



PROJECT PERIODIC REPORT

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Interim report: 1st ☒ 2nd ☐ 3rd ☐ 4th ☐

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Name, title and organisation of the scientific representative of the project's coordinator:

Research Professor Dr Georgios Stamatakis
Institution of Communication and Computer Systems (ICCS)
National Technical University of Athens

Tel: +30 210 772 2287

Fax: +30 210 772 3557

E-mail: gestam@central.ntua.gr

Project website address: www.chic-vph.eu

Declaration by the scientific representative of the project coordinator

I, as scientific representative of the coordinator of this project and in line with the obligations as stated in Article II.2.3 of the Grant Agreement declare that:

- The attached periodic report represents an accurate description of the work carried out in this project for this reporting period;
- The project (tick as appropriate):
 - ☒ has fully achieved its objectives and technical goals for the period;
 - ☐ has achieved most of its objectives and technical goals for the period with relatively minor deviations.
 - ☐ has failed to achieve critical objectives and/or is not at all on schedule.
- The public website, if applicable
 - ☒ is up to date
 - ☐ is not up to date
- To my best knowledge, the financial statements which are being submitted as part of this report are in line with the actual work carried out and are consistent with the report on the resources used for the project and if applicable with the certificate on financial statement.
- All beneficiaries, in particular non-profit public bodies, secondary and higher education establishments, research organisations and SMEs, have declared to have verified their legal status. Any changes have been reported under section 2 (Project Management) in accordance with Article II.3.f of the Grant Agreement.

Name of scientific representative of the Coordinator: Research Professor Dr. Georgios Stamatakos

Date: 29 / 5 / 2014

Signature of the coordinator:



Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology

PUBLISHABLE SUMMARY OF THE MAIN RESULTS ACHIEVED DURING THE 1st YEAR OF THE PROJECT IMPLEMENTATION

Georgios S. Stamatakos
CHIC Project Coordinator

30 May 2014

I. Summary of the project context and objectives

In silico medicine (*ISM*) [http://en.wikipedia.org/wiki/In_silico_medicine], an emergent scientific and technological domain based on clinically driven and oriented multiscale biomodelling, appears to be the latest trend regarding the translation of mathematical and computational biological science to clinical practice through massive exploitation of information technology. *In silico* (i.e., on the computer) experimentation for each individual patient using their own multiscale biomedical data is expected to significantly improve the effectiveness of treatment in the future, since reliable computer predictions could suggest the optimal treatment scheme(s) and schedules(s) for each separate case. Due to the predominant manifestation of cancer in *all* spatiotemporal scales of biocomplexity, *in silico* oncology (*ISO*) appears to be the paradigm *par excellence* of *in silico* medicine. The CHIC project aims at advancing *ISM* through the paradigm of *ISO* in the following aspects: 1. Fundamental Science (development of clinically driven and oriented complex hypermodels and oncosimulators by different modelling groups) 2. Information Technology (semantic description of cancer models and hypermodels, development of a secure technological infrastructure and tools and services supporting the semi-automatic accessibility and resusability of models as well as the building of hypermodels) 3. Clinical Medicine (clinical drive of hypermodel building, clinical adaptation and partial clinical validation of hypermodels and oncosimulators). The actual components being developed by CHIC include a hypermodelling infrastructure consisting primarily of a hypermodelling editor and a hypermodelling execution environment, an infrastructure for semantic metadata management, a hypermodel repository, a hypermodel-driven clinical data repository, a distributed metadata repository and an *in silico* trial repository for the storage of executed simulation scenarios. Multiscale models and data are semantically annotated using the ontological and annotating tools under development. An image processing and visualization toolkit, and cloud and virtualization services are also being developed. The CHIC tools, services, infrastructure and repositories will provide the community with a collaborative interface for exchanging knowledge and sharing work in an effective and standardized way. A number of open source features and tools under development will enhance usability and accessibility. In order to ensure clinical relevance and foster clinical acceptance of hypermodelling in the future, the whole endeavour is driven by the clinical partners of the consortium. Cancer hypermodels being collaboratively developed by the consortium cancer modellers are providing the framework and the testbed for the development of the CHIC technologies. Clinical adaptation and partial clinical validation of hypermodels and hypermodel oncosimulators will be undertaken.

II. Description of the work performed so far and the main results achieved

Overall progress of the project implementation

The project has fully achieved the targets foreseen for the first year of its implementation with a few minor adjustments. In the following subsections important representative progress and result examples from all workpackages are provided. A more comprehensive and detailed listing of the achievements is provided in the first annual project periodic report.

Work Package 1 (WP1) : Project Management

The project management is going very well. The collaboration between the coordinating institution, ICCS, and the project management partner Eurice, has been so far effortless and efficient. Representative examples of the 1st year achievements include the following: The Grant Agreement and the Accession Forms have been signed by all partners. The Consortium Agreement has been concluded and signed before the official start of the project on 1 April 2013. The Kick-off Meeting (milestone MS1) took place in Athens on 10-12 April 2013. The 1st Progress Meeting (MS2) was held in Heraklion on 17-18 October 2013. A 6-month interim review was held in Brussels on 15 November 2014. The 2nd Progress Meeting (MS2) took place in Luton on 20-21 February 2014. A web-based password-protected management tool (ProjectAngel) has been set up within the scope of developing the CHIC website in order to centrally store templates for presentations and reporting, project relevant information and data. The first European Commission (EC) payment of 3,703,700€ was received by the coordinator after the start of the project and timely and duly distributed to the partners.

Work Package 2 (WP2): User Needs and Requirements

Scenario based user needs and requirements have been finalized. The requirements for the validation of hypermodels are currently in an iterative process of optimization by all members of the CHIC consortium. Clinical, imaging, histological and molecular data for the major CHIC hypermodelling scenarios are being collected. Additional scenarios and use cases are under development by the clinical partners in close interaction with non clinical partners. They have been dissected into granular modules. A systematic interaction with the p-medicine project has been established.

Work Package 3 (WP3) : Clinical and Translational Science Scenarios

The detailed specifications of the multiscale (i.e. imaging, histological, molecular, clinical and treatment) data provided by the clinical partners have been produced for the paradigmatic clinical scenarios of CHIC. These refer to nephroblastoma, glioblastoma multiforme and lung cancer. The clinical trial management system ObTIMA primarily developed within the framework of the p-medicine project has been extended in order to support part of the CHIC project needs. Ethical approval has been granted for the clinical scenarios. Initial data sets have been provided to the modelling partners

Work Package 4 (WP4) : Legal and Ethical Framework

An initial data protection and data security framework for the project has been developed in compliance with ethical and legal requirements on the reuse of pseudonymized and anonymized data within the European Union. A position paper on the current data protection issues was drafted early on in the project (for further consideration by the Virtual Physiological Human (VPH) initiative) in order to allow researcher concerns and experience to be fed directly and in a timely way into the current legislative reform process. Data on the licenses of the tools have been collected and are undergoing legal analysis. Data protection contracts - contracts for data providers, end users, and the trusted service provider have been drafted and circulated to the partners.

Work Package 5 (WP5): IT Architecture

A Technological Architecture Board has been established and the basic operating procedures have been defined. A review of the existing information technology (IT) architectural styles prevalent in the biomedical informatics and the Virtual Physiological Human (VPH) domains has been undertaken. An initial CHIC IT architecture has been designed and documented. An initial data protection (security) framework within the CHIC environment has been developed. The most appropriate technologies for the implementation of private or hybrid cloud infrastructures have been selected and an in depth evaluation has been carried out. An initial deployment of the CHIC cloud infrastructure for testing with the hypermodelling infrastructure has been implemented. A private cloud infrastructure for productive usage has been installed and deployed. This infrastructure will soon be released for use by all partners.

Work Package (WP6): Cancer Models and Hypermodel Design

The overarching cancer hypomodelling and hypermodelling strategies have been refined and crystallized. An initial generic conceptual platform to serve as a standardized framework for the design and the development of multi-research group (multimodeller) multiscale hypermodels has been developed and agreed on by the cancer modelling partners. A large number of cancer models previously developed by the modelling partners (e.g. in the framework of ACGT, ContraCancrum, TUMOR, p-medicine and other projects) has been tabulated and served as a starting point for the technology developers. A formal description of any cancer model (being either a hypomodel or a hypermodel) based on 13 perspectives has been proposed and adopted by the consortium. A finalized version of a CHIC project related glossary is about to be completed. A basic version of the glossary is already accessible on the CHIC intranet. A clear way of linking subcellular multiscale models with cellular and supercellular models has been established. Available Wilms tumour multiscale data is being exploited by

relevant models. An initial machine learning model to be used as the statistical modelling approach for glioblastoma multiforme immunotherapy combined with chemotherapy and radiation therapy has been shaped. This model will serve as the starting point of a mechanistic model of the same biomedical problem. A lung cancer scenario to serve as the driver for the first multi-modeller multiscale hypermodel demonstrator has been formulated. The components of the biomechanical model and the related scientific and technological requirements have been defined. The initial process of integration of biomechanics modelling into discrete-entity discrete-event multiscale cancer modelling has been designed. A feasibility study regarding the collection of blood samples from prostate cancer patients undergoing radiotherapy in order to correlate tumour markers with clinical outcome is under way.

Work Package 7 (WP7): Hypermodelling infrastructure

The required attributes pertaining to the component models (hypomodels) that will ultimately allow implementation of the latter on the CHIC hypermodelling framework as well as the generic stub which will define connectivity between model components have been defined. The cloud infrastructure has been deployed and is ready to be tested and used by the interested partners. A list of component models with their technology specifications including control and data flows has been produced. A test object for the development of the basic tag management system has been developed. The set of 13 perspectives, proposed by WP6, from which each model should be viewed and a corresponding (semantic) metamodel should be created has been adopted by WP7. The VPH-HF, being the core technology for the CHIC hypermodelling IT architecture, has been successfully installed. This will provide a valuable resource for further developmental work in the rest of the WP7 implementation. The interactions between WP7 components and components being developed by other workpackages has been analysed. The hypermodelling specifications have been consolidated.

Work Package 8 (WP8): Model and Data Repositories

The requirements of the model and tool repository have been analysed. The database framework for the data repository has been selected. The multiscale data has been specified and described from the repository viewpoint. Fake multiscale data has been collected. Pertinent technologies for the development of the *in silico* trial repository have been reviewed. Existing model integration examples have been analysed. The initial integration of the data repository with the CHIC security framework has been completed. The first version of the REST (REpresentational State Transfer) services has been implemented. Tools for automatic pseudonymization and uploading of clinical data to the data repository have been reviewed. Existing ontologies pertinent to the CHIC project have been reviewed. Knowledge representation requirements for multiscale cancer biology and oncology have been collected. A semantic interoperability framework which is based on the above requirement collection and is coherent with the standards development process in industry has been designed.

Work Package 9 (WP9) : Image Processing and Visualization

User requirements for multimodal brain tumour segmentation have been finalized. The major components of the image registration tool have been identified and initial trials on clinical images have been conducted. The input and output of the Doctor Eye software and the new CHIC image processing modules have been defined. A literature review on advanced features and MRI imaging modalities has been conducted. The reuse of the visualization module for hybrid volume/surface visualization has been evaluated and the data input module has been re-implemented. All important decisions regarding the software platform for the assessment of tumour treatment response have been taken with close clinical interaction. Initial tools for perfusion diffusion MRI data analysis are ready for testing. The image processing and visualization needs of the WP6 models have been defined.

Work Package 10 (WP10): Integrated Platform

A portal being the main “point of entrance” to the CHIC platform, offering access to the model repositories for publishing and discovery of models and hypermodel and providing links to specific tools (e.g. for anonymization), supporting the upload of new data sets and the management of the existing ones, assisting the creation of new hypermodels by linking existing ones, etc. has been implemented. Interoperable interfaces for retrieving model and hypermodel descriptions from the corresponding repositories are in the process of definition.

Work Package 11 (WP11): Clinical Adaptation and Validation

Evaluation and validation criteria for enhancing clinical adaptation of hypermodels have been formulated. These criteria will be applied during the advanced stages of the project implementation when hypermodels will be ready for clinical adaptation and validation.

Work Package 12 (WP12): Dissemination and Exploitation

A clear plan and set of tools for the dissemination of the CHIC results have been defined. The most important features of the CHIC project identity (logo, colours, flyer) are available. The updated project website www.chic-vph.eu is running. A project dissemination kit can be downloaded by the partners on the management platform. The first annual newsletter is currently under preparation. Dissemination of the overall purpose of the CHIC project to audiences comprising academics from several disciplines, as well as clinicians working in the field of oncology and representatives from industry has started. Partners have actively started to disseminate CHIC-related content both with presentation at conferences and peer-reviewed journal publications. Concerning exploitation, preliminary activities have started with the identification of intellectual property rights (IPR) issues. An industry workshop with the goal of achieving a communal standard for multiscale anatomy knowledge representation relevant to CHIC has been organized. A discussion about sustainability and maintenance issues has started. Further exploitation and sustainability details are provided in section III.

III. Expected final results and their potential impact and use (including socio-economic impact and wider societal implications of the project so far)

The major expected results of the project can be summarized as the implementation of its objectives outlined in section I. These include the development, the clinical adaptation and the partial clinical validation of a series of cancer models, hypermodels, technological tools, services and secure infrastructure. Regarding the impact of the project, CHIC is expected to have a major influence on the following sectors: 1. Fundamental Science (quantitative decomposition of complex biological phenomena into elementary biomechanisms, mathematical and computational modelling of each biomechanism, virtual (re)synthesis of complex phenomena via hypermodelling) 2. Clinical Medicine (conduction of virtual clinical experiments instead of eventually ethically forbidden real ones on the level of a single patient or a clinical trial) 3. Industry (provision of models, hypermodels, technological infrastructure, tools and oncosimulators to be utilized for the development of patient individualized decision support and treatment planning systems and *in silico* clinical trial platforms. 4. Society (expected achievement of increased life expectancy and improved quality of life through the conduction of experiments *in silico* aiming at the optimization of the treatment strategy in the patient individualized context, reduction of the experimental cost due to the partial replacement of costly *in vitro* and *in vivo* experiments by *in silico* experiments, conduction of virtual clinical experiments instead of real ones.). Within the first year of the project implementation several actions aiming at facilitating the exploitation of the project outcomes were taken. These include discussions relating to the IPR issues for the MAF (Multimode Application Framework) used in a number of previous projects including VPHOP. The latter will serve as a core technology for the CHIC hypermodelling technological framework. In order to guide and understand CHIC specific IPR issues a questionnaire has been prepared and completed by the consortium. The questionnaire focuses on the expected results to be obtained during the implementation of CHIC, how to secure these results and where to locate these results on the innovation chain or regarding potential commercialization. A cross-industry workshop for pharmaceutical companies to work towards a communal standard for multiscale anatomy knowledge representation relevant to the semantic interoperability requirements of CHIC was organized on Oct 30-31 2013. Discussions at the whole-consortium level in support of the long-term sustainability of the CHIC platform were also held during the 2nd progress meeting. The focus was on the application of the CHIC cancer hyper-modelling approach as part of the pharmaceutical drug discovery pipeline (known as pharmaCHIC). Other broader exploitation related issues were also addressed by all partners. A discussion on the sustainability and maintenance of the CHIC project via the proposed Study Trial and Research Institute (STaRC) that is part of the maintenance program of the p-medicine project is in progress. Further discussions are needed and will be integrated into the exploitation planning report of CHIC in the next reporting period. In interaction with the Thomson Reuters company, an exploration of possible exploitation scenarios of the CHIC outcome by the wider biomedical research and clinical industry has started. It is noted that Thomson Reuters is a member of the External Advisory Committee of the CHIC project.

IV. Address of the public website

<http://chic-vph.eu/>

Table of Contents

1. Work progress and achievements during the period	3
1.1 Work Package 1: Project Management	3
1.2 Work Package 2: User Needs and Requirements	3
1.3 Work Package 3: Clinical and Translational Science Scenarios.....	8
1.4 Work Package 4: Legal and Ethical Framework	12
1.5 Work Package 5: IT Architecture	15
1.6 Work Package 6: Cancer Models and Hypermodel Design.....	18
1.7 Work Package 7: Hypermodelling infrastructure	22
1.8 Work Package 8: Model and Data Repositories.....	27
1.9 Work Package 9: Image Processing and Visualization	31
1.10 Work Package 10: Integrated Platform	34
1.11 Work Package 11: Clinical Adaptation and Validation.....	37
1.12 Work Package 12: Dissemination and Exploitation	40
1.12.1 Dissemination activities and publications.....	47
Press activities.....	50
Publications.....	51
2. Deliverables and milestones tables	55
2.1 Deliverables.....	55
2.2 Milestones.....	62
3. Project management	66
4. Explanation of the use of the resources	72
4.1 Budget Overview.....	73
4.2 Budget Explanations	76
4.3 Planned versus actual efforts.....	76

1. Work progress and achievements during the period

1.1 Work Package 1: Project Management

Regarding Work Package 1 reference is made to section 3 “Project Management” in this report.

1.2 Work Package 2: User Needs and Requirements

Main objectives of this WP

WP2 elaborates on the user needs and requirements for the proposed technological and clinical research infrastructure to develop an environment that is able to run hypermodels composed of existing and newly developed models by different end users (e.g. clinicians) with the goal to drive common clinical practise to preventive, predictive and participate medicine. This will provide the clinical perspective of the project and will take into account the state of the art, the state of research and the state of practice in the healthcare domains addressed by the project. This WP will address the needs for developing secure and consistent hypermodels and it will address the technological requirements (in conjunction with all other WPs) from a clinical application standpoint facilitating VPH research. The project will take into account existing infrastructures already developed for VPH like the p-medicine and the VPH-share infrastructure dealing with heterogeneous data and models. As requirements might change during the evolution of the project, the specification of user needs and requirements will continuously be updated.

As the VPH vision suggests the creation of repositories where a huge number of models are stored that describe and simulate different physiological processes, interoperability issues between these models are of utmost importance. Knowledge management models are needed to cope with this extreme complexity to build new integrative models. This WP will investigate the following:

1. Which models exist and how they can be accessed and used;
2. Which metadata do exist for these models and for models in general
 - a. regarding annotation and
 - b. interoperability issues;
3. What kind of data are needed to execute models;
4. Which ontologies are available and needed for proposed data, tools and models;
5. Which markup languages do exist that can be used for building hypermodels.

In this WP user requirements and specifications for the interaction with existing infrastructures will be defined and applicable use cases for the system validation will be developed within the clinical domains of the project. In case of usage of hypermodels within clinical trials GCP compliance will be addressed and solutions provided. The certification of tools and hypermodels is beyond the scope of this project. Nevertheless actions will be defined to allow seamless integration in daily clinical practice.

Active tasks in this reporting period:

- T2.1, State of the Art Knowledge for Building Hypermodels (M1-8)
- T2.2, Scenario based user needs and requirements (M1-8)
- T2.3, Requirements for enhancing hypermodels beyond the domain of cancer (M1-18)

Work has started early in the following task:

- T2.4, How to get acceptance of hypermodels by patients and physicians (M12-42)

Summary of progress achieved towards objectives

FORTH initiated a discussion regarding the state of the art knowledge for building hypermodels, which also continued on the plenary meeting (1st Progress Meeting) that was hosted on FORTH's premises. This process is documented in the deliverable D2.1, submitted to the EC in mid-January 2014.

Major work was done in T2.2 and T2.4. Deliverable D2.2 was written in an effective iteration process with all involved partners and mainly driven by clinical partners and with a template provided by **ICCS**. The deliverable was finalized and submitted in January 2014. The short delay had no impact on further work and progress in CHIC. The additional time was needed to focus on the clinically relevance of the scenarios. The main objective of D2.2 was the elaboration of the scenario based user needs and requirements. For each of the cancer domains within CHIC one scenario was selected for building a hypermodel. The selection as well as the description of the scenarios were discussed during different meetings and telephone conferences between clinicians but also between other stakeholders, especially IT people. **USAAR** is responsible for the scenarios in nephroblastoma and lung cancer. For all cancer domains data are defined and the collection of data has already started. **CUSTODIX** critically followed up on the development of scenarios under security issues. **CUSTODIX** also followed up on the scenarios and attended corresponding meetings. Sharing and joining of data will be initiated as soon as the legal framework is in place.

Besides double blind validation and the initial interaction with the musculoskeletal modelling community no major work for enhancing hypermodels beyond the domain of cancer is done up to now. Regarding double-blind validation **UPENN** presents a computational modelling and simulation approach to delineate molecular-level mechanisms of activation of protein receptor tyrosine kinases and describe clinical implications of mutations in the Anaplastic Lymphoma Kinase (ALK) receptor tyrosine kinase in paediatric neuroblastoma. They show here that their results shed molecular-level insight into the various mechanisms governing such transforming mutations at the level of kinase activity and are remarkably consistent with experimental observations. In particular, **UPENN's** computational predictions matched experimental measures of kinase activity with over 85% accuracy in the mutations investigated from neuroblastoma patients.

In Task 2.4 **USAAR** is analysing the requirements for the validation of hypermodels. This is done in close cooperation with Task 2.3 and Task 11.1 as tools, models and hypermodels will only be used in the clinical setting and beyond the domain of cancer if they are validated. For that reason a questionnaire is developed to find ways of bringing models and hypermodels into clinical practice. Further important requirements in this task are addressed on the legal side including mainly IP issues of composed hypermodels. In addition requirements for sustainability and maintenance of hypermodels are elaborated. Within Task 2.3 mechanisms to use in silico models and hypermodels in clinical settings is elaborated. An additional report to D2.3 will cover the general requirements for the validation of hypermodels and is currently in preparation. The additional report will be made available on the CHIC intranet and will be submitted to the EC with D2.3 at the latest.

All clinical partners started to collect data from the different cancer domains, including clinical data, imaging data, and molecular data. A questionnaire was developed to ask stakeholders about features that are essential for usage of hypermodels. Results are awaiting.

USAAR started discussions about possible interactions with the p-medicine environment. **ICCS** has had initial discussions with **USFD** regarding the possible reuse of the hypermodeling infrastructure (approach) by the musculoskeletal modelling community.

Summary of details for each task

■ Task 2.1: State of the Art Knowledge for Building Hypermodels

FORTH lead this task and they organized a series of discussions through emails and Skype teleconferences for collaboration, interaction and feedback. **FORTH** submitted deliverable D2.1, which focuses on the state of the art knowledge for building hypermodels. Initial discussions with the consortium converge on approaching the SOA through three distinct viewpoints: a) the systems biology/clinical, b) the engineering design and c) the software architecture focusing on semantic interoperability. Critical questions have been defined and were further discussed in the plenary meeting (held on 17, 18 October at FORTH premises). **ICCS** participated in the discussions related to the deliverable D2.1 “State of the Art of Knowledge for building hypermodels” and its preparation. In this task **USAAR** started the collaboration with p-medicine including questions of infrastructures, modularity and granularity of tools, the ethical and legal framework as well as interoperability issues and questions regarding sustainability of CHIC via the proposed Study Trial and Research Centre that is part of the maintenance program of p-medicine.

Different methods to catalogue and computationally assess the mutational landscape of proteins in human cancers exist. Most of these efforts have been adaptations of methods developed for predicting whether a single nucleotide polymorphism is deleterious to protein structure and function. In cases where the mechanism of protein activation and regulation is understood, it can be possible for structure-based computational approaches to predict the effects of point mutations. This method is most appropriate when a relatively small number of driver mutations account for a large portion of the observed cancer somatic mutations. However, many patients will present with mutations that are not one of the major known drivers, and being able to assess which of the relatively infrequent mutations are drivers would aid clinical treatment decision. Machine learning techniques are most appropriate in this situation to help recognize and illuminate mutational patterns in a clinical dataset. In the molecular Model of **UPENN**, they classified the type of the mutation (hydrophilic to hydrophobic, polar to non-polar etc.) and its location (A-loop, C-helix, P-loop, N-loop etc.) and ascribed a mechanism-based functional significance of the mutation on the kinase activation. **UPENN** already has demonstrated the success of this approach on the effect of mutations on the activation mechanisms of ErbB family kinases. Analysing the effects of each activating mutation on ALK protein dynamics helps to reveal how the mutation functionally changes the intramolecular interactions within the kinase. In order to optimize the accuracy of the prediction and automate the analysis, **UPENN** implemented a machine-learning algorithm for the prediction of activation and trained our model on retrospective clinical genomic data.

Task T2.1 has finished and provided the deliverable D2.1 as required in the Technical Annex.

■ Task 2.2: Scenario based user needs and requirements

Scenario based user needs and requirements were elaborated in an iterative way with all members of the CHIC project. Especially the participation of clinicians in this process guaranteed clinical relevant scenarios. For each cancer domain one hypermodel scenario was developed. This was further discussed during telephone conferences and several meetings, including consortium meetings. According to results of previous projects all scenarios and use cases are dissected according to the finest possible granularity. This results in different modules that can be combined to higher level scenarios and use cases. A list of existing models and new models provided by WP6 is dissected in that way and ranked according to clinical usage. In addition we started to define standardized, open interfaces and functionality descriptions, so that a user can easily build new models as a composition of existing granular tools. Such an approach will guarantees the re-use of already developed tools and models and avoids rebuilding of tools and models from scratch.

Data for the scenarios are defined and collection of data already started.

■ **Task 2.3: Requirements for enhancing hypermodels beyond the domain of cancer**

ICCS has had initial discussions with USFD regarding the possible reuse of the hypermodeling infrastructure (approach) by the musculoskeletal modelling community. Within this framework the coordinator has planned to participate in the 7th World Congress on Biomechanics to take place in Boston US on 6-11 July 2014. UPENN has devised a double-blind validation protocol for assessing the accuracy of our predictive algorithm by computing ROC (receiver operating characteristic) curve. The prediction of the activation status is based on the results of text mining, evolutionary analysis of the protein sequence, and based on specific interactions (hydrogen bonds etc.) in the dynamics simulations. The double-blind comparison validates these predictions with in vitro and cellular assays of kinase activation in different mutants. A molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations was established by UPENN. As part of the task a multiscale method to combine the molecular studies with signalling network studies was developed. The following publications describe the accomplished work in detail.

- Multiscale Cancer Modeling and In Silico Oncology: Emerging Computational Frontiers in Basic and Translational Cancer Research, G. S. Stamatakis, N. Graf, R. Radhakrishnan, J. Bioengineering and Biomed. Sci., 2013, 3(2), 1000e114.
- Computational Methodology for Mechanistic Profiling of Kinase Domain Mutations in Cancers, P. J. Huwe, and R. Radhakrishnan, Proceedings of the IEEE, 5th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation, Eds. G. S. Stamatakis, D. D. Dionysiou, 2013, pp1-4. Print ISBN: 978-1-4673-5024-2
- Computational Delineation of Tyrosyl-Substrate Recognition and Catalytic Landscapes in the Epidermal Growth Factor Receptor Tyrosine Kinase Domain, Y. Liu, R. Radhakrishnan, Molecular Biosystems, 2014, in press. DOI: 10.1039/C3MB70620F
- Integrative functional assessment of ALK mutations for therapeutic stratification in neuroblastoma, D. Weiser, S. Bressler, P. J. Huwe, R. Radhakrishnan, M. A. Lemmon, Y. Mosse, 2014, submitted to Cancer Cell.
- In silico profiling of activating mutations in cancer, E. Jordan, R. Radhakrishnan, 2014, submitted to Integrative Biology.

Deliverable 2.3, Requirements for enhancing hypermodels beyond the domain of cancer (due M18) is under development.

■ **Task 2.4: How to get acceptance of hypermodels by patients and physicians**

The requirements for the acceptance of hypermodels by patients and physicians are under elaboration in an iterative process with all members of the CHIC project. USAAR is leading this task. A questionnaire was developed and sent around. As there are overlapping topics between WP2 and WP11 dealing with this task, deliverable D11.1 will be written in parallel and submitted at month 14.

The most important requirement for the validation of models and hypermodels are the availability of data. In this reporting period we started with the collection of data for the different cancer domains. At the moment these data are still locally hosted by the clinical partners as long as the legal and ethical framework is not in place and a user interface is missing for the upload of data to the CHIC platform.

Summary of significant results

Scenario based user needs and requirements have been finalized and the corresponding deliverable was submitted. The requirements for the validation of hypermodels are currently in an iterative process of optimization including all members of the CHIC consortium.

Cancer Genomics: One of the grand challenges of the understanding of cancer progression is to find mechanistic links between molecular alterations and the hallmarks of cancers. As we gather clinical data in a large scale aimed at molecular profiling of patients or patient cohorts, functional annotation of data or deriving mechanistic insights from the data, which can be useful for clinical decision making gets ever more challenging. We provide an integrative framework for combining the state-of-the-art in two different fields, namely structural biology and machine learning, in order to delineate hitherto unknown mechanisms and relationships in cancer genomes, which has the potential to make clinical impact in oncology. Machine learning techniques are most appropriate in this situation to help recognize and illuminate mutational patterns in a clinical dataset. Although structure based and machine-learning methods have enjoyed success on their own, therein is hitherto unexplored opportunity to combine them. However, in order to relate to the clinical context, these molecular profiling methods need to be combined with multiscale methods to incorporate the molecular effect on cell phenotypic outcomes.

We started to collect clinical, imaging and molecular data.

Scenarios and use cases are under development by clinical partners and in close interaction with all other partners. They are dissected into granular modules.

Interaction and collaboration started with p-medicine and USFD.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

Deliverable D2.2 was submitted 3 months later without any impact on the project.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

The delay in submission was caused by a missing but crucial contribution to the deliverable as well as the Christmas/New Year's break.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP2			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	2.00	1.00	1.40
3-USAAR	25.00	6.00	3.77
7-FORTH	3.00	1.00	2.00
9-UPENN	5.00	1.50	1.50
13-CUSTODIX	1.00	0.25	0.46
14-PHILIPS	4.00	0.50	0.00
Total	40.00	10.25	9.13

1.3 Work Package 3: Clinical and Translational Science Scenarios

Main objectives of this WP

The objectives of WP3 are to validate the CHIC environment by focusing on three different cancer types. The selected diseases are Wilms tumor, glioblastoma multiforme (GBM) and non small cell lung cancer (NSCLC). These particular diseases are selected to address different aspects of the project. For all three cancer types, clinically relevant cases are defined. Data from these cases will be stored within the infrastructure of CHIC in a secure and anonymized way according to the legal and ethical framework of CHIC. The data from these concrete clinical scenarios will undergo processing within the environment, and validation of the environment will be based on the clinical and oncologic data produced by the same scenarios.

Active tasks in this reporting period:

- Task 3.1, Wilms tumor (M1-48)
- Task 3.2, Glioblastoma multiforme (M1-48)
- Task 3.3, Non small cell lung cancer (M1-48)

Work has started early in the following task:

- T3.4, Applying the CHIC infrastructure to other cancer types (M12-36)

Summary of progress achieved towards objectives

For tasks 3.1 and 3.3, **ICCS** performed the exploitation of Wilms tumor and lung cancer patients' multiscale data. **ICCS** initiated discussions regarding micro-RNA data to be provided.

At **USAAR**, major work was done in defining the data that will be used in the nephroblastoma scenario. ObTiMA was further developed and data collection could start within ObTiMA. After the legal framework is in place data can be shared for usage by developers of the hypermodel.

In task 3.2, **ICCS** defined the specific multiscale data to be used by the glioblastoma multiforme multiscale models to be developed. At **KULeuven**, major work was done in defining data that will be used in the glioblastoma multiforme scenario. Fake prototype data from patients with glioblastoma multiforme, enrolled in the HGG-2010 clinical trial, were collected and provided to CHIC partners.

In task 3.3, **USAAR** defined the data that will be used in the Non-Small-Lung-Cell Cancer (NSLCC) scenario. ObTiMA was further developed and data collection could start within ObTiMA. After the legal framework is in place data can be shared for usage by developers of the hypermodel. At **UPENN**, a molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations was established and implemented to study EGFR mutations in non-small-cell lung cancer. The accomplished work is described in the publications mentioned below.

Work has started early in task 3.4. At **UNITO** networking activity and data collection have been initiated in different institutions. Also, the ethical approval for the retrospective studies was obtained. A molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations as well as machine learning methods, was established by **UPENN** and implemented to study ALK mutations in paediatric neuroblastoma. The accomplished work is described in the publications mentioned below.

Summary of details for each task

- **Task 3.1: Wilms tumor**

ICCS: Exploitation of Wilms tumor patients' multiscale data, already provided by USAAR in the framework of previous research projects, is in progress. Discussions regarding the provision of micro-RNA data are under way. Continuous interactions of ICCS with USAAR have taken place.

USAAR: Within the SIOP Renal Tumor Study Group, a new clinical trial is under development. This trial will use ObTiMA as the data management system. Corresponding CRFs are developed.

Imaging data (DICOM) are collected from patients with nephroblastoma at the time of diagnosis and after 4 weeks of preoperative chemotherapy. Part of these DICOM data are post-processed by rendering the tumor using DoctorEye.

A doctoral thesis is under way building a tool for automatic annotation of Wilms Tumor. This tool is under validation in a feedback loop with the developer.

All data that are collected so far are locally stored until the legal and ethical framework is in place for CHIC and a user interface is built for easy upload of the data. Ethical approval for the collection of the data for the CHIC project is given by the Ärztekammer des Saarlandes (No.: 104/10, dated: 19th August 2013).

Together with WP2 data for the nephroblastoma hypermodel were defined. Data collection already started with ObTiMA. Release of data is possible after the legal framework is in place and functioning. The hypermodel was defined in an iterative process together with WP2.

■ Task 3.2: Glioblastoma multiforme

ICCS: Continuous interactions of ICCS with KULeuven and other partners have led to the definition of the specific multiscale data to be provided by KULeuven. The latter will guide the development of the specific glioblastoma multiforme multiscale models.

KU LEUVEN: At April 1st 2014 there were 120 patients with glioblastoma multiforme included in the HGG-2010 trial. This clinical study will serve as the data source for task 3.2. An informed consent was obtained for each of the 120 patients and they are treated according to the study protocol and followed regularly.

Our first goal was to make a list with all data available within the HGG-2010 trial. Together with WP2 the glioblastoma multiforme scenario and the data for the glioblastoma multiforme hypermodel were defined (D2.2).

We are exploring which data management system for collecting and locally storing the data will serve best for all parties involved (FileMaker or ObTiMA). Imaging data (DICOM) are stored in the hospital's PACS system. Data concerning tumour parameters (e.g. genotyping) and immune monitoring are still in experimental phase.

An excel test version of a comprehensive data base model has been built with fake prototype data and has been transferred to different partners in CHIC.

Data are locally stored until consensus is obtained about the data management system, until the legal and ethical framework of the CHIC environment is in place and until a user interface is built for easy upload of the data.

An extra application for sharing the data in the CHIC consortium was done at the local ethical committee on March 17th, 2014. Approval is given by the Commissie Medische Ethiek UZ KULeuven on April 7th, 2014.

■ Task 3.3: Non small cell lung cancer

ICCS: Exploitation of lung cancer patients' multiscale data, already provided by USAAR in the framework of previous research projects, is in progress. Continuous interactions of ICCS with USAAR have taken place.

USAAR: Together with WP2 data for the Non-small cell lung cancer hypermodel were defined. Data collection has started for Non-Small-Lung-Cell-Cancer. This includes clinical data, pathology data and molecular data (EGFR, KRAS, BRAF and echinoderm microtubule-associated protein-like 4-ALK (EML4-ALK)). All these data are stored locally up to now until the legal and ethical framework is in place for CHIC and a user interface is built for easy upload of the data. Release of data is possible after the legal framework is in place and functioning. The hypermodel was defined in an iterative process together with WP2.

UPENN: The following publications describe the accomplished work in detail.

- Molecular Modeling of the ErbB4/HER4 Kinase in the Context of the HER4 Signaling Network Helps Rationalize the Effects of Clinically Identified HER4 Somatic Mutations on the Cell Phenotype, S. E. Telesco, R. Vadigepalli, R. Radhakrishnan, Biotechnology Journal, 2013, 8, 1452-1464. DOI: 10.1002/biot.201300022
- Computational Delineation of Tyrosyl-Substrate Recognition and Catalytic Landscapes in the Epidermal Growth Factor Receptor Tyrosine Kinase Domain, Y. Liu, R. Radhakrishnan, Molecular Biosystems, 2014, in press. DOI: 10.1039/C3MB70620F
- Multiscale Computational Models in Physical Systems Biology of Intracellular Trafficking, R. W. Tourdot, R. P. Bradley, N. Ramakrishnan, R. Radhakrishnan, 2013, submitted to IET Systems Biology.

A computational modelling and simulation approach to delineate molecular-level mechanisms of activation of protein receptor tyrosine kinases is presented. Also, clinical implications of EGFR mutations in non-small-cell lung cancer are described. These results shed molecular-level insight into the various mechanisms governing such transforming mutations at the level of kinase activity and are remarkably consistent with experimental observations. It is expected that the current study on EGFR will transform the computational approach to enable future predictions of driver oncogenic mutations with low false-positive rates, and can hence serve an important *in silico* tool toward personalized cancer therapy.

■ Task 3.4: Applying the CHIC infrastructure to other Cancer types

UNITO has started to collect data and define models for prostate cancer not applicable in first reporting period.

Networking activity has started: a group of Urologic Surgery Units (Cuneo general hospital, Gradenigo private general hospital, Orbassano university hospital, Novara university hospital, Molinette university hospital, Maria Vittoria hospital, Mauriziano hospital, Aosta general hospital) and Radiotherapy Units (Orbassano University Hospital, Asti general Hospital, Ivrea general Hospital, Candiolo Scientific Cancer Center, Novara University hospital) already met and agreed to cooperate for two retrospective studies on radical surgery and radiotherapy for prostate carcinoma collecting about 4000 cases each.

Approval of the Ethical Committee for the retrospective studies was obtained. Data collection already started in all the institutions cited above.

UPENN: The following publications describe the accomplished work in detail.

- Computational Methodology for Mechanistic Profiling of Kinase Domain Mutations in Cancers, P. J. Huwe, and R. Radhakrishnan, Proceedings of the IEEE, 5th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation, Eds. G. S. Stamatakis, D. D. Dionysiou, 2013, pp1-4. Print ISBN: 978-1-4673-5024-2
- Integrative functional assessment of ALK mutations for therapeutic stratification in neuroblastoma, D. Weiser, S. Bressler, P. J. Huwe, R. Radhakrishnan, M. A. Lemmon, Y. Mosse, 2014, submitted to Cancer Cell.

- In silico profiling of activating mutations in cancer, E. Jordan, R. Radhakrishnan, 2014, submitted to Integrative Biology.

A computational modelling and simulation approach to delineate molecular-level mechanisms of activation of protein receptor tyrosine kinases is presented. Also, clinical implications of mutations in the Anaplastic Lymphoma Kinase (ALK) receptor tyrosine kinase in paediatric neuroblastoma are described. These results shed molecular-level insight into the various mechanisms governing such transforming mutations at the level of kinase activity and are remarkably consistent with experimental observations. It is expected that the current study on ALK will transform the computational approach to enable future predictions of driver oncogenic mutations with low false-positive rates, and can hence serve an important *in silico* tool toward personalized cancer therapy.

Summary of significant results

Exploitation of Wilms tumor and lung cancer patients' multiscale data.

Definition of the specific multiscale data to be provided for glioblastoma multiforme modelling.

Continuous interaction of ICCS with the clinicians regarding the details of the provision and checking of the multiscale data.

Further development of ObTiMA and collection of the first data with ObTiMA.

All data for usage in the hypermodels of nephroblastoma and Non-small cell lung cancer are defined and collection of data has already started.

Ethical approval for data collection for CHIC is given for nephroblastoma.

The glioblastoma multiforme scenario and the data for the GBM hypermodel were defined and a comprehensive data base model has been built with fake prototype data and this has been transferred to different partners in CHIC.

Ethical approval of HGG-2010 study was already given and also ethical approval for data sharing in the legal and ethical framework of the CHIC environment was obtained.

The *in silico* profiling algorithm correctly predicts the activation status in ALK with over 85% accuracy. Analysing the effects of each activating mutation on EGFR and ALK protein dynamics helps to reveal how the mutation functionally changes the intramolecular interactions within the kinase. Our studies completed show that not all mutations have the same mechanism of constitutive activation. Collectively, the results are helpful in the rational design of mutant-specific inhibitors and to rationalize the effect of mutation on inhibitor (crizotinib) sensitivity in a given cohort of patients in neuroblastoma and inhibitor sensitivity (erlotinib, gefitinib, and lapatinib) in non-small-cell lung cancer.

The Ethical committee approval has already been obtained and the data collection activity is effective since last July.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

Work has started early in Task 3.4: Applying the CHIC infrastructure to other cancer types (M12-36). This will not have any effect on the overall project plan or on available resources.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP3			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	2.00	0.50	0.80
3-USAAR	49.00	6.00	5.72
4-KULeuven	68.00	8.50	8.50
9-UPENN	2.00	0.50	0.50
11-UNITO	14.00	4.00	4.24
Total	135.00	19.50	19.76

1.4 Work Package 4: Legal and Ethical Framework

Main objectives of this WP

This work package has five objectives:

- To set up an ethical/legal framework to guarantee compliance with existing rules governing the field of patients' medical data. This framework will help partners to process data on valid legal grounds within the project.
- Establish necessary legal and organizational measures including drafting relevant contracts for the sharing of sensitive data within the project.
- To clearly define the intellectual property rights relating to the models, data, background and foreground brought in or generated in the project. Specific attention will be given to the fact that CHIC involves amalgamation of models which adds additional complexity. A deep analysis will be done about the protectability and the pros and cons of copyright protection in the field. Contracts that can be concluded between project partners as well as with interested third parties on copyright protection of the works developed will be provided.
- To help the project to stay compliant with the relevant legislation and jurisdiction and will therefore act as a permanent legal advisor to the other partners.
- To do legal research on the necessary development of the existing European regulatory framework, in order to foster VPH-research initiatives such as CHIC in the areas of data protection, clinical trials regulation and intellectual property. A position paper for the VPH community was prepared and circulated in M4, and a whitepaper on these issues for the use of the European Commission and other political stakeholders will be produced in M36. Specific focus will be on the amalgamation of models in the field.
- Being legal advisor for all not yet foreseen legal and ethical questions for all partners for the whole duration of the project.

Active tasks in this reporting period:

- Task 4.1, Initial analysis of the ethical and legal requirements on the reuse of pseudonymized and anonymized data within CHIC (M1-6)
- Task 4.2, Initial analysis of the copyright-related legal requirements for the sharing of data and amalgamation of models within CHIC (M1-9)
- Task 4.3, Development of a data protection and copyright framework for CHIC (M1-42)

Summary of progress achieved towards objectives

The initial analysis of the ethical and legal requirements for the sharing of data has been completed as described in Task 4.1. A deliverable (D4.1) has been submitted on time in September 2013 (M6), containing the details of the analysis. **LUH** led the team on this task. **ICCS**, **CUSTODIX**, and **USAAR** contributed to the discussion on this task as well as in the preparation and review of the corresponding deliverable. **USAAR** has also obtained Ethical approval for data collection and sharing within CHIC was given by the Ärztekammer des Saarlandes for nephroblastoma.

In task 4.2, initial information relating to the licences envisaged to be used in the project has been collected by **LUH** and deliverable D4.2 has been submitted in M9 outlining a preliminary analysis of the information obtained. **ICCS**, **CUSTODIX**, and **USAAR** were involved in the discussions.

Task 4.3 is ongoing till M42. So far, an initial analysis of the data protection requirements has been carried out and **ICCS**, **CUSTODIX**, and **USAAR** contributed to the discussions on this task. A first iteration of the data protection and copyright framework for CHIC will be submitted in M14, and the full framework will be completed in M42 of the project.

Summary of details for each task

■ **Task 4.1: Initial analysis of the ethical and legal requirements on the reuse of pseudonymized and anonymized data within CHIC**

a) **A questionnaire has been developed and distributed to the project partners in order to gather information on the nature of data to be processed and its flow**

The questionnaire consisted of 14 questions aimed at eliciting details on which partners will provide which kind of data for the project, – personal, pseudonymised, anonymised, whether data will be prospective (collected in the future) or retrospective (already collected), whether informed consent covers the use of the data in CHIC, whether real data will be required to test the tools and models to be developed in the project, and details of licences under which the tools and models to be used in the project development may be released.

b) **Evaluation of the legal and ethical requirements relating to the use of health data within the CHIC project**

This task evaluated European data protection and data security requirements on the processing of sensitive data. Provisions of the Data Protection Directive 95/46/EC on the processing of sensitive data and the security requirements such as Article 8 and 17 were evaluated, to examine the impact of pseudonymisation and anonymisation on the application of the Directive. National transpositions of the Directive and other relevant international and national regulations on data protection also formed part of the evaluation. Other relevant Directives such as the Clinical Trials Directive 2001/20/EC, Good Clinical Practice Directive 2005/28/EC and Medicinal Products Directive 2001/83/EC were also analysed. In addition, due to the consortium's composition, Swiss and US law have been under investigation, to assess the implications of a possible transfer of personal data to and from these countries within the project. Furthermore, ethical requirements that are relevant, in addition to the legal data protection rules, for carrying out medical research using health data were also evaluated such as the Declaration of Helsinki.

c) **Following I and II above, the presentation of an initial data protection and data security schema for the project**

On the basis of the overall evaluation of the relevant legal and ethical norms, an initial schema of data exchange was outlined in chapter 7 of deliverable D4.1 (which will be further developed in the first iteration data protection and copyright framework in M14). The schema proposes to establish a network of trust within a community of researchers involved in the CHIC project for data sharing. A core aspect of this, to be further developed in the M14 framework, is of taking care of the project development in two phases – the development/validation phase and the exploitation phase.

In the first phase, data will be used by researchers in anonymous form when developing the tools and models. To achieve the level of anonymity required for the project, the clinical and the research domain will be separated from each other to maintain privacy and the required control mechanism relevant to both domains. Data in the research domain will undergo a second pseudonymisation process. In addition to this double pseudonymisation the following pillars will be further used to obtain a result that leads to anonymity in a legal sense:

- i. Research data sets will be stripped of any direct identifiers;
- ii. Confidentiality obligation will be imposed on the users by binding contracts;
- iii. A trusted third party will be used for the second pseudonymisation process before data is used within the CHIC research domain;
- iv. A data protection office will be re-used for the project;
- v. Access to the research domain will be limited/restricted to only authorised persons from each partner institution;
- vi. Technical security measures such as traceability/logging capabilities, encryption, etc, will be maintained;
- vii. There will be no publication of personal identifiers in the research results generated.

Towards the end of the development phase (M36) when the tools will be validated and tested with real data (tantamount to personal data in the understanding the Data Protection Directive), this framework will be reviewed, and updated to take care of the validation aspects of the development phase as well as the exploitation phase of the project.

d) A position paper on the proposed General Data Protection Regulation has been drafted and sent to the VPH Share community

The position paper shows how data reuse under the proposed General Data Protection Regulation may impact medical research. Three key problems for medical researchers wishing to use health data for non-interventional research were identified, namely terminological and factual difficulties in deciding if some given health data qualify as personal or not; difficulty in deciding when the patient data subject should be approached for consent to data use (and what counts as appropriate consent); and difficulty in deciding when to obtain ethical review of the proposed research using the data. In this regard a closer look was taken at the putative impact of Art 81 and 83 of the Regulation in their original draft form. The paper concluded that, as well as providing specific solutions to the above problems, the rules in the Regulation must also make sense in ethical and professional terms to researchers and other actors in the research community operating on the ground (including ethics review committees).

■ **Task 4.2: Initial analysis of the copyright-related legal requirements for the sharing of data and amalgamation of models within CHIC**

Licenses for the tools to be used in the project have been collected via a questionnaire, and analysed in D4.2. A preliminary examination and assessment of the licenses and other copyright issues that may emerge with the amalgamation of tools and models has been carried out, and published in a deliverable D4.2, (initial analysis of the copyright-related legal requirements for the sharing of data) in M9 of the project. Following further one-to-one telco discussions with the project partners, a follow up analysis of the IPR issues will form part of deliverable D4.3.1 in M14.

■ **Task 4.3: Development of a data protection and copyright framework for CHIC**

An initial analysis of the data protection framework has been carried out. A full framework incorporating the copyright aspect will be completed in M42 of the project.

An initial analysis of the data protection framework has been made in M6. A similar analysis of the intellectual property framework has been completed in M9. Task 4.3.1 which is a first iteration of the whole data protection and IPR framework is on-going. Currently, individual discussions concerning IPR during the project and possible exploitation issues are being undertaken. This will

feed into deliverable D4.3.1 in M14. Similarly, data protection contracts - contracts for data providers and end users, have been drafted and circulated to the partners.

Summary of significant results

An initial data protection and data security framework for the project has been developed in compliance with ethical and legal requirements on the reuse of pseudonymized and anonymized data within the EU.

A position paper on the current data protection was drafted early on in the project, for further consideration by the VPH initiative, so as allow researcher concerns and experience to be fed directly and in a timely way into the current legislative reform process.

Data on the licenses of the tools have been collected and are undergoing legal analysis.

Data protection contracts - contracts for data providers, end users, and the trusted service provider have been drafted and circulated to the partners.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

Not applicable.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP4			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	2.00	0.70	0.70
3-USAAR	4.00	0.00	0.00
8-LUH	48.00	12.00	16.07
9-UPENN	2.00	0.50	0.50
13-Custodix	2.00	0.50	1.21
Total	58.00	13.70	18.48

LUH have distributed their person month efforts linearly across the four reporting periods of CHIC. The overperformance of the first project year is due to the starting phase of the project which created a surplus of work in WP4. This has no effect on any tasks in WP4 or any other WPs.

Custodix: due to overlap in work between both WP4 and WP5, Custodix have logged most of their effort under WP4 instead of WP5 as there was a deliverable in WP4.

1.5 Work Package 5: IT Architecture

Main objectives of this WP

WP5 will focus on the definition of the architecture for subsequent implementation and integration. The architecture specification will provide the software architecture design patterns to effectively

guide and support the construction of a coherent and consistent system. Particular emphasis will be given to the definition of appropriate interfaces among the modules to enable interoperability. This work-package ensures that the legal and ethical restrictions defined on WP4 are met by the system through the definition and implementation of the appropriate policies and security mechanisms. In this work-package also the relevant existing standards with impact on the system will be identified, analyzed and selected. We will also investigate and provide techniques to build a private cloud infrastructure to support data processing by utilizing resources within individual institutions. This can potentially facilitate a lot of legal and ethical issues concerning data privacy in remote computing.

Active tasks in this reporting period:

- Task 5.1, Reference Architecture (M1-42)
- Task 5.2, Security tools and services (M1-28)
- Task 5.3, Private cloud infrastructure (M1-27)

Summary of progress achieved towards objectives

The Architecture Board has been formed. Existing architectures have been reviewed and security related issues were studied. An initial CHIC architecture has been designed, while an initial data protection (security) framework has also been developed and deployed. Finally the evaluation of the private cloud technologies, to be endorsed by the consortium has been done. The installation and deployment of the private cloud infrastructure for productive usage is also completed and has been released for initial experimentation.

Summary of details for each task

■ **Task 5.1: Reference Architecture Definition**

Since **TEI-C** is the leader of WP5, the individual activities have been assigned to the participants in order to perform a review and evaluation (mainly by **FORTH**) of existing architectures and work on the architecture definition. The steps in order to process data from WP2, WP3 and WP4 have been taken. The Architecture Board has been established which now operates through regular (usually bi-monthly) Skype meetings. In parallel, efforts have been devoted towards the elaboration – through a series of telephone and Skype conferences – of the Semantic aspects of the architecture. In parallel significant efforts have been devoted (primarily through partner **ICCS**) in making sure that the overall CHIC reference architecture is compatible with the basic science aspects of hypermodel development taking place within WP6. Further input was provided by **USFD** (along with partner **CINECA**) related to the technical specifications of the pre-existing VPH-HF framework, which will provide the core hypermodelling architecture for the CHIC project. Finally, the initial CHIC architecture has been prepared and has been documented in D5.1.1.

■ **Task 5.2: Security tools and services**

Efforts in defining the security view of the architecture have taken place. The work mainly focused on analysing a variety of scenarios for the elaboration of security related aspects ranging from user authentication, authorization, and auditing, over data integrity and privacy to pseudo anonymization and re-identification of patient data. In conjunction with WP4 an initial data protection (security) framework has been developed and deployed within the CHIC development/test environment (**CUSTODIX**). **ICCS** collaborated with **CUSTODIX** for the integration of the single-sign-on security mechanism into the models repository (initial phase).

■ **Task 5.3: Private cloud infrastructure**

FORTH, **TEI-C** and other involved partners (**UBERN** etc.) have completed an in depth evaluation of available competing technologies for the implementation of a private or hybrid cloud based infrastructure supporting scientific computation and/or big data management. The selection of the

most prominent technologies has been completed and a focused evaluation of their comparative strengths and weaknesses was performed. An initial deployment of the CHIC cloud infrastructure has been made, for tests with the hypermodelling infrastructure (MS15). After the initial tests, progress is being made in releasing the cloud infrastructure for productive usage by all CHIC partners. Initial efforts on transforming the Wilms tumor simulation model code for local cloud deployment have been done (ICCS, BED).

Summary of significant results

Formation of the Architecture Board and definition of its operating procedures. Review of existing architectural styles prevalent in the Biomedical Informatics and VPH domains. Design and documentation of an initial CHIC architecture. Development and deployment of an initial data protection (security) framework within the CHIC development/test environment. Selection of most appropriate technologies for the implementation of private or hybrid cloud infrastructures and in depth evaluation. Initial deployment of the CHIC cloud infrastructure for tests with the hypermodelling infrastructure. Installation and deployment of the private cloud infrastructure for productive usage, which will be soon released for usage by all partners.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

The submission of D5.1.1 has been delayed from its due date (M12), and an extension has been requested with the approval of the WP leader and the CHIC coordinator.

One point worth reporting is the fact that newly hired staff hired by partner **USFD** has been included in the Architecture Board and will be strongly included in the upcoming work for Tasks 5.1 and 5.2. Every effort to technically align the CHIC architecture with what already has been developed in the sites of specific partners will be made.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

All critical objectives and milestones of the WP have been achieved.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP5			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	3.00	0.80	1.00
5-BED	19.00	5.00	5.00
6-USFD	12.00	0.00	0.00
7-FORTH	10.00	3.00	9.00
12-UBERN	4.00	0.50	0.30
13-Custodix	12.00	2.00	0.70
14-Philips	15.00	2.00	1.10
17-TEI-C	15.00	4.00	3.96
Total	90.00	17.30	21.06

For **FORTH**, the discrepancies between the planned and the actual PMs are large in WP5, as FORTH had planned the budget on higher salary, experienced post-docs at an average rate given by the central administration, but eventually, no appropriate senior post-docs could be hired and instead a larger number of less experienced engineers (Graduates) was hired for the project at lower rates. The result was an increase in the number of actual PMs for FORTH. These new circumstances have no effect on FORTH's overall budget.

Custodix: due to overlap in work between both WP4 and WP5, Custodix have logged most of their effort under WP4 instead of WP5 as there was a deliverable in WP4.

1.6 Work Package 6: Cancer Models and Hypermodel Design

Main objectives of this WP

The main objectives of WP6 are: To develop clinically driven multiscale cancer models. To use these models along with already existing ones in order to produce elementary models (hypomodels or component models) of fundamental biological processes (biomechanisms). To standardize the latter according to the guidelines to be provided by WP7. To subsequently produce hypermodels (integrated models) as demonstrators of the VPH hypermodelling methodology in the cancer domain. To test and validate all models.

Active tasks in this reporting period:

- Task 6.1, Cancer hypomodelling and hypermodelling strategies and elementary models (M1-36)
- Task 6.2, Subcellular cancer modeling (M1-36)
- Task 6.3, Biomechanics enhanced tumour modeling (M1-36)
- Task 6.4, The clinical modeling paradigms of nephroblastoma, glioblastoma and lung cancer (M6-46)
 - SubTask 6.4.a: The nephroblastoma paradigm
 - SubTask 6.4.b: The glioblastoma paradigm
 - SubTask 6.4.c: The lung cancer paradigm
- Task 6.5, The colon cancer modeling paradigm (M6-46)
- Task 6.6, The prostate cancer modeling paradigm (M6-46)

Summary of progress achieved towards objectives

In **task 6.1**, extensive work has been done regarding cancer hypomodelling and hypermodelling strategies. **ICCS** proposed an initial generic conceptual platform to possibly serve as a standardized framework for the design and development of multi-research group multiscale hypermodels. **Moreover**, **ICCS** proposed a formal description of any cancer model (including hypomodel and hypermodel) based primarily on 13 perspectives. The modelling partners (**ICCS**, **UOXF**, **UPENN**, **UNITO**, **FORTH**, **UBERN**) have provided the detailed description of a large number of cancer models. **ICCS** produced the core content of the CHIC glossary, which was expanded by other partners. All modelling partners contributed extensively to the discussions on the mid- and long-term project strategy. **ICCS** proposed the lung cancer scenario to serve as the driver for the first multi-modelling group multiscale hypermodel demonstrator. All modelling partners are revisiting their developed or under development hypomodels in order to enable their linking and re-writing in the context of hypermodelling.

In **Task 6.2**, discussions were continued between **ICCS**, **UPENN** and **USAAR** on the linking of the subcellular and the cellular and supercellular levels of biocomplexity. A clear way of linking subcellular multiscale models with cellular and supercellular models has been established. Descriptions of several subcellular cancer models developed by **UPENN** and **UOXF** have been

included in Deliverable D6.1. **UPENN** established a molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations. As part of the task a multiscale method to combine the molecular studies with signalling network studies was developed. **UPENN** developed a physically based multiscale modeling platform for predictively analysing the role played by the external cell environment on intracellular trafficking in mammalian cells. **UNITO** has been working on prostate cancer modelling at the subcellular level. A feasibility study is currently open to collect blood samples from prostate cancer patients undergoing radiotherapy IRCC-Candiolo in order to correlate tumour markers with clinical outcome (related project to be submitted to the Ethical Committee on May 2014).

In **Task 6.3**, possible extensions of previous work done within the framework of the Contra Cancrum project have been explored. **ICCS** made concrete suggestions regarding the integration of biomechanics modelling into discrete-entity discrete-event multiscale cancer modelling. The main components required for the biomechanical modelling have been identified by **UBERN** in collaboration with **ICCS**. The model behaviour has been defined and requirements to run the model have been defined.

In **Task 6.4**, **UNITO** has carefully investigated similarities and differences of the three clinical modelling paradigms of CHIC compared to their prostate cancer modelling, in order to share knowledge with the rest of the CHIC modelling partners.

In **SubTask 6.4.a**, the partners explored the integration of micro-RNA related mechanisms into the multiscale model developed by **ICCS**. Exploitation took place of already available Wilms tumor patients' multiscale data, provided by **USAAR** within the framework of previous projects.

In **SubTask 6.4.b**, an initial machine learning model was shaped to be used as the statistical modelling approach (**ICCS** in collaboration with WP3). **ICCS** carried out an in-depth comparative study of several machine learning techniques that could potentially be recruited and adapted in order to address the particular problem.

In **SubTask 6.4.c**, the partners exploited already available data, provided by **USAAR** within the framework of the Contra Cancrum project. **ICCS** proposed the lung cancer scenario to serve as the driver for the first multi-modelling group multiscale hypermodel demonstrator.

In **Task 6.5**, there was interaction of **ICCS** with **UOXF** regarding the clarification and implementation of several components of colon cancer modelling.

Finally, in **Task 6.6**, **UNITO** has almost completed data collection from the Urological and Radiotherapy departments in Regione Piemonte. Development of a hypermodel which connects the tissue level (tumor growth according to PSA level) to the cellular level (response to therapies) to the subcellular level (prediction of the response according to the detected biomarkers level) is in progress. **ICCS** collaborated with **UNITO** regarding the clarification and implementation of several components of the prostate cancer modelling. **ICCS** provided guidance to **UNITO** regarding overall modelling characteristics that could render the prostate model compatible with the CHIC modelling framework.

Summary of details for each task

■ **Task 6.1, Cancer hypomodelling and hypermodelling strategies and elementary models:**

Extensive work has been done regarding cancer hypomodelling and hypermodelling strategies. An extensive outline of this process is included in the deliverable D6.1 "Cancer hypomodelling and hypermodelling strategies and initial component models" (submitted and accepted). The deliverable provides an extensive list of models already developed or under development by the consortium modellers (**ICCS**: 22 models at the cell and tissue level. **UOXF**: 3 models at the molecular level and 3 models at the cell and tissue level. **UPENN**: 4 models at the atomic level. **UNITO**: 4 models at the cell and tissue level. **FORTH**: 2 models at the cell and tissue level. **UBERN**: 1 model at the cell and tissue

level). These models will provide the starting point and the basis for the development of several CHIC hypomodels and hypermodels through metamodeling.

ICCS proposed an initial generic conceptual platform to possibly serve as a standardized framework for the design and development of multi-research group multiscale hypermodels and produced a corresponding *internal document* entitled “*The core of a generic conceptual framework for building cancer hypermodels*”.

Furthermore, **ICCS** proposed a formal description of any cancer model (including hypomodel and hypermodel) based primarily on 13 perspectives. Corresponding *internal document*: “*Characterizing a (cancer) model and defining the boundaries between a metamodel and a model*”.

ICCS produced the core content of the CHIC glossary to be expanded by other partners. The partners can access the glossary via the CHIC intranet (ProjectAngel).

All modelling partners contributed extensively to the discussion on the mid- and long-term project strategy that took place during the February 2014 plenary meeting in Luton.

All modelling partners are revisiting their developed or under development hypomodels in order to enable their linking and re-writing in the context of hypermodelling.

■ **Task 6.2, Subcellular cancer modeling:**

Discussions between **ICCS**, **UPENN** and **USAAR** on the linking of the subcellular and the cellular and supercellular levels of biocomplexity have led to a joint publication.

A clear way of linking subcellular multiscale models with cellular and supercellular models has been established.

Descriptions of several subcellular cancer models developed by **UPENN** and **UOXF** have been included in Deliverable D6.1.

UNITO has been working on prostate cancer modelling at the subcellular level. A feasibility study is currently open to collect blood samples from prostate cancer patients undergoing radiotherapy IRCC-Candiolo in order to correlate tumour markers with clinical outcome (related project to be submitted to the Ethical Committee on May 2014).

■ **Task 6.3, Biomechanics enhanced tumour modeling:**

Possible extensions of previous work done within the framework of the Contra Cancrum project have been explored.

The main building blocks for the biomechanical simulations have been identified by **UBERN** in collaboration with **ICCS**. The description of the model has been summarized, including description of the model, the list of input/output components as well as the software requirements.

ICCS has made concrete suggestions regarding the integration of biomechanics modelling into discrete-entity discrete-event multiscale cancer modelling in order to refine the tumor shape prediction.

■ **Task 6.4, The clinical modeling paradigms of nephroblastoma, glioblastoma and lung cancer:**

UNITO has been carefully investigating similarities and differences of the three clinical modelling paradigms of CHIC compared to their prostate cancer modelling, in order to share knowledge with the rest of the CHIC modelling partners.

- **SubTask 6.4.a, The nephroblastoma paradigm:** Exploration of the integration of micro-RNA related mechanisms into the multiscale model developed by **ICCS**. Exploitation of already available Wilms tumor patients’ multiscale data, provided by **USAAR** within the framework of previous projects. Extensive discussions regarding the planned use of micro-RNA data by the nephroblastoma hypermodel Oncosimulator.

- **SubTask 6.4.b, The glioblastoma paradigm:** Shaping of an initial machine learning model to be used as the statistical modelling approach (**ICCS** in collaboration with WP3).
- **ICCS** has made an in-depth comparative study of several machine learning techniques that could potentially be recruited and adapted in order to address the particular problem.
- **SubTask 6.4.c, The lung cancer paradigm:** Exploitation of already available data, provided by **USAAR** within the framework of the Contra Cancrum project, has triggered improvements on the discrete event based model of lung cancer developed by **ICCS**.

Following a rigorous exploration of the type of clinical multiscale data provided or to be provided by the clinicians, as well as the corresponding data provision timing, **ICCS** has proposed the lung cancer scenario to serve as the driver for the first multi-modelling group multiscale hypermodel demonstrator.

■ **Task 6.5, The colon cancer modelling paradigm:**

There has been a continuous interaction of **ICCS** with **UOXF** regarding the clarification and implementation of several components of colon cancer modelling.

■ **Task 6.6, The prostate cancer modelling paradigm:**

UNITO has almost completed data collection from the Urological and Radiotherapy departments in Regione Piemonte, and around 1500 complete follow-up pertaining to prostatectomized or radically radiotreated patients are available for model validation. Development of a hypermodel which connects the tissue level (tumor growth according to PSA level) to the cellular level (response to therapies) to the subcellular level (prediction of the response according to the detected biomarkers level) is in progress.

There was interaction between **ICCS** and **UNITO** regarding the clarification and implementation of several components of the prostate cancer modelling. **ICCS** provided guidance to **UNITO** regarding some overall modelling characteristics that should be addressed in order to render the prostate model compatible with the CHIC modelling framework.

Summary of significant results

Extensive work has been done regarding cancer hypomodelling and hypermodelling strategies.

Proposal of an initial generic conceptual platform to serve as a standardized framework for the design and development of multi-research group multiscale hypermodels.

Detailed description of a large number of cancer models included in Deliverable D6.1.

Proposal of a formal description of any cancer model (including hypomodel and hypermodel) based primarily on 13 perspectives.

The CHIC glossary has been started. A basic version of the glossary is accessible on the CHIC intranet. The partners are currently editing the document.

Clear way of linking subcellular multiscale models with cellular and supercellular models has been established.

Exploitation of already available Wilms tumor patients' multiscale data.

Shaping of an initial machine learning model to be used as the statistical modelling approach for glioblastoma multiforme immunotherapy. In depth comparative study of several machine learning techniques.

Proposal of the lung cancer scenario to serve as the driver for the first multi-modelling group multiscale hypermodel demonstrator.

The components of the biomechanical model and the related scientific and technological requirements have been defined. The initial integration of biomechanics modelling into discrete-event multiscale cancer modelling has been designed.

Feasibility study currently open to collect blood samples from prostate cancer patients undergoing radiotherapy IRCC-Candiolo in order to correlate tumour markers with clinical outcome

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

UBERN: The development of the biomechanical model for the brain has been delayed due to recruitment problems. Currently all the positions have been filled and the progress will shortly converge to the initial planning.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

The recruitment delay at **UBERN** will have minimal impact on other tasks, available resources and planning. There is sufficient time to meet the milestones. Based on the knowledge of the biomechanical model, the interfaces with the other components have been defined (such as input/output component), which eliminates the impact on the other partners.

Corrective actions

See point 6 above.

Statement on the use of the resources

Planned versus actual efforts in WP6			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	44.00	13.00	13.72
7-FORTH	9.00	2.50	7.61
9-UPENN	61.00	15.00	15.00
10-UOXF	46.00	0.20	0.36
11-UNITO	14.00	1.00	1.08
12-UBERN	20.00	0.50	0.40
14-Philips	1.00	0.00	0.00
Total	195.00	32.20	38.09

For **FORTH**, the discrepancies between the planned and the actual PMs are large in WP6, as FORTH had planned the budget on higher salary, experienced post-docs at an average rate given by the central administration, but eventually, no appropriate senior post-docs could be hired and instead a larger number of less experienced engineers (Graduates) was hired for the project at lower rates. The result was an increase in the number of actual PMs for FORTH. These new circumstances have no effect on FORTH's overall budget.

1.7 Work Package 7: Hypermodelling infrastructure

Main objectives of this WP

Develop the ICT hypermodelling infrastructure, intended as a set of services and technologies that make possible to build and execute integrative models, formed by component models and relation models, coherent with the vision of VPH.

Active task in this reporting period:

- Task 7.1, Models execution (M1-27)
- Task 7.2, Metamodels annotation (M7-36)
- Task 7.3, Hypermodels execution (M7-42)
- Task 7.5, Hypermodelling infrastructure (M7-42)

Summary of progress achieved towards objectives

In **Task 7.1**, **USFD** actively engaged in the process of defining the information required (e.g. input/output, flow, resources....) for each of the component models proposed to be implemented in the CHIC hypermodelling architecture. We have also contributed to discussions and documentation extension related to the definition of the generic stub.

In this first reporting period, **CINECA** worked at the activities for the definition of the CHIC-HF hypermodel component, generic stub. In particular, training activities were carried out with **USFD** staff on the hypermodel technology previously developed within the VPHOP project and that will be the base for the CHIC developments. The activities included meetings to introduce the technology and its use and support the installation of the hypermodelling framework on the USFD hardware. These activities were also the base for the start of Task 7.3 and 7.5 activities and to create a common understanding of the available technologies. **FORTH** defined the “generic model stub” and prepared a design document that was discussed and agreed upon with the WP7 partners. **ICCS** provided to **USFD**, **FORTH** and **CINECA** an initial list of component models, including their technology specifications for control and data flow, to serve as preliminary drivers for the development of the execution platform. **ICCS** also reviewed the Component Model Generic Stub developed by **FORTH**.

In **Task 7.2**, **BED** released the first version of the basic annotation and tag management service. **USFD** provided to partner **BED** a test bed for annotation, and user-tested the basic tag management system provided by **BED**. **UCL** designed and planned the HOT Maps knowledge management effort. This effort, carried out by **UCL**, Bedfordshire, Saarland and Leuven, will carry out the text mining of cancer literature as a means to link cancer mechanism knowledge to annotations of CHIC elementary process models. **ICCS** prepared and distributed a preliminary review of existing ontologies pertinent to the CHIC project. **ICCS** has also proposed 13 perspectives from which each model should be viewed and a corresponding metamodel should be created.

In **Task 7.3**, **CINECA** worked in particular on the revision of the VPH-HF for the analysis and definition of the CHIC-HF components. **USFD** replicated on their cluster the VPH-HF software stack that was originally developed in the VPHOP project, and which will be used as starting point for the CHIC hypermodelling framework. Partners **CINECA** and **USFD** completed a basic model test run on this installation, and we have carried out a reciprocal test on the installation created on the CINECA PLX. We have also drafted the structure of and contributed to Deliverable 7.1 – Hypermodelling Specifications. Under **FORTH's** supervision, an initial design of the interaction between the Hypermodelling Editor and the execution framework has been agreed among the relevant partners (**FORTH**, **CINECA**, and **USFD**).

ICCS contributed in the analysis of the various interactions between the components developed in WP7 and those developed in the context of other workpackages. **ICCS** also worked for the consolidation of the hypermodelling specifications gathered by WP7 developers. Under the coordination of **ICCS** all partners contributed to the production of Deliverable D7.1: “Hypermodelling specifications”.

Finally, in **Task 7.5** **USFD** co-ordinated activity between **FORTH** and **CINECA** who are the primary partners involved in the initial stages of this task.

FORTH provided an initial cloud infrastructure for the deployment of the hypermodel execution framework. **ICCS** has provided the initial hypermodelling strategy for the cancer domain to be used as a driver for the development of the hypermodelling infrastructure.

Summary of details for each task

■ **Task 7.1: Models execution**

D6.1 “Cancer hypomodelling and hypermodelling strategies and initial component models”, which includes i.e. a list of component models with both their basic science and the technical specifications, including control and data flow was written in collaboration with WP7. The technology specifications of the models, to be used by WP7, include execution time, memory requirements, source code language etc. This list of model descriptions is to be used as a reference basis for the development of specific hypermodeling technologies in WP7. Upon receiving the first draft from **ICCS**, **USFD** made a number of suggestions including:

- i. Limiting the number of models to be implemented in the first instance and instead implementing the models in phases;
- ii. The attributes of the different component models that needed to be explicitly defined in order to allow the component models to be implemented on the CHIC hypermodelling architecture. Specifically, these included: input and output parameters and files, coding language, operating system required, external dependencies and hardware requirements.

These suggestions were implemented in the second draft of the component model list. **USFD** staff attended a WP6 workshop at **UOXF** on defining the initial set of hypomodels for implementation on 10-11th April 2014. **FORTH** released an initial version of the definition of a generic stub interface for the execution of models, based on prior experience on the field. This work has been also presented and discussed in the plenary meeting of the consortium. **ICCS** in collaboration with several partners revised the deliverable.

■ **Task 7.2: Metamodels annotation**

USFD provided feedback to **CINECA** on a first draft of a proposed tagging scheme. We implemented a mathematical (ODE-based) model from the literature in Matlab and provided **BED** with the necessary set of information relating to this model in order to implement the first basic annotation system. **ICCS** prepared and distributed a preliminary review of existing ontologies pertinent to the CHIC project. **ICCS** also proposed 13 perspectives from which each model should be viewed and a corresponding metamodel should be created. Apart from those perspectives additional crucial information including the input and the output of each model is to be provided for each model. **BED** developed the first version of the tagging system, which was tested by **CINECA** and **USFD**.

■ **Task 7.3: Hypermodels execution**

USFD replicated on their cluster the VPH-HF software stack that was originally developed in the VPHOP project, and which will be used as starting point for the CHIC hypermodelling framework. Such replication highlighted a number of problems, primarily related to different versions of supporting libraries, and to the limitations of configuration that a large HPC resource typically imposes to its users, which have now been resolved. A basic model test run was completed by partners **CINECA** on this installation and we have carried out a reciprocal test on the installation created on the **CINECA** PLX. Test workflows consisting of two orchestrated exemplar hypomodels are due to be executed on both installations by the end of the month. **USFD** drafted the overall structure of the document for Deliverable 7.1 Hypermodelling Specifications, which was agreed by all WP7 partners. We have provided Section 3 relating to Use Case Scenarios for this deliverable. In this task **CINECA** has worked in particular to the revision of the VPH-HF for the analysis and definition of the CHIC-HF components. In particular the functional requirements and the expected APIs have been

defined. The results of this work are reported in D7.1. However, D7.1 will be submitted 15 days after submission of “D5.1: 1 The CHIC technical architecture-initial version”, in order to ensure consistency between the CHIC architecture described in D5.1.1 and the components participating in the Hypermodelling Infrastructure, which is a subset of the overall architecture. The responsible partner for D7.1 (ICCS) has already received a draft version of the D5.1.1, but the final version of D5.1.1 is needed in order to finalize D7.1 as well.

At the same time, a shared collaboration environment has been created on CINECA HPX cluster (PLX) with the deployment of the current implementation of the VPH-HF to be the base for the next developments. In order to test the deployment, the correct working and fix issues so to be ready for the deployment on the **FORTH** system, a replica of the deployment has been carried out on USFD system (Iceberg). The testing and comparison between the two systems deployment will be completed before starting the one at **FORTH**. Joint development between **CINECA**, **USFD** and **BED** team has also started under an Agile development process (eXtreme Programming). Physical meetings are organised every three months to analyse requirements (users’ stories) to be implemented, discuss technical solutions, prioritise and assign specific programming activities. **ICCS** contributed to the analysis of the various interactions between the components developed in WP7 and those developed in the context of other workpackages; contribution in the corresponding documentation. **ICCS** also worked to the consolidation of the hypermodelling specifications gathered by WP7 developers and for the production of Deliverable D7.1: “Hypermodelling specifications”. **ICCS** provided indicative preliminary models to support the design of the model execution platform.

■ Task 7.5: Hypermodelling infrastructure

USFD have co-ordinated activity between **FORTH** and **CINECA** who are the partners with the primary roles in developing the hypermodelling infrastructure. We are in the process for developing a VPH-HF installer for the platform specified by **FORTH**. **FORTH** has established an initial deployment of the CHIC cloud infrastructure (MS15) after the evaluation of the existing solutions and the selection of OpenStack. We are now progressing towards having an initial deployment of the hypermodelling platform using the cloud infrastructure. **ICCS** has provided the initial hypermodelling strategy for the cancer domain to be used as a driver for the development of the hypermodelling infrastructure.

In order to ensure fine-grained project management for WP7, necessary due to the challenging implementation issues to be dealt with in this workpackage, we have activated an eXtreme Project Management (XPM) model that complement that Classic Project Management model used by the coordinator. Each output of WP7 is exploded into sub-tasks that are negotiated with the participating partners, which act as providers or as users, depending on the sub-task.

Summary of significant results

USFD – Contribution to the required attributes pertaining to the component models, which will ultimately allow implementation of the latter on the CHIC hypermodelling framework, and also of the generic stub which will define connectivity between model components.

FORTH - The generic stub will be the basis for the model implementations and the CHIC execution framework. The cloud infrastructure has been deployed and is ready to be tested and used by the interested partners.

ICCS - Production of a list of component models with their technology specifications, including control and data flow.

USFD – Provision of a test object for development of the basic tag management system.

ICCS - Proposal for 13 perspectives from which each model should be viewed and a corresponding metamodel should be created.

USFD - Successful installation of VPH-HF, the core technology for the CHIC hypermodelling architecture, at USFD. This will provide a valuable resource for further developmental work in the rest of WP7.

ICCS - Analysis of interactions between WP7 components and components developed in the context of other work packages.

ICCS - Consolidation of the hypermodelling specifications.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

During the process of implementing hypomodel test cases for the initial installations of the hypermodelling architecture, it became apparent that the current method of hypomodel wrapping (associated with the pre-existing VPH-HF) is not optimal. USFD and CINECA have taken the decision that refactoring the template wrapper is required and CINECA are currently exploring options for doing this. A firm decision on the revised wrapper structure will be made before PM24. This refactoring is not anticipated to cause any significant issues with the development of the hypermodelling environment, particularly as it was always planned to revise the definition of the generic stub throughout the course of the project.

Small delay of Deliverable D7.1 “Hypermodelling specifications” (originally due M12, i.e. 31.03.2014): the submission of the deliverable in mid-April was requested, since, in the plenary meeting at Luton in late February 2014, there have been important interactions between the involved partners which needed to be incorporated in D.7.1. The deliverable will be submitted 15 days after submission of “D5.1: 1 The CHIC technical architecture-initial version”, in order to ensure consistency between the CHIC architecture described in D5.1.1 and the components participating in the Hypermodeling Infrastructure, which is a subset of the overall architecture. The responsible partner for D7.1 (ICCS) has already received a draft version of the D5.1.1, but the final version of D5.1.1 is needed in order to finalize D7.1 as well.

No impact on other tasks as well as on available resources and planning is expected.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

All critical objectives have been achieved in the first year of the CHIC project.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP7			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	6.00	1.50	1.70
3-USAAR	4.00	0.00	0.02
5-BED	19.00	4.00	4.00
6-USFD	128.00	30.00	30.19
7-FORTH	6.00	1.50	2.00
15-UCL	24.00	3.00	2.26
16-CINECA	42.00	12.00	11.56
Total	229.00	52.00	51.73

WP7 was expected to start immediately, but delays in the recruitment procedures forced **USFD** to compensate in the first six months with other staffs, and with the recruitment on the project of a PhD student, who will continue to work in the project for the next two years. Because of this **USFD** plan a considerable increase of effort in WP7, that will raise from 88 PM as planned in the DoW to 128 PM; however, this will not involve any increase of cost, due to the lower salary scale of the PhD student.

1.8 Work Package 8: Model and Data Repositories

Main objectives of this WP

This work package focuses on the development of various kinds of repositories, including the design and implementation of the corresponding infrastructures and interfaces which will cover the needs of the CHIC project.

This involves the development of:

- a repository of cancer models, spanning from models of generic fundamental biomechanisms involved in cancer progression and treatment response, such as cell cycle and cell metabolism, to complex multiscale models of various types of cancer;
- a repository of multiscale data exploitable by the models, either by physically storing the data in the project's data repository, or by providing links to other, already existing, data repositories or warehouses;
- a repository of in silico trials for various types of cancer;
- a distributed RDF repository to store metadata from each partner, including the corresponding interfaces for annotating and querying.

The aforementioned repositories will be tailored to the needs/clinical scenarios of the project. At the same time they will be generic enough to be reusable by several different medical scenarios.

Active tasks in this reporting period:

- Task 8.1, Development of the model/tool repository (M1-48)
 - SubTask 8.1.a, Development of the model/tool repository
 - SubTask 8.1.b, Development of the data repository
 - SubTask 8.1.c, Development of the in silico trial repository
- Task 8.2, Infrastructure for Semantic Metadata Management (M1-48)
 - Subtask 8.2.a, RDF storage solution for semantic metadata
 - Subtask 8.2.b, A core knowledge base to support semantic querying of metadata
 - SubTask 8.2c, Resource annotations
- Task 8.3, Integration with the security and the legal/ethical framework (M10-48)

Summary of progress achieved towards objectives

In **SubTask 8.1.a**, **ICCS** has performed a requirement analysis on the model/tool repository.

In **SubTask 8.1.b**, **ICCS** analysed the specifications of the clinical data that will be hosted in models/tools repository and coordinated the collection of representative sets of fake data. **UBERN** identified the data repository framework. An initial version is running and will be available shortly for clinicians to store medical image datasets. **UBERN** has also finalized the specification of the RESTful communication as well as the implementation of the most critical functions.

In **Subtask 8.1.c**, **ICCS** provided the requirements of the *in silico* trial repository and has reviewed the technologies to be used for its development.

In **Subtask 8.2.a**, **ICCS** analysed existing model integration examples.

In **Subtask 8.2.b**, **ICCS** prepared and distributed a preliminary review of existing ontologies pertinent to the CHIC project. **ICCS** designed and prepared the deliverable D6.1 “Cancer hypomodelling and hypermodelling strategies and initial component models” so as to provide certain initial semantic descriptions of the models. **ICCS** has also provided a system of formal description of each cancer model based on 13 perspectives and additional information including i.a. the input and output parameters of the model. **UCL** initiated, at consortium level, the articulation and collection of requirements for the knowledge representation for integrative models and associated data. **UCL** also ensured the coherence of the CHIC semantic interoperability framework with metadata frameworks in the pharmaceutical R&D industry and carried out a first assessment of the applicability of Functional Tissue Unit knowledge in support of multiscale integrative models in cancer. A first assessment of the applicability of the ApiNATOMY knowledge representation in support of flow process metadata management has been also carried out. **USAAR** started discussions with the p-medicine project on how to collaborate in the area of semantic interoperability. In addition ‘HOT Maps’ of tumour-specific hallmark knowledge is under discussion with several partners, led by **UCL**.

In **Subtask 8.2.c**, **ICCS** is investigating the requirements for a possible connection of the RICORDO infrastructure with the CHIC model repository to be developed. **UCL** initiated the design of the underlying RICORDO implementation adapted to the project requirements collected in subtask 8.2.b. **UCL** established a simple online graphical user interface to illustrate: (i) the creation of RICORDO annotations and (ii) the display of multiscale anatomy knowledge over which semantic metadata can be organized and visualized.

In **Task 8.3**, **ICCS** had a close collaboration with **LUH** in order to adopt a proper legal/ethical procedure for the collection of clinical data. **ICCS** also reviewed the tools that can be used for the automatic pseudonymization and uploading of clinical data to the data repository. **UBERN** completed the initial integration of the data repository within the CHIC security framework.

Summary of details for each task

■ **Task 8.1: Development of Repositories**

SubTask 8.1.a: Development of the model/tool repository

ICCS has performed a requirement analysis on the model/tool repository, including:

- collection of information concerning the characteristics of CHIC component models (existing and/or to be developed)
- classification of the component models with respect to: biological scale, software requirements, hardware requirements
- review of the technologies to be used in the development of model/tools repository.

SubTask 8.1.b: Development of the data repository

ICCS provided the major multiscale data categories which drive the development of the repository and has contributed to the discussions concerning the creation of the latter. **ICCS** analysed the specifications of the clinical data that will be hosted in models/tools repository.

ICCS coordinated the collection of representative sets of fake data from **the clinical partners**. The collection of real data presupposes the availability of the data protection framework, which will be ready on month 14.

ICCS analysed the aforementioned data and categorized them into structural data (numerical or textual) and files (documents, spreadsheets-CSV, imaging data, etc.)

At **UBERN**, a database framework has been selected as the data repository. The repository can be easily adapted to store medical images for the project as well as the results of the image processing steps (i.e. image segmentation). The different datasets can be linked together. An additional object type should be added to enable the system to store other medical information.

A development environment has been setup by **UBERN**, which can be used by third party instances to integrate the REST service of the data repository within their application. The REST uploader currently supports the following file formats: DICOM (Digital Imaging and Communications in Medicine), Metalmage, Analyze, Niftii, and HDF5 (Hierarchical Data Format). Chunked encoding will be applied to support the upload of large files. The first integration has been selected and will be the data upload of anonymous patient information from the Trusted Third Party.

SubTask 8.1.c: Development of the in silico trial repository

ICCS provided the requirements of the *in silico* trial repository and has reviewed the technologies to be used for its development.

■ **Task 8.2: Infrastructure for Semantic Metadata Management**

Subtask 8.2.a: RDF storage solution for semantic metadata

ICCS analysed existing model integration examples.

Subtask 8.2.b: A core knowledge base to support semantic querying of metadata

ICCS prepared and distributed a preliminary review of existing ontologies pertinent to the CHIC project. The deliverable D6.1 “Cancer hypomodelling and hypermodelling strategies and initial component models” prepared by **ICCS** in collaboration with several other partners has been designed in such a way as to provide certain initial semantic descriptions of the models. **ICCS** has also provided a system of formal description of each cancer model based on 13 perspectives and additional information including i.a. the input and output parameters of the model.

UCL initiated, at consortium level, the articulation and collection of requirements for the knowledge representation for integrative models and associated data. **UCL** also ensured the coherence of the CHIC semantic interoperability framework with metadata frameworks in the pharmaceutical R&D industry and carried out a first assessment of the applicability of Functional Tissue Unit knowledge (see publication in WP12 report for **UCL**) in support of multiscale integrative models in cancer. A first assessment of the applicability of the ApiNATOMY knowledge representation in support of flow process metadata management has been also carried out.

USAAR started discussions with p-medicine on how to collaborate in the area of semantic interoperability. In addition ‘HOT Maps’ of tumour-specific hallmark knowledge is under discussion with different partners led by **UCL**. **USAAR** organized a related workshop in Homburg in December 2013. The HOT Maps effort will establish an expert-checked knowledge base linking specific Tumours (T) to tumourspecific cancer process Hallmarks (H) by mapping H and T terms to terms from an independent reference set of Ontologies. The HOT Maps will be further developed in an iterative process with input from all clinical partners. This work is carried out with the Dr Inventor project.

Subtask 8.2.c: Resource annotations

ICCS is investigating the requirements for a possible connection of the RICORDO infrastructure with the CHIC model repository to be developed.

UCL initiated the design of the underlying RICORDO implementation adapted to the project requirements collected in subtask 8.2.b. **UCL** established a simple online graphical user interface to illustrate: (i) the creation of RICORDO annotations and (ii) the display of multiscale anatomy knowledge over which semantic metadata can be organized and visualized.

■ **Task 8.3: Integration with the security and the legal/ethical framework**

ICCS had a close collaboration with **LUH** in order to adopt a proper legal/ethical procedure for the collection of clinical data. **ICCS** also reviewed the tools that can be used for the automatic pseudonymization and uploading of clinical data to the data repository.

UBERN: The data repository has been integrated with the external security framework provided by **CUSTODIX**. Shibboleth has been used to support single sign-on within the CHIC domain on the web-based solution of the data repository. The technical implementation of the authentication mechanism for the REST service has been defined and will be based on SAML token. REST clients are responsible for retrieving a SAML token from the Security Token Service (STS) provided by **CUSTODIX** and then passing it through a HTTP authorization header to the REST service.

Summary of significant results

Requirement analysis on the model/tool repository.

Database framework selected for data repository.

Clinical data specification analysis.

Fake clinical data collection.

Review of technologies for the development of the *in silico* trial repository.

Analysis of existing model integration examples.

Initial integration of data repository with CHIC security framework completed. First version of the REST services has been implemented.

Review of the tools for automatic pseudonymization and uploading of clinical data to the data repository.

Preliminary review of existing ontologies pertinent to the CHIC project.

Collection of knowledge representation requirements for multiscale cancer biology.

Design of a semantic interoperability framework based on the above requirements collection that is coherent with developing standards in industry.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

Not applicable.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP8			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	14.00	4.00	4.20
3-USAAR	3.00	0.00	0.00
7-FORTH	6.00	1.50	2.00
9-UPENN	3.00	1.00	1.00
12-UBERN	15.00	3.00	4.50
13-Custodix	3.00	0.50	0.00

14-Philips	7.00	1.00	0.00
15-UCL	48.00	3.00	4.28
Total	99.00	14.00	15.98

UBERN: WP8 started earlier than initially planned in order to accelerate the development and installation of the clinical data repository. This updated schedule will be beneficial to the project and should accelerate the transfer of data to the consortium (as soon as the legal issues have been settled).

UCL: Preparations for the model and data annotation strategy had to be slightly accelerated as it became apparent that progress in WP7 was dependent on this effort in WP8

1.9 Work Package 9: Image Processing and Visualization

Main objectives of this WP

This work package will concentrate on the visualization and image analysis support to the project. The objectives are:

- To provide a set of visualization tools for model and data analysis;
- To provide a set of image analysis tools for image data processing;
- To provide tools for assessing the tumor change from functional tomographic data.

Active tasks in this reporting period:

- Task 9.1, User requirement analysis (M1-6)
- Task 9.2, Scalable visualization techniques (M3-18)
- Task 9.5, A general image processing development toolkit (M6-18)
- Task 9.6, Image registration tools (M3-36)

Summary of progress achieved towards objectives

The deliverable D9.1 which includes the user requirements on the visual analysis suite and image analysis tools has been completed and submitted. **ICCS** provided the major requirements of the models with regards to image processing and visualization.

The SQL database has been mapped on BED's local server in order to test data and design effective visualization approaches (e.g. ContraConcnum). The possibility of reusing the ContraCancrum visualisation plugin has been analysed. DoctorEye has been chosen as the basis of further development software for visualizing 3D and 4D tumor shape. There has been a significant clinical interaction work especially in collaboration with the clinical partners. Objectives of nephroblastoma segmentation have been identified into three stages: identification of region of interest, measurement of tumor growth and decrease after treatment. The images registration pipeline for monomodal and multimodal images has been identified and tested based on the clinical needs and technical specifications. A literature review on advanced feature selection for supervised classification approaches, as well as an extensive literature review on advanced MRI modalities, including diffusion and perfusion imaging has been conducted. The WP9 team visited the radiology department within a dedicated meeting and the general analysis framework for therapy assessment has been designed. This includes the pharmacokinetic analysis of the MRI data to derive tumor perfusion markers and sophisticated diffusion analysis tools.

Summary of details for each task

- **Task 9.1: User requirement analysis:**

The task has been completed, and the related deliverable D9.1 was submitted.

This task gathers user requirement on the visual analysis suite and image analysis tools. Typical approaches and examples that are expected to get benefit from the use of visualization and image analysis are identified and analysed. We have looked into current problems and needs in the model and data analysis and understand the scales of the model and data repositories. Some questionnaires were developed for collecting information from relevant stakeholders regarding acceptance, user needs and requirements. Documentation of the requirement and analysis have been prepared.

Within the framework of a close collaboration with **BED**, **ICCS** has provided the major requirements regarding image processing and visualization of the multiscale models of WP6 and contributed to the production of the corresponding deliverable D9.1 “User requirements for the visualization toolkit and image analysis toolkits”. The content of the deliverable D6.1 “Cancer hypomodelling and hypermodelling strategies and initial component models” also provides useful information for the specific needs of WP9.

The deliverable D9.1 (User requirement for the visual analysis suite and image analysis toolkit) was reviewed and discussed with all partners of WP9.

■ **Task 9.2: Scalable visualization techniques:**

UBERN’s SQL database has been mapped on the local server of **BED** in order to test data and design effective visualisation approaches. Storytelling visualization techniques have been investigated. Web-based timeline visualization of the medical images in the database has been proposed and the initial design is in progress.

ICCS provided model predictions at several levels of biocomplexity in order to serve as examples of requirement providers for the development of scalable visualization techniques.

■ **Task 9.3: Uncertainty data visualization:**

The possibility of reusing the ContraCancrum visualisation plugin has been analysed. The implementation of time-varying hybrid volume/surface visualization has been started. The data input module has been separated from the visualization module and replaced. The potential and effective algorithms to deal with uncertainty are under investigation with regards to the uncertainty reference model.

ICCS described several possible sources of uncertainty during tumour growth and treatment response simulation and their expected impact on the predictions.

■ **Task 9.5: A general image processing development toolkit**

The Doctor eye suite for multimodal image visualization and processing will be the basis of further development of modular functionalities regarding tumor visualization and analysis in 3D and 4D (spatio-temporal analysis). An I/O to expand the functionality of the suite in a modular and flexible manner has been devised.

BED has identified and summarized the objectives of nephroblastoma segmentation into three aspects: identification of region of interest, measurement of tissue volume to measure growth of tumor, measurement of decrease in size of tumor with treatment. In order to reach these objectives, state-of-the-art medical image segmentation approaches had been investigated, including meanshift, graph-based segmentation, active contour and MRF segmentation. We used a C++ based computer vision library Blepo to evaluate the effect of meanshift and graph-based segmentation methods on 8 patients’ DICOM image dataset. The initial results reflect that with meanshift and graph-based segmentation methods work well with 50% of dataset as a result of identifiable tumour region and demarcated tumour boundary. Active contour methods and MRF approaches are interactive mode, which requires manual indication of foreground or background of images. Active contour methods work well when user indicates a fine prior of foreground, but with low time efficiency for

computation. MRF approaches are based on traditional mixture gaussian model for colour image, it has a poor performance on given dataset. Also, these methods are implemented and evaluated on 2D basis not 3D basis, the future work will investigate the possibility of using 3D medical image segmentation, like supervoxels.

■ **Task 9.6: Image registration tools**

The main components of the image registration pipeline have been identified. The registration metric for monomodal and multimodal image registration has been selected. The registration model has been selected based on clinical needs and technical specifications. Both, fully automatic and landmark-assisted multimodal demons-based intensity-based registration approaches have been tested on clinical cases.

■ **Task 9.7: Multimodal and longitudinal brain tumor image analysis**

A literature review on advanced feature selection for supervised classification approaches, as well as an extensive literature review on advanced MRI modalities, including diffusion and perfusion imaging has been conducted.

■ **Task 9.8: A software platform for the Assessment of Tumor Treatment Response**

There has been a significant clinical interaction work especially in collaboration with **KULeuven**. WP9 team visited the radiology department within a dedicated meeting and the general analysis framework for therapy assessment has been designed. This includes the pharmacokinetic analysis of the MRI data to derive tumor perfusion markers and sophisticated diffusion analysis tools. A number of models and software components have already been implemented for assessing therapy changes based on perfusion and diffusion MRI data and WP9 is awaiting the legal issues to be resolved for initial testing of the tools.

Summary of significant results

User requirements were finalized for multimodal brain tumor segmentation.

First components for image registration tool were identified and first trials on clinical images conducted.

The definition of I/O for Doctor Eye and new CHIC image processing modules was established.

A literature review on advanced features and MR imaging modalities was conducted.

UBERN SQL database has been mapped on the local server in order to design the effective visualization approach.

Reuse of the visualization module for hybrid volume/surface visualization has been evaluated and data input module has been reimplemented.

All the important decisions regarding the software platform for the Assessment of Tumor Treatment Response have been taken with close clinical interaction; initial tools for perfusion diffusion MRI data analysis are ready for testing.

Definition of the image processing and visualization needs of WP6 models.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

Not applicable.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP9			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	3.00	0.70	0.70
3-USAAR	15.00	0.00	0.00
5-BED	36.00	3.00	5.00
7-FORTH	20.00	5.00	19.79
12-UBERN	12.00	3.00	6.00
17-TEI-C	1.00	0.00	0.00
Total	87.00	11.70	31.49

For **FORTH**, the discrepancies between the planned and the actual PMs are large in WP9, as FORTH had planned the budget on higher salary, experienced post-docs at an average rate given by the central administration, but eventually, no appropriate senior post-docs could be hired and instead a larger number of less experienced engineers (Graduates) was hired for the project at lower rates. The result was an increase in the number of actual PMs for FORTH. These new circumstances have no effect on FORTH's overall budget.

UBERN: In the framework of a Master project on brain tumor segmentation, Mr. Raphael Meier was initially hired as a Master student and then contractually moved to a PhD position. This resulted in extra 3PM that we were able to allocate into WP9.

1.10 Work Package 10: Integrated Platform

Main objectives of this WP

This work package will be responsible for the implementation of the system architecture of CHIC and its realization as a distributed software platform. The main challenge of this package is to build an IT infrastructure that is able to support the implementation of the VPH scenarios of the CHIC project in an efficient, well documented, and secure way. The main objectives of this work package are:

- To provide the end user portal application for the CHIC users to enter the platform and use its facilities;
- To define the programmatic interfaces for accessing the model and hypermodel repositories;
- To develop and document the access to the private CHIC cloud infrastructure and its services for the management of the data;
- To support and facilitate the orchestration of the models into the integrative hypermodels by providing the necessary tools for their efficient construction and execution.

Active tasks in this reporting period:

- Task 10.1, Portal (M1-8)
- Task 10.2, Interoperable interfaces for retrieving model and hypermodel descriptions from corresponding repositories (M1-18)
- Task 10.3, Data Management and Computational infrastructure (M7-36)
- Task 10.4, Data and hypermodel orchestration (M7-44)

Summary of progress achieved towards objectives

In the current reporting period there were four active tasks.

In Task 10.1 we have selected the portal framework, we have set up a development installation of the CHIC portal and the integration of the corresponding tools from other WPs and we delivered the deliverables foreseen in the Technical Annex and additionally we compiled an Appendix with technical guidelines. This task finished on M8.

In Task 10.2 preparation has been done in order to define the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repositories (initial phase) and work progresses as planned.

In Task 10.3 work has been done to the definition of the proper interfaces with the other software layers, collection of the necessary description of the underlying data and the major usage scenarios.

In Task 10.4 work has been done on the collection of the requirements for the development of a clinical workflow environment and the corresponding preliminary discussions.

Summary of details for each task

■ **Task 10.1: Portal**

FORTH has conducted an evaluation of portal frameworks and technologies which led to the selection of the Liferay portal framework. **FORTH** also set up a development installation of the portal to be used for CHIC.

FORTH prepared and submitted the deliverable D10.1 (due on M8) which documents the process and knowledge gathered from the work described above. **ICCS** and **USAAR** also contributed and proofread the D10.1.

FORTH prepared the appendix D10.1.A aiming to support the developers of the portal by providing manuals, guidelines and all the necessary technical information, such as security integration guidelines, for the portal development. **ICCS** also collaborated with **FORTH** in order to ensure proper integration of various components developed by **ICCS** into the CHIC portal. Although the task officially finished in M8, **FORTH** and **all involved partners** continue supporting the development and integration of the CHIC portal by continuing updating the appendix D10.1.A which will be used as a working document of the portal implementation and integration documentation.

■ **Task 10.2: Interoperable interfaces for retrieving model and hypermodel descriptions from corresponding repositories**

In this task **ICCS** collaborated with **PHILIPS** in order to define the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repositories (initial phase).

Initial work which relates also to the objectives of this task has been performed by partner **FORTH** also in parallel in the context of WP7, with the production and documentation of an initial description of a generic model stub specification.

PHILIPS has conducted work on the definition of a data model on how to describe the VPH models and what metadata is necessary to expose in order to provide a uniform and interoperable representation.

■ **Task 10.3: Data Management and Computational infrastructure**

The activities related to this task started in M7. During this period work was mainly devoted by **CINECA** to the definition of the proper interfaces with the other software layers in conjunction with the definition of the architecture and its components taking place in the other technical WPs. In particular, in association with WP7 a draft metadata schema has been defined as starting point for the tagging services development.

ICCS also provided the type of data to be collected for the needs of the CHIC project and the major scenarios of their utilization within the supporting computational infrastructure.

■ Task 10.4: Data and Hypermodel orchestration

This task started on M7. **FORTH** has already conducted initial work on the objectives of this task in parallel in WP7 and the development of the hypermodelling editor.

ICCS provided FORTH with the requirements for the development of a clinical workflow environment and participated in preliminary discussions on the integration therein of the various components developed by ICCS. ICCS provided paradigms of combinations of data and hypermodels as well as typical execution workflows at the conceptual level in order to serve as drivers of the data and hypermodel orchestration infrastructure.

Summary of significant results

Task 10.1 finished successfully after completing all the foreseen work described in the Technical Annex. Task 10.2 progresses as planned towards defining a standardized and interoperable description of the model interfaces. Tasks 10.3 and 10.4, which recently started, progress as planned.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

Not applicable.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP10			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	7.00	1.80	2.10
3-USAAR	7.00	0.00	0.00
7-FORTH	21.00	5.00	17.29
12-UBERN	3.00	0.00	0.00
14-Philips	18.00	0.00	0.00
16-CINECA	8.00	1.00	0.78
Total	64.00	7.80	20.17

For **FORTH**, the discrepancies between the planned and the actual PMs are large in WP10, as FORTH had planned the budget on higher salary, experienced post-docs at an average rate given by the central administration, but eventually, no appropriate senior post-docs could be hired and instead a larger number of less experienced engineers (Graduates) was hired for the project at lower rates. The result was an increase in the number of actual PMs for FORTH. These new circumstances have no effect on FORTH's overall budget.

1.11 Work Package 11: Clinical Adaptation and Validation

Main objectives of this WP

According to the different goals and requirements of this project specified in detail in the different WPs and tasks, a clinical adaptation and validation process within the project will be carried as a major part of quality control and guarantee for further usage of tools and models, including the Oncosimulator. The spectrum ranges from testing of tools and models up to their usage in clinical trials. Hence, this WP will identify objectives that need to be specifically tested in each case. For that reason proper evaluation criteria will be defined. This WP is crucial in that it will continuously assess the quality of all services and tasks of the CHIC environment and iteratively gives feedback to all responsible persons. In the first 18 months a set of guidelines and check-lists to support evaluators will be created to standardize the clinical adaptation and validation process including standardized reports. Such reports will suggest possible improvements, modifications and other functionalities to the technical WPs in a feedback loop. During that period corresponding checklists from other projects will be studied and if possible adapted to the specific requirements of CHIC. Furthermore, workshops are to be held to perform dedicated evaluation sessions engaging both users and developers. Besides these task-specific evaluations, another task is to provide combined evaluations covering the whole integrated CHIC environment and their clinical adaptation and validation. In general, this WP will:

- Formulate criteria for clinical adaptation and validation and feedback report guidelines
- Coordinate validation activities by partners and feedback reports
- Evaluate the developed tools and models by testing functionalities, accessibility, respect of user needs, data integration and execution times
- Verification of GCP (Good Clinical Practice):
 - protection of human rights as a subject in the CHIC environment
 - standards on how data storages, data sharing and hypermodels will be used in clinical care
 - clinical audits: performance will be regularly reviewed to ensure scheduled activities will be properly executed enhancing clinical adaptation of tools and models

Specifically this WP will:

- clinically adapt and partly clinically validate the three Oncosimulator multiscale models (Wilms tumor, glioblastoma, non small cell lung cancer) based on data to be provided by the clinical partners of the consortium (USAAR and KU Leuven)
- clinically check the four cancer multiscale model paradigms (biochemical and molecular interactions, prostate cancer, colon cancer, glioblastoma biomechanics) based on published data and mathematical models
- give a quantitative indication about how safely an active surveillance strategy can be applied
- perform a quantitative validation of the effectiveness of standardized therapies (mainly radiotherapy, chemotherapy and hormonal therapy) versus innovative ones.

Active tasks in this reporting period:

- T11.1, Formulate evaluation and validation criteria for enhancing clinical adaptation of hypermodels (M1-12)
- T11.2, Coordinate evaluation activities by partners (M6-18)

Work has started early in the following task:

- T11.3, Clinical adaptation of the CHIC infrastructure as a whole (M12-48)

Summary of progress achieved towards objectives

In **Task 11.1** **USAAR** started together with **ICCS** to define evaluation and validation criteria for enhancing the clinical adaptation of hypermodels. This was done in close collaboration with all partners of WP11. A questionnaire was developed in an iterative process together with WP2. In addition **UPENN** is developing a comprehensive double-blind validation strategy to validate the predictions of molecular models on the activation status of a given clinical mutation in genes relevant to targeted therapy. Deliverable 11.1 is under development. Because of a close linkage to WP2 the deliverable will take the results of WP2 into consideration.

In **Task 11.2**, coordination of evaluation activities by partners was initiated by **ICCS**. All enrolled partners gave contributions to the coordination of the evaluation activities during the kick-off meeting and subsequently on several physical meeting occasions as well as through electronic correspondence.

In **Task 11.3**, despite the fact that this task opens at month 12, **UNITO** already started to work on the clinical adaptation of the CHIC infrastructure as a whole.

Summary of details for each task

- **Task 11.1: Formulate evaluation and validation criteria for enhancing clinical adaptation of hypermodels**

ICCS, in collaboration primarily with the clinical partners, has initiated the formulation of the basic policies for the evaluation and validation of hypermodels. Analyses of evaluation and validation criteria from other EU projects (p-medicine and EURECA) are under review. The identification of specific application objectives started after D2.1 was finalized. In linkage to task 2.3, **UPENN** has devised a double-blind validation protocol for assessing the accuracy of their predictive algorithm by computing ROC (receiver operating characteristic) curve. The prediction of the activation status is based on the results of text mining, evolutionary analysis of the protein sequence, and based on specific interactions (hydrogen bonds etc.) in the dynamics simulations. The double-blind comparison validates these predictions with in vitro and cellular assays of kinase activation in different mutants. Adaptation to different stakeholders is under discussion. Writing of deliverable D11.1 (Evaluation and validation criteria for clinical adaptation) has started by **USAAR**.

- **Task 11.2: Coordinate evaluation activities by partners**

ICCS contributed to the coordination of the evaluation activities during the kick-off meeting and subsequently on several physical meeting occasions as well as through electronic correspondence. **All partners of WP11** were involved in this activity despite the fact that this task starts at month 6.

- **Task 11.3: Clinical adaptation of the CHIC infrastructure as a whole**

Despite the fact that this task opens at month 12, **UNITO** already started to work on the clinical adaptation of the CHIC infrastructure as a whole by engaging in the following topics:

- Identification, in collaboration with the clinical partner **IRCCS-FPO Cancer Center of Candiolo**, Radiotherapy Unit, of 27 potential hospital departments (17 Urology and 10 Radiotherapy Units) interested in the storage of clinical, serological and pathological data of patients treated in the past 15 years;
- Organization of three clinical meetings: one between urologists in April 2013, one between radiotherapists in June 2013 and one between radiotherapists, radiologists, pathologists and molecular biologists in January 2014; the first gathering was set at the Physiology Institute,

Neuroscience Department, University of Torino, while the second and third ones were held at the IRCCS-FPO Cancer Center of Candiolo, Radiotherapy Unit;

- Selection of the departments suitable for data collection: 13 Urology Units (Molinette University Hospital of Torino, Novara University Hospital, San Luigi University Hospital of Torino, San Giovanni Bosco Hospital of Torino, Gradenigo H, Aosta H, Cuneo H, Mauriziano H, Maria Vittoria H, Asti H, Ivrea H, Cirié H, Biella H) and 10 Radiotherapy Units (IRCCS-FPO Cancer Center, Novara University Hospital, San Luigi University Hospital of Torino, IEO Cancer Center of Milano, Pisa University Hospital, Ivrea Hospital, Biella H, Asti H, Como H, Verbania H);
- Submission in June 2013 of two retrospective multi-centric clinical studies on prostate cancer: EUREKA-1 (concerning surgical patients) and EUREKA-2 (relating irradiated patients);
- Approval of the protocols EUREKA-1 and EUREKA-2 by the Ethical Committee of the IRCCS-FPO Cancer Center of Candiolo on July 9th, 2013;
- Start of data collection on August 1st, 2013;
- Data collection ongoing in all the participating hospitals: 13/13 Urology Units and 10/10 Radiotherapy Units;
- Data collection already finished in six centers (five in EUREKA-1 and one in EUREKA-2);
- Data homogenization into the common database already started (on March 30th, 2014, around 650 clinical cases homogenised);
- Foreseen end of data collection: April 30th, 2014 for EUREKA-1 and July 31st, 2014 for EUREKA-2. On March 30th, 2014, approximately 6,000 case histories open, of whom 2,500 complete for clinical, pathological and follow-up data.

Summary of significant results

Work in task 11.1 has started by all involved partners. There is a close interaction with WP2 task 2.1. UPENN presents a computational modelling and simulation approach to delineate molecular-level mechanisms of activation of protein receptor tyrosine kinases and describe clinical implications of mutations in the Anaplastic Lymphoma Kinase (ALK) receptor tyrosine kinase in paediatric neuroblastoma. They show here that their results shed molecular-level insight into the various mechanisms governing such transforming mutations at the level of kinase activity and are remarkably consistent with experimental observations. In particular, UPENN's computational predictions matched experimental measures of kinase activity with over 85% accuracy in the mutations investigated from neuroblastoma patients.

The collaboration within the consortium and this WP is excellent. The formulation of the basic policies for the evaluation and validation of hypermodels is initiated and shows good progress.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

Deliverable D11.1 will be delayed for 2 months. This will have no impact on the project.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP11			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	7.00	1.00	0.70
3-USAAR	25.00	2.00	1.78
5-BED	8.00	0.00	0.00
7-FORTH	3.00	0.50	0.57
9-UPENN	5.00	1.00	1.00
11-UNITO	20.00	3.00	3.27
12-UBERN	3.00	0.00	0.00
13-PHILIPS	3.00	0.00	0.00
Total	74.00	7.50	7.32

Due to recruitment problems, **UBERN** has not been able to participate in Task 11.1. Planning of resources has therefore been revised by UBERN and the recruitment problems have now been solved.

1.12 Work Package 12: Dissemination and Exploitation

Main objectives of this WP

The objectives of this work package are the following:

- to coordinate the dissemination of this project's outputs, approaches and results to target groups, new users and communities;
- to coordinate the exploitation of the project results and to guarantee their sustainability;
- to exchange information and establish relationships with current projects and initiatives;
- to coordinate training activities and thereby promote the use of tools and methods created through workshops, conferences and publications.

Active task in this reporting period:

- Task 12.1, Dissemination activities (M1-48)
- Task 12.2, Exploitation and IPR issues (M1-48)

Summary of progress achieved towards objectives

In **Task 12.1**, D12.1, "Dissemination Plan", which was prepared by CINECA with contribution from Eurice and all partners, was submitted to the EC on the 2nd of October 2013.

Eurice was responsible for the layout and set-up of the project website, www.chic-vph.eu, which went online on the 28th of June 2013 and has been updated with the latest news ever since. ICCS provided core text and updates for the CHIC website as well as established wiki platform for collaborative document creation and editing.

CINECA and Eurice worked to the selection of the appropriate software tool, collection of material, editing, creation of contacts list, and distribution of four issues of the CHIC e-mail newsletter. A special download section for the newsletters has been set up by Eurice on the front page of the CHIC website. Contributions to the content of the newsletter were provided by all partners, and in particular by ICCS.

Eurice developed material for a dissemination kit to be used by the project partners, including the poster and the flyer by ICCS. The corresponding deliverable, D12.2, describing the content of the kit, was written by Eurice in collaboration with CINECA and submitted to the EC on time.

A number of dissemination channels including peer-reviewed publications (18 in total published or in press), media and alternative media publications, and presentations have been completed by the consortium; a complete list of dissemination activities is included in this report after the management section.

Continuous interaction was carried out with the following EU-funded projects: TUMOR, p-medicine, MyHealthAvatar, DrTherapat, and VPH-Share. Moreover, CHIC has been presented and promoted in the clinical and academic context of Regione Piemonte by UNITO.

In **Task 12.2**, an IPR questionnaire was prepared and sent to all the partners for collection of information. The questionnaire was supported by interviews with partners in collaboration with LUH and WP4.

USFD has held discussion with CINECA relating to the IPR associated with the existing MAF source code and future developments that will take place during the CHIC project. Discussion with p-medicine has started about sustainability issues. Contributions were made by all partners to the discussions on the CHIC project exploitation and to the hypermodelling IPR issues discussions in terms of current and future licensing policies of the models and software components.

Frequent interaction with Thomson Reuters, member of CHIC EAB, took place. Exploration of exploitation scenarios of CHIC outcomes was initiated.

Summary of details for each task

■ **Task 12.1: Dissemination activities**

Subtask 12.1.a: Strategic dissemination planning

During the CHIC project dissemination activities will have a central role in order to foster the widespread awareness as well as strong cooperation and exchange with research communities inside and outside of the EU.

The wider dissemination activities will embrace informing all relevant target groups about the project results and the implications that these results might have for clinical, industrial and societal users as well as for the research community. It will also aim for increasing awareness among other target groups, namely “all stakeholders” in general, the scientific community, industry, clinical practice and the public at large.

CINECA has defined the CHIC dissemination strategic plan and, in particular, the communication model, the target groups, the dissemination channels and the associated responsibilities. The outputs of this analysis were reported in D12.1 submitted at month 6. All partners have contributed to the deliverable with the list of planned dissemination events, target conferences and peer-reviewed journals. Eurice contributed to the section on the project corporate identity, also providing an explanation about the usefulness of a coherent and highly visible design for dissemination and exploitation purposes. Moreover, Eurice wrote the section about the project website, which will be more thoroughly described in Subtask 12.1.b. Section 5.4.3 of the deliverable deals with the CHIC Newsletters and was written in close cooperation by CINECA and Eurice.

Detailed information on the achieved dissemination events will be collected at every reporting period according to the defined communication model. Consequently the Dissemination Plan will be updated annually throughout the project’s lifetime (corresponding deliverables: D12.3, D12.4, D12.5).

All partners also contributed to a discussion on the strategic dissemination plan and future activities that took place during the February 2014 plenary meeting at Luton.

UCL started development work with **BED**, **USAAR** and **KULeuven** on an outreach and dissemination plan known as HOT Maps with the aim of approaching global cancer experts to interact with CHIC knowledge management tools.

SubTask 12.1.b: Web presence

The layout of a professional project website was set up by Eurice, in close cooperation with the coordinator. The design of the website incorporates elements of the CHIC corporate identity, such as the defined CHIC colours and the CHIC project logo. As outlined in the Description of Work, the website features an external as well as an internal part. On the external website, users are informed about the project in general, its objectives, strategy and structure, the consortium members and the latest news and events within the VPH community and beyond. Moreover, a download section has been installed to provide newsletters and further material to be defined in the course of the project. Publications originating from the work done in CHIC as well as relating to the project will be listed on the respective section of the website. The textual parts of the website have been kept updated with core text provided by ICCS but it still have to be improved. Eurice is currently working on this task. The information is to be presented in a lighter and more concise way in order to attract not only scientists but generate interest in the general public as well.

The internal part of the website features an online tool for project management which was developed by Eurice specifically for the management of EU funded research projects. The consortium members have access to mailing lists and a large document repository featuring the most important shared project documents, deliverables, publications and other dissemination activities. Moreover, templates for presentations and project reporting are also provided on the internal management tool. More detailed information on the CHIC website can be found in deliverable D12.1, "Dissemination Plan". The progress of the website development will be recorded in the forthcoming deliverables of WP12.

In terms of web presence, CINECA created also a building on the Biomed Town community portal, which will be used during the project to re-post news of general interest to a wider biomedical community. CINECA will in the next period create a CHIC presence also on the most important social media, like Facebook, Google+, and Twitter.

In parallel, ICCS established the internal WIKI platform of the project for collaborative document writing and update.

SubTask 12.1.c: Newsletter

Eurice supported CINECA in the collection of material, editing and distribution of four issues of the CHIC e-newsletter. The newsletter is issued every two months and sent out by e-mail to the subscribers by relying on the MailChimp online service, which allows also collecting statistics. This frequent communication provides a short and concise overview of news and events related to CHIC, allowing the readers to not only follow the project's immediate progress but also to participate in the "project life". The newsletter accommodates the latest news from the past two months from CHIC as well as the wider VPH community (related projects, initiatives, conferences and other important issues) and a list of noteworthy forthcoming events in which CHIC partners are actively participating or which might be of interest to anybody working in this field. A detailed description of the bi-monthly newsletters is given in deliverable D12.1, "Dissemination Plan". From the first issue, we had continuous increase in the number of subscribers to the newsletter (from 41 to 61) with also an increasing open rate, which is now higher than 50%.

The first annual CHIC newsletter, a deliverable (D12.6) originally due after M12, had to be postponed due to considerable time constraints and an unforeseen heavy workload at Eurice as well as at contributing partner institutions. The EC officer, Dr. Jaakko Aarnio, was informed of this delay on time and an extension of the submission deadline was requested by Eurice at the beginning of

March. The first newsletter will focus on the clinical perspective in the CHIC project, thereby highlighting the practical implications of the rather complex project. The newsletter is intended to disseminate the CHIC research not only among the relevant scientific communities but also attract the attention of a wider public – thus the choice to present the more tangible aspects of CHIC. The editing and layout of the final newsletter sections will be done by Eurice, while the material itself will be provided by the project partners. Like the bi-monthly newsletters, the annual CHIC newsletter will be available for download on the CHIC public website. It will also be distributed to partner projects.



Figure 1: Newsletter section on the CHIC public website

SubTask 12.1.d: Dissemination Kit

Eurice developed material for a dissemination kit to be used by the project partners. So far, the kit consists of a professional project logo, a consistent corporate design reflected on various templates (ppt template, template for meeting agendas, etc.), an introductory CHIC ppt presentation and the e-mail newsletter, a flyer and various posters for distribution and advertising at various conferences mainly from ICCS. The CHIC project logo is always clearly visible on all these items.

As stated in the DoW, the dissemination kit is available to all partners via the CHIC intranet/management platform. The dissemination kit will be continuously updated and complemented with new material over the whole duration of the project.

The content of the Dissemination Kit at the end of the first year is reported in D12.2 “Dissemination Kit”, which was successfully submitted to the EC services.

SubTask 12.1.e: Conferences, exhibitions, workshops

CHIC partners already started to actively present CHIC-related contents at conferences and workshops. The list of the events attended in the first year of the project is included in this report on p 48.

SubTask 12.1.f - Scientific & Technical Papers Publications

CHIC partners already started to actively describe CHIC-related outputs on relevant technical and scientific publications in a wide variety of peer-reviewed journals; the complete list of publications (18 in total) for the first year of the project is included in this report on p 52.

SubTask 12.1.g – Interfacing with other projects

ICCS had continuous interaction with the following projects: TUMOR, p-medicine, MyHealthAvatar, DrTherapat. ICCS participated in the AVICENNA project (A Strategy for in silico Clinical Trials) 1st event, Rome, Italy, 21 March 2014. CINECA is interacting with VPH-Share in order to understand if and how CHIC can become part of the VPH-Share infrastructure beta user programme. Moreover, CHIC has been presented and promoted in the clinical and academic context of Regione Piemonte by UNITO.

■ Task 12.2 - Exploitation and IPR issues

USFD and **CINECA** held discussions relating to the IPR for MAF (Multimod Application Framework) – the basis for the hypermodelling framework used in a number of previous projects including VPHOP, which will form the core technology for the CHIC hypermodelling framework. The outcome was that the software developed will be subject to either BSD like or Apache 2 licensing. Any libraries used are under LGPL, BSD or Apache 2 licenses. This information has been communicated also to LUH, who are responsible for overseeing licensing issues on the CHIC project via email correspondence and a number of teleconferences, which have been organised with different software developing partners.

In order to guide and understand CHIC specific IPR issues a questionnaire has been prepared by CINECA with **Eurice** support. The questionnaire focuses on expected results obtained during CHIC, how to secure these results and where to locate these results on the innovation chain or regarding potential commercialization. The goal of the questionnaire is to collect preliminary information on any licensing issues, which might arise during exploitation of the project results. The questions include expected results, expected stage of development of the results at end of project, plans for securing Intellectual Property Rights, potential for commercial application, licence associated to potential public results, etc. The questionnaire has been distributed to all partners and information is now being collected and categorised. The analysis of this questionnaire will be performed by CINECA and a concise summary of the partners' answers will be provided in the first official report. The questionnaires responses were shared with LUH team to support the interviews on IPR that have been carried out with partners developing models and tools current and future licencing policies.

UCL organized a cross-industry workshop (on Oct 30-31 2013) for pharmaceutical companies to work towards a communal standard for multiscale anatomy knowledge representation relevant to the semantic interoperability requirements of CHIC; and initiated discussions at whole-consortium level in support of the long-term sustainability of the CHIC platform. In particular, the focus is on the application of CHIC cancer modelling as part of the pharmaceutical drug discovery pipeline (known as pharmaCHIC).

A discussion about sustainability and maintenance of the CHIC project via the proposed Study Trial and Research Institute that is part of the maintenance program of p-medicine has started. Further discussions are needed and must be integrated into the exploitation planning report of CHIC in the next reporting period.

ICCS, in frequent interaction with Thomson Reuters, has started the exploration of exploitation scenarios of CHIC outcome by the wider biomedical research and clinical community. It is noted that Thomson Reuters is a member of the EAB committee of CHIC.

All partners also contributed to the mid- and long term discussion on the CHIC project exploitation that took place in the February 2014 plenary meeting at Luton.

Summary of significant results

CINECA with the strong support of Eurice and all partners have defined a clear plan and set of tools for the dissemination of the CHIC results (D12.1).

The most important features of the CHIC project identity (logo, colors, flyer) are available. The project website www.chic-vph.eu is running and for issues of the bi-annual e-mail newsletter are available online. A project dissemination kit can be downloaded by the partners on the management platform set up by Eurice. The first annual newsletter is currently under preparation.

Dissemination of the overall purpose of the CHIC project has started to audiences comprising academics from several disciplines, as well as clinicians working in the field of oncology and representatives from industry.

Partners have actively started to disseminate CHIC-related content both with presentation at conferences and peer-reviewed journal publications.

Concerning exploitation, preliminary activities have started with the identification of IPR issues.

The organization by UCL of an industry workshop with the goal of achieving a communal standard for multiscale anatomy knowledge representation relevant to CHIC;

A discussion about sustainability and maintenance issues has started.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning

Deliverable D12.6, the CHIC Periodic Newsletter (issue 1) had to be postponed. This will not have any impact on other tasks as well as on available resources and planning.

Reasons for failing to achieve critical objectives and/or not being on schedule and the impact on other tasks as well as on available resources and planning

D12.6 had to be postponed due to an unforeseen, but nevertheless massive workload at Eurice and at other partner institutions in early 2014. However, the rest of the newsletters to be issued during the project's lifetime, are still scheduled as originally foreseen in the DoW.

Corrective actions

As the postponement of the newsletter does not affect any other work packages and/or tasks, no corrective actions will be necessary.

Statement on the use of the resources

Planned versus actual efforts in WP12			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	8.00	1.60	1.40
2-Eurice	12.00	4.00	4.16
3-USAAR	3.00	0.00	0.00
5-BED	6.00	0.00	0.00
6-USFD	7.00	0.60	0.57
7-FORTH	6.00	1.00	0.00

8-LUH	6.00	0.50	0.00
9-UPENN	6.00	1.50	1.50
10-UOXF	6.00	0.00	0.00
11-UNITO	6.00	1.00	1.00
12-UBERN	5.00	0.00	0.00
13-Custodix	6.00	0.50	0.00
14-Philips	6.00	0.50	0.10
15-UCL	2.00	0.50	0.11
16-CINECA	6.00	2.00	3.21
17-TEI-C	1.00	0.00	0.00
Total	92.00	13.70	12.05

USFD plan a small increase of PM over the DoW (7 PM instead of 6 PM), in relation to the CHIC dissemination within the Insigneo Showcase, especially in the third and fourth year.

1.12.1 Dissemination activities and publications

As an overview of the dissemination of foreground, a list of dissemination activities (divided into workshops/conferences and press) as well as a list of publications produced in the current reporting period are provided below.

Workshops and conferences

Title	Type	Main leader/Participants	Event	Venue	Date
Data collection for models validation: application to prostate cancer - clinical aspects	Conference	UNITO	IEEE-EMBS International Conferences on Biomedical and Health Informatics (BHI)	Valencia, Spain	1-4 June 2014
Computational medicine: Current and Future prospects	Conference	FORTH	eHealth Forum 2014	Athens, Greece	12-14 May 2014
Presentation of the CHIC project on a special leaflet	Showcase event	USFD	Insigneo Institute first anniversary showcase event	Sheffield, UK	08 May 2014
Poster presentation of CHIC	Showcase event	USFD	Insigneo Institute first anniversary showcase event	Sheffield, UK	08 May 2014
Presentation of the CHIC project	Workshop	USFD	Collaborations Workshop 2014 (CW14) - software in your reproducible research	Oxford, UK	26 April 2014
Long-term survival data in patients with glioblastoma and relapsed malignant glioma after tumor vaccination: is the paradigm slowly shifting?	Conference	KULeuven	Annual scientific meeting of the Belgian Society of Neurosurgery	Brussels, Belgium	29 March 2014
Immuntherapie bei Hirntumoren des Kindes- und Jugendalters	Conference	KULeuven	HIT-TAGUNG	Essen, Germany	28 March 2014

Title	Type	Main leader/Participants	Event	Venue	Date
Presentation of the CHIC project	Workshop	USFD	Collaborations Workshop 2014 (CW14) – software in your reproducible research	Oxford, UK	26-27 March 2014
Presentation of the potential of CHIC for being used as an in silico clinical trials platform was presented.	Conference	ICCS	The AVICENNA project (A Strategy for in silico Clinical Trials) 1st event	Rome, Italy	21 March 2014
Multiscale Cancer Modeling and in Silico Oncology: Emerging Technological Solutions.	Conference	UNITO, CINECA	Database in Medicine	Torino, Italy	14 March 2014
Presentation of the CHIC project	Conference	USFD	Innovations in Healthcare Industry Open Day	Sheffield, UK	06 March 2014
Immunotherapy for brain tumors: an update	Conference	KULeuven	SIOPE-BTG High grade glioma working group meeting	Göttingen, Germany	27 February 2014
An update of immunotherapy translational research program at KU Leuven	Conference	KULeuven	8 Rostock symposium on tumor immunology in pediatrics	Rostock, Germany	14 February 2014
Multiscale Models for Intracellular Trafficking	Conference	UPENN	ASME 2014 3 rd Global Congress on Nanoengineering for Medicine and Biology	San Francisco, USA	2-5 February 2014
Workshop in medical imaging	Workshop	UBERN	Microsoft Research Workshop	Cambridge, UK	17-18 November 2013
Multiscale Cancer Modeling and Insilico Oncology: Emerging Computational Frontiers in Basic and Translational Cancer Research	Conference	UPENN	2013 AIChE Annual Meeting	San Francisco, USA	3-8 November 2013
Multiscale modeling of membrane sculpting by the protein exo70	Conference	UPENN	2013 AIChE Annual Meeting	San Francisco, USA	3-8 November 2013

Title	Type	Main leader/Participants	Event	Venue	Date
Protein-Sorting, Curvature-Induction and Curvature Sensing in Lipid Membranes: Quantification of Free Energies in a Mesoscale Cell Membrane Model	Conference	UPENN	2013 AIChE Annual Meeting	San Francisco, USA	3-8 November 2013
The use of free energy methods to study morphological transitions in vesicles and cells induced by membrane modelling proteins	Conference	UPENN	2013 AIChE Annual Meeting	San Francisco, USA	3-8 November 2013
Cross-Industry Workshop	Workshop	UCL	Cross-Industry Workshop	London, UK	30-31 October 2013
11th HGG-IMMUNO-Meeting	Conference	KULeuven	11th HGG-IMMUNO-Meeting	Leuven, Belgium	21 October 2013
Computational Methods in Cancer Research	Workshop	USFD	Computational Methods in Cancer Research	Sheffield, UK	11 October 2013
Presentation and Discussion	Workshop	ICCS	Computational Methods in Cancer Research	Sheffield, UK	11 October 2013
Modelling solid tumour growth: from in vitro to in vivo via in silico	Workshop	UOXF	Computational Methods in Cancer Research	Sheffield, UK	11 October 2013
Brain Tumor Segmentation Challenge	Workshop	UBERN (obtained second place in this competition)	Brain Tumor Segmentation Challenge, MICCAI 2013, Nagoya, Japan	Nagoya, Japan	22 September 2009
Computational methodology for mechanistic profiling in kinase domain mutations in cancer	Video Conference	UPENN	Transborder Educators E-seminar to University of Ghana	Online	19 September 2013
American Chemical Society Annual Meeting	Conference	UPENN	Computational Structural Biology Session	Indianapolis, IN	8-12 September, 2013
Understanding mutation-driven kinase activation of ALK in neuroblastoma patients	Conference (Poster)	UPENN	The 27th Annual Symposium of The Protein Society	Boston, MA	20-23, July, 2013

Title	Type	Main leader/Participants	Event	Venue	Date
In Silico Oncology: Exploiting Clinical Studies to Clinically Adapt and Validate Multiscale Oncosimulators	Conference	ICCS, FORTH, USAAR, Philips,	EMBC 2013	Osaka, Japan	6 July 2013
Invited special session talk	Workshop/Discussion	USAAR	EMBC 2013	Osaka, Japan	3-7 July 2013
Clinical multi-model studies on prostate cancer	Workshop	UNITO	2 nd Summer School in Computational Oncology	Wadern, Germany	25 June 2013
The Continuous Mathematics Based Oncosimulator: A demonstrator for the case of Glioblastoma Multiforme. Clinical validation aspects.	Workshop	ICCS	2 nd Summer School in Computational Oncology	Wadern, Germany	25 June 2013
The Generic Oncosimulator as an integrative platform for In Silico Oncology: The CHIC project paradigm	Workshop	ICCS	2 nd Summer School in Computational Oncology	Wadern, Germany	25 June 2013
Legal and ethical challenges in ICT for health scenarios and how security can help to solve them	Lecture	LUH	2 nd Summer School in Computational Oncology	Wadern, Germany	26 June 2013
Security and privacy challenges for clinical research IT	Lecture	Custodix	2 nd Summer School in Computational Oncology	Wadern, Germany	26 June 2013
CASyM (Coordinating Action Systems Medicine) modelling Workshop	Workshop	ICCS	CASyM 2013	Heidelberg, Germany	11 June 2013
Mathematical modelling: an effective weapon for fighting cancer?	Workshop/ Seminar	UOXF	Centre for Systems Biology, Stuttgart University	Stuttgart, Germany	June 2013

Press activities

Title	Type	Main leader	Reference	Date
CHIC project featured in The Parliament Magazine	Online article		Link: http://www.vph-institute.org/news/chic-project-featured-in-the-parliament-magazine.html	05 May 2014

Title	Type	Main leader	Reference	Date
Computational Horizons in Cancer (CHIC)	Newspaper/magazine article	ICCS	Link to an online issue of The Parliament Magazine, Issue 389: http://viewer.zmags.com/publication/6eced2e8#/6eced2e8/36	28 April 2014
Multi-disciplinary Penn Research Identifies Protein Required for Cell Movement	Online article	UPENN	http://www.upenn.edu/pennnews/news/multi-disciplinary-penn-research-identifies-protein-required-cell-movement	12 August 2013
Optimising cancer treatment through in-silico oncology	Online article	Eurice	Link: http://eurice.eu/news/details/article/optimising-cancer-treatment-through-in-silico-oncology/	28 May 2013
New Horizons in Cancer Treatment	Newspaper Article	ICCS	http://www.tovima.gr/society/article/?aid=507213	11 April 2013
A Novel Cancer (Related) Project	Newspaper Article	ICCS	http://news.kathimerini.gr/4Dcgi/4Dcgi/_w_articles_columns_2_10/04/2013_516943	10 April 2013
Complex Mathematics Against Cancer	Newspaper Article	ICCS	http://www.enet.gr/?i=news.el.article&id=356570	10 April 2013
5th IARWISOCI workshop	Online news item		http://www.vph-institute.org/news/available-in-open-source-the-proceedings-of-the-2012-5th-international-advanced-research-workshop-on.html	22 November 2012
5th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation	Online news item		http://www.ehealthnews.eu/events/3187-5th-international-advanced-research-workshop-on-in-silico-oncology-and-cancer-investigation	30 August 2012

Publications

Title	Contact person	Involved Institutions	Reference	Category	Publication date	Co-Authors	Status
Integrative functional assessment of ALK mutations for therapeutic stratification in neuroblastoma	Ravi Radhakrishnan	UPENN	Cancer Cell	Peer-reviewed publications	2014	D. Weiser, S. Bressler, P. J. Huwe, R. Radhakrishnan, M. A. Lemmon, Y. Mosse	Submitted
In silico profiling of activating mutations in cancer	Ravi Radhakrishnan	UPENN	Integrative Biology	Peer-reviewed publication	2014	E. Jordan	Submitted

Multiscale Computational Models in Physical Systems Biology of Intracellular Trafficking	Ravi Radhakrishnan	UPENN	IET Systems Biology	Peer-reviewed publication	2014	R. W. Tourdot, R. P. Bradley, N. Ramakrishnan	Submitted
Defining the Free Energy Landscape of Curvature Inducing Proteins on Membrane Bilayers	Ravi Radhakrishnan	UPENN	Physical Review E	Peer-reviewed publication	2014	R.W. Tourdot, N. Ramakrishnan	In press
Computational Delineation of Tyrosyl-Substrate Recognition and Catalytic Landscapes in the Epidermal Growth Factor Receptor Tyrosine Kinase Domain	Ravi Radhakrishnan	UPENN	Molecular Biosystems, DOI: 10.1039/C3MB70620F	Peer-reviewed publication	2014	Y. Liu	In press
Mesoscale computational methods for membrane remodeling by curvature inducing proteins”, Physics Reports, 2014, in press	Ravi Radhakrishnan	UPENN	Physics Reports	Peer-reviewed publication	2014	N. Ramakrishnan, P.B. Sunil	In press
Enabling multiscale modeling in systems medicine	Georgios Stamatakis	ICCS, UOXF	Genome Medicine 6:21	Peer-reviewed publication	2014	O. Wolkenhauer, C. Auffray, O. Brass, J. Clairambault, A. Deutsch, D. Drasdo, F. Gervasio, L. Preziosi, P. Maini, A. Marciniak-Czochra, C. Kossow, L. Kuepfer, K. Rateitschak, I. Ramis-Conde, B. Ribba, A. Schuppert, R. Smallwood, F. Winter, and H. Byrne	Published
The Technologically Integrated Oncosimulator: combining multiscale cancer modelling with information technology in the in silico oncology context	Georgios Stamatakis	ICCS, TEI-C, FORTH, USAAR	IEEE J. Biomed Health Inform. doi: 10.1109/JBHI.2013.2284276	Peer-reviewed publication	May 2014	Dionysiou D, Lunzer A, Belleman R, Kolokotroni E, Georgiadi E, Erdt M, Pukacki J, Rueping S,	Published

						Giatili S, Donofrio A, Sfakianakis S, Marias K, Desmedt C, Tsiknakis M, Graf N.	
Dendritic cell vaccination for glioblastoma multiforme: review with focus on predictive factors for treatment response	Stefan Van Gool	KULeuven	Immuno Targets and Therapy 2014:3, 55-66, http://dx.doi.org/10.2147/ITT.S40121	Peer reviewed publication	13 March 2014	J. Dejaegher, S. De Vleeschouwer	Published
The Virtual Skeleton Database: An Open Access Repository for Biomedical Research and Collaboration	Philippe Büchler	UBERN	Journal of Medical Internet Research	Peer-reviewed publication	13/11/2013	M. Kistler, S. Bonaretti, M. Pfahrer, R. Niklaus	Published, open access
A Hybrid Model for Multimodal Brain Tumor Segmentation	Mauricio Reyes	UBERN		Peer-reviewed publication	2013	S. Bauer, J. Slotboom, R. Wiest	Accepted (in press)
Computational Methodology for Mechanistic Profiling of Kinase Domain Mutations in Cancers	Ravi Radhakrishnan	UPENN	Proceedings of the IEEE, 5th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation	Conference Proceedings	2013	P. J. Huwe	Published
In Silico Oncology: Exploiting Clinical Studies to Clinically Adapt and Validate Multiscale Oncosimulators	Georgios Stamatakis	ICCS, FORTH, USAAR	doi: 10.1109/EMBC.2013.6610806	Peer-reviewed publication	2013	D Dionysiou, A Lunzer, R Belleman, E Kolokotroni, E Georgiadi, M Erdt, J Pukacki, S Rueping, S Giatili, A d'Onofrio, S Sfakianakis, K Marias, C Desmedt, M Tsiknakis, and N Graf	Published

The Technologically Integrated Oncosimulator: Combining Multiscale Cancer Modeling with Information Technology in the In Silico Oncology Context	Georgios Stamatakos	ICCS, FORTH, TEI-C, USAAR	J Biomed Health Inform. 2013 [Epub ahead of print]	Peer-reviewed publication	02/10/2013	D Dionysiou, A Lunzer, R Belleman, E Kolokotroni, E Georgiadi, M Erdt, J Pukacki, S Rueping, S Giatili, A d'Onofrio, S Sfakianakis, K Marias, C Desmedt, M Tsiknakis, and N Graf	Published, open access
Molecular modeling of ErbB4/HER4 kinase in the context of the HER4 signaling network helps rationalize the effects of clinically identified HER4 somatic mutations on the cell phenotype	Ravi Radhakrishnan	UPENN	Biotechnology Journal, 2013, in press. (Published Online) http://doi.wiley.com/10.1002/biot.201300022	Peer-reviewed Article	2013	S.E.Telesco, R. Vadigepalli, R. Radhakrishnan	In Press (Published Online)
Multiscale Cancer Modeling and In Silico Oncology: Emerging Computational Frontiers in Basic and Translational Cancer Research	Georgios Stamatakos	ICCS, USAAR, UPENN	J Bioengineer & Biomedical Sci, vol. 3, no. 2	Peer-reviewed publication	2013	N. Graf, R. Radhakrishnan	Published
Editorial: Multiscale Cancer Modeling and In Silico Oncology: Emerging Computational Frontiers in Basic and Translational Cancer Research	Georgios Stamatakos	ICCS, USAAR, UPENN	J Bioengineer & Biomedical Sci, vol. 3, no. 2				
Functional tissue units and their primary tissue motifs in multi-scale physiology	Bernard de Bono	UCL	Biomed Semant, vol. 4, no. 1 doi:10.1186/2041-1480-4-22	Peer-reviewed publication	2013	P. Grenon, R. Baldock, P. Hunter	Published

2. Deliverables and milestones tables

2.1 Deliverables

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date Annex I	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
D2.1	State of the art knowledge for building hypermodels	2	7-FORTH	R	PU	30.11.2013		Yes	05.02.2014	FORTH, the partner leading this deliverable, informed the coordinator that a one-month extension would be necessary, a request to which the coordinator agreed and which was passed on to the EC project officer. The main issue of delay was that although the partners started the discussion on this deliverable at a very early stage there was slow progress especially due to the preparation of the critical 6 month-project review in November. Since this deliverable has a deep impact on the architectural design and most aspects of the project the partners preferred to delay its submission in order to continue the internal discussions and agree on its content.
D2.2	Scenario based user needs and requirements	2	3-USAAR	R	PU	30.11.2013		Yes	13.01.2014	Due to the missing contributions of a crucial partner, the deliverable was delayed.
D2.3	Requirements for enhancing hypermodels beyond the domain of cancer	2	14-PHILIPS	R	CO	30.09.2014		No		A supplementary report outlining the requirements for the validation of hypermodels is currently in preparation and will be handed in with D2.3 at the very latest.

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date Annex I	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
D2.4	Acceptance of hypermodels by patients and physicians	2	3-USAAR	R	PU	30.09.2016		No		
D3.1	Report on Scenarios and data from defined patients	3	4-KULEUVEN	R	PU	31.03. 2016		No		
D3.2	Report on Scenarios and data from other cancer types for usage by the CHIC infrastructure	3	11-UNITO	R	PU	31.03.2016		No		
D3.3	Demonstration of the developed Meta- and Hyper-Multiscale Models and Repositories	3	1-ICCS	O	PU	31.03.2017		No		
D4.1	Initial analysis of the ethical and legal requirements for the sharing of data	4	8-LUH	R	PU	30.09.2013		Yes	30.09.2013	
D4.2	Initial analysis of the copyright-related legal requirements for the sharing of data	4	8-LUH	R	PU	31.12.2013		Yes	06.01.2014	
D4.3.1	Development of the data protection and copyright framework for CHIC first iteration	4	8-LUH	R	PU	31.05.2014		No		

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date	delivery from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
D4.3.2	Development of the data protection and copyright framework for CHIC - second iteration	4	8-LUH	R	PU	30.09.2016		No		
D4.4	Whitepaper Recommendations for an amended European legal Framework	4	8-LUH	R	PU	31.03.2016		No		
D5.1.1	The CHIC technical architecture – initial version	5	7-FORTH	R	PU	31.03.2014		Yes	13 June 2014	The partners asked for an extension of the deadline of D5.1.1 in order to incorporate adequate amounts of feedback from an end-user perspective as requested in the 6-month review meeting of CHIC. A request for extension was sent to the EC. The final version of D5.1.1 was submitted to the EC on 13 June 2014.
D5.1.2	The final CHIC technical architecture (including the security tools and cloud infrastructure)	5	7-FORTH	R	RE	30.09.2016		No		
D5.2	Security guidelines and initial version of security tools	5	13-CUSTODIX	R	CO	30.09.2014		No		
D5.3	Techniques to build the cloud infrastructure	5	5-BED	R	PU	31.03.2015		No		

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date Annex I	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
	available to the community									
D6.1	Cancer hypomodelling and hypermodelling strategies and initial component models	6	1-ICCS	R	CO	30.09.2013		Yes	22.10.2013	D6.1 is a very extensive report and is expected to serve as the initial scientific basis for the entire project. The coordinator firmly believes that the quality, the extent and the depth of the document will have an important impact on most of the subsequent CHIC work and deliverables. Therefore, D6.1 should be of the highest quality possible and an extension of the deadline for submission proved to be necessary.
D6.2	CHIC cancer component models: initial tested versions	6	1-ICCS	R	CO	30.11.2014		No		
D6.3	Initial standardized cancer hypermodels	6	1-ICCS	R	CO	31.05.2016		No		
D6.4	Clinical adaptation and partial validation of hypermodels	6	1-ICCS	R	CO	31.01.2017		No		
D7.1	Hypermodelling Specifications	7	1-ICCS	R	PU	31.03.2014		No	June 2014	Deliverable D7.1 will be submitted 15 days after submission of “D5.1: 1 The CHIC technical architecture-initial version”, in order to ensure consistency between the CHIC architecture described in D5.1.1 and the components participating in the Hypermodeling Infrastructure, which is a subset of the overall architecture. The responsible partner for D7.1 (ICCS) has

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date Annex I	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
										already received a draft version of the D5.1.1, but the final version of D5.1.1 is needed in order to finalize D7.1 as well.
D7.2	First Release Hypermodelling framework deployed on test nodes	7	16-CINECA	P	RE	31.03.2015		No		
D7.3	Hypermodels annotation services	7	15-UCL	P	RE	31.03.2016		No		
D7.4	Final Hypermodelling framework deployed on test node	7	16-CINECA	O	RE	31.08.2016		No		
D8.1	Design of the CHIC repositories	8	1-ICCS	R	CO	31.07.2014		No		
D8.2	Prototype implementation of the CHIC repositories	8	12-UBERN	O	CO	31.03.2015		No		
D8.3	Implementation of the interfaces of the CHIC repositories	8	15-UCL	R	PU	30.09.2015		No		
D8.4	Report on the final system	8	1-ICCS	R	PU	30.09.2016		No		
D9.1	User requirements for the visualization toolkit and image analysis toolkits	9	5-BED	R	PU	30.09.2013		Yes	01.10.2013	
D9.2	A model and data visualization toolkit	9	5-BED	P	RE	31.01.2017		No		
D9.3	A multimodal and	9	12-UBERN	P	RE	31.01.2017		No		

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date Annex I	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
	longitudinal brain tumour image analysis tool									
D9.4	The tumor response quantitative platform	9	7-FORTH	P	RE	31.03.2016		No		
D10.1	The CHIC portal	10	7-FORTH	O	RE	30.11.2013		Yes	02.12.2013	
D10.2	Design of the orchestration platform, related components and interfaces	10	14-PHILIPS	O	PU	30.09.2014		No		
D10.3	The CHIC Encryption Services	10	13-CUSTODIX	O	CO	31.03.2015		No		
D10.4	The Physiomics-enabled storage on public clouds	10	7-FORTH	R	CO	31.03.2016		No		
D10.5	The CHIC integrated platform	10	7-FORTH	P	RE	30.11.2016		No		
D11.1	Evaluation and validation criteria for clinical adaptation	11	3-USAAR	R	PU	31.03.2014		Yes	02.06.2014	In accordance with the coordinator, D11.1 has been postponed by 2 months. The new foreseen delivery date is 31 May 2014.
D11.2	Report on the first evaluation workshops round	11	3-USAAR	R	RE	30.09.2014		No		
D11.3	Report on the second evaluation Workshops round	11	3-USAAR	R	RE	31.03.2015		No		
D11.4	Validation of CHIC	11	1-ICCS	R	RE	31.03.2017		No		

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date	delivery from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
	infrastructure as a whole									
D12.1	Dissemination Plan	12	16-CINECA	R	PU	30.09.2013		Yes	01.10.2013	
D12.2	Dissemination Kit available	12	2-EURICE	O	PU	31.03.2014		Yes	25.03.2014	
D12.3	Preliminary Plan for the Use and Dissemination of Foreground	12	16-CINECA	R	CO	31.03.2015		No		
D12.4	Draft Plan for the Use and Dissemination of Foreground	12	16-CINECA	R	CO	31.03.2016		No		
D12.5	Final Plan for the Use and Dissemination of Foreground	12	16-CINECA	R	CO	31.03.2017		No		
D12.6	Periodic Newsletters	12	2-EURICE	R	PU	31.03.2014 31.03.2015 31.03.2016 31.03.2017		No	June/July 2014	The first issue of the periodic newsletter is unfortunately delayed but currently in preparation. Task leader Eurice is making an effort to issue the newsletter as soon as possible. The delay has been caused by a massive and unscheduled workload at the participating partner institutions (e.g. review meeting preparations for CHIC partner projects, periodic reports and other contractual obligations). The bi-monthly newsletters are largely unaffected by this delay and have been issued throughout the first year of the project.

2.2 Milestones

Table 2. Milestones							
Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I dd/mm/yyyy	Achieved Yes/No	Actual/ Forecast achievement data dd/mm/yyyy	Comments
MS1	Kick-Off Meeting	1	2-Eurice	01.04.2013	Yes	10-12/04/2013	The Kick-Off Meeting was held at the Royal Olympic Hotel in Athens, Greece from 10-12 April 2013
MS2	Progress meetings	1	2-Eurice	30.09.2013	Yes	17-18/10/2013 20-21/02/2014	1 st progress meeting of CHIC at FORTH, Heraklion, Greece, from 17-18 October 2013 2 nd progress meeting at BED, Luton, UK, from 20-21 February 2014
MS3	User needs and Requirements are defined	2	3-USAAR	30.11.2013	Yes	13/01/2014	The delay was caused by a delay occurring in D2.2.
MS4	Hypermodels are accepted by users	2	3-USAAR	30.09.2016	No		
MS5	Scenarios and data from nephroblastoma, GBM and NSCLC are available	3	4-KULEUVEN	31.03.2015	No		
MS6	Exploitation of the CHIC infrastructure by further cancer types	3	4-KULEUVEN	31.03.2016	No		
MS7	Meta- and Hyper-Multiscale Models can be Demonstrated	3	4-KULEUVEN	31.03.2017	No		
MS8	The CHIC Data protection and intellectual property framework	4	8-LUH	31.05.2014	No		
MS9	Initial CHIC Architecture and security guidelines	5	7-FORTH	30.09.2014	No		
MS10	Final version of the CHIC Architecture	5	7-FORTH	30.09.2016	No		
MS11	Initial component models	6	1-ICCS	30.09.2013	Yes	22.10.2013	D6.1 is available

Table 2. Milestones							
Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I dd/mm/yyyy	Achieved Yes/No	Actual/ Forecast achievement data dd/mm/yyyy	Comments
	available for all cancer modelling branches						
MS12	Rational, numerical and clinical experience based check of the component models complete	6	1-ICCS	30.11.2014	No		
MS13	Availability of hypermodels for all clinical scenarios compliant w. the guidelines to be prov. by WP7	6	1-ICCS	31.07.2016	No		
MS14	All hypermodels have been quantitatively clinically adapted	6	1-ICCS	31.01.2017	No		
MS15	First hypermodel infrastructure deployed	7	7-FORTH	31.03.2014	No	June 2014	MS15 will be reached when D7.1 has been finalized and submitted to the EC. Since D7.1 can be finalized only after the final version of D5.1.1 has been issued, the CHIC consortium expects a delay of about 2 more weeks. D7.1 is expected to be ready in mid-June, therefore, MS15 will also be considered achieved in mid-June.
MS16	Folksonomy and Ontology annotation and search services deployed	7	5-BED	31.03.2015	No		
MS17	Hypermodel editor, development and execution application ready	7	7-FORTH	31.03.2016	No		
MS18	Metahypermodels annotation completed	7	6-	31.03.2017	No		
MS19	Design of the CHIC repositories	8	1-ICCS	31.07.2014	No		

Table 2. Milestones							
Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I dd/mm/yyyy	Achieved Yes/No	Actual/ Forecast achievement data dd/mm/yyyy	Comments
	completed						
MS20	Deployment of the CHIC repositories	8	15-	31.07.2015	No		
MS21	Integration with security and ethical framework	8	1-ICCS	30.09.2016	No		
MS22	Scalable & uncertainty visualization techniques	9	5-BED	31.03.2015	No		
MS23	Image segmentation & registration techniques	9	12-	30.09.2014	No		
MS24	Initial version of the tumor response quantitative platform	9	7-FORTH	31.03.2015	No		
MS25	The CHIC Orchestration Platform and Encrypted Data Services	10	7-FORTH	31.03.2015	No		
MS26	Public cloud Deployment	10	7-FORTH	31.03.2016	No		
MS27	Evaluation and validation criteria for clinical adaptation are ready	11	3-USAAR	31.03.2014	Yes	02.06.2013	D11.1 is available.
MS28	First evaluation Workshop	11	3-USAAR	30.09.2014	No		
MS29	Second evaluation Workshop	11	3-USAAR	31.03.2016	No		
MS30	Internal collaborative area and external website	12	2-EURICE	30.06.2013	Yes	28.06.2013	Website is online and operational: www.chic-vph.eu
MS31	First CHIC summer School	12	3-USAAR	30.09.2014	No		The first CHIC training workshop will be held in the context of the 6 th IARWISOCI workshop in Athens from 3-4 November 2014. Therefore, the consortium will switch MS31 and MS32, as a dedicated CHIC Summer School is planned for 2015.

Table 2. Milestones							
Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I dd/mm/yyyy	Achieved Yes/No	Actual/ Forecast achievement data dd/mm/yyyy	Comments
MS32	CHIC workshop	12	1-ICCS	30.09.2015	No		The first CHIC training workshop will be held in the context of the 6 th IARWISOCI workshop in Athens from 3-4 November 2014. Therefore, the consortium will switch MS31 and MS32, as a dedicated CHIC Summer School is planned for 2015.
MS33	Second CHIC summer school	12	3-USAAR	30.09.2016	No		

3. Project management

Consortium management tasks and achievements

The consortium management is covered by WP1 and includes

- Task 1.1: Decision making management (M1-48)
- Task 1.2: Administrative coordination (M1-48)
- Task 1.3: Financial management (M1-48)
- Task 1.4: Contractual management (M1-48)
- Task 1.5: Assessment of progress and results (M6-48)

All in all, project management in CHIC is going very well. The collaboration between the coordinating institution, **ICCS**, and the project management partner **EURICE**, has so far been effortless and efficient.

ICCS has been in continuous daily electronic contact with **EURICE** for all the decision making managerial needs of the project (e.g. regarding project meetings and technical meetings). The project coordinator has been in regular contact with the project officer regarding several administrative issues such as the agreement on the review meeting dates and the technical annex amendments.

ICCS has been scientifically coordinating the entire project through a series of communication procedures such as emailing, teleconferencing, Skype-conferencing and a number of physical meetings with various consortium members. Decisions at the consortium level have been reached through electronic voting or preference stating platforms such as doodle.

The following achievements were made during the first year of the project:

The **Grant Agreement** and the Accession Forms were signed by all partners with only a slight delay caused by the 100% acquisition of former consortium partner SCS Srl by the new consortium member CINECA. Further details on this acquisition are given below. A complete copy of the Grant Agreement including Accession Forms was distributed to all partners for their files. The Consortium Agreement, on the other hand, was concluded and signed before the official start of the project on 1 April 2013. On 16 May 2013 CINECA acceded to the Consortium Agreement via Attachment 2, "Accession document".

Non-disclosure confidentiality agreements have been signed by ICCS, as the coordinator, and the members of the External Advisory Committee, in order to facilitate mutual interaction within the context of CHIC.

A request for an **amendment** to the Grant Agreement was filed by the CHIC Coordinator, ICCS, in November 2013. The Coordinator's bank account had changed and the necessary modifications were made in the NEF tool after an amendment session had been opened by the EC on 22 January 2014. The updated version of the financial identification form generated by NEF was duly signed, dated and stamped by ICCS's authorized representative as well as by a representative of ICCS's new bank, Alpha Bank, and then sent to the European Commission. The amendment N1 was formally closed on 12 March 2014.

The **Kick-off Meeting (MS1)** was organized by the coordinator ICCS in cooperation with EURICE and took place on 10-12 April 2013 at the facilities of the Royal Olympic Hotel in Athens, Greece. The meeting laid the foundation for the work of the first year with thorough and fruitful discussions on how to start and connect the activities in the different work packages.

A **1st Progress Meeting (MS2)** was held on 17-18 October 2013 at FORTH in Heraklion, Greece where the work done so far was presented and the work anticipated for the upcoming months was discussed. Following the 1st Progress Meeting, a first **technical meeting** was held at FORTH on 19 October 2013. Its purpose was to define responsibilities within the technical work packages of CHIC and further coordinate the workplan for the upcoming months. Detailed meeting minutes, attendance lists and ppt presentations are available for all meetings in the internal management tool, which is introduced in the following paragraph.

A 6-month **interim review** was held in Brussels on 15 November 2014. The reviewers' recommendations as well as the signed outcome letter were sent to the coordinator on 22 January 2014. The recommendations were distributed to the CHIC partners immediately. Two specific recommendations from the reviewers were directed at all the technical work packages in CHIC: the set-up of a comprehensive Gantt Chart, outlining the availability of all the CHIC services and the development of a glossary of technical and legal terms connected to the CHIC project. Both tasks are currently tackled collaboratively by the consortium. Working documents are in place and are stored on the project intranet.

The **2nd Progress Meeting (MS2)** took place from 20-21 February 2014 at BED in Luton, United Kingdom. A total of 46 consortium members attended the progress meeting. Moreover, David Ingram from the external advisory board joined the meeting on day 1 to provide his advice and ideas. Like at the first progress meeting in Heraklion, the ongoing work done in CHIC was presented by the work package leaders and/or other key partners involved. The meeting agenda was structured alongside the recommendations provided by the reviewers after the 6-month interim review of CHIC in November 2013. The work package leaders were given the task to identify means of dealing with the recommendations until the first official CHIC review and beyond. Details of how the individual work packages deal with the reviewers' recommendations can be found in the individual work package reports. The project management team reminded UBERN and UOXF to solve their recruitment problems as soon as possible. On the scientific side, the partners agreed to establish a comprehensive Glossary of terms related to hypermodeling as well as a Gantt chart documenting which services are available to the clinicians when and from where until the next review. Both documents are currently in preparation and will be made available on the CHIC intranet. The glossary will also be shared on the public website.

The **1st official CHIC review** is scheduled for 3 September 2014 at the European Commission in Brussels. During the review the progress made in the first year of CHIC will be assessed. The reviewers will evaluate in how far the consortium has adapted the recommendations made after the interim review in November 2013. Moreover, several demonstrators will be presented.

The **3rd progress meeting (MS2)** is currently planned. It will be hosted by CHIC partner KULeuven on 15-17 October 2014. The meeting will include a one-day technical meeting, where the various work groups can meet individually and develop their presentations/ summaries of work to be presented at the General Assembly meeting scheduled for the two following days. This way, the General Assembly meeting will be much more effective and the consortium will be less pressed for time, which is a key factor in a consortium this large. The EAB members will also be invited to the meeting to provide their ideas and advice.

A web-based password-protected management tool (*ProjectAngel*) was set up within the scope of developing the CHIC website to centrally store templates for presentations and reporting, project relevant information and data. It includes a reporting tool specifically adapted to the latest FP7 reporting guidelines and the partners were asked to use this tool for the preparation of this report (for more information on the website and the features of the internal project management platform, reference is made to deliverable D12.1 "Dissemination Plan").

The first EC payment of 3,703,700€ was received by the coordinator after the start of the project and timely and duly distributed to the partners according to the table below:

Project Number: 600841				Project Title: CHIC			
Participant Number in this project	Participant Short name	Fund. %	Total Costs	Requested EU Contribution	% of Total EU Contribution/ Pre-financing	Pre-financing	Cost Claims 1st report
1	ICCS	60.0	1.386.800 €	1.128.800 €	10,67%	395.080,00 €	177.447,00 €
2	EURICE	85.0	645.498 €	645.498 €	6,10%	225.924,30 €	110.605,00 €
3	USAAR	60.0	1.689.301 €	1.282.996 €	12,12%	449.048,60 €	100.130,00 €
4	KULeuven	60.0	814.000 €	625.000 €	5,91%	218.750,00 €	60.612,00 €
5	BED	60.0	857.800 €	659.800 €	6,24%	230.930,00 €	71.172,00 €
6	USFD	60.0	1.215.675 €	941.825 €	8,90%	329.638,75 €	158.387,00 €
7	FORTH	87.0	888.106 €	688.031 €	6,50%	240.810,85 €	159.592,00 €
8	LUH	60.0	608.794 €	474.928 €	4,49%	166.224,80 €	90.036,00 €
9	UPENN	62.0	742.206 €	573.282 €	5,42%	200.648,70 €	120.883,00 €
10	UOXF	60.0	561.120 €	446.591 €	4,22%	156.306,85 €	10.363,00 €
11	UNITO	60.0	597.000 €	462.998 €	4,38%	162.049,30 €	49.597,00 €
12	UBERN	60.0	844.000 €	651.000 €	6,15%	227.850,00 €	98.980,00 €
13	CUSTODIX	50.0	303.000 €	245.375 €	2,32%	85.881,25 €	15.595,00 €
14	PHILIPS	149.0	1.019.116 €	566.120 €	5,35%	198.142,00 €	16.671,00 €
15	UCL	60.0	1.060.364 €	804.156 €	7,60%	281.454,60 €	53.154,00 €
16	CINECA	20.0	596.307 €	325.560 €	3,08%	113.946,00 €	125.530,00 €
17	TEI-C	60.0	78.880 €	60.040 €	0,57%	21.014,00 €	17.510,00 €
			13.907.967 €	10.582.000 €	100,00%	3.703.700,00 €	1.436.264,00 €

Problems which have occurred and how they were solved or envisaged solutions

All in all, no particular problems have occurred during the first twelve months of the project. This is noteworthy, as the consortium is very large and requires careful, steady and reliable management and communication.

Changes in the consortium

None.

List of project meetings, dates and venues

Title	Date	Venue	Local organizer	Participants
2 nd modeller's meeting	June 2014	Foundation for Research and Technology Hellas, Crete/Greece	FORTH	
Architecture Board telephone conference	05 May 2014 and 22 May 2014	Skype conference	ICCS	Architecture Board members
1 st modellers' meeting	10-11 April 2014	Oxford University, United Kingdom	UOXF	ICCS, FORTH, UNITO, UBERN
Architecture Board	13 March 2014	Skype conference	ICCS	Architecture

telephone conference	and 27 March 2014			Board members
Release planning meeting	28 February 2014	University of Sheffield, United Kingdom	USFD	BED, CINECA
2 nd Progress Meeting	20-21 February 2014	University of Bedfordshire, Luton, United Kingdom	BED	Consortium
Architecture Board telephone conference	23 January 2014	Skype conference	ICCS	Architecture Board members
Clinical workshop	06 December 2013	Saarland University Hospital, Homburg, Germany	USAAR	UCL, UOXF
Release planning meeting	26 November 2013	Consorzio Interuniversitario CINECA, Bologna, Italy	CINECA	USFD
WP7 meeting	12 November 2013	University of Sheffield, UK	USFD	ICCS
CHIC (WP6+WP7+WP8)-CHASTE meeting	11 November 2013	Oxford University, UK	UOXF	ICCS, UCL, USFD
WP7+WP9 meeting	8 November 2013	University of Bedfordshire, Luton, UK	BED	ICCS
1 st Progress Meeting	17-18 October 2013	Foundation for Research and Technology Hellas, Heraklion, Greece	FORTH	Consortium
1 st Technical Meeting	19 October 2013	Foundation for Research and Technology Hellas, Heraklion, Greece	FORTH	Consortium
D2.1/D2.2, State of the art knowledge for building hypermodels	17 September 2013	Skype conference	USAAR	USFD, ICCS, UCL, FORTH, TEI-C, CINECA
Bilateral meeting	22-25 July 2013	Consorzio Interuniversitario CINECA, Bologna, Italy	CINECA	USFD
Workgroup meeting	17 June 2013	UZ Gasthuisberg, Leuven, Belgium	KULeuven	ICCS
Bilateral meeting (CINECA and USFD)	3-5 June 2013	University of Sheffield, Sheffield, UK	USFD	CINECA
WP9 meeting	22 May 2013	UZ Gasthuisberg, Leuven, Belgium	KULeuven	WP9 members
WP3 & WP6 meeting	17 May 2013	UZ Gasthuisberg, Leuven, Belgium	KULeuven	ICCS
Kick-off Meeting	10-12 April 2013	Royal Olympic Hotel, Athens, Greece	ICCS	Consortium

Related documentation is available in the project management tool.

Cooperation with other projects/programmes

For cooperation with other projects/programmes reference is made to SubTask 12.1.g “Interfacing with other projects” described in the WP12 report.

Project planning and status

In general, the project’s work plan was implemented as foreseen.

ICCS together with the WP leaders and with the support of EURICE has been controlling and monitoring work package status measured against deliverables and milestone planning in order to ensure a timely and accurate work plan follow-up, allow for early identification and troubleshooting of possible technical and organisational problems. Only occasional slight extensions of the foreseen deliverable deadlines have occurred up to now.

ICCS reviewed project reports and deliverables to ensure their quality and verify their consistency with technical and contractual requirements before transmitting them to the Commission.

Minor deviations from the original work plan are described in the following paragraphs.

Work has started early/is starting late in the following tasks:

- T2.4, How to get acceptance of hypermodels by patients and clinicians (M12-42): Initial work has been done in this task, which includes the discussion of requirements for the validation of hypermodels and the start of data collection for different cancer domains. An additional report is currently written in the context of Tasks 2.3 and 2.4 outlining the requirements for the validation of hypermodels. This report will be a supplement to D2.3.
- T3.4, Applying the CHIC infrastructure to other cancer types (M12-36): in this task, UNITO has started the collection of data for prostate cancer.
- T11.3, Clinical adaptation of the CHIC infrastructure as a whole (M12-48): despite the fact that this task opens at month 12, **UNITO** already started to work on the clinical adaptation of the CHIC infrastructure as a whole

Change of person months:

In work package 7, partner **USFD** have elected to engage a PhD student at less cost and more effort. There will be no net effect on the budget, simply more effort applied to this work package overall. The total effort for partner USFD in WP7, originally planned to be 88 person/month, is now projected to be 128PM. In WP1, Project Management, USFD has now increased the number of PM from 4PM to 7.4PM due to a less senior management staff than originally planned at a similar cost. In WP12, Dissemination and Exploitation, USFD have increased their PM efforts to 7PM.

In some WPs the discrepancies between the planned and the actual MMs are big, as **FORTH** had planned the budget on higher salary, experienced post-docs at an average rate given by the central administration, but eventually, no appropriate senior post-docs could be hired and instead a larger number of less experienced Engineers (Graduates) was hired for the project at lower rates. The result was an increase in the number of actual MMs for FORTH. But there are no deviations in the cost budget. For more detail, reference is made to the reports on the work packages. This deviation does not have any negative impact on other tasks and do not influence the resources originally planned.

Impact of possible deviations from the planned milestones and deliverables

In the first twelve months of the project, most deliverables and milestones have been submitted or achieved as foreseen in Annex I. If a delay was expected, the consortium partners informed the coordinator as well as the project management partner Eurice who then immediately informed the EC project officer about the delay and the reasons for the delay. However, the delayed deliverables did not have any significant impact on the overall progress in CHIC, so no contingency measures had to be put in place.

Any changes to the legal status of any of the beneficiaries

From 1 March 2013 onwards, i.e. shortly before the official start date of the CHIC project, former partner SCS Srl, an SME based in Milano, was taken over by Consorzio Interuniversitario CINECA, a non-profit consortium of 54 Italian universities, the National Institute of Oceanography and Experimental Geophysics, the National Research Council and the Ministry of Education, University and Research. The takeover was organized along the regulations concerning the partial transfer of rights and obligations from one entity to another. Accordingly, CINECA agreed to perform all of SCS's task and responsibilities in the CHIC project. Following a formal communication between CINECA and the European Commission (dated 15 February 2013), the CHIC budget and Description of Work were adapted to the new partner. CINECA then acceded to the CHIC Grant Agreement as well as the CHIC Consortium Agreement and the project negotiations could be closed.

Development of the Project website

The first version of the CHIC website went online in June 2013 and is available under www.chic-vph.eu. The website has been set up to ensure the smooth information and communication within the consortium as well as with the public. It is therefore divided into a publicly accessible information platform and a password protected internal area for project management. It has been continuously updated over the past months to reflect the progress of the project. Especially the news section has been used on a regular basis to keep the public informed about the on-goings in CHIC. Participation in conferences is always announced in the events section to give interested the scientific community the opportunity to meet and connect with CHIC partners. In addition, a Wiki has been installed to provide a feature for the partners where they can share instant information, discuss topics on the spot and create as well as edit documents between the partners. As the project continues over the next 3 years, the website will be constantly revised and updated to reflect the project's progress and meet the consortium's requirements.



More detailed information on the features of the website is available in Deliverable D12.1 "Dissemination Plan".

Statement on the use of the resources

Planned versus actual efforts in WP1			
Partner	Planned PM Total	Planned PM Period 1	Actual PM Period 1
1-ICCS	8.00	2.00	1.85
2-Eurice	38.00	9.50	8.72
6-USFD	7.40	2.00	2.05
7-FORTH	2.00	0.50	0.53
10-UOXF	2.00	0.90	1.11
16-CINECA	1.00	0.40	0.40
Total	58.40	15.30	14.66

USFD in the DoW has 4 person months (PM) in WP1. Due to a less senior management staff than originally planned, USFD expect a mildly larger effort (7.4 PM) at a similar cost. The actual effort reported in WP1 is 2.05 PM, in line with this new effort projection.

4. Explanation of the use of the resources

The costs presented in the explanation of the use of the resources in this interim report are based on estimates and serve the purpose of having a good overview on how the budget has been used so far to see problems as early as possible and take corrective action where required.

4.1 Budget Overview

Cost Budget Follow-up Table						
Contract n°	600841	Project acronym		CHIC		
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)		Percentage spent	Remaining Budget (EUR)
			Period 1	Total	Total/ Budget	
			M1-M12			
ICCS	Total Person-month	106,00	30,27	30,27	29%	75,73
	Personnel	636.000,00	117.446,00	117.446,00	18%	518.554,00
	Other direct costs	227.000,00	22.114,00	22.114,00	10%	204.886,00
	Subcontracting	6.000,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	517.800,00	83.734,00	83.734,00	16%	434.066,00
	Total Costs	1.386.800,00	223.294,00	223.294,00	16%	1.163.506,00
Eurice	Total Person-month	50,00	12,88	12,88	26%	37,12
	Personnel	324.500,00	65.313,00	65.313,00	20%	259.187,00
	Other direct costs	39.173,00	5.314,00	5.314,00	14%	33.859,00
	Subcontracting	6.000,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	275.825,00	39.978,00	39.978,00	14%	235.847,00
	Total Costs	645.498,00	110.605,00	110.605,00	17%	534.893,00
USAAR	Total Person-month	135,00	11,29	11,29	8%	123,71
	Personnel	725.498,00	64.750,00	64.750,00	9%	660.748,00
	Other direct costs	326.764,00	18.692,00	18.692,00	6%	308.072,00
	Subcontracting	5.682,00	0,00	0,00	0%	5.682,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	631.357,00	50.065,00	50.065,00	8%	581.292,00
	Total Costs	1.689.301,00	133.507,00	133.507,00	8%	1.555.794,00
KULeuven	Total Person-month	68,00	8,50	8,50	13%	59,50
	Personnel	340.000,00	41.421,00	41.421,00	12%	298.579,00
	Other direct costs	167.500,00	9.090,00	9.090,00	5%	158.410,00
	Subcontracting	2.000,00	0,00	0,00	0%	2.000,00
	Adjustments		0,00	0,00	0%	0,00
	Indirect costs	304.500,00	30.306,00	30.306,00	10%	274.194,00
	Total Costs	814.000,00	80.817,00	80.817,00	10%	733.183,00
BED	Total Person-month	88,00	14,00	14,00	16%	74,00
	Personnel	484.000,00	52.323,00	52.323,00	11%	431.677,00
	Other direct costs	49.000,00	6.988,00	6.988,00	14%	42.012,00
	Subcontracting	5.000,00	0,00	0,00	0%	5.000,00
	Adjustments		0,00	0,00	0%	0,00
	Indirect costs	319.800,00	35.586,00	35.586,00	11%	284.214,00
	Total Costs	857.800,00	94.897,00	94.897,00	11%	762.903,00

Cost Budget Follow-up Table						
Contract n°	270089	Project acronym				
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)		Percentage spent	Remaining Budget (EUR)
			Period 1	Total	Total/ Budget	
			M1-M6			
USFD	Total Person-month	110,00		0,00	0%	110,00
	Revised number of PM	154,40	32,81	32,81	21%	121,59
	Personnel	679.296,00	115.475,00	115.475,00	17%	563.821,00
	Other direct costs	78.001,00	12.986,00	12.986,00	17%	65.015,00
	Subcontracting	4.000,00	0,00	0,00	0%	4.000,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	454.378,00	77.076,00	77.076,00	17%	377.302,00
	Total Costs	1.215.675,00	205.537,00	205.537,00	17%	1.010.138,00
FORTH	Total Person-month	86,00	60,79	60,79	71%	25,21
	Personnel	412.800,00	105.586,00	105.586,00	26%	307.214,00
	Other direct costs	110.170,00	17.911,00	17.911,00	16%	92.259,00
	Subcontracting	6.000,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	359.136,00	87.636,00	87.636,00	24%	271.500,00
	Total Costs	888.106,00	211.133,00	211.133,00	24%	676.973,00
LUH	Total Person-month	54,00	16,07	16,07	30%	37,93
	Personnel	350.622,00	72.235,00	72.235,00	21%	278.387,00
	Other direct costs	28.000,00	2.795,00	2.795,00	10%	25.205,00
	Subcontracting	3.000,00	0,00	0,00	0%	3.000,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	227.173,00	45.018,00	45.018,00	20%	182.155,00
	Total Costs	608.793,00	120.048,00	120.048,00	20%	488.745,00
UPENN	Total Person-month	84,00	21,00	21,00	25%	63,00
	Personnel	391.564,00	72.110,00	72.110,00	18%	319.454,00
	Other direct costs	63.501,00	24.241,00	24.241,00	38%	39.260,00
	Subcontracting	5.000,00	0,00	0,00	0%	5.000,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	282.140,00	59.738,00	59.738,00	21%	222.402,00
	Total Costs	742.204,00	156.089,00	156.089,00	21%	586.115,00
UOXF	Total Person-month	54,00	1,47	1,47	3%	52,53
	Personnel	289.077,00	6.217,00	6.217,00	2%	282.860,00
	Other direct costs	59.184,00	735,00	735,00	1%	58.449,00
	Subcontracting	3.902,00	0,00	0,00	0%	3.902,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	208.956,00	4.171,00	4.171,00	2%	204.785,00
	Total Costs	561.119,00	11.123,00	11.123,00	2%	549.996,00
UNITO	Total Person-month	54,00	9,59	9,59	18%	44,41
	Personnel	270.000,00	35.978,00	35.978,00	13%	234.022,00
	Other direct costs	100.000,00	3.227,00	3.227,00	3%	96.773,00
	Subcontracting	5.000,00	0,00	0,00	0%	5.000,00
	Adjustments		0,00	0,00	0%	0,00
	Indirect costs	222.000,00	23.522,00	23.522,00	11%	198.478,00
	Total Costs	597.000,00	62.727,00	62.727,00	11%	534.273,00

Cost Budget Follow-up Table						
Contract n°	270089	Project acronym		ACTUAL COSTS (EUR)		Percentage spent
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	Period 1	Total	Total/ Budget	Remaining Budget (EUR)
			M1 -M6			
UBERN	Total Person-month	62,00	11,20	11,20	18%	50,80
	Personnel	465.000,00	71.512,00	71.512,00	15%	393.488,00
	Other direct costs	60.000,00	10.972,00	10.972,00	18%	49.028,00
	Subcontracting	4.000,00	0,00	0,00	0%	4.000,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	315.000,00	49.490,00	49.490,00	16%	265.510,00
	Total Costs	844.000,00	131.974,00	131.974,00	16%	712.026,00
CUSTODIX	Total Person-month	24,00	2,37	2,37	10%	21,63
	Personnel	180.000,00	12.227,00	12.227,00	7%	167.773,00
	Other direct costs	33.000,00	1.790,00	1.790,00	5%	31.210,00
	Subcontracting	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	90.000,00	6.777,00	6.777,00	8%	83.223,00
	Total Costs	303.000,00	20.794,00	20.794,00	7%	282.206,00
PHILIPS	Total Person-month	54,00	1,20	1,20	2%	52,80
	Personnel	398.466,00	11.276,00	11.276,00	3%	387.190,00
	Other direct costs	25.000,00	0,00	0,00	0%	25.000,00
	Subcontracting	3.000,00	0,00	0,00	0%	3.000,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	592.650,00	19.418,00	19.418,00	3%	573.232,00
	Total Costs	1.019.116,00	30.694,00	30.694,00	3%	988.422,00
UCL	Total Person-month	74,00	6,65	6,65	9%	67,35
	Personnel	497.978,00	39.837,00	39.837,00	8%	458.141,00
	Other direct costs	161.000,00	4.214,00	4.214,00	3%	156.786,00
	Subcontracting	6.000,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	395.386,00	26.430,00	26.430,00	7%	368.956,00
	Total Costs	1.060.364,00	70.481,00	70.481,00	7%	989.883,00
CINECA	Total Person-month	57,00	15,95	15,95	28%	41,05
	Personnel	228.000,00	56.196,00	56.196,00	25%	171.804,00
	Other direct costs	54.408,00	5.258,00	5.258,00	10%	49.150,00
	Subcontracting	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	313.899,00	92.025,00	92.025,00	29%	221.874,00
	Total Costs	596.307,00	153.479,00	153.479,00	26%	442.828,00
TEI-C	Total Person-month	17,00	3,96	3,96	23%	13,04
	Personnel	37.400,00	10.527,00	10.527,00	28%	26.873,00
	Other direct costs	11.900,00	4.065,00	4.065,00	34%	7.835,00
	Subcontracting	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	29.580,00	8.755,00	8.755,00	30%	20.825,00
	Total Costs	78.880,00	23.347,00	23.347,00	30%	55.533,00
Total	Total Person-month	1.177,00	260,00	260,00	22%	917,00
	Personnel	6.710.201,00	950.429,00	950.429,00	14%	5.759.772,00
	Other direct costs	1.593.601,00	150.392,00	150.392,00	9%	1.443.209,00
	Subcontracting	64.584,00	0,00	0,00	0%	64.584,00
	Adjustments	0,00	0,00	0,00	0%	0,00
	Indirect costs	5.539.580,00	739.725,00	739.725,00	13%	4.799.855,00
	Total Costs	13.907.963,00	1.840.546,00	1.840.546,00	13%	12.067.417,00

The revised number of PM efforts at **USFD** is justified as follows:

According to the CHIC DoW, USFD has 4 PM in **WP1**. Due to a less senior management staff than originally planned, USFD expect a mildly larger effort (7.4 PM) at a similar cost. The actual effort reported in WP1 is 2.05 PM, in line with this new effort projection.

WP7 was expected to start immediately, but delays in the recruitment procedures forced USFD to compensate in the first six months with other staffs, and with the recruitment on the project of a PhD student, who will continue to work in the project for the next two years. Because of this USFD plan a considerable increase of effort in WP7, that will raise from 88 PM as planned in the DoW to 128 PM; however, this will not involve any increase of cost, due to the lower salary scale of the PhD student.

Regarding **WP12**, USFD plan a small increase of PM over the DoW (7 PM instead of 6 PM), in relation to the CHIC dissemination within the Insigneo Showcase, especially in the third and fourth year.

4.2 Budget Explanations

Reference is made to the budget explanations given in the Use of Resources table generated in NEF.

4.3 Planned versus actual efforts

Planned versus actual efforts are included in each work package report.