/VPHFET

users and all the information available. This will primarily revolve around advanced interactive multi-scale visualisation and human-machine interface technologies.

2.1.2 Blender of information

The DP as a blender of information: Information blending, generating new information through algorithms, information fusion. Information arrives in a fragmented way, and the DP provides an integrative representation of such information. Here the accent is on integration, the ability to combine, integrate, fuse information in a synergistic way, and to return such fusion to the user visually. This involves knowledge management, data fusion, image processing, multimodal visualisation and visualisation of uncertainty.

2.1.3 Patient Avatar

Towards a Patient Avatar: clinical knowledge blending, new knowledge about the patient from patient-specific and population-specific information and knowledge.

Literally, 'avatar' means 'embodiment', and the Virtual Physiological Human is embodied by a *Virtual Body*. Here the accent is on modelling of physiological and pathological processes and their representation in a way that fosters understanding, exploration, and possibly the production of new knowledge.

The *VPH Network of Excellence (VPH NoE) Strategic Vision*[7] document contained the concept of the Patient Avatar, but there it was called 'the Digital Me'. It was described as: 'a coherent digital representation of each patient that is used as an integrative framework for the consolidation within the European research system of fundamental and translational Integrative Biomedical Research and the provision to European Citizens of an affordable Personalised, Predictive, and Integrative Medicine'.

The Integrated Project *VPH-Share* expresses the vision that 'within ten years every person will have such an Avatar which will be used as the basis of the presentation to the investigator (clinician or researcher) of all patient information, and it will serve as the basis of predictive simulations to evaluate the probability of a certain disease developing or progressing, as well as predicting the effects of present or future interventions.'

One of the powerful aspects of the Patient Avatar is that it is *a repository of all of the clinically-relevant information* that has been collected about the individual. The vision promoted by VPH-Share is of a *structured* Avatar that is able to contain all data items, and at the least personalised level this Avatar will contain population averages, or even best guesses. Over the years the Avatar becomes an increasingly accurate representation of the individual as new measurements are made, or as inferences are made about missing items by operations on the information that *is* available. Here we use 'inference' in a very general sense: it could include the operation of very complex computational models from which new information is extracted.

At the root of the VPH vision, the concept of "Integrative model" is defined as a model "made of component idealizations and of relational idealizations defining the relations between components"[8].

[7] VPH Vision & Strategy (16.12.2009) http://www.biomedtown.org/biomed_town/VPH/vphonoe_strategic_report_2009

[8] Viceconti M.: A tentative taxonomy for predictive models in relation to their falsifiability. Phil. Trans. R. Soc. A 2011 369, 4149-4161

Within this document we use the term '**hypermodel**' to describe a concrete instance of an integrative model, built as the orchestration of multiple computer models that might run on different computers at different locations, using different simulation software stacks. Typically a hypermodel is a *computational model that might operate on multiple spatial scales, perhaps from molecular through cellular to organ and patient level, and/or on multiple temporal scales, from acute response upwards, and/or might include descriptions of physical, chemical and biological processes*.

Section 2.2 of this roadmap focuses on the issues of presentation to, and use of, this information by the clinician or, indeed, the patient, whilst section 2.3 describes specific infrastructural and technological challenges in the realisation of the Patient Avatar.

2.2 The clinical use of Digital Patient technology

The second dimension is that related to the use in clinical practice. The DP technologies will be used to support:

- Decision-making - the clinical specialist decides the best course of action,
- Explanation - the clinical specialist explains his/her decision to others: peers, GP, carers, patient him/herself,
- Execution - the clinical specialist plans, carries out and monitors the treatment.

In the following section, these categories are explained with reference to the highest level of maturity, the Patient Avatar.

2.2.1 Patient Avatar: DECISION

As a decision support system (DSS), the Patient Avatar will represent a considerable evolution over current DSS that are based on VPH technology. The primary difference is that, in VPH DSS, the designers have reduced the potentially massive simulation outputs to a single or to a small set of indicators (risk factors, expected outcome, go / no go recommendations). While this is useful in many contexts, this does not leverage the ability of clinical specialists to receive and process large amounts of heterogeneous information and fuse it into a clinical decision.

With the Patient Avatar we can *expose the entire set of information about the patient, including results produced by a hypermodel and provide the clinical specialist with a user-interface that makes possible to explore such a vast information space or, on demand, to reduce this to a small number of selected indicators tailored to the needs of the individual clinician*.

Some of the technological research challenges that have been identified in relation to this clinical dimension are:

1. **Interface for exploration of large results space**: visual analytics and similar visualisation techniques to explore very large, multi-dimensional and heterogeneous collections of simulation results.

2. **Multiscale visualisation**: as above, but for results that need to be represented through visualisation that are defined over radically different space-time scales.

3. **Generalised stochastic/probabilistic frameworks**; quantitative predictions should be presented together with an associated confidence interval or intrinsic physiological variability.

4. **Reasoning querying**: the option to query the hypermodel to find out which knowledge sets have been used to develop each component module, with links to

the relevant literature, validation results, etc. This will include clearly defined limits of validity of hypermodelling reasoning related to the limits of validity for the entire hypermodel.

2.2.2 *Patient Avatar: EXPLANATION*

The explanation concerns a *formalisation of the clinical decision, and its presentation to peers, carers, or the patient him/herself*.

Some of the technological research challenges that have been identified in relation to this clinical dimension are:

1. **Representing complex processes at variable level of detail**: imagine a very complex process that involves various organ systems and/or space-time scales.

   On one extreme we can represent this process as cartoon-like animation where simplified drawings represent the essential parts of the system, and other visual clues show if their status changes over time.

   On the other extreme, for each component, there are ultra-detailed and ultra-specialised visual representations for each result set produced by each sub-model. Can we imagine a *"Load on Demand (LoD)"* mechanism where, by moving a slider, we can go from the cartoon that everyone can understand to progressively more, and more, complex and more detailed visual representations?

2. **Logical zoom**: the possibility to be able to hide entire branches of the sub-model leaving only those outputs that affect other branches visible.

   For example, for pulmonary hypertension: the full hypermodel involves a sub-branch for the lungs, and one for the right ventricle of the heart. The cardiologist would see the full sub-model relative to the heart, with pulmonary function represented as a generic compartment with pulmonary impedance and oxygenation; the pneumologist would see the detailed pulmonary sub-model with the heart branch represented in terms of a compartment that shows pressure and flow.

3. **Search the match**: in multi-specialty consultations the clinicians usually base their decisions on previous experience.

   A highly individualised Avatar could be used as a search template to identify similar cases within the hospital database. Of course this requires a definition of similarity, and this will depend on the question posed. For example in some situations patient age will be important, in others ethnicity, in others anatomical descriptors, and in others combinations of all of these factors. Work is required on formalisation of the process of establishing similarity within the Patient Avatar.

   Provide rapid-prototyping of exploratory interfaces, whereby a significant number of patients are mapped by match closeness with the current case, treatment selection, and outcome, with each element defined by a user-selected metrics/categorisation.

4. **Avatar lookalike**: develop rapid, automatic, and low-cost strategies to individualise the physical appearance of the Avatar to that of the patient.

   Parametric scaling with body weight, height; patient picture textured on a generic avatar face; incorporation of data captured by rapid, low-cost body scanners.

   Avatar similarity provides emotional intensification in the patient-doctor communication; exploratory analysis of psychological impact.

5. **Show the outcome (treatment)**: use the Avatar to simulate the possible outcomes of the various treatment options, and represent the outcome as a functional animation, of an older man that walks very slowly, for example, or of a failing heart that has a limited cardiac output capability, etc.
6. **Show the outcome (lifestyle)**: use similar animation technologies to show the patient the predicted effect of certain inappropriate life-style choices, and lack of compliance with treatment or, to demonstrate the positive effects of compliance/improved life-style choices.

2.2.3 Patient Avatar: EXECUTION

Here the Patient Avatar is used to plan the treatment, by simulating it on the Avatar, and viewing the outcome predicted by the hypermodel. The outcome hypermodel is revised during the intra-operative session and refined - in the light of observations - during the follow-up, but also using it to record any unexpected deviations that indicate the occurrence of unrecognised processes/events.

Some of the technological research challenges that have been identified in relation to this clinical dimension are:

1. **Real-time or quasi-real time VPH hypermodel response**; surrogate modelling, efficient execution of multi-scale models. Efficient restart of pre-computer hypermodels to support q sessions, i.e. where hypermodels are embedded in surgical simulation environments.
2. **Self-refining Avatar by intra-operative measures**: detailed measurements collected during the treatment are used to refine the hypermodel and improve its predictive accuracy for the treatment outcome.
3. **Self-refining Avatar by monitoring**: post-treatment monitoring data are used to refine the long-term outcome prediction and feedback to the knowledge repository when significant deviations are observed between predicted and actual outcomes.

As already noted, Table 1 on the following page presents in a Matrix an initial overview of the potential scope of use of DP technology of different levels of maturity and sophistication in the clinical practice.

TABLE 1: DP TECHNOLOGIES: OVERVIEW OF MATURITY LEVELS AND CLINICAL USE GOALS

CLINICAL USE **DP maturity level**	**DECISION** Clinical specialist decides the best course of action	**EXPLANATION** Clinical specialist explains his/her decision to others: peers, GP, carers, patient him/herself	**EXECUTION** Clinical specialist plans, executes and monitors the treatment
Interface to information	*Interface to combined, heterogeneous information; visualisation, interaction*		
Blender of information	*Generating new information through algorithms, information fusion*		
Patient Avatar	*Clinical knowledge blending, new knowledge about the patient from patient-specific and population-specific information and knowledge*		
	User interface to expose & explore the entire information space about a patient, incl. results produced by a hypermodel or, on demand, reduced to selected indicators	Formalisation of the clinical decision, and its presentation to peers, carers, or the patient him/herself	Treatment simulation on the Avatar, viewing the outcome predicted followed by outcome hypermodel revision
	• Interface for exploration of large results space: visual analytics • Multiscale visualisation of results defined over different space-time scales • Generalised stochastic/probabilistic frameworks • Reasoning querying (of hypermodel; limits of validity)	• Representing complex processes at variable level of detail o Load on Demand • Logical zoom • Search the match • Avatar lookalike • Show the outcome	• Real-time VPH hypermodel response • Efficient execution of multi-scale models • Hypermodels embedded in surgical simulation environments • Self-refining Avatar o By intra-operative measures o By monitoring

2.3 Further insight on specific S&T challenges

2.3.1 Infrastructure for the Digital Patient

The key challenge facing the Digital Patient paradigm is the creation of an *in silico* environment that integrates the *knowledge* (as determined by the research communities and medical professionals) with clinical records, and channels it into a technology that augments clinical diagnostic, therapeutic and preventative medicine. The ambition here is patient-specific medical care, based on a patient-doctor interaction, supported up by *in silico* modelling and 'Digital Patient' data.

The concept of 'Digital Patient' data was explored during the recent DP workshop held in Barcelona (March 30, 2012). This ideally requires 'good quality' data that includes not only images and EHRs but all other available data, i.e., laboratory data, genotypic profiling, etc, extracted from 'dirty data' or 'real data'. In summary: can we produce **'acceptable' DP datasets for modelling, understanding, prediction**? An alternative (that should not be discarded *a priori*) is to develop tools that are able to cope with all kinds of 'real' or 'dirty' data where total accuracy and completeness cannot be ensured.

The unifying influence of a DP helps to address issues associated with piecing together heterogeneous data from fractured and fragmented patient clinical records. Particular challenges of a DP implementation include:

i. Construction of an **integrating infrastructure** capable of assembling a coherent representation of patient health status from fragmented information dispersed across the healthcare system.

ii. The construction of **user-interfaces that promote interactive and intuitive navigation of the unified patient data-space** assembled by (i) above, permitting extraction of relevant data for clinical benefit (identification of cohorts, disease progress etc.)

iii. The **capacity to manipulate Digital Patient information** made available by (i) and (ii), above, with supporting DP tools that aid clinical interpretation and prediction of patient outcome (through simulation, visualization etc.) and thereby augment diagnostic, therapeutic and preventive medicine.

The DP relies upon the combination of disparate sources of EHR information, requiring not just technical integration, but also **semantic harmonisation**. Fortunately, this challenge is one on which many initiatives are presently aligned, including[9]:

- the existence, and gradual adoption, of EHR interoperability and communication standards
- research projects on semantic interoperability
- the development of ontologies to represent not only the data items themselves, but also the associations between them
- research and development projects on the re-use of EHR data for research
- investments in many national eHealth programmes on EHR infrastructure and on clinical adoption of EHRs

[9] For EC co-funded projects see: EHR4CR: Electronic Health Records for Clinical Research (www.ehr4cr.eu/), SemanticHealthNet: Semantic Interoperability for Health NoE (www.semantichealthnet.eu/), TRANSFoRm: Translational Research and Patients safety In Europe (www.transformproject.eu/), RICORDO: Researching Interoperability using Core Reference Datasets and Ontologies (www.ricordo.eu), etc.

There remains, however, a significant challenge for needs such as semantic interoperability to be reflected in systems and services that are already deployed and widely used.

Another challenge is to extend the avatar to represent not only the data and information that is present in a typical EHR, but to enrich it with the sort of **data that comes from the hypermodels** described in earlier sections. As a community, as yet, we do not have generic approaches to this integration challenge, but a comprehensive description of the issues, together with a description of a Patient Avatar for four, very specific, clinically-orientated workflows, is available from VPH-Share on BiomedTown[10].

The success of the DP is also dependent upon being able to make accurate and safe predictions using data that might not be "clean": i.e. with missing values, imprecise or uncertain clinical findings and occasionally errors.

Another dimension that will need to be explored is the extent to which **access controls** to EHR information, which might vary depending upon the status and role of each clinician, will impact on the data that a Digital Patient Avatar can access. For example, might the DP need to adapt depending upon what data each user is permitted to access? This has patient safety implications as well as usability issues.

New generation health software will be expected to conform to **regulatory requirements** such as the European Medical Device Directive (which now applies to stand-alone software used in healthcare, especially if the software makes or supports clinical decisions)[11]. A European level clarification is needed of the regulatory requirements for innovations such as the DP, which will inevitably be evolutionary and progressively improve in reliability, in contrast to definitive medical device products that are version-controlled and where established methods are in place to inform testing.

An effort has been, and continues to be, made to address issues such as security, access, authorisation, annotation, interoperability, **ethical and legal issues**, etc., through a variety of projects across the VPH and beyond and it is clear that regulatory policies have a significant role to play here[12]. Certainly harmonization and clarification of current European-wide Directives would help. This has direct bearing on points (ii) and (iii) above in relation to clinical software development and deployment.

For instance, the creation of DP accessible data, populated by high-fidelity data, must address the highly contentious issues of patient anonymity, data protection, informed consent, etc. There is a continuous tension between the need to distribute data and information to support research, and indeed to inform clinical practice by sharing information about prognoses, interventions and outcomes, and the need to protect the privacy of the patient. It is a social and political challenge to **set the guidelines under which data and information can and will be shared**. At a technical level it is

[10] VPH-Share Integrated Project: Patient-Centred Multiscale Computational Workflows, Deliverable: D5.1 Patient Avatar Defined for Flagship workflows, 30 November 2011, https://www.biomedtown.org/biomed_town/vphshare/reception/public_repository/deliverables/VPH-Share_D51_1v2.pdf

[11] Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices. See also Commission communication in the framework of the implementation of the Council Directive 93/42/EEC of 14 June 1993 - OJ C 123 of 27/04/2012, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2012:123:0006:0030:EN:PDF

[12] Policy Brief on Policy needs and options for a common approach towards Modelling and simulation of human physiology and diseases with a focus on the Virtual Physiological Human Transatlantic Observatory for Meeting Global Health Policy Challenges through ICT-Enabled Solutions - ARGOS eHealth.

important to develop processes that make it easy to expose and to find data (and indeed tools and models), if and when this is allowed and supported, ensuring that **appropriate governance** is maintained. It is also important to recognise the challenges of federation of data across many centres, particularly when access might be restricted to particular purpose by the terms of access. Cloud computing offers many advantages in terms of cost and efficiency of utilisation of computational resource, but as a community we are still learning how to harness the power of the cloud in the confined and security-conscious atmosphere of potentially sensitive patient information. **Security** is a major concern, but not more so than the establishment of guidelines to indicate what level of security is required for specific purposes. Traditionally a division has been made between data that is identifiable and associable with a particular individual and data that is regarded as non-identifiable. This distinction becomes blurred as increasing amounts of data become available and the potential for integration to re-identify the individual emerges.

The DP concept must deal with adoption issues within the clinical work place. In certain areas (pharma, devices) rigorous standards apply provide a regulatory framework and also encourage responsible development by clear specifications of appropriate standards. However, VPH and DP tools fit uncomfortably within this framework because these technologies suffer from a range of regulatory uncertainties, despite a revision of the European Medical Devices Directive which became active in 2010[13]. CE marking is required for clinical use of certain categories of software that 'could fall' within the medical devices categories. Unfortunately the interpretation of EU regulation by the individual States' Competent Authorities and the Notified Bodies is only just beginning to emerge and, as yet, there are no test cases for modelling software. Clarification is anticipated from a further revision of the Directives in 2012, but its potential impact is still unclear. Thus, at the present time, it is difficult to envisage how the broader DP vision will be regulated and approved. This will need to be addressed. There will undoubtedly be challenges associated with software that incorporates self-learning learning processes as proposed during the first consultation event; current legislation invariably requires strict software version control with changes requiring a potentially costly re-approval process.

2.3.2 Understanding information, visualisation and human-machine interaction

One key question from a clinical point of view is: "Given my patient's progression of symptoms and test results, what is the likely pathology and outcome?" This diagnostic question is important, because it categorises the pathology and predicts outcome, and thereby suggests a therapeutic pathway. An 'average' patient with classic presentation and progression of the disease is likely to respond predictably to the 'standard' therapeutic regimen. Whereas non-classical symptoms and test results may prompt alternative approaches. The clinician's expertise and experience of the pathology usually mitigates the need for broad data searches across the hospital. The clinician can, of course, choose to pursue a broad search, if that need arises; but such a search may involve a multitude of independent systems. Alternatively, the clinician can consult published case studies in clinical literature. These present informed opinion to the clinical community, providing statistics of the evolution and response of pathologies in the context of various patient cohorts. Reading a peer-reviewed article is far easier than unravelling connections between hospital records. However, it is self-explanatory why this is an unsatisfactory and inefficient approach.

[13] See footnote 10.

Electronic Health Record databases, PACS, and billing systems contain rich information about patients with multiple attributes and temporal events such as diagnosis dates and the dates and details for various symptoms, treatments and outcomes. The challenge of searching for desired information within such a large quantity of heterogeneous data is critical to address. There is great need to **support data exploration by using novel tools for visual presentations and data exploration**. Currently, most of the existing techniques do not aggregate information and therefore they face problems in scalability. Challenges still remain largely unsolved in the area.

The issue of identifying relevant information from large (and ever-growing) datasets is crucial. Medicine is not the only discipline suffering from information overload, and the challenges here resonate with problems experienced in other disciplines, such as, astronomy (i.e., navigating through increasingly large astronomical object catalogues), making sense of financial time-varying data in the financial sector, etc. Solutions have already been sought in these areas. Methods, including, **subspace clustering combined with visual analytics**[14] have attracted recent research attention. For example, a meaningful cohort of patients may have common attributes related to their ethnicity, symptoms, geographical locations, etc. This is intimately linked to issues identified in the data and infrastructure sections, where quality 'DP' data is necessary. Given a dataset with high dimensionality, the number of possible sub-spaces is tremendously high and although automatic machine learning has been used, it is inefficient in order to identify clusters. However there might be a way forward by incorporating human judgement in this process, which will involve the incorporation of human-machine interaction tools, bringing in elements of computer science, behavioural sciences, design and several other fields of study such as look and feel, usability, interfaces,[15] etc. This aspect is crucial in the decision-making process of the DP and could be used to explore inter-patient differences based on longitudinal information sets within cohorts, to guide differential diagnosis and refine treatment plans.

Augmented reality (AR) could be used for better visualization of a patient's anatomy during surgery to help guide surgeons, or a way to get medical history of a patient by examining them and seeing what areas have had medical supervision or diagnosis before by superimposing x-rays and other images over these specific areas. This technology could also be used for medical teaching, to help in providing medical care to remote locations or locations under duress (e.g., war or natural disaster). Additionally, AR could be used to address issues of patient compliance, for example, patients with chronic disease that needs to be managed pharmacologically in which case a "virtual nurse"/"virtual doctor" could help monitor the treatment by keeping these patients to the recommended dosages and on the right timetable.

Last but not least, in order to understand and support clinical decisions, an interesting opportunity is presented in the concept already explored during the VPH-FET exercise of a 'Web of Models'.[16] Such a web of models will allow the creation of integrative models

[14] Heer J, Agrawala M: Design Considerations for Collaborative Visual Analytics. Information Visualization, 7(1), pp. 49-62, 2008, http://vis.berkeley.edu/papers/design_collab_vis_ivs/2008-DesignCollabVis-IVS.pdf

[15] The use of user interfaces might contain also elements of gaming. Interfaces that are 'realistic' or that have a 'realistic feel' would be necessary, in particular, augmented reality, where the 'user' (doctors) would be able to see the real world, with virtual objects superimposed upon or composited with the real world hence, supplanting reality rather than completely replacing it, with virtual and real 'objects' coexisting in the same space. Additionally, multi-player gaming allowing different specialists/teams to 'play' would offer opportunities impossible to start imagining today.

[16] Web of models. In: VPH-FET Research Roadmap: Advanced Technologies for the Future of the Virtual Physiological Human. Editors: Marco Viceconti, Gordon Clapworthy, September 2011, p. 70. www.biomedtown.org/biomed_town/VPHFET

and the reproduction of the complex workings of human biology, at different levels of detail. Simulated populations will be created. Medical problems developed by virtual populations will be studied according to models, relations among models, and individual risk profiles. The web of models will support the provision of insights into the anatomy, pathology, disease progression and the most suitable treatments; and, through the development of clinical decision support systems, will allow the prediction of conditions and aid clinicians to accomplish their goals.

In summary, key issues related to the challenge of user-friendly interface to combined, heterogeneous information, visualisation and interaction include:

- Unified and clean visuals of "dirty" data
- Standardisation of EHRs
- Fast access to all data, clustered by areas in order to help visuals
- Interaction with this data via mobile devices
- This data must be accessible from different places
- Time-history of patients and unified charts or evolution of biomarkers, acute events and disease progression
- Starting from genotype as the baseline, visualisation of the disease progression via accepted clinical indexes
- The interface should use touch-screen technology, 3D visualisation techniques with user-friendly interfaces and, in the future, interactive holograms
- The information about the patient must include a wide range of data (environmental, genetic, etc.) and also population data for direct comparison. Overlapping of markers at the individual and population level will be useful if they take a graphical form. We must move away from using numbers alone.
- Information must be combined using sophisticated individual predictions, producing a 'fan' of possible scenarios for further exploration. This information must be displayed using the interfaces described in the 'decision support' category.
- Possible 'gaming' approaches, in much the same way that multi-player games work online. This would allow access by different specialists at different locations. Each 'game' would be recorded and re-played if necessary. This would include; bringing up information that specialists deem necessary from the EHR, videos, conversations with patients, etc or adding professional 'knowledge' (information that the clinicians know and is not documented but that needs to be contextualised, written in mathematical form and displayed in a graphical manner). Automatic programming techniques might be needed in order to address this.
- Online and mobile applications allowing patients to upload data and to keep track of progress. Constant feed to EHRs. This technology must be easy to use and intuitive.
- Applications should involve advanced graphics in order to create an illusion of 'reality'.
- Identification of the patient with their own DP will involve sophisticated human-machine interaction techniques and substantial technical developments in the implementation of self-perception theory in the DP Avatar. Online representations of ourselves – like our Avatars on Xbox 360 or our Miis on the Nintendo Wii– can affect individual behaviour, including healthy behaviour.

2.3.3 Data & sensing

Advances in methodology for **capturing and sharing large amounts of data** synergise with advances in core analytical, learning, and inferential tools that consume such data. New approaches in **applied statistics and machine learning** can transform opaque or 'dirty' data into knowledge and then into decision policies that can provide guidance on ideal actions by consumers, healthcare providers, and taxpayers. Large-scale and systematic inclusion of patients in both observational and interventional research studies would greatly accelerate our ability to detect subtle findings that may be small but could nevertheless translate into substantial cost and quality benefits at the population level. Such studies can lead to guidelines on the effective allocation of scarce resources in a context-sensitive manner, identifying how best to make investments that will ideally enhance the quality and cost-effectiveness of healthcare.

Studies in support of such goals will often require the extraction, storage, and fusion of multiple classes of data from disparate sources and contexts—data that are drawn in a secure manner in accordance with patients' preferences about privacy. As previously mentioned, new computational techniques are needed at multiple steps to meet this challenge, drawing from such sub-disciplines as machine learning and reasoning, systems, databases, cryptography, and human-computer interaction.

A great deal of information with potential relevance to the optimisation of healthcare delivery is currently being wasted. New kinds of data sensing and perception will be necessary to capture and to pool previously uncollected data—and these data may be important for building insights and constructing predictive and causal models. Data must be captured in situ and in ways that are automatic, unobtrusive, and easy to use. **Networks of small special-purpose sensors and convenient mobile devices** are examples of the new technologies that can be brought to bear to capture data. At a higher level, fundamental advances are needed to enable the **automated capture and comprehension** of context, situations, events, and systems. For example, information about the actions, assessments, and flow of activity among members of a surgical team during a surgery procedure, about the post-surgical course, and about the patient's post-discharge experiences are available to different people at different times—and such data is largely volatile and currently not captured. New kinds of tools for recognition, tracking, and recording could capture and pool such data at low cost and make it available to an **analytical pipeline**. Also, new kinds of annotations about the sources and reliability of data need to be maintained and relayed with the core data. Just as an example, the evidence about a heart murmur documented by a cardiologist differs from the evidence provided about that same murmur by a medical student. Advances in the ability to capture information from these multiple sources and extract knowledge from them will help to end the chronic wastage of valuable data and experience in health delivery – for individuals and populations.[17]

2.3.4 Advanced biomedical and biological imaging for model personalisation and disease/population characterisation

Biomedical imaging remains the main sensing strategy to map three-dimensional structural and functional information, in some cases even dynamically, of the biological and physiological mechanisms and across a wide range of observational scales. Additionally, imaging is used both for understanding fundamental mechanisms (e.g.

[17] Computing Community Consortium: Information Technology Research Challenges for Healthcare: From Discovery to Delivery. May 25, 2010, http://cra.org/ccc/docs/init/Information_Technology_Research_Challenges_for_Healthcare.pdf

advanced light microscopy techniques), to develop biomarkers for disease diagnosis and stratification, and also in surgical and interventional therapies for planning and guidance purposes. Consequently, imaging data will be a central element in developing the DP forward. Im-aging is crucial for personalisation of models. But imaging can also be carried out at population level as is being tackled in certain initiatives (e.g. the Rotterdam Scan Study) where citizens of a given region are follow-up over time and scanned at regular intervals. Such studies do not only provide imaging information for each and every individual in-volved in the study but they enable gaining systematic knowledge on the manifestations and the natural history of specific diseases through imaging biomarkers.

There are a number of challenges associated with the use of biomedical and biological imagery (let alone the technological challenges for developing new imaging systems which are outside the scope of this roadmap):

i. **Data assimilation and model personalisation**: There is a need to develop algorithms at the interface between image computing and computational modelling that enable transformation of state-of-the-art imagery of specific subjects into model parameters. Although initial steps have been made in this direction, there are still challenges associated with parameter estimation in large-scale non-linear and sometimes discrete models from imaging data. In addition to challenges associated to complex inverse problems, some of the difficulties stem from the need to establish appropriate relationship between the model parameters and the parameters actually measurable through imaging. One would want to have specific ontologies that enable conceptual mapping between imaging modalities and model parameters so that it would be possible to fully streamline the process of model building and its personalisation.

ii. **Image-based characterisation of disease and populations**: This requires the availability and processing of large-scale databases which enable understanding of structural and functional changes across subjects and over time. Methods for image-based group com-parison and image feature registration are needed that can run robustly on massively large databases. Construction of statistical population atlases and reliable computation of biomarkers (and their statistics) through high-throughput and image analytics are other two areas of relevance. Ideally, one would be interested in being able to automatically transform a massive population image database, including individual and temporal varia-tions, into clusters representing specific diseases with the average phenotype and its principal directions of variability in terms of image-based biomarkers.

iii. **Multiscale image computing for multiscale modelling**: So far, the emphasis has been primarily on medical imaging as a source of patient-specific data. However, a number of relevant pieces of information in building accurate biophysical and biological models require information that cannot be obtained in clinical imaging systems. Biological imaging, in turn, can provide the required level of detail but this is usually in samples of very small size. The challenge is thus how to combine information from small-level detail obtained with tissue or cellular imaging with the tissue-to-organ level data we are able to derive through imaging systems.

2.4 Facilitating development and adoption

2.4.1 Verification, validation, technology assessment

Fundamental to the vision of the DP are the scientific and methodological challenges that the correctness of the developed predictive models in biomedical research pose.

Developers and users are rightly concerned with whether a model and its results are "correct". The correctness needs conceptualization – in a highly interdisciplinary field of science that is at the crossroads between biological, medical, physical and engineering sciences.[18]

This challenge not only affects scientific quality and the definition thereof, but it has highest relevance for clinical acceptance and adoption (see above), and entails political and economic consequences. Clinicians have expressed their concerns that some VPH ideas are "too virtual", caused by a methodological gap between clinical research standards and physics-based approaches to model validation.

The lack of a common understanding and semantics between the physical and the medical world about what is meant by "model validation" – and even worse, ignorance of this lack – has become a serious inhibitor for advancing VPH technologies to clinical deployment. Promises by VPH developer of validated models disillusion clinicians, while funding agencies can be taken by misguided evaluation criteria. Presently, the most advanced VPH technologies can be better interpreted as delivering pre-clinically validated models, i.e. some form of prototype demonstration with the use of real patient data, but not clinical validation in a clinical environment, which can only be achieved with prospective clinical trials.

Validation methodology of physics-based simulation models

- 'Model validation' is the process of demonstrating that the model matches experimental reality - normally done by the author of the model as part of the scientific publishing process.
- 'Model verification' is the process of ensuring that the claimed model outputs can be achieved for the specified inputs (model, parameters, data) - i.e. someone else other than the model developer can verify that the model behaves as expected (even if the model bears no relation to reality - i.e. has not been validated).

New health technologies are usually subjected to experimentation, refinement, and increasingly realistic testing, which, in the case of VPH technologies, refers to clinical testing. The testing for correctness ranges from:

- the technical capability assessment (verification, sensitivity, validation),
- via accuracy (prediction uncertainty),
- to efficacy and clinical effectiveness assessment).

The combination between physics-based model validation methodology and clinical research validation approaches could be achieved with the following table.

[18] See also Viceconti, M. (2011) "A tentative taxonomy for predictive models in relation to their falsifiability." Philos Transact A Math Phys Eng Sci 369(1954): 4149-61.

Model validation steps	Clinical Development Phase
Basic principles observed and reported	*Basic research*
Technology concept, application or hypotheses formulated	
Analytical & experimental critical function and/or characteristic proof-of-concept	
Sub-Model design and construction in laboratory environment	*Experimental verification and validation (inherent accuracy[19])*
Sub-Model parameterisation and configuration in laboratory environment	
Sub-Model validation in laboratory environment	
Multiscale integration through hypermodel successfully validated in laboratory environment	
Sub-model or prototype demonstration in a relevant environment (clinical observation or laboratory observation using patient input data)	*Pre-clinical verification and validation*
Hypermodel prototype demonstration in a relevant environment (clinical observation or laboratory observation using patient input data)	
Prototype demonstration in clinical environment/ pre-Phase I clinical trial for safety completed	*Clinical validation and assessment (clinical accuracy[20])*
Hypermodel prototype demonstration in clinical environment/ pre-Phase I clinical trial for safety completed	
Hypermodel completed and tested/validated in full clinical trial	
Actual model proven through decision support system successfully used in clinical environment	*Operational*

The challenge of validating multi-model simulations poses an additional challenge to validation methodology. This key element for VPH contains the concept of integrative reasoning, where new knowledge is produced by composing models into a new integrative model. However, how can the models be applied as a whole integrated tool, when they are produced in isolation and at a specific level/organ site? How can the validity of basic models be translated into validity of the combination of models, i.e. a hypermodel?

Validation methodology in medical sciences

The central method in medical sciences for testing medical technologies is a clinical trial, which can be defined as a scientific study, or an organised test, of procedures for diagnosing or experimental treatments involving patient and non-patient human volunteers.

Clinical trials are conducted to allow safety and efficacy data to be collected for health interventions:

- These trials can take place only after satisfactory information has been gathered on the quality of the nonclinical safety.
- Health outcomes are measured primarily in terms of changes in mortality (death rate) or morbidity (disease rate).

[19] How accurately the technology can estimate a quantity, while it is used under the most ideal conditions, i.e. in laboratory conditions. For predictive models based on mathematical formulations solved numerically, the inherent accuracy is determined through verification, sensitivity analysis, and validation (V&SA&V).

[20] How accurately the technology can estimate a quantity, while the technology is used under clinical conditions.

However, to gain initial acceptance in the clinical world, DP technologies need to be tested for their safe use on patients with pre-clinical studies or small phase 1 clinical trials. Furthermore, the use of DP technologies in healthcare does not absolve physicians and other healthcare workers of liability for care decisions; liability is a major concern, it can be a roadblock to technology adoption. Validation, in this sense, forces DP developers to incorporate a higher standard of reliability. Long-term impacts on the legal standards of care have to be considered, yet it is only one approach to improve trust by formal medical clearance procedures DP technologies should undergo. Answers of legal nature have to be found the question if the existence of the technology changes what is legally expected of physicians.

Validation and technology assessment

A research-roadmap-driven taxonomy with a deployment perspective should provide an initial structure for identifying respective so-called technology readiness level of a technology, and assessment approaches deemed appropriate and applicable at the various development and innovation stages:

- verification and physics-based validation of simulation models relate to their technical merit (is it feasible/does it "work"?),
- a socio-economic assessment perspective facilitates the development and testing of clinical application scenarios,

For evidence-informed implementation and diffusion decisions, the assessment taxonomy should further be complemented by:

- clinical efficacy assessment,
- clinical validation,
- dynamic benefit-cost modelling, reflecting value-propositions for key stakeholders involved,
- development of successful exploitation plans and business models.

2.4.2 Clinical acceptance and adoption

The regulatory approval of DP technologies, their integration into the EHR systems and clinical applications, and appropriate authorisations and access to EHR data, are all pre-conditions to their deployment into clinical care and patient self-management settings. However there are other important steps that need to be taken before a DP solution can actively be used to inform clinical or lifestyle decisions, to support team communications or to educate. Necessary steps for clinical acceptance that have surfaced from interactions with different stakeholders so far include:

- Identifying the EHR information feeds that are likely to provide the best quality data to populate DP models
- Measuring the robustness of the models in the event of missing or poor quality data
- Determining the precise clinical scenarios in which a given DP model or Avatar is suitable, and when it is not suitable to be used (e.g. if the model is only suited to patients within a certain age range, to conditions of a particular severity, if co-morbidities can be accommodated etc)
- How DP advice or predictions are to be used alongside other information and knowledge sources that are currently used to make the same decisions
- If the use of DP solutions are acceptable to clinicians and patients from a usability point of view

- If DP-informed decisions result in any alteration to clinical outcomes (hopefully favourably)
- If DP technologies are cost effective

Some of these questions might be explored via workshops, usability testing, safety testing etc. Others will require formal clinical trials along the same design principles as for any other healthcare intervention. Economic (cost benefit) analyses will also be needed.

Unfortunately, since most of the budget supporting VPH research is for primary development (R&D, with more emphasis on the R), and since without initial evidence of benefit health services are unlikely to fund large scale studies, there is no clear sponsor for the necessary clinical evaluations to generate trust and enable wide scale adoption.

Clinicians taking part in the first Consultation Workshop in Barcelona unequivocally identified **evidence of rigorous validation as a pivotal component of the pathway to their adoption** of DP technology in the clinic. This ***translational research gap*** requires urgent attention from funding bodies such as the European Commission.

Clearly this introduces an alarming degree of uncertainty into the translation of these tools to the DP paradigm. 'Digital patient' tools will have a difficult path for clinical uptake, as they are dependent on adoption on the basis of their own merit and being able to overcome the administrative and regulatory barriers in place in order to deploy them. Moreover, even when the DP technology is able to pass these hurdles, it still may not be embraced by the clinical community. There is no evidence that technology translation and clinical acceptance will occur by itself. On the contrary, anecdotal evidence suggests that this process needs to be managed if it is to be successful. There are many good reasons as to why research tools might not be welcomed by clinicians. This raises important questions... 'What is required of research software if it is to be acceptable to the clinic? How should it be configured if it is to stand any chance of clinical adoption? What hurdles need to be overcome, what processes engaged, which standards adopted before a tool can be considered 'clinically acceptable'? And very importantly: how can we ensure that all tools and models used in DP research and DP/VPH related repositories are properly validated if they do not belong to any clear-cut regulatory category?

Additionally, the lifecycle model of DP technology must recognise and implement 'adoption models'. The process of adoption over time is likely to be described by a classical normal distribution. Following the description technology diffusion mode proposed by [Beal, Rogers and Bohlen][21] the first group of people to use this technology (called "innovators") are the ones performing the research, followed by "early adopters." Next come the early and late majority, and the last group to eventually adopt a product are called "laggards." If we follow this, then the DP technology will soon need to find a way to identify *flagship products* and *key players, hospitals and industries* that will champion these. Strategic cooperation agreements at a high level might be the way forward.

[21] Beal, George M., Everett M. Rogers, and Joe M. Bohlen (1957) "Validity of the concept of stages in the adoption process." Rural Sociology 22(2):166–168

2.4.3 The business perspective

2.4.3.1 Developing awareness for and creating a business perspective

To facilitate reaching the demanding objectives, it was emphasised that it is imperative to not only raise awareness, but also to identify clear priorities for further model and CDSS development, such as putting a focus on support for prevention – where, at the same time, it was acknowledged that it may be difficult to identify a business-case providing a win-win situation for all stakeholders.

2.4.3.2 Assessing socio-economic benefits and costs

To approach and achieve such goals, the VPH Community acknowledged its responsibility to raise awareness of issues related to exploitation, which in turn needs the development of business cases and the undertaking of business planning exercises.

VPH technology will have to meet two key challenges *en route* to routine clinical application: it has to prove both its clinical and socio-economic benefits, and it needs sustainable business models. More and more, funding agencies will require such activities as an integral part of ongoing research to ensure that the output will indeed meet the needs of clinical users, the health system, industry, and society.

In biomedical research, methods assessing the clinical and socio-economic impact of complex technologies such as multi-scale computer modelling of human physiology have rarely, if ever, been applied. However, to build a realistic business case for future exploitation of VPH results and outcomes, like the VPH Avatar, such information is indispensible.

Whereas conventional health technology assessment (HTA) is usually only applied to incre-mental, almost established technological innovations (which are studied as a well-defined alternative intervention at specific decision-points in a treatment algorithm), VPH technology may lead to the complete transformation of diagnosis and treatment pathways and thus of the relevant Clinical Guidelines. The assessment of such complex, multi-faceted health technology innovations during their early phases of development will also require innovation in clinical and socio-economic impact assessment.

2.4.3.3 Business models

Such approaches will, at the same time, ensure a well-founded and structured framework for collecting key data needed to develop the business case and sustainable business models for healthcare provider organisations as well as industry. At the end of the academic and laboratory development phase, industry will have to take over and deliver the complex integrated systems that will ultimately be needed to render VPH technology a not only viable, but also a highly beneficial alternative to present medico-technical solutions. The reliable, theory-guided collection of financial and non-financial data on benefits, costs and risks, on impacts perceived by clinical users, patients, healthcare providers and payers, on required organisational and behavioural changes etc, and their acceptance to key participants will pave the way towards defining the business case and identifying appropriate business models.

A core suggestion made during the workshop was to consider developing the DP as an open platform, which constantly grows through contributions by the global VPH com-munity at large, like other Open Source endeavours. Anyhow, it will never be a single-purpose finished product, tool, or service, but rather a dynamic, multi-purpose platform build on a central concept and kernel, but open for multiple application purposes adapting over time to new (clinical) needs as well as to new technical opportunities. By building in feed-back loops and options to integrate new knowledge created by applying the Avatar to real patients, it could become a kind of self-learning system.

Market analyses to assess, from an individual actor perspective, the longer term business potential and the related development of exploitation strategies were mentioned as measures to support the translation, commercialisation and diffusion of 'disruptive' VPH technologies. To extract value from an innovation, a project like creating the VPH Digital Patient needs an appropriate business model. At this stage it is too early to specify distinct business models which deliver added value to customers or clients. But business modelling will need to become an inherent dimension in the socio-economic impact assessment framework of future activities. The involvement of industrial partners in research consortia will strongly support this perspective and facilitate eventual exploitation.

A further analytical dimension noticed concerns the 'business' case at the societal level. Empirical evidence shows that in many, if not most, instances new system technologies do not necessarily imply a win-win situation for all participants, but rather that some of them may lose, and (if they have a powerful position within the healthcare system) may even act as so-called 'veto players' being able to block innovations in spite of their overall convincing return to society. It is to be expected that disruptive VPH technologies may fall into such a category, requiring complex interventions at the health system level and compensation for those who otherwise may be able to block diffusion.

One of the major goals behind future exploitation perspectives for the DP must be to elucidate the market and clinical potential of both its core platform and its multiple application purposes – like serving as interface to access and present VPH models and infrastructures. This implies that as part of its roadmap DISCIPULUS needs to gain a first rough over-view of the market segments and stakeholders it may cater to.

Needless to say that priority applications of DISCIPULUS are to be explored in future tasks as discussed earlier. In addition, we need to assume that no single market exists for such an Avatar; rather one may expect that there exist or can be developed a multitude of different markets, each with its own and unique market features and forces, The upturn, on the other hand, resides in exactly the very chance to eventually create new demand and hence a market, and exploit successfully the commercial opportunities that innovative healthcare solutions can have the power to offer.

In particular, necessary steps envisaged are the need to explore in some detail the potential impact on, value propositions for and exploitation opportunities with respect to these stake-holder groups:

- Scientific/academic stakeholders and communities
- Clinical stakeholders
- Industrial stakeholders

3 Towards recommendations for R&D actions

3.1 First consultation meeting with clinicians and other stakeholders: results

The following material summarises the discussions in seven breakout groups and fishbowl discussions that took place during the First Consultation Workshop in Barcelona in March 2012. The focus of this summary is the relevance to, and adoption by, clinicians of the VPH and the future Digital Patient.

The discussion on 'data' spans a technological and clinical dimension. Although there is a great deal of discussion about 'data', in reality, there is 'data' and 'information'. Although both terms are used interchangeably, they mean different things. Both data and information are types of knowledge or something used to attain knowledge. There are many differences between the meanings of these two words.

Data refers to the lowest abstract or a raw input which when processed or arranged makes meaningful output. It is the group or chunks that represent quantitative and qualitative attributes pertaining to variables. Information is usually the processed outcome of data. More specifically speaking, it is derived from data. Information is hence *a concept*.

In a clinical setting, information is the interpretation of raw data but it could also be a mental stimulus, perception, representation, knowledge, or even an instruction. Information can be explained as any kind of understanding or knowledge that can be exchanged with people. It can be about facts, things, concepts, or anything relevant to the topic concerned.

Data are facts, analysis, or statistics. In computer terms, symbols, characters, images, or numbers are data. In the clinical domain these can be for example, lab analysis, free text, images or even pictures. A collection of these data, which conveys some meaningful idea, is information. It may provide answers to questions like who, which, when, why, what, and how. These are the inputs for the system to give a meaningful interpretation. In other words, data in a meaningful form is information. If data is at the lowest level in the series, information is placed at the next step. Information is obtained is a result of analysis, communication, or investigation.

The inputs that will be brought together to deliver the DP, for example as an Avatar or in the knowledge blender, include both data and information, such as, the patient clinical and family history, image data, genetics, biomarkers, lifestyle and environmental factors, literature/peer review, databases public/private and clinical experience.

There is great need to have DP quality data but also, to have tools able to analyse the 'raw' data and to include in the mix the experience and knowledge of the clinicians and patients' history (both expressed as a narrative rather than hard facts). There is a chasm between the analytic approaches applied in the hard sciences vs. the semi-empirical approach used in the medical profession. Although doctors use hard facts to help in their decision-making process, there is a great deal of information that is encapsulated in the 'experience' box. However, in order to achieve a hyper-sophisticated clinical decision support system (the 'medical avatar'), both approaches will need to meet in the middle. Since knowledge is by definition, incomplete, we will need to find a way to fill in the gaps by incorporating 'experience' in the medical avatar.

Whilst not the main target of the consultation process the discussions identified significant enthusiasm for developing the DP Avatar as an educational tool.

The VPH Network of Excellence and VPH-MIP have already begun to address the potential exploitation of VPH Technology in training applications. Feedback, at this stage, suggests that funding for educational uses of DP technologies, perhaps as part of the exploitation plans, in future projects would be well received.

From the industry perspective, VPH is a fascinating area taking into account that the technology is available to be applied into the DP. Industry should provide an integrative decision support tool, which is able to test different scenarios. As a first step the emphasis should be on acquiring enough data to be populate the DP. Once the data is acquired quality must be assessed and industry should also concentrate on how to present the information, making clear to clinicians with the limits of accuracy of the information. Also the information should be made accessible for interdisciplinary teams, taking into account the end-user needs and focusing on usability. One of the main problems we are facing is the fact that since the extent of maturity of VPH and DP is very low; this is inevitably perceived by industry as a long-term objective, hence immediate investment remains low.

3.1.1.1 What are the opportunities for DP technologies

Understanding the Technology

Technologies like VPHOP, @neurIST, MySpine, euHeart and PreDICT were discussed.

The majority of attendees at the Workshop were familiar with one or more of these technologies and how they operated.

It was proposed that before considering the potential use of VPH, the electronic health record (HER) interoperability standards need to be considered.

The importance of the issue of patient consent for use of their data, its accessibility for the purpose of VPH research and the related legal considerations were discussed. There was a strong emphasis on the need to invest time, energy and money to address these issues in order to speed up the process of patient consent and involvement for the progress of research projects.

It was suggested that there were a large number of models and algorithms but the processes needed for the path from model to clinical practice had yet to be addressed.

What data is going to come together here?

- Image Data
- Patient History
- Genetics
- Lifestyle
- Literature/peer review
- Databases public/private

Discussion of clinical scenario examples

1. Clinical scenario - Stroke

Stroke is currently the second leading cause of death in the Western world ranking after heart disease and before cancer and causes 10% of deaths worldwide. It has a strong social impact as the disability it brings affects not only the patient and their family members but also society. For strokes, prevention is the key: with the right tools it could be possible to anticipate the problem.

Current clinical practice is to collect information from EGCs, duplex scans, MRI, cardiovascular investigations and other tests. The cases are then discussed at multi-disciplinary meetings attended by clinicians from different specialities, to which each brings their own specific knowledge, so as to be able to make a better decision. It is important to understand the whole patient history by gathering; clinical data, genetic data, environmental factors, complaints, imaging etc and developing an avatar of this patient. Once all this information is available doctors will make an assessment. At present, largely due to lack of infrastructural support and time pressures, it is very difficult to identify patterns, and the data is not available at the moment it is needed.

Current challenges:

- modelling challenges
- molecular biology should be considered
- some data are difficult to grasp such as patient complaints and the treatment outcomes (Is the patient going back to work after the intervention? Are they able to live a normal life?)

- Neuropsychological aspects are very difficult to represent digitally

2. Clinical scenario - Breast Cancer

Breast cancer (malignant breast neoplasm) is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk.

The decisions are:

- Which images need to be taken
- To collect data – size of tumour, imaging and so on.
- To decide on surgical treatment - when to perform surgery.
- To decide on what other treatment they should they have
- The clinician needs to decide - How often do I need to see this patient? (they need to know the risk)

The introduction of modelling into the clinic will improve slowly but steadily.

The system creates a risk classification – the patient is classified according to risk

We need models to fit the data and to place it in relation with other data and we need ways to put data into the system (does the patient speak the truth?)

If all the data was available, clinicians could filter the population at risk first and then apply 2nd stage diagnostic screening (blood sample, genetics). As a next step the probability of disease could be predicted – with imaging => integrate VPH approach into prediction of disease (= decision support).

Finding an example where a technology could be useful in Clinical Practice

Model nominated: VPHOP - The Osteoporotic Virtual Physiological Human

The VPHOP research project worked to develop, validate and deploy the next generation of technology to predict the absolute risk of fracture in patients with low bone mass, thereby enabling clinicians to provide better prognoses and to implement more effective treatment strategies (both pharmacological and interventional).

Clinical area for application: osteoporosis patients requiring drug treatment or surgery. It is envisaged that this could be used preventively as well as therapeutically.

The clinician needs to make the following decisions:

- Prediction of bone fracture
- Decision of operating therapeutic as well as preventive surgery.
- Anti-osteoporotic drug treatment …preventive measure for fracture and bone pain.

What is their ability to make rapid decisions tailored to the specific patient?

The clinicians require computational resources for imaging and simulations tailored to the specific patient.

How able is the clinician to integrate clinically-relevant information/knowledge from a variety of sources?

At present, such integration is very difficult and time consuming. Integration with other relevant information like activity level and stress level/factors is also necessary. There is a need for a tool to integrate medical, biological, lifestyle and social information.

What kinds of cross-speciality communication is involved? How easy is it for the clinician to take a systemic perspective?

- Radiology/Imaging
- Pathology
- Physiotherapy
- Biotechnology and biomechanics
- Prosthetic device manufacturers

Opportunities for the technology to enhance or replace what already exists in orthopaedic clinics

- The VPHOP technology may be introduced into orthopaedic clinics.
- Update/integrate medical education accordingly.
- This will take imaging to another level of simulations/integration with other relevant information
- E.g., a 60 year old female with advanced osteoporosis. Should you start anti-osteoporotic drug treatment?
- E.g., 72 year old female with severe osteoporosis with a history of falls. Should she undergo preventive surgery for hip replacement/hemiarthroplasty of the hip?
- Model can also possibly guide physiotherapists/occupational therapists.

How models can help in medicine:

- Common access to information collected in other specialisms.
- Provide information about other pathologies that the patient may have, but that are outside the domain of the specialty.
- Automatically generate comparisons of quantities over time.
- To predict the onset of a problem.
- Integrate information gathering to reduce the duplication of testing or use prediction to replace tests, especially invasive tests.
- A model which can help by advising which treatment may be most effective
- Predicting the progression of the pathology.
- The explanation and understanding of the condition: Visual communication, e.g. the effect of treatment on the function of the heart.
- A simulation to 'tune' treatment.
- Plug-in models for each of the different organs, interfacing with each other, and coupled.
- Comorbidity and risk prediction for future pathologies.
- Tools to save time, which can integrate and link data.

What would industry be interested in?

- Tools for tailor-made (patient specific) devices.
- Needs to be a benefit assessment in order to get uptake and investment (in a new technology).

- There is an opportunity to use models to speed up the benefit assessment process for medical devices, and treatments.
- Reduce, but not replace, the need for extensive animal testing, and the need for animal trials.

Can modelling change the healthcare paradigm?

- There is a need for standardisation and sharing of patient data.
- It is the glue which binds diverse information.
- There is a risk of isolated adoption, where clinics/hospitals introduce software ad-hoc.
- It is difficult to envisage a system-wide adoption, particularly in some countries (e.g. Spain), where a risk of disruption to current practice, or an aversion to change exists.
- We need to find a way of providing more useful information. The target should be to provide an environment to support decision making, not a decision system.
- Scientists need a clear specification for the technology to be produced.
- Can experience be generalised? Can we translate experience into mathematical equations?

3.1.1.2 Feedback of issues

Medical/Clinical

1. "The idea, work in progress and future prospects of VPH should be introduced in Medical Education" (Lecturer in Medicine from Sheffield)
2. "See it as positive step towards integration of clinical data, genetics, physiological models, and its application in relevant clinical problems" (CHIME, UCL researcher)
3. Benefit for training in medicine.
4. "Repository for digital images shall have scope/need for computational modelling of the images. These computational models could be part of VPH" (Medical student)
5. Clinicians in different part of the world came to the similar conclusion that it is possible to capture this value into a computerized system. Time is changing: before patients come to the clinic we should have all the images, all the patient info collected and only in a second stage meet the patient in person (vascular surgeon at UCL Hospital).
6. Clinicians are interested in easily accessible integrated data that would be complete and reliable. Prevention, early diagnosis, correct treatment, avoiding complications and knowledge of prognosis are the key factors (clinician from DG).

Industry

1. "I see it as a business idea" (IBOS representative).
2. "VPH is a fascinating area taking into account the technology is available to be applied into the DP" (MK representative).
3. Unlike other industry sectors where the spend is close to 10%, at present, only between 2-4% of the healthcare budget is spent on IT. This means that there

is a huge potential for introducing technology in our field in order to improve quality indicators, processes and to achieve a high socioeconomic impact in global terms.

4. "Industry should provide an integrative decision support tool, which is able to test different scenarios. As a first step industry should concentrate in acquiring enough data to be put into the digital patient (such as blood flow, fluid structure interaction, estimation on the tissue properties of the vessel walls….) using imaging but also different techniques" (SIEMENS).
5. Once data is acquired we should assess its quality.
6. "We see the DP as a decision support system. Once collected all the data, industry should also concentrate on how you present them, making clear to clinicians what to do with the information. Also the information should be made accessible for interdisciplinary teams" (PHILIPS)
7. In this process it needs to be very clear what clinicians need, how they need to visualize the info, what measure parameters they need.
8. "The key aspect is usability". In order to help clinicians in the decisional process a clinician forum could be created to collect different point of view based on the real life data. One of the main problems we are facing is the fact that since the extent of maturity of VPH and DP is very low; this implies that low investment is expected to happen at least from the industry point of view.
9. "How can we make the outcome of this technology valuable? We need to validate the models before they can be used in the real clinical setting" (Siemens Corporate Research).
10. "How do you get clinicians to understand there is a missing mile from the development of the technology to its adoption into the clinical practice? "(AMC Research Council)
11. "How to develop a business model: how can a product be put in the market? How can we earn money out of it?" (KUL)
12. From the clinical perspective "hospital management also needs to be involved" (HTK representative).
13. A key factor of the VPH technologies success is their adoption in the clinical practice" (Vice President of Philips Research).
14. A joint venture between clinicians/researchers and the industry for the co-creation of meaningful products is the best way forward (Vice President of Philips Research).
15. "I am concerned about the VPH technologies benefits as at this stage they are not very clear. We need examples to prove the adoption of these technologies can be good in other fields, that there is real value in order to convince people to invest in this area" (Toshiba representative).
16. "There is a deluge of data, there is a lot coming in, but not all of it is correct. Need to make good technology that will benefit clinician and provide intelligence storage and IT that is able to archive and handle data over time. Stakeholders need to work together" (IBM representative).

Research

1. "How comfortable are we (clinicians/researchers) with the simulations and their application?" Their concern is reliability and acceptability and the rate of adoption? (Researcher in biomechanics from Sheffield).
2. Various kinds of imaging integrated with e individual patients clinical data would provide the updated and integrated view of digital patient.

Insurance companies

1. Insurance companies are interested in prevention.
2. Aid in identification of underlying factors/predisposing factors for a disease would help prevention of the same.
3. Early diagnosis and treatment can prevent complications.

Pharmaceutical companies

1. Pharmaceutical companies have finances.
2. They are interested in selling drugs.
3. They need to meet regulatory requirements.
4. They may be forced to collect more population health information to meet regulatory requirements.

Summarising the feedback

What do clinicians need?

In this process it needs to be very clear what clinicians need, how they need to visualize the information and what parameter measures they need. The key aspect is usability. Surgeons want a simple tool based on statistics. The decision-making time is very limited, so the interpretation of the data should be as simple as possible. Feedback is required to help the system learn. There needs to be a continuous cycle of self-learning, on-going development, needs-policing and checking.

How could industry contribute to the process of building the digital patient?

Industry should provide an integrative decision support tool which is able to test different scenarios. As a first step industry should concentrate in acquiring enough data to be put into the digital patient (such as blood flow, fluid structure interaction, estimation on the tissue properties of the vessel walls) by using imaging but also different techniques. Once data is acquired we should assess its quality and how you present them, making clear to clinicians what to do with the information. Also the information should be made accessible for interdisciplinary teams.

The Opportunities

- The digital patient technologies could be useful for rapid decision making, the example given was a prediction of tissue death after myocardial infarction. In this case a sufficiently fast model could determine if stenting or bypass is needed.
- As a tool for understanding the features of complex diseases. For example a parametric analysis of the components of a model can help a clinician to get a feel for the impact that various disease features have.
- The DP represents an opportunity to move from risk-factor parameters to a mechanistic prediction. The example given: currently ventricular size is used as a

surrogate measure for heart function, but we would get more important/direct information if we simulate the haemodynamics, and obtain measures such as flow rates, pressures, etc.

- For the insurance industry, models can help to improve the prediction of likelihood of hospitalisation, which currently relies on epidemiology. This is especially true as models become more integrated, and hence a cardiovascular model, say, could influence an Alzheimer's model.
- There is a clear opportunity for the DP as learning and training tool, for medical students and new scientific researchers.
- There are two economic drivers: avoiding treatments that are likely to fail, and so avoid and delays and side effects and outcome-based reimbursement of treatment

The Challenges

- Any predictive model used for decision-making must be shown to be equally good as, or better than, current clinical practice and be validated and trustworthy. For clinicians relying on these models it will be essential that issues of liability are addressed.
- How can the models be applied as a whole integrated tool, when they are produced in isolation and at a specific level/organ site?
- The challenge of validating multi-model simulations was noted.
- As an example of the IT challenge facing healthcare, it is reported from one cardiology department in a paediatric hospital that 15TB of data are generated each year.
- Any DP technologies must be adaptable to the requirements of different users. Many clinicians will have different needs, even within the same specialisms. This is also true for different countries/institutions, which use different data systems, protocols, etc. It was suggested that they should be adaptable at the user-interface level, i.e. that tools could be tailored.
- The new tools, which come from DP, should integrate with current interfaces as much as possible.
- How do we manage to introduce the DP in hospitals?
- How do we identify the early adopters and how do we integrate them in the community?
- Initial cost may increase, but social care cost may decrease. Overall budget needs to be considered

Action Points

- The benefits (in terms of general patient health) should be established first, preferably on the specific models, before integration.
- There should be a focus on patient needs based on a formal process of benefit assessment.
- The definition of, and requirements for, validation should be explored extensively. Formal clinical validation (i.e. a clinical trial) may not be necessary, for example, when using tools for learning and understanding.
- Communication between 'tribes' is not optimal, and could be improved by a greater understanding of each other's language. In particular, the step of

specification of needs for the technology is critical. This requires clinical input at an early stage.

- Demonstrator projects would be required to prove its validity.
- To extract the data it needs to process from existing EHR systems, first the EHR interoperability between existing systems will need to be sorted.
- The data that is stored and its analyses and evidence can be used as basis to inform development of apps and other technologies. In building the trust – as soon as the physician has more knowledge he has the trust. Therefore we need to enable the physician to have access to correct and required information.
- Education on how to access the information, its evidence base and references.
- Clinical phases/trials will need to be funded, estimated cost - few million Euros.
- Suggestion: there needs to be industrial partner involvement
- The following indicators have to be accomplished: efficacy, safety, speed, clinical accountability, clinical validation on large set of patients, medical clearance, clinician personalization (feeding in clinician's own practice experience) and standardization of data formats (so that it is exchangeable and readable in other systems).

3.2 Next steps

The evolving DP roadmap draws upon the outcomes of all other workpackages. Concrete clinical scenarios are being developed with clinicians, including what data sources would need to be integrated, what decisions will need to be made, and what kinds of DP solution might be helpful (WP3: Clinical Acceptance, Translation and Exploitation). This will help guide development of illustrative Avatar materials within the scientific/technological challenges workpackage (WP2: Identification of Scientific and Technological Challenges).

In other words, the technological agenda will be developed top-down, from the maturity levels, down to core technologies needed. Clinical examples will be used as test-benches for the relevance of the technological discussion.

The clinical agenda will be developed bottom-up from examples of clinical applications clustered into macro-groups. The technology descriptions will provide a feasibility framework to the clinical applications discussion.

Emphasis will be put on understanding the data sources needed to feed the DP Avatar, their availability and quality; how multi-professional clinical decisions utilising the DP will be best captured, preserved and shared; identifying the requirements and constraints for successful use in clinical care and for patient empowerment.

As a next step, the consortium is working with the clinicians who have expressed interest in supporting the road mapping process to further develop in detail clinical use scenarios (through meetings, clinician interviews, online wiki). The resulting clinical case storyboards will help promote the potential of the DP to a wider audience.

DISCIPULUS is using a dedicated forum to engage the scientific community in prioritising the key open issues identified for further R&D, and identifying the key actors that need to get involved (incl. also interface research community, health ICT, etc.) in order to develop concrete recommendations for R&D actions in Europe and globally. For more information on the process, please refer to WP4, D4.1 "Community Building Work-plan".

Main issues to discuss over the coming months can be summarised as follows:

Open issues / priorities	What to address first, prerequisites	Actions needed	Tools, resources required	Whom to involve	Structures, processes needed	Drivers & facilitators	Barriers	Timeline

The key areas for targeted research to advance the capability and functionality of Digital Patient representations will be defined with respect to both inter-mediate and longer-term milestones.