



ARGOS – VPH Position paper¹

Rationale

This document will provide the basis for the policy brief that will be produced as a result of the ARGOS project. Whereas the policy brief will target the policy makers, the present document targets the community of academic, clinical, and industrial stakeholders of the VPH initiative. The primary difference is the language: here we use a technical language, whereas the policy paper will use more broadly understood language.

eHealth 2020: a vision of the future of cyber-enhanced healthcare

Context

The penetration of Information Technology (IT) in healthcare has been slower than in other domains, but as in other domains is the integration of IT will in the long run become inevitable and, according to many observers, pervasive. We are moving toward a time when everything in our life will involve information technology, including every aspect of the healthcare process.

Currently, information technology is present in healthcare in three distinct and largely independent manifestations:

- *Medical informatics* deals primarily with the management of the information inside healthcare organizations. Historically IT penetrated hospitals first on the administrative side, and from there it spread to the management of any information in the hospital, including clinical information. It is the most established and mature branch of what has become known in Europe and Canada as eHealth and is often known in the U.S. as Healthcare Informatics.
- *Bioinformatics* deals primarily with the use of IT for data integration, query and analysis in molecular biology and genomics, where it is used not only to manage the information, but also to mine and analyze biological data to generate new knowledge and hypotheses. Developed in the context of biomedical scientific research, bioinformatics has evolved independently of medical informatics. With the emerging use of genomic and proteomic measurements in healthcare, new concepts of *clinical bioinformatics* or *biomedical informatics* are receiving emphasis in academic medical centers².
- *Computer-Aided Medicine* deals with the use of computing directly within healthcare delivery systems. Computers are now widely used in prevention, diagnosis, prognosis, treatment planning and execution, monitoring, rehabilitation, and assisted living. Exciting research horizons of computer-aided medicine are arising from the use of predictive computational models in the delivery of personalized healthcare. In particular, the notion of using predictive models as repositories of knowledge on human physiopathology opens up entirely new possibilities for knowledge and information integration, and the promise of more fully integrated approaches to patient care as well as accelerated development of new diagnostics, devices and therapeutics. In this vision, computer-aided medicine is moving closer to bridging medical informatics with bioinformatics, suggesting a future in which all these terms may be replaced by the broader eHealth concept, in which IT tools are used to integrate all the available data, information,

¹ This project is funded by the European Union within the framework of the Pilot Project on Transatlantic Methods for Handling Global Challenges in the European Union and the United States. The general objective of the Pilot Project, created through a European Parliament initiative, is to promote mutual understanding and learning among EU and US policy researchers and policymakers on a number of challenges with a global dimension.

² Witness, for example, the new Clinical Translational Science Awards made recently by the NIH (<http://www.ctsaweb.org/>)

knowledge and accumulated experience on patient health, in order to provide more *personalized, predictive, and integrative healthcare*.

Let's go digital

We can expect by 2020 to see the complete digitalization of essentially all healthcare information, at least in the developed world. Despite the costs involved, the lack of a digital information workflow within the healthcare enterprise will eventually incur a much higher cost in the effectiveness of healthcare delivery, which could threaten to create a *digital divide* between fully digital healthcare providers that will benefit from this integration trend, and those that are not. This issue could be amplified by the increasing demand from patients for secure online access to personal health records. By 2020, the elderly population will comprise citizens who retired in the '90s or later, the vast majority of whom will expect to have the same degree of digital access to all their health information as they do for all their other personal information.

Investments in healthcare IT in the next few years must account for the trend toward **integration of all available data**, and they should emphasize solutions that facilitate integration; the idea that the information system of a hospital is an island, isolated from the rest of the digital world, is becoming untenable.

Let's get personal

Modern medical science is all about populations. The diagnostic signs of a disease, the efficacies of a drug, the appropriateness or the risks associated to a therapy, are always defined over populations and then applied to individuals.

But as our therapies become more and more targeted to increasingly complex pathological mechanisms, the best option for an individual patient is a balance between opposing factors; what is effective for most patients might not be for every individual.

The solution is personalization of therapy. While popular literature emphasizes customization of diagnosis and pharmacological treatment on based on the patient's genome, effective personalization will require that every event in the provision of healthcare be informed by all relevant patient-specific data. Suffice to say, the **integration of all available information** on the patient will be necessary.

Explanation-based medicine

Everyone can hold unsubstantiated beliefs; but in science, we consider only opinions that are supported by reproducible observations (evidence). This is why, in its slow transformation from art to science, medicine has sought become "evidence-based". Evidence is necessary but not sufficient: we say to know something only when we can explain *why* what we observe is happening. This is the next Holy Grail: *explanation-based medicine*.

The best way to confirm (or refute) a theory is still largely debated. But following Karl Popper's logical positivism, a well accepted strategy is to attempt to falsify the theory as systematically as possible, and consider every un-falsified theory at best temporarily valid. In this light, the best possible way to express a theory is that which makes the falsification process as straightforward as possible. Quantitative predictive models are among the most falsifiable ways to represent a theory, and this is why we think that the future of explanation-based medicine will require quantitative and personalised *predictive* models. Far from replacing the cornerstone of evidence-based medicine, the clinical trial, the use of predictive models will also inform clinical trial design and improve the interpretation of trial data in the context of the individual patient and patient-to-patient variability.

The use of predictive modeling is already common practice in many other domains: to know if an airplane is safe we do not crash thousands of airplanes under all possible conditions; we make models

of all airplane systems, validate them by attempting multiple falsifications with controlled experiments, and then use them to predict how safe the airplane will be under a wide range of conditions. And it works well.

While a human body as a whole is vastly more complex and variable than an airplane, some physiological functions of the human body are already predicted with very good accuracy under widely varying conditions using computer models. As the power of our computers and the sophistication of our models increase, it is reasonable to expect that in a few years personalised computer models will reliably predict a variety of clinically relevant scenarios.

But a problem remains. Most relevant physiological and pathological processes that we study emerge from complex systematic interaction between components of complex networks and systems that operate over widely divergent space and time scales. It is popularly appreciated that the effect of a coding error in the DNA molecule can produce changes in cells, that result in alterations in the tissues, that influence the organs, and in turn affect the whole organism. But we are also starting to observe many “inverse causation” mechanisms, where what happens at the organism level, interacts downward producing changes at the molecular scale, i.e. affecting the expression genes, and their translation into proteins. Even if we can make computer models that accurately predict the behaviour of the molecule, cell, tissue, organ, and organism, it will only be when we combine all these models to **integrate all the knowledge that** each model contains, that these complex systemic processes can be predicted.

Integration will rule them all

At the root of this revolution is the integration of available, data, information, and knowledge. Thus, **the key element of eHealth 2020 is integration**. We need to integrate data, metadata, and models stored in whatever location, in whatever format, in whatever size and complexity. We need to make the results accessible by anyone from everywhere and through whatever IT interface. And we need to do this without compromising the security, confidentiality, and integrity of personal health information, among the most sensitive information IT systems can treat.

But this trend for integration acts also on other axes. One very important axis is the integration between biomedical research and clinical medicine. This relationship is already close, but the vision of explanation-based medicine requires that this relationship becomes even closer. In particular, it would be enabling if biomedical information obtained during routine care could be integrated with data from clinical research.

Another related aspect is the integration of skills, to cope with the increased complexity of diagnosis and disease management and avoid the need for excessive specialization. While the body of knowledge will continue to expand, not only in size but also in breadth (i.e. involving knowledge about molecular biology, computer sciences, advanced technologies, etc.), there is a demand from the many patients for a more holistic approach to their health and welfare, that accounts for all aspects of their health history, life style, etc. The only viable solution is to recognize that the care can be provided now only by a team of professionals, physically remote and culturally heterogeneous..

And the patient? In the centre!

A key concept that is recurring in debates on the future of healthcare delivery is the need to keep the patient at the centre of the information cloud. In reality, the relationship between the patient and the doctor remains the metaphysical core of medicine, which will never be reducible or simplifiable. In relation to age, culture, social status, and geographical location, some patients will always expect to transfer the major part of their health responsibility to their doctor, whereas others will fight to retain total control, even when this is ill-advised. This issue ultimately must balance the needs of the individual with those of society and of the other stakeholders, which often becomes a complex political issue. While technology cannot address these problems, it is reasonable to expect eHealth in 2020 will be able to accommodate the full range of possibilities outlined above.

Example #1: Personalised, Predictive, and Integrative medicine to fight chronic and rare musculoskeletal diseases

The primary function of the musculoskeletal system is to support, protect, and move the body during its interaction with the rest of the physical world. Not surprisingly, the most important chronic (osteoarthritis, osteoporosis) and rare (osteogenesis imperfecta, bone sarcomas, osteopetrosis) disorders impair the ability of the musculoskeletal system to fulfil this function.

The primary objective for computer-based Personalised, Predictive, and Integrative (PPI) medicine in these diseases is the ability to predict how the disease has reduced or will reduce these support, protection and mobility functions, and how pharmacological, surgical, regenerative, and rehabilitative treatments may reduce or eliminate this functional impairment.

Seemingly, the functions of the various organs forming the musculoskeletal system are quite simple: the musculotendinous complexes must contract with the necessary force and speed when activated by their innervations; the bones must withstand internal and external forces without fracturing and without exhibiting excessive deformation; the joints must ensure minimally resisted motion in certain directions, and progressive stiffness in the other directions. However, these apparently simple functions are the result of complex interactions between processes defined at radically different spatiotemporal scales, from the whole body down to the molecular level.

For example in osteogenesis imperfect (OI), an inherited genetic mutation interferes with the ability of many cells to secrete properly formed procollagen proteins, that assemble into the collagen fibres that form all musculoskeletal tissues³. These molecular alterations produce devastating changes in the functional capabilities of the skeleton. Owing to complex coupling mechanisms, bone mineralisation is also impaired. Here the growing ability to model the effects of these molecular changes on the biomechanical properties of the bone tissue, combined with the ability to use medical imaging and anatomical modelling to follow the evolution of the skeleton in OI children opens up new research perspectives, and generates interesting new clinical opportunities.

Or in osteoporosis, where approximately half of the spontaneous fracture we observe in clinical practice can be explained with the progressive alternation of the bone tissue morphology induced by altered cellular activity, whereas the other half require additional cofactors, such a progressive degradation of whole body neuromotor control, that increases the risk of falling, and the risk of overloading the skeleton during normal movements. This alone would require an integration between organism-scale models and organ-scale models, but if we want to account also for the evolution of disease over time, or predict the effects of a pharmacological treatment, we must also model the tissue, cell, and constituents scales, as the evolution of the disease emerges from the systemic interaction of processes observed at all these different scales⁴.

Example #2: Personalised, Predictive, and Integrative medicine to fight chronic and rare cardiovascular diseases

Increasingly sophisticated models of the heart and circulation that integrate from molecular functions to three-dimensional simulation of intact cardiovascular system physiology have started to emerge in recent years. Given that these scales bridge a key gap between bench biology and clinical medicine, we expect to see continued growth in the number and scope of translational applications of multi-scale

³ Gautieri A, Vesentini S, Redaelli A, Buehler MJ. Single molecule effects of osteogenesis imperfecta mutations in tropocollagen protein domains. *Protein Sci.* 2009 Jan;18(1):161-8.

⁴ Cristofolini L, Taddei F, Baleani M, Baruffaldi F, Stea S, Viceconti M. Multiscale investigation of the functional properties of the human femur. *Philos Transact A Math Phys Eng Sci.* 2008 Sep 28;366(1879):3319-41

models in this category including patient-specific modelling for diagnosis and therapy planning in cardiovascular disease.

The origins of these impressive examples in computational cardiovascular biology research are many, but there are at least two important foundations underlying the progress in this field. One is the legacy of Hodgkin and Huxley, whose ionic model of the nerve cell in 1952 became the foundation for systems models of the cardiac muscle cell that appeared as early as 1960⁵ and have been continually extended and enhanced in detail and complexity in close conjunction with experimental studies of cardiac cell biophysics for the past half century. The other is the fact that the primary functions of the heart and circulation are mechanical and have lent themselves to analysis using advanced computational tools developed by engineers and applied mathematician for mechanical, chemical and structural engineering. We would have a much poorer understanding of pressure and flow in the cardiovascular system without the benefit of solving the underlying physical conservation laws (in this case expressed as the Navier-Stokes equations for fluid flow). Today, the availability of detailed non-invasive clinical cardiovascular imaging data from a wide variety of modalities is driving new developments in computational model-based diagnosis and treatment planning such as computational models for predicting and optimizing outcomes of surgical procedures for correcting congenital heart defects, such as the Fontan operation.

In cardiac electrophysiology, biologically detailed multi-scale models of cardiac arrhythmia mechanisms now promise to provide insights into rare life-threatening disorders. For example, a recent multi-scale model based on measurements from oocytes expressing ion channels harbouring a human gene mutation made predictions about whole cell, tissue and organ scale gene mutations⁶. Some of the alterations in the electrocardiogram predicted by this computational model of life-threatening genetic Long-QT Syndrome were actually first reported in human subject⁷ the year *after* the model was published. This is one of the first examples of a computer model predicting a phenotype of a rare genetic disease before it had been recognized clinically.

Congestive heart failure, in contrast, is reaching epidemic proportions in the Western world. In a large fraction of heart failure patients, their condition is complicated by cardiac electrical conduction disorders, leading to dyssynchronous heart failure. Over the past decade, clinical experience has shown cost effective improvements in survival and quality of life in dyssynchronous heart failure patients who receive cardiac resynchronization therapy (CRT), which employs cardiac pacing technology. But a third or more of candidates fail to respond to CRT for reasons that are poorly understood. Teams in the USA, Europe are making excellent progress developing mechanistic patient-specific models intended to help identify CRT candidates and optimize patient outcomes. The continued progress and translation of this research to clinical practice will better require access to clinical data and patient tissue samples together with well-designed clinical trials.

⁵ Noble D (1960) Cardiac action and pacemaker potentials based on the Hodgkin-Huxley equations. *Nature* 188:495-497.

⁶ Saucerman JJ, Healy SN, Belik ME, Puglisi JL, McCulloch AD (2004) Proarrhythmic consequences of a *kcnq1* akap-binding domain mutation. Computational models of whole cells and heterogeneous tissue. *Circ Res* 95:1216-1224.

⁷ Darbar et al. Images in cardiovascular medicine. Himalayan T waves in the congenital long-QT syndrome. *Circulation* (2005) vol. 111 (11) pp. e161

ARGOS Position paper on VPH Research

Cyberinfrastructure for VPH Research

This vision of a personalized, predictive, and integrative medicine will become a reality only when a comprehensive framework of methods and technologies for analyzing organisms as integrated systems has been developed. In Europe, this framework has been sponsored by the European Commission's 7th framework and named the *Virtual Physiological Human*. In the USA, there is no similar coordinated large-scale effort, but similar goals have been articulated in a variety of publications and venues, notably the Multi-Scale Modeling (MSM) consortium of investigators supported by the 8 participating agencies of the Interagency Modeling and Analysis Group (IMAG).

The investments that many European and United States funding agencies are making in this direction are transforming what was formerly the dream of a handful of visionaries into a reality, which is starting to bear fruit. But as the vision of a whole new generation of methods and technologies that enable integrative biomedical research becomes more concrete, concern is also rising in the research community worldwide for the long-term support and viability of the "cyberinfrastructure"⁸ consisting of new tools, services, and data collections that will be needed for the widespread adoption of integrative approaches within the existing research infrastructure.

While the mechanisms exist to maintain the infrastructures already available for biomedical research worldwide, the concern is that the revolutionary nature of the VPH cyberinfrastructure, will require special policies to its long-term sustainability.

In particular three aspects appear of fundamental relevance: *maintenance*, *service*, and *outreach*.

- *Maintenance*: we need to transform the research prototypes developed in the various technological research projects into consolidated resources, through a process of re-engineering, consolidation, standardization, and maintenance. Such activities cannot be supported with the funding mechanisms available from most funding agencies, though there are isolated programs supported by NIH and other agencies for maintaining specific software and data resources. And recently the NSF has recognized this problem through its establishment of the Scientific Software Innovation Institutes.⁹ By their nature in order to be effective there should also be strong international collaboration in these projects.
- *Service*: we need to deploy these consolidated technologies into services that are operated and curated in ways that ensure their persistence, reliability, security, etc. This is an essential requirement if we want the vision of integrative biomedical research, with all its advantages, to percolate deeply into the worldwide practice of research, and into its most relevant clinical applications.
- *Outreach*: motivated organizations must be established and supported not only to operate these services, but also to promote an outreach campaign that: a) ensures the widest possible adoption and utilization of the computational model based research technologies; b) provides training and re-training to researchers and medical professionals in these technologies and methods, to ensure their most effective and appropriate usage; and c) monitors the development and the adoption of information and computational modeling technologies in research and healthcare, providing decision-makers with factual and up-to-date evidence on which to base policy decisions and to communicate the impact of investments made in this domain.

⁸ *Cyberinfrastructure Vision for 21st Century Discovery*, NSF 07-28, March 2007. <http://www.nsf.gov/pubs/2007/nsf0728/index.jsp?org=NSF>

⁹ <http://nsf.gov/si/>

The role of the VPH Cyberinfrastructure in biomedical research

The role that such cyberinfrastructure can play for research is already quite clear. Biomedical research in most of its branches and articulations is progressing toward comprehensive digitization of experimental observations and the associated meta-information; this will make it possible to share with our peers not only the conclusions we draw from such observations, but also the raw data themselves. By speeding up the circulation of data, we can expect a better peer reviewing process, and the reuse of experimental data in new contexts and applications, reducing the costs of research. This process is already under way.

But the VPH vision goes much beyond this. With predictive models it is possible to capture in a digital and reusable form the tentative knowledge we produce as scientists. A global cyberinfrastructure where such models can be accessed, used to elaborate other data, and combined to form an integrative understanding of complex systemic processes could be a real breakthrough for biomedical research.

First of all, it would make possible an effective replication of those studies that involve the use of simulation, a known issue with current publication system where the simple description of the simulation rarely provide enough information to reproduce the experiment and the results reported in the paper. The ability for the community to replicate computational experiments in full, will improve the quality and reliability of simulation-based research.

Secondly, it will make possible the reuse of large bodies of knowledge captured in a shared model by different researchers. This could substantially improve the efficiency of research in those strongly multidisciplinary areas where the circulation of new knowledge is slowed by the burden that the replication of other studies poses in mastering of skills (such programming, algorithm design, physical or chemical modeling, etc) that might not be part of the education of biomedical researchers.

The same reasoning applies when reusable models are combined to describe processes that involve more than one organ system, or many spatial and temporal scales. Owing to the specialization of biomedical research, it is a rare expert in cardiovascular biology that is also well versed in neuroscience or orthopedics for example, despite the critical interactions between these systems. So it should not be a surprise to find out that the vascularization of the bones tissue, in spite of being a vital process both in physiological and pathological conditions, has been poorly investigated to date.

But it is probably the last point the most exciting of all. There is increasingly strong evidence that biological processes are characterized by unexpectedly complex upward and downward causations that link processes and events that occur at radically different space-times scales, across sub-systems, and involving different bodies of knowledge. Consider for example the exploding knowledge on non-coding RNA or epigenetics. In some cases, it is now clear that what we observe is the emergence of the systemic interaction of a complex system; this means that studying any part of the process will never fully explain the observations we make. This realization is also driving the “omic” approach to personalized medicine. Only by studying the system, made of all its parts, will we be able to obtain good explanations of what we observe. But how can this vision of an integrative biomedical research can be done in practice? The VPH cyberinfrastructure will help make it possible to create accurate models of each part of the system, store it in a digital artifact, share it electronically, so as to allow the combination of these parts into models of models (called integrative models) capable of capturing complex systemic interactions that could be otherwise defy intuitive explanation.

The role of the VPH Cyberinfrastructure in clinical practice

The VPH cyberinfrastructure will impact clinical practice in two ways. The first is *clinical decision support*, where Internet-based services based on fully validated integrative models will be used by properly trained clinical users to integrate the data and information available on the patient with the existing knowledge relevant to the clinical problem, which is captured in the integrative model, so as

to provide support and assistance during prevention, diagnosis, prognosis, treatment planning and execution, monitoring, and rehabilitation. Already today, VPH models are being used to help identify responders to cardiac resynchronization therapy and make it a more cost-effective repeatable and reliable treatment for patients with dyssynchronous heart failure. Similar results are being reported in pre-clinical or early clinical trials in other domains such as treatment planning in acute myocardial infarction, diagnosis of the risk of fracture in osteoporosis, model guided ablation of liver tumors, etc.

A second way that the VPH cyberinfrastructure promises to impact clinical practice is via the biomedical therapeutics industries. The large-scale availability of data and models about human physiology and pathology will make it easier to investigate the safety and the efficacy of new medical devices *in silico*, to reduce risks and costs associated with clinical trials. VPH models will also make it easier to test whether modifications to existing therapies might produce unintended consequences. In pharmacology, molecular and cellular modeling are transforming drug discovery. For example, one of the EU VPH projects, PreDICT, is developing an *in-silico* environment to test the risk of cardiotoxicity for new compounds. As the VPH cyberinfrastructure develops, it will become easier and more effective for regulatory authorities to verify that the pre-requisite conditions exist to start new clinical trials, through the availability of standard simulation benchmarks that all products of a given category must pass. Scenarios are also emerging where medical technologies for diagnosis, planning, or treatment are augmented with VPH models that can transform patient data into predictions of the natural history of disease, treatment outcomes, and prognosis. There is now also considerable penetration of population-based modeling in developing clinical guidelines, healthcare policies and designing clinical trials.¹⁰

Impact on the VPH cyberinfrastructure on the other ARGOS topics

The VPH cyberinfrastructure will have to enable the integration of highly diverse biomedical data sets, information and knowledge, including those contained in hospitals PACS and HER systems. This is why the VPH initiative aims to follow closely the standardization efforts of the information contained in electronic health records. On the other hand, the VPH is already now discussing the interoperability of types of data and information that may soon become part of mainstream healthcare, and thus part of the HER; the work VPH does should provide an useful starting point for any extension effort by the HER standardization organisms.

On the problem of quantifying the adoption, usage, and cost-benefit of eHealth technologies, the contribution of the VPH cyberinfrastructure will be primarily related to the development of new health technology assessment approaches that do not have to begin only after the technology is fully deployed, but before when the technology is in the research and development phase. This will help steer public and private research investments towards those approaches that show the highest potential for efficacy and cost benefit.

Benchmarking

If we consider the VPH in general there are three separate indicators that can benchmark the development of this international research initiative:

- a) The number of international peer-reviewed publications on VPH-related research and technology development. This indicator quantifies how important this work is becoming within the research community.

¹⁰ IMAG Futures report, 2010. http://www.imagwiki.org/mediawiki/index.php?title=IFM_Feedback

- b) The number of international peer-reviewed publications targeting biomedical researches where VPH-related technologies were used to unravel relevant research questions. This indicator quantifies the impact of the VPH vision onto biomedical research at large.
- c) The number and size of clinical trials that aim to evaluate the clinical accuracy, clinical efficacy, and clinical impact of VPH-related technologies and services. This indicator quantifies the rate of translation of VPH-derived technologies to clinical practice.
- d) The number and size of VPH-based medical technology products and services that enter the market. This indicator quantifies the level of adoption of VPH-based technologies in clinical practice.

Referring more specifically to the VPH cyberinfrastructure, the success of the initiative can be benchmarked by monitoring the levels of offer and demand:

- a) The number of sites, portals, and services that share as digital artifacts data, information, and knowledge captured into models, concurring the global VPH cyberinfrastructure, as well the number of artifacts that the cyberinfrastructure deploys;
- b) The number of users of the artifacts the VPH cyberinfrastructure distributes, and their number of accesses, clustered by research, clinical and industrial applications.

Governance model

The distributed, international, loosely coupled nature of the VPH Cyberinfrastructure recalls a famous sibling: the Internet. The network of the networks has a governance model that has been revised and adjusted over the years, while enabling the Internet to grow rapidly and flourish beyond all expectation.

With this inspiration, we propose the following governance steps.

1) Establish a Multistakeholder Advisory Group (IS/MAG) to:

- a) Constantly revise the goals of the Cyberinfrastructure;
- b) Promote the development of standards for interoperability and integrability;
- c) Maintain an worldwide research roadmap;
- d) Develop regulatory guidelines and processes in cooperation with regulatory bodies.

Such an advisory group could be established at the very beginning of the initiative, perhaps hosted by the VPH Institute, an international non-profit organization based in Brussels that is being established to foster the development and the best use of the VPH technology.

Its structure would include a master board where all stakeholders are properly represented, and a series of work groups, much like the Internet Engineering Task Force, that would produce technical recommendations and specifications related to the operations of the VPH Cyberinfrastructure.

2) Establish a globally distributed cyberinfrastructure:

- a) Whose backbone is operated by a private no-profit organization;
- b) Whose leaves are voluntarily interconnected cyberinfrastructures operated at regional, state, and/or federal levels.

Essentially, we propose to minimize the role of the centralized authority, delegating this role to a private non-profit organization, designed on the model of @ICANN, that would be responsible to ensure through training, certification, and auditing services that all peripheral nodes of the VPH Cyberinfrastructure correctly comply with the agreed interoperability standards, and provide the global

integration level services such as management of the VPH cyberinfrastructure main portal, and global services such as ID management, directory, namespaces resolution, etc.

Most of the work would be done by the peripheral nodes, which would be operated, governed and funded autonomously by the various local authorities.

3) Commit the financial support

We expect that research funding agencies will initially need to provide financial support for the Cyberinfrastructure, though much of this support might be provided in kind by allocating existing staff and infrastructures, where reorganization plans de-allocate some of them from other mission (i.e. the re-organization of HPC centers that is happening in many countries in relation to the changes in the demand of high-performance computing). However, we also feel that because of the research efficiencies and high translational potential for this research, the Cyberinfrastructure should eventually derive most of its financing from the pharmaceutical, medical device and healthcare industries that benefit from its deployment.

The ARGOS observatory

Presentation

The “Transatlantic Observatory for Meeting Global Health Policy Challenges through ICT-Enabled Solutions” (ARGOS) is a pilot project funded the European Commission / DG RELEX - Relations with the US and Canada. The project is coordinated by the EuroRec Institute for Health Records, and sees the participation of Empirica, Istituto Ortopedico Rizzoli, and the American Medical Informatics Association. Among the contributing organisations are listed the University at Buffalo, Ontology Research Group, the University of California, San Diego, the Certification Commission of Health Information Technology, the European American Business Council, the Center for Information Technology Leadership (CITL), and the American Health Information Management Association.

The overall goal of this Pilot Project is to contribute to establishing a “Transatlantic Observatory for Meeting Global Health Policy Challenges through ICT-Enabled Solutions” in order to develop and promote “Common Methods for Responding to Global eHealth Challenges in the EU and the US”. EU and US care about the global challenges because (a) citizens travel and migrate globally and there is a wish to foster good health-care everywhere (b) the EU and US wish to refine their products to better penetrate global markets (c) experiences and lessons learned globally are useful in Europe and the US. The Observatory will promote mutual understanding and learning among the EU and the US policy researchers and policy makers on the following general challenges with global dimension: (1) Improving health and well-being of citizens through accelerating eHealth strategy development and through supporting large scale eHealth infrastructure implementations; (2) Supporting R&D in eHealth to promote the benefits from the pursuit of consistent strategies.

In the ARGOS project, the following specific target areas will be addressed:

- Interoperability in eHealth and Certification of Electronic Health Record systems (EHRs);
- Definition of a common, consistent approach and Identification of Indicators and tools for measuring the adoption, usage and cost-benefits of eHealth;
- Modelling and simulation of human physiology and diseases with a focus on the Virtual Physiological Human (VPH) and the use of such solutions to support the diagnosis and treatment of rare diseases.

Key outputs for each of the three topics are:

- a comparative analysis of current US and EU approaches;
- workshops in the US and the EU involving the different stakeholder groups;
- interim reports and publications (Policy Briefs: one per target area, three separate brochures) documenting the subprojects’ findings and recommendations (in web- and printed version);
- the “ARGOS project finale” global conference.

ARGOS VPH activity

The activity relative to the VPH topic will be coordinated by Marco Viceconti, responsible of the VPH NoE outreach program and coordinator of the VPHOP Integrated project, and by Andrew McCulloch, member of the IUPS Physiome project and of the Multi Scale Modelling consortium of the USA Interagency Modelling and Analysis Group.

The policy brief will be the result of the work of these two experts, plus eventually a small editorial committee of VPH experts in USA and Europe that are willing to contribute to the editorial process, plus two expert panels formed in USA around the MSM group of the IMAG, and in Europe around the VPH NoE. Last, but not least the draft brief will be opened to the public debate and every stakeholder will be invited to comment it as part of enlarged consensus process similar to that used for the VPH Research roadmap.

Another group of stakeholders will have to be generated around the application of VPH to diagnosis and treatment of rare diseases. In USA we should probably try to establish a link with the NIH Office of Rare Diseases: <http://rarediseases.info.nih.gov/> and with USA National Organisation for rare Diseases (NORD) <http://www.rarediseases.org/>. In Europe the patient organisation is Rare Diseases Europe (EuroDIS) <http://www.eurordis.org/> while in the EC the unit should be the SANCO C2, but this needs to be verified.

There is also a Rare Diseases day on February 28th, worldwide, that we probably should target with some dedicated actions within the VPH community (to be discussed): <http://www.rarediseaseday.org/>.

The activity will be organised in the following macro-phases:

- 1) Draft of the position paper on VPH, preparatory of the policy brief
- 2) Presentation and discussion of the draft with selected experts in USA and Europe.
- 3) Presentation and discussion of the revised draft at key IMAG and VPH NoE meetings
- 4) Presentation and discussion of the revised draft at the ARGOS meeting in DC
- 5) Publication and call for comments of the draft policy brief
- 6) Consolidation and presentation of the policy brief

Scope

The policy brief should not replicate the scope of other road-mapping efforts in Europe or in USA, but focus only on the specific aspects of ARGOS:

- Provide a observatory of VPH research, pointing to relevant documents for details
- Revise critically these experiences, and point where the residual challenges are
- With respect to such challenges understand where a US-EU cooperation is necessary
- Identify which changes in policy would foster such cooperation

In addition to the 2007 VPH Research Roadmap, the primary starting points will be the recent vision document from the VPH NoE and the meeting brief for the IMAG Future meeting, that is being written in these days.

Process

January 2010 - Kick-off TC: agreement on the procedures and the first steps of the activity plan. This task has been completed.

February 2010 – First draft Position Paper: MV and AmC issue a first draft. This should provide primarily a trace, to be of support for the experts’ panel and the editorial committee.

March 2010 – first ARGOS consortium meeting: as part of the WoHIT meeting in Barcelona, in 15th March 2010 first internal meeting, but one hour will be open to the public where we shall inform all VPH stakeholders of what ARGOS is about. Creation of the editorial committees with those colleagues of are willing to be more involved in the editorial process.

July 2010 – ARGOS VPH US consensus: the draft Position Paper is presented by AmC to a group of USA experts, and comments are received. This could happen in conjunction with the next IMAG meeting, which might be hosted by SIAM Life Science conference, July 12-15, 2010 Pittsburgh, Pennsylvania <http://www.siam.org/meetings/ls10/>. If this date is not confirmed AmC will find another suitable situation to present and debate the draft with the USA colleagues before the end of September 2010.

September 2010 – ARGOS VPH EU consensus: before VPH2010 MV will organise the same type of consensus event for the European colleagues; this might happen on Sept. 29th, 2010, the day before VPH2010 in Brussels.

October 2010: ARGOS workshop. According to the proposal we should have it in USA, linked to AMIA 2010 Annual Symposium, November 13-17, 2010, Hilton Washington & Towers, Washington, DC. Local contact is meryl@amia.org. Since we plan to have our meetings separately, we could use this slot to present the draft position paper, updated of the inputs we collected in the regional consensus meetings. We might also invite selected stakeholders that can be reached only with an event in DC. The primary scope of this meeting, with respect to the VPH aspects, will be to synchronise with the other ARGOS topic groups, in particular with respect to the aspects of research/healthcare data integration and their implication for the electronic health record, and the aspects of dynamics technology assessment of VPH technology.

December 2010: the VPH policy brief goes into public review; we aggressively disseminate to all stakeholders.

April 2011: ARGOS Finale, Brussels. Editorial committee members (topic leaders will act as EU-US “rapporteurs”), invited experts and delegates from all interested stakeholder groups (with free access but limited audience) will be involved.

May 2010: drafting and dissemination of final recommendations.

June – December 2011: presentation of the recommendations at EU and US events.

2012: Official presentation of the recommendations at the EU-US Summit of 2012.

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