



## PROJECT PERIODIC REPORT

### Preliminary version!

**Grant Agreement number:** 600841

**Project acronym:** CHIC

**Project title:** Computational Horizons in Cancer – Developing Meta- and Hyper-Multiscale Models for In-Silico Oncology

**Funding Scheme:** Collaborative Project

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**Interim report:** 1<sup>st</sup> ☐ 2<sup>nd</sup> ☒ 3<sup>rd</sup> ☐ 4<sup>th</sup> ☐

**Period covered:** from 1 April 2014 to 31 March 2015

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## 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) <sup>1</sup>:
  - ☒ 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 (section 3.4) 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 3.2.3 (Project Management) in accordance with Article II.3.f of the Grant Agreement.

Name of scientific representative of the Coordinator: *Georgios S. Stamatakis, Research Professor*.....

Date: .....1...../ .....6...../ .....2015.....



For most of the projects, the signature of this declaration could be done directly via the IT reporting tool through an adapted IT mechanism.

<sup>1</sup> If either of these boxes below is ticked, the report should reflect these and any remedial actions taken.

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## Publishable Summary

### I. Summary of the project context and objectives

*In silico* medicine (*ISM*) [[http://en.wikipedia.org/wiki/In\\_silico\\_medicine](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 during the 2<sup>nd</sup> year of the project's implemetation and the main results achieved

#### Overall progress of the project implementation

The project has fully achieved the targets foreseen for the second 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 second annual project periodic report.

#### Work Package 1 (WP1): Project Management

The following major achievements were made during M13-M24: The **2<sup>nd</sup> CHIC review (first annual review)** took place on 3 September 2014. The assessment included in the Review Report was very positive. The reviewers saw the project on track and considered the goals of the 1st year achieved. The CHIC consortium members agreed with the CHIC Project Officer at the European Commission to schedule the **3<sup>rd</sup> CHIC review** (after M24) on 8 July 2015. A **3rd Progress Meeting (MS2)** was held on 16-17 October 2014 at KULeuven). A special focus of the meeting was the recommendations made

during the annual CHIC review and the discussion of a work plan/schedule to meet the recommendations. A dedicated technical meeting was also held at KULeuven on 15 October 2014. The **4<sup>th</sup> progress meeting** (MS2) of CHIC was held in Turin on 26-27 March 2015. The CHIC partners presented their work of the past six months and discussed obstacles, solutions and options within all workpackages. A special focus of the meeting lay in the preparation of the 3<sup>rd</sup> CHIC review meeting which is to take place in July 2015. The CHIC members identified various demonstrators to be presented at this review. These include a clinical demonstrator (clinical data and pseudonymization workflow), an integrated lung cancer multi-modeller hypermodel as well as a demonstration of the overall technological workflow through the use of special cancer toy models. The meeting was accompanied by a clinical workshop primarily dedicated to prostate cancer and organized by the CHIC partner UNITO (University of Turin) on 28 March 2015. In terms of **financial monitoring**, the CHIC consortium received their first periodic payment from the European Commission (EU) after the successful conclusion of the annual review meeting. General financial monitoring is done throughout the project by Eurice. Regarding **contractual management**, the management team closely followed the development and signing process of the CHIC Memorandum of Understanding (MoU). The final signed CHIC MoU will be an addition to the CHIC Consortium Agreement and will be made available to all CHIC partners via the CHIC intranet. Given the fact that several modifications had to be made to the original CHIC DoW, the CHIC Consortium is currently preparing for an **amendment**, which will be officially requested by the CHIC coordinator after the submission of the 2<sup>nd</sup> periodic report. This decision was taken in order not to cause any delays in the reporting schedule.

#### **Work Package 2 (WP2): User Needs and Requirements**

The following major actions were accomplished: Requirements for hypermodels beyond the domain of cancer were developed and documented. Collection of clinical, imaging and molecular data continued. All CHIC partners contributed to the requirements analysis for enhancing hypermodels beyond the domain of cancer. Scenarios and use cases were further developed and refined by the clinical partners in close interaction with all other partners. Scenarios were dissected into granular modules. Interaction and collaboration with the p-medicine project continued. The CHIC project was presented in clinical workshops and conferences such as the EUREKA prostate cancer workshop held in Turin, Italy on 28 March 2015. Extensive interaction with clinicians outside the CHIC consortium regarding the clinical acceptance of hypermodels took place. Of special importance for the CHIC project is the domain of cancer genomics: one of the grand challenges of the understanding cancer progression is to find mechanistic links between molecular alterations and the hallmarks of cancer. Gathering large scale clinical data aims at profiling patients or patient cohorts at the molecular level. Functional annotation of data and derivation of mechanistic insights are particularly useful for clinical decision making. In this context we provided an integrative framework for combining the state-of-the-art in two different fields, namely structural biology and machine learning, in order to delineate mechanisms and relationships in cancer genomes.

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

The following major activities related to WP3 took place: Exploitation of Wilms tumor and lung cancer patients' multiscale data. Definition of the specific multiscale data to be provided for glioblastoma modelling. Continuous interaction of the modellers with the clinicians regarding the details of the provision, checking and usage of the multiscale data. Definition of all data to be used by the hypermodels of nephroblastoma and non-small cell lung cancer. Collection of data. Further development of the ontology-based clinical trial managing system ObTiMA to collect data also for glioblastoma. Addressing of legal and ethical issues for sharing glioblastoma data in the CHIC framework. Consensus was obtained for using ObTiMA as the data management system for glioblastoma multiforme data. Case Report Forms (CRFs) were prepared and 82 glioblastoma data sets were introduced into ObTiMA. The necessary information regarding the clinical, radiological, standard therapy, immunotherapy, pathological and patient self-reporting data regarding



glioblastoma was made available in the source documents. Images were made available on the UZ Leuven (University Hospital of Leuven) PACS server. Interaction with involved modellers resulted in a better understanding between clinical and cancer modelling partners. The data collection on prostate cancer patients treated by radical surgery or radiotherapy was completed (EUREKA-1 and EUREKA-2). The clinical database resides on the server of UNITO and FPO-IRCCS Cancer Center of Candiolo, Turin, Italy and will be shared with other members of the CHIC project according to the signed agreement. The beta release of the model based on the phenomenological universalities is ready. Decomposition of the model into hypomodels is in progress.

#### **Work Package 4 (WP4): Legal and Ethical Framework**

During the second year of the CHIC project implementation the first iteration of the data protection and copyright framework was completed. An Intellectual Property Rights (IPR) memorandum of understanding was developed. The concluding phase of data protection agreements between the CDP and partners was reached. A mapping of the data evaluation and privacy profile for the transfer of data to the CHIC research environment was produced.

#### **Work Package 5 (WP5): IT Architecture**

Several important results for the successful implementation of the project were produced. In particular, the final stage of the initial version of the CHIC technical architecture has been completed. The second phase of the integration of the single-sign-on security mechanism into the model/tool repository and the *in-silico* trial repository has been initiated. Integration with the CHIC security framework has been extended and support for the production of identity provider has been added to enable single sign-on. A black-box testing of the new integrated authentication module for VPH-HF (Virtual Physiological Human – Hypermodelling Framework) version alpha 0.2 has been passed. An in depth analysis of the details for the integration plan between the CHIC security services and the VPH-HF has been performed and the technical work for this integration has been completed. The final version of the security guidelines and an initial version of security tools has been produced. The design of the private cloud infrastructure has been completed and put into production providing data storage and computational resources to all of the technical partners of the consortium. Techniques to build the cloud infrastructure available to the community have been formulated.

#### **Work Package (WP6): Cancer Models and Hypermodel Design**

The lung cancer multi-modeller hypermodel was delineated and is currently under implementation. Extensive *in silico* experimentation, analyses and explorations using the available nephroblastoma data were performed. A mechanistic model of the response of glioblastoma to immunotherapy treatment is under development. An alternative mathematical approach to the phenomenon of glioblastoma invasion to surrounding tissues based on the Brownian motion was developed and published. Advanced numerical checking and exploration of an existing model of non-small cell lung cancer response to treatment was performed. An automatic meshing tool was made available. A multi-scale coupling of a biomechanical with a cellular bio-model integrated into a single configurable package was achieved. A hypermodel validation strategy was devised. The “coupled simulator” of tumour growth and biomechanics has been partly tested on certain cases of lung cancer patients. New components of vasculature growth with a focus on the interaction with the tumour growth component model have been formulated. Hybrid and continuum partial differential equation (PDE) models of angiogenesis have been developed. The angiogenesis and molecular components are under integration into the composite hypermodel. Additionally, the relationship between certain particular genes and the good or bad response of prostate tumours to hormone therapy was studied. Mutation based models have been applied in different contexts including lung prostate and cancer. Prostate cancer data collection has been completed. Preliminary related studies are under way. A molecular scale methodology and protocol for the computational profiling of kinase mutations using molecular dynamics simulations has been established. As part of the task a multiscale method to combine the molecular studies with signalling network studies has been developed. An *in silico*

profiling algorithm correctly predicting the activation status in Alk with over 85% accuracy was developed. 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. The 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, crizotinib, and lapatinib) in non-small-cell lung cancer and pediatric neuroblastoma. Molecular models regarding metabolism have also been developed.

#### **Work Package 7 (WP7): Hypermodelling infrastructure**

The following activities took place: Deployment of an exemplar set of hypomodels supplied by project partners and development of black box hypomodels representative of an initial test set as agreed with WP6 which is dedicated to cancer hypermodelling at the basic science level. Deployment of a set of hypomodels supplied by WP6 which constitutes the first CHIC exemplar lung cancer multimodeller hypermodel. Revision of the generic stub.Consolidation of the first version of the metadata schema used to annotate data and resources to be used in VPH-HF. Construction of an initial version of folksonomy tagging service. Successful implementation and deployment of the first release of the revised VPH-HF and demonstration of test workflows on two test nodes. Provision of models and hypermodels for testing purposes as well as their wrapping and annotation. Development of software for the easy deployment of an alpha version of hypermodelling environment on a remote machine. Reaching of an agreement on a revised architecture for the beta version of the framework, optimised for the needs of the CHIC project.

#### **Work Package 8 (WP8): Model and Data Repositories**

The following actions were completed: Finalization of the information model and the technologies for the model/tool and the *in silico* trial repositories. Design of the back-end of the model/tool and the *in silico* trial repositories. Completion of the advanced phase of the definition of the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repository. Development of components of the back-end of the model/tool and *in silico* trial repositories and deployment on the CHIC's private cloud. Completion of the second phase of the integration of the single-sign-on security mechanism into the model/tool and the *in silico* trial repositories. Integration of the data repository with the first version of the CHIC data protection framework. Initial integration of an external timeline tool into the data repository interface. Extension of REST (Representational State Transfer) services with more functionality in line with the defined milestones. Support for clinical study datasets. Initiation of the integration with the RICORDO framework. Evaluation of available triple-store databases to determine the database (Virtuoso) most appropriate for CHIC. Development of a software interface in the form of its "RDF(Resource Description Framework)Store" API (Application Programming Interface) which allows creation of user-friendly templates from SPARQL (SPARQL Protocol and RDF Query Language) queries. Development of OWLKB (Ricordo semantic reasoner server). Selection of a set of reference ontologies for CHIC. Development of cutting-edge technology to deal with the problem of ambiguous terms. Development of the "RDFStore" system and accompanying API. Review of the way in which p-medicine is dealing with semantic interoperability. Progress in the development of 'HOT (Hallmarks-Ontologies-Tumor) Maps' of tumour-specific hallmark knowledge.

#### **Work Package 9 (WP9): Image Processing and Visualization**

Several partners worked on the definition of the basic science expectations from WP9. WP9 developed software for the preprocessing of imaging datasets according to the needs of the CHIC hypermodel Oncosimulator. Both the timeline and CCGVIS (a 3D volume rendering software) have been internally tested by certain partners. Most of the technologies have been integrated into the DrEye image processing platform. Preparatory tasks have been performed in order to enable all

partners to use the DrEye tool as the single integrated imaging platform of CHIC. For this purpose, documentation, API and other material have been provided through a dedicated repository. The ktrans DCE-MRI (Dynamic contrast-enhanced MRI) biomarker has been tested providing promising results. Full implementation of monomodal and multimodal registration routines using a point-wise mutual information metric has been carried out. A fully operative plug-in for the DrEye software to perform automatic segmentation of brain tumours from multimodal MRI has been developed. Automated tumour volumetry has leveraged the design of biomarkers for patient survivability and neuro-navigation. A high potential to improve the current state of the art in current RANO (Response Assessment in Neuro-Oncology) criteria for tumour assessment has been identified. The model and the data repositories have been evaluated by clinical partners regarding usability. Feedback has been provided. The development of a tool for the automatic rendering of the tumour volume in glioblastoma and neuroblastoma has started. The latter will be integrated into the DrEye software.

#### **Work Package 10 (WP10): Integrated Platform**

The following actions were completed: Definition of the programmatic interfaces for accessing the model repositories. It is noted that the interfaces will be implemented and used not only by the internal components of the CHIC platform but will also enable interoperability with external research organizations. Implementation of the CHIC Data Upload tool for the secure uploading of sensitive patient data to the CHIC platform. Further development of the current PhysiomeSpace encryption services with state of art encryption algorithms. Initial design of the CHIC Hypermodelling Editor. Preliminary integration results and exploration for supporting “strongly-coupled” models.

#### **Work Package 11 (WP11): Clinical Adaptation and Validation**

Work started in an iterative way and the evaluation process will continue throughout the whole lifetime of the project. The collaboration within the consortium has been excellent. The first round of evaluation tests of the CHIC components has been completed. Cloud resources have been used for the evaluation activities of CHIC, proving to be a valuable tool for the objectives of WP11. With the technical knowledge earned through this process it is expected that it will also be used in the future for such activities with even better results. The first multi-modeller hypermodel of lung cancer has served as a first complete example for the fine-tuning of the CHIC infrastructure based on the corresponding multiscale clinical data. The first round of evaluation tests of the CHIC components took place in Leuven, Belgium and its results have been reported in deliverable D11.2. A first version of the BraTumIA software as a DrEye Plugin has been created.

#### **Work Package 12 (WP12): Dissemination and Exploitation**

The project website is up to date and regular dissemination of news and highlights via the CHIC newsletters is ongoing and effective. The 2nd annual newsletter is currently in the making. 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, is actively ongoing. A clinical workshop primarily dedicated to prostate cancer was organized by the CHIC partner UNITO in Turin on 28 March 2015. Most CHIC clinical partners, modellers and the CHIC coordinator participated in it disseminating CHIC to the wider clinical community. About forty clinicians from Italy and other European countries actively participated in that highly successful event. A discussion about sustainability and maintenance issues of the CHIC project via the proposed Study Trial and Research Centre (STaRC) that is part of the maintenance program of the p-medicine project has started and exploitation related activities are in progress. Relevant discussions are ongoing. Their outcome will be integrated into the exploitation planning report of CHIC. A first version of the Preliminary Plan for the Use and the Dissemination of Foreground (PUDF) was submitted to the EC. Training activities, most notably the CHIC Summer School 2015, have also started or are currently being organized.



### 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 second year of the implementation of the project several actions aiming at facilitating the exploitation of the project outcomes were taken. A discussion about sustainability and maintenance issues of the CHIC project via the proposed Study Trial and Research Centre (STaRC) that is part of the maintenance program of the p-medicine project has been initiated and exploitation related activities are progressing. Relevant discussions among all partners are ongoing. Their conclusions will be integrated into the exploitation planning report of CHIC. An initial version of the Preliminary Plan for the Use and the Dissemination of Foreground (PUDF) was submitted to the EC. Training activities, most notably the CHIC Summer School 2015, have also started or are currently being organized.

### IV. Address of the public website

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

## 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:

- T2.3, Requirements for enhancing hypermodels beyond the domain of cancer (M1-18)
- T2.4, How to get acceptance of hypermodels by patients and physicians (M12-42)

### Summary of progress achieved towards objectives

The requirements for enhancing hypermodels beyond the domain of cancer were developed and documented. Activities among the contributing members were coordinated mainly by Philipps. They include identifying the necessary set of requirements that need to be fulfilled in order a not-cancer-focused hypermodel to be developed and executed in the CHIC platform. The final document includes requirements regarding the development of biological models, about all the layers of the CHIC architecture and the requirements from the ethical and legal framework. ICCS contributed to the requirements analysis for enhancing the model/tool repository and the *in silico* trial repository beyond the domain of cancer from the technical perspective. In addition all participants of WP2 contributed to the preparation of deliverable “D2.3: Requirements for enhancing hypermodels beyond the domain of cancer” from the modelling perspective. From the clinical perspective USAAR and other clinical partners contributed extensively. In task 2.4 USAAR is analysing the requirements to get acceptance of hypermodels. This is done in close cooperation with all partners, 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 further 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. Together with task 2.3 mechanisms to use *in silico* models and hypermodels beyond the domain of cancer are elaborated and written in D2.3. All partners of the CHIC consortium are included in these discussions.

The work of UPENN is related to Tasks 2.1, 2.3, 2.4: State of the Art of Knowledge for building hypermodels: To identify topology of signalling networks with feedback interactions in receptor tyrosine kinase mediated signalling in cells harbouring wildtype and mutant forms of the receptors. The deregulation associated with signaling of EGFR family receptors has been implicated in other serious health conditions, such as atherosclerosis, and an inherited loss-of-function mutation was recently reported to result in multi-organ inflammation. Several of the mutants have constitutive tyrosine kinase activity, which can further be stimulated by ligand treatment. Hence our study of EGFR mutations and signalling can be extended to domains beyond cancer. UPENN has built a script-based platform, which mines the genomic information (retrospective clinical data) in cancer atlases (COSMIC) and performs analysis on somatic and germline mutations in tissues in different cancers. We have also implemented a machine-learning algorithm that predicts the activation state of a given gene based on the underlying mutation. This algorithm is multiscale, as it uses protein evolutionary data as well as data from physics-based (molecular dynamics) simulations to build classifiers. 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 has been validated against a panel of ALK mutations in neuroblastoma.

### Summary of details for each task

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

From the clinical perspective USAAR contributed extensively in elaborating D2.3. Specifically USAAR worked on the following parts of this deliverable: Overview, Ethical and legal framework, Validation of hypermodels in clinical trials, and requirements for biological models.

In this task, Philips identified, designed and developed the requirements for enhancing hypermodels in other domains. This is achieved by identifying, along with the contributing members, the necessary set of requirements that need to be fulfilled in order a not-cancer-focused hypermodel to be developed and executed in the CHIC platform. The final document includes requirements regarding

the development of biological models, about all the layers of the CHIC architecture and the requirements from the ethical and legal framework. The necessary process of the formal validation of those hypermodels will be documented in deliverable D2.3.

ICCS has contributed to the requirements analysis for enhancing the model/tool repository and the *in silico* trial repository beyond the domain of cancer from the technical perspective. ICCS contributed to the preparation of deliverable “D2.3: Requirements for enhancing hypermodels beyond the domain of cancer” from the modelling perspective. General requirements for the enhancement of the hypermodels have been defined. The deliverable also included specific examples where such enhanced models could be used in the future for numerous non-cancer diseases and physiological functions.

FORTH contributed to D2.3 by providing the necessary requirements and restrictions from the technical architecture perspective in order to enhance and extend the CHIC platform beyond the domain of cancer.

USAAR and other clinical partners enhanced the requirements from the clinical perspective. USAAR participated in iterative discussions on how to develop the repositories (WP8) in a way that meets clinical needs. In addition, the way to upload data to the data repository was discussed and optimized in an iterative way with all stakeholders. The web-based user interface was evaluated and feedback given in an iterative way for usability issues. A meeting dealing with data upload was held in Homburg in December 2014.

Different methods to catalog 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 UPENN’s molecular Model, 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 have 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 their model on retrospective clinical genomic data.

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

The requirements for getting acceptance of hypermodels are under further elaboration in an iterative process with all members of the CHIC project. USAAR is leading this task. A questionnaire is being further elaborated. ICCS took part in initial discussions on how to gain acceptance of hypermodels. Presenting the work performed in CHIC in clinical oriented conferences was proposed. The CHIC coordinator (G. Stamatakis, ICCS) and Norbert Graf were invited in the workshop entitled “Prostate Carcinoma: Reports from EUREKA Studies (CHIC studies)” that took place in Turin, Mar 28, 2015 in the IRCC-FPO Istituto Scientifico di Candiolo. He presented the CHIC project and intensely interacted with the about 40 participating clinicians regarding the clinical acceptance of hypermodels.

The most important requirement for the validation of models and hypermodels is the availability of data. In this reporting period all clinical partners continued with the collection of data for the different cancer domains. At the moment the clinical partners still locally host these data. As soon as the legal and ethical framework is in place and a user interface is functional for the upload of data to the CHIC platform these data will be shared to all other partners. This will happen before the next consortium meeting in 2015.

Double-blind validation: UPENN presented 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. UPENN showed 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.

### **Summary of significant results**

- Requirements for hypermodels beyond the domain of cancer were developed and documented.
- We continued to collect clinical, imaging and molecular data. All partners of CHIC give contributions to the requirements analysis for enhancing hypermodels beyond the domain of cancer.
- Scenarios and use cases are under further development by clinical partners and in close interaction with all other partners. They are further dissected into granular modules.
- Interaction and collaboration continued with p-medicine and USFD.
- Presentation of the CHIC project and interaction with clinicians regarding the clinical acceptance of hypermodels.
- 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.

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

The submission of the D2.3 has been slightly delayed (M18) and an extension was requested with the approval of the WP leader and the CHIC coordinator. The document was delivered on the extended deadline (M21). There was no impact on other tasks or to 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**



Not applicable.

#### Corrective actions

Not applicable.

#### Statement on the use of the resources

Planned versus actual efforts in WP2			
Partner	Planned PM Total	Planned PM Period 2	Actual PM Period 2
1-ICCS	2.00	0.60*)	0.80
3-USAAR	25.00	7.00	1.65
7-FORTH	5.00**)	1.00	1.00
9-UPENN	5.00	1.00	1.00
13-CUSTODIX	1.00	0.25	0.00
14-PHILIPS	4.00	2.00	2.00
<b>Total</b>	<b>40.00</b>	<b>11.85</b>	<b>6.45</b>

\*) New PM effort planning after an internal revision of efforts at ICCS. The revision was performed as the future work in the remaining 2 periods of CHIC became clearer.

\*\*) New planned PM efforts resulting from a revision by FORTH which was carried out after the 2<sup>nd</sup> CHIC review. The new PM effort table was sent to the EC on 11 December 2014. The CHIC partners are currently working towards an amendment to incorporate these changes in the CHIC DoW.

USAAR have moved planned efforts in this WP to comply with the need to fulfill all the demands of WP3. There is no influence on the outcome of WP2.

### 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:

- T3.1, Wilms tumor (M1-48)
- T3.2, Glioblastoma multiforme (M1-48)
- T3.3, Non small cell lung cancer (M1-48)
- T3.4, Applying the CHIC infrastructure to other cancer types (M12-36)

#### Summary of progress achieved towards objectives

For Wilms tumor, ICCS started the exploitation of Wilms tumor patients' multiscale data. Preparatory work was done regarding micro-RNA data to be provided. Major work was done at USAAR after defining the data to be used in the nephroblastoma to start collecting them and in addition to render

tumour volumes of nephroblastoma. After the legal and technical framework is in place these data can be shared for usage by developers of the hypermodel. ObTiMA is used for data collection. New functionalities are needed for ObTiMA that are under programming by IT staff from USAAR. For Glioblastoma multiforme, ICCS defined the specific multiscale data to be used by the glioblastoma multiforme multiscale models to be developed. Together with KU Leuven USAAR discussed how glioblastoma data can be collected with ObTiMA. For that purpose new functionalities are needed for ObTiMA. At KULeuven, major work was done in collecting data that will be used in the glioblastoma multiforme scenario. Data management systems were extensively explored and CRFs were constructed. ObTiMA will be used for data collection; 82 data sets were already entered. Close interaction with ICCS modellers was also continued. For Non small cell lung cancer, ICCS began the exploitation of lung cancer patients' multiscale data. Major work was done by USAAR after defining the data that will be used in small cell lung cancer scenario. Collection of data from patients with Non-Small-Lung-Cell Cancer (NSCLC) has been started. After the legal and technical framework is in place these data can be shared for usage by developers of the hypermodel.

At UNITO, the data collection from patients undergoing prostatectomy has been closed in May 2014. Checking these data has been completed in September 2014. Data on anamnesis, biopsy, pathology, surgical and medical therapies, follow-up are recorded in the EUREKA-1 database (UNITO & FPO-IRCCS Cancer Center of Candiolo). The data collection from patients undergoing radical radiotherapy has been closed in December 2014. Checking these data has been completed in February 2015. Data on anamnesis, biopsy, radiotherapy and androgen depriving drugs, follow-up are recorded in the EUREKA-2 database (FPO-IRCCS Cancer Center of Candiolo & UNITO). The beta release of the model based on the Phenomenological Universalities to be applied to the clinical data on prostate cancer has been completed.

A script-based platform was built by UPENN, which mines the genomic information (retrospective clinical data) in cancer atlases (COSMIC) and performs analysis on somatic and germline mutations in tissues in different cancers. A machine-learning algorithm that predicts the activation state of a given gene based on the underlying mutation has also been implemented. This algorithm is multiscale, as it uses protein evolutionary data as well as data from physics-based (molecular dynamics) simulations to build classifiers. A double-blind validation protocol for assessing the accuracy of the predictive algorithm by computing ROC (receiver operating characteristic) curve has been devised. 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 has been validated against a panel of ALK mutations in neuroblastoma.

### Summary of details for each task

#### **Task 3.1: Wilms tumor**

Exploitation of Wilms tumor patients' multiscale data is in progress at ICCS. Preparatory work for the provision of micro-RNA data are under way. Continuous interactions of ICCS with USAAR.

Within the SIOP Renal Tumor Study Group a new clinical trial is further developed by USAAR. 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 tool for automatic annotation of Wilms Tumor is further optimized and still under validation in a feedback loop with the developer. miRNA data in addition are collected and locally stored. They can be submitted to other partners as soon as they are acknowledged by the legal and ethical framework of CHIC and the user interface allows upload of the data. A dedicated workshop took place in Homburg at the 11<sup>th</sup> and 12<sup>th</sup> of December 2014.

Data collection and post-processing of data continued with ObTiMA. Release of data is possible after the legal framework is in place and functioning. The hypermodel was further elaborated in an iterative process together with WP2.

### Task 3.2: Glioblastoma multiforme

Continuous interactions of ICCS with KU Leuven and other partners have led to the definition of the specific multiscale data to be provided by KU Leuven. The latter are continuously guiding the development of the specific glioblastoma multiforme multiscale models. Together with KU-Leuven USAAR discussed data collection with ObTiMA. For that purpose new functionalities were programmed for ObTiMA by IT specialists from USAAR.

At KU Leuven, the HGG-2010 clinical trial will serve as the data source of glioblastoma multiforme data for task 3.2. An informed consent was obtained for all 136 patients. An extra application for sharing the data in the CHIC consortium was done at the local ethical committee on March 17<sup>th</sup>, 2014. Approval is given by the *Commissie Medische Ethiek UZ KU Leuven* on April 7<sup>th</sup>, 2014. KU Leuven also signed the *CHIC Data Provider Agreement* on May 23<sup>th</sup> 2014 and by this means data protection agreements for sharing data are fulfilled.

Different data management systems for storing the glioblastoma multiforme data were explored extensively by KU Leuven. *FileMaker* was studied locally but did not satisfy the CHIC partners for practical and for technical reasons (the format for exporting data). *OpenClinica* was studied in more detail and a big effort was done in making accurate CRFs for the HGG-2010 trial. After examining this system in practice and discussing ObTiMA with other CHIC partners, the latter system was chosen as the system we will use for storing the glioblastoma multiforme data. Discussions and meetings with USAAR partners were held to learn to work with ObTiMA. The already tested CRFs were optimised and re-evaluated in the *ObTiMA test server*.

An extra effort was done for collecting a huge amount of material of different kinds. As part of the clinical trial an update on the completion of source documents of all patients was done; this was documentation containing clinical, radiological, pathological, standard of care, immunotherapy and patient self-reporting information. This information will be updated every 6 months.

Imaging data (DICOM format) are stored in the hospital's PACS system. The primary endpoint of the study (and the primary question in the CHIC project for GBM) is being determined, based on these imaging data.

Analysis of some immunotherapy related aspects (FACS acquisitions) was started and will provide extra immunotherapeutic data for sharing. Also the patient self-reporting information was processed.

Preparation was done for upcoming biological and immunological research on tumor and blood samples.

The data sets of 82 HGG-2010 trial patients were entered in a pseudonymised way in the *ObTiMA production server* and are up-to-date to at least December 2014. The corresponding anonymised images are also available.

Intense interaction between modellers from ICCS and clinicians at KU Leuven took place during this entire period. Providing them with information on the theory and the experimental background resulted in a clear understanding between both partners.

Now, all the software and infrastructure needs to be tested and made available in order to share the data sets with the consortium.

### Task 3.3: Non small cell lung cancer

Exploitation of lung cancer patients' multiscale data is in progress, which also requires continuous interactions of ICCS with USAAR. Together with WP2, USAAR further elaborated data for the Non-small cell lung cancer hypermodel. Data collection continued: 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 were given for upload according to the legal and ethical framework of CHIC.

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

ICCS is in contact with UNITO in order to adapt various models being developed primarily by UNITO to the CHIC framework, in particular regarding the multiscale nature of prostate models. This concerns the following tasks:

- collecting data from patients histories assessing their individual variability and the common features in terms of developmental phases
- defining a model, based on the general 'Phenomenological Universalities', linking an overall growth law with 'growth spurts', corresponding to organ invasion, host invasion, near and distant metastasis occurring at proper average $\pm$ SD times
- including the specific model in the more general context of multivariate-multiscale models proposed by the CHIC projects

A discussion started at USAAR how ObTiMA can be used for data collection for other cancer types.

In EUREKA-1 data of a total of 3538 patients from 13 clinical Urology Divisions (sending from 65 to 513 cases) with a median follow up of 57 months are collected by UNITO. In EUREKA-2 data are collected of a total of 3776 patients from 10 clinical Radiotherapy Divisions (sending from 76 to 1195 cases) with a median follow up of 65 months. EUREKA-1 and EUREKA-2 studies have been amended in November 2014 by FPO-IRCCS Cancer Center of Candiolo Ethical Committee in order to pursue data collection and will be updated until March 2017. A software has been supplied to the participating centers of EUREKA-1 and EUREKA-2 studies, in order to update their data; the goal to be reached within December 2016 is that of recruiting a total of 8000 patients with a median follow-up of 84 months.

Applications of the modelling activities prostate cancer are in progress: both statistics (bottom up) and mathematics (top down) approaches are investigated. Applications to lung cancer have been discussed with CHIC partners at the Progress meeting in Leuven.

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 and EGFR mutations in non-small-cell lung cancer. We show here that our 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. We expect that the current study on ALK and EGFR will transform our 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. (See also publications mentioned above) In the double-blind validation our computational predictions matched experimental measures of kinase activity with over 85% accuracy in the mutations investigated from neuroblastoma patients.

### 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.

Definition of all data for usage in the hypermodels of nephroblastoma and non-small cell lung cancer. Further development of ObTiMA to collect data (also for glioblastoma).

Legal and ethical issues for sharing data in the framework are cleared.

Consensus was obtained for using *ObTiMA* as the data management system for glioblastoma multiforme data. CRFs were prepared and 82 data sets were entered in *ObTiMA*.

The information for the clinical, radiological, standard therapy, immunotherapy, pathological and patient self-reporting data are available in the source documents. Images are available on the UZ Leuven PACS server. The primary endpoint is being determined for all patients.

The data collection on prostate cancer patients treated by radical surgery or radiotherapy has been completed (EUREKA-1 and EUREKA-2).

The clinical database is resident on the server of UNITO and FPO-IRCCS Cancer Center of Candiolo and will be shared with the other members of the CHIC project according to the signed agreement.

The beta release of the model based on the Phenomenological Universalities is ready. Decomposition in hypomodels is in progress.

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. 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, crizotinib, and lapatinib) in non-small-cell lung cancer and pediatric neuroblastoma.

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

Some experimental work from KU Leuven still needs to be done. This results in a delay for the availability of the experimental data, but all partners involved are aware of this. Nevertheless, the 82 data sets containing all clinical data were entered in time in ObTiMA. The data sets (containing the clinical data) are ready to be shared with the consortium, so there is no delay in the planning for that.

#### 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 2	Actual PM Period 2
1-ICCS	2.00	0.70*)	0.90
3-USAAR	49.00	16.00	35.98
4-KULeuven	68.00	20.00	20.00
9-UPENN	2.00	0.50	1.50
11-UNITO	14.00	4.00	4.33
<b>Total</b>	<b>135.00</b>	<b>41.20</b>	<b>62.71</b>



\*) New PM effort planning after an internal revision of efforts at ICCS. The revision was performed as the future work in the remaining 2 periods of CHIC became clearer.

USAAR needed more resources than originally planned in WP3 due to data creation and data provision for the different scenarios covered. In order to minimize the effect on the total planned efforts of USAAR in the second reporting period, PM efforts were deducted from other WPs to meet this additional need in WP3.

## 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:

- T4.3, Development of a data protection and copyright framework for CHIC (M1-42)
- T4.4, Whitepaper preparation on "Recommendations for an amended European legal framework on patients' and researchers' rights and duties in E-health related research" (M14-28)

### Summary of progress achieved towards objectives

LUH – Led in the development of the data protection and copyright framework first iteration which has been completed and Deliverable D4.3.1 submitted in that respect. Work is on-going for the second iteration towards the end of the project. LUH also developed the Memorandum of Understanding covering IPR issues which is currently being signed by the CHIC partners.

Research is being conducted that will lead to whitepaper recommendations for amending the European legal framework on patients' and researchers' rights and duties in E-health related

research. This is a follow-up of the initial position paper developed in month 3, taking account of the on-going reform debate in the area of data protection.

USAAR contributed in the submission of D4.3.1 as well as in the discussion and refinement of how to pseudonymise/anonymise data needed for the nephroblastoma and small lung cell cancer hypermodel.

CUSTODIX contributed in the development and deployment of the initial data protection framework including the pseudonymisation and security tool as applicable to task 4.3 first iteration.

ICCS contributed to the clarification of the definition of composite work in the context of hypermodelling in CHIC as well as review of the Memorandum of Understanding (MoU).

UPENN contributed to the IPR discussion and have procured the necessary software licenses for the hypermodels and frameworks.

### Summary of details for each task

#### **Task 4.3, Development of a data protection and copyright framework for CHIC**

This task is divided into two parts – the first and the second iteration of the data protection and copyright framework. In the first iteration, the data protection and copyright framework has been developed and completed. Deliverable D4.3.1 was submitted on time in that respect. The framework includes the development of pseudonymisation and security framework for deploying data to the CHIC platform. Data protection agreements developed for this task have been concluded between the CDP and the partners who will require access to the CHIC data. Privacy profiles mapping and data validation have commenced for DICOM files to be sent to the CHIC research environment. In respect of the IPR, the clarification of the definition of joint and composite work in the context of CHIC as well as potential IPR issues arising from the gap in the CA and GA have been investigated and a Memorandum of Understanding (MoU) drafted to take care of the identified problems. Negotiations on the terms of the MoU have been completed and the document is currently being signed by the CHIC partners. Work is on-going for the second iteration towards the end of the project.

#### **Task 4.4, Whitepaper preparation on “Recommendations for an amended European legal framework on patients’ and researchers’ rights and duties in E-health related research”**

Research is being done by LUH for a whitepaper recommendation for amending the European legal framework on patients' and researchers' rights and duties in E-health related research. This is a follow-up of the initial position paper developed in M3 relating the on-going reform in the area of data protection. Initial research in this task has taken place and will be completed in M36.

### Summary of significant results

The first iteration of the data protection and copyright framework was completed.

Development of the IPR Memorandum of Understanding.

Concluding phase of data protection agreements between the CDP and partners.

Data evaluation and privacy profile mapping for the transfer of data to the CHIC research environment

### 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 2	Actual PM Period 2
1-ICCS	2.00	0.70*)	0.90
3-USAAR	4.00	1.50	0.01
8-LUH	48.00	12.00	17.01
9-UPENN	2.00	0.50	1.00
13-Custodix	2.00	0.50	0.55
<b>Total</b>	<b>58.00</b>	<b>15.20</b>	<b>19.47</b>

\*) New PM effort planning after an internal revision of efforts at ICCS. The revision was performed as the future work in the remaining 2 periods of CHIC became clearer.

In order to cope with the additional effort needed in WP3, USAAR's involvement in WP4 was minimal. However, USAAR will work more in the next two periods of the project, to evaluate the Legal and ethical framework within the scenarios and with all the provided data. This it without influence of the outcome of WP4.

LUH have originally distributed their person month efforts linearly across the four reporting periods of CHIC. This explains the differences between planned and actual PM efforts in the reporting periods. This has no effect on any tasks in WP4 or any other WPs.

## 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 initial Reference Architecture has been established and is now being implemented through the technical work packages. Feedback from the developers and further requirements from the end users is being collected, in order to enhance and update the architecture.

Moreover, the initial version of the CHIC security framework has been deployed. The security framework has been integrated in the data upload flow. Authentication and security protocols already in place for the VPH-HF were included. In parallel the integration between the data repository within the CHIC security framework has been extended in terms of authorization.

The installation of the private cloud infrastructure is complete. Feedback and requirements from the end users are being collected for further support and the necessary upgrades.

The data repository deployed to the CHIC private cloud infrastructure was adapted in order to accept the production Identity Provider (IdP) provided by CUSTODIX.

### Summary of details for each task

#### **Task 5.1, Reference Architecture**

TEI-C, as the leader of WP5, continued to provide a coordinated implementation of the work in WP5. The Architecture Definition Board that was established in the previous period, was fully functional during the reporting period. Regular biweekly SKYPE meetings were held, with a focus on well prepared technical issues under discussion, taking decisions on several fronts in order to update and enhance the initial Reference Architecture definition, with contributions from all partners.

FORTH participated and contributed in all CHIC WP5 activities relevant to the Reference Architecture definition. They took the leading role in the implementation and integration of the architectural components. FORTH is currently active in gathering and applying contributions regarding the refinement of the architecture. ICCS was also active in the preparation of a plan regarding the time of availability of the CHIC services to the clinical end users. The analysis of the basic science and legal information is following.

The final version of Deliverable D5.1.1: “The CHIC technical architecture – initial version” has been delivered.

#### **Task 5.2, Security tools and services**

ICCS and CUSTODIX, with contributions and supervision from TEI-C, collaborated closely for the integration of the single-sign-on security mechanism into the model/tool repository and the *in-silico* trial repository (second phase). In collaboration with the WP4, an initial data protection (security) framework has been developed and was deployed in production within the CHIC development and test environment.

The data repository has been previously integrated in the external security framework provided by CUSTODIX with a focus on authentication. During this period, the aim was to integrate the authorization mechanisms to restrict the data access to specific users. For this purpose, additional attributes were placed by the Identity Provider within the tokens exchanged during the authentication process. Those attributes are automatically extracted and translated/mapped by the repository to authorize or reject the data access request made by the respective users. For the task 5.2, the data repository deployed to the CHIC private cloud infrastructure (<https://cdr-chic.ics.forth.gr/>) was adapted by UBERN in order to replace the previously accepted development Identity Provider by the production Identity Provider. This adaptation enables the Single Sign-On (SSO) functionality in the productive environment.

The final version of Deliverable D5.2: “Security guidelines and initial version of security tools” has been submitted. USFD has also contributed with input to this deliverable. In more detail, USFD carried out a survey of the authentication and security protocols already in place for the VPH-HF, which is being developed to provide the CHIC hypermodelling execution environment. This was done

in collaboration with project partner CINECA (who is not formally involved in WP5, but played a key role in developing the VPH-HF services). Key features of the existing services were documented. CINECA is looking on how their preliminary release can be extended so to be easily integrated with the protocols in place in VPH-HF. The integration plan has been clearly defined with intermediate implementation steps for CUSTODIX and CINECA to be achieved in the next reporting period. An update of D5.2 has also been prepared with latest developments and integration guidelines.

USFD also participated in testing the integration of the authentication module for the refactored version (alpha 0.2) hypermodelling execution framework (developed by CINECA) with authentication services developed by CUSTODIX. The tests were carried out on the key components, Director and Storage Management System of VPH-HF (v0.2). The authentication module has passed the black-box testing from USFD.

### **Task 5.3, Private cloud infrastructure**

In the context of this task, the WP5 partners have a) investigated the applicability of open source technologies for the implementation of a private biomedical cloud infrastructure with a special focus on the specific requirements of the biomedical domain which has strict requirements for reliability, availability, performance and security; b) selected the most suitable from the variety of cloud offerings that are available in order to be used in the biomedical domain; c) developed a private cloud infrastructure – mainly using open source platforms; and d) investigated the extend, complexity and benefits of using private (community) clouds in the biomedical domain.

Having completed the installation and configuration of the production cloud environment, FORTH continued supporting the cloud infrastructure, providing resources and technical support to the consortium. Feedback and requirements are being gathered from the end users of the cloud infrastructure in order to perform necessary enhancements and upgrades. The infrastructure is based on Openstack,

BED has provided a state-of-the-art overview of technologies in cloud computing and private community cloud by harvesting existing IT facilities with a focus open source platforms. The results support the architectural decision that has been made, that the project will use the private cloud based on Openstack.

The relevant deliverable D5.3: “Techniques to build the cloud infrastructure available to the community”, has been submitted. Contrary to the CHIC DoW, however, it was agreed that FORTH would lead this deliverable as the lead of task 5.3 also went to FORTH. The EC project officer was informed of this change upon submission of D5.3.

### **Summary of significant results**

Several critical results, for the successful implementation of the project, have been produced during the second year of project implementation. Namely:

- The final version of Deliverable D5.1.1 “The CHIC technical architecture – initial version” has been delivered.
- A refined version of the CHIC reference architecture is being produced.
- The second phase of the integration of the single-sign-on security mechanism into the model/tool repository and the in-silico trial repository has begun.
- Integration with CHIC security framework has been extended and support for production Identity Provider added to enable Single Sign-On.
- Black-box testing of new integrated authentication module for VPH-HF version alpha 0.2 has been passed.
- In task 5.2, an in depth analysis of the details for the integration plan between the CHIC security services and the VPH-HF has been performed and the technical work for this integration has been done.



- The final version of Deliverable “D5.2: Security guidelines and initial version of security tools” has been produced, gone through internal evaluation and submitted.
- Design of the private cloud infrastructure has been completed and was put into production, providing data storage and computational resources to all of the technical partners of the consortium.
- Deliverable “D5.3: Techniques to build the cloud infrastructure available to the community” has been submitted.

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

The efforts in Task 5.2 originally planned to be allocated on USFD were shared between USFD and CINECA as CINECA was the original developer of the security part of VPH-HF. In order to better reflect how the software development tasks are distributed between partners USFD and CINECA, it was agreed to swap 6 PM between the two partners and between WP5 and WP7. As a result of this adjustment the effort of partner USFD is reduced of 6pm in WP5, and increased 6 pm in WP7. Symmetrically, the effort of partner CINECA is reduced of 6pm in WP7 and increased of 6pm in WP5.

Task 5.3 was initially planned to finish on M27, followed by the deployment of the CHIC technical infrastructure to a public cloud. Taking into consideration the reviewer’s recommendations as well as the strong indications from the legal and ethical partners that use of a public cloud infrastructure is not advisable, the CHIC consortium has agreed to extend the Task 5.3 until the end of the CHIC project, so that a the CHIC private cloud, offered, managed and extended by partner FORTH, will be available to the end of the project. This managerial decision implies that additional effort will be required by partner FORTH, which was not foreseen in the Technical Annex and has an impact on the available resources and planning. As a result, FORTH will act as the Task leader for T5.3 and will need to increase its personnel month in Task 5.3 in order to run, maintain and potentially extend the CHIC private cloud in line with the evolving project requirements. BED is expected to slightly reduce its activity in this task. This change will not affect the deliverables described in the DoW. Actions are in progress with the CHIC partners and the management team for an amendment of the Technical Annex in order to reflect and alleviate this change of 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

Not applicable.

#### Corrective actions

Not applicable.

#### Statement on the use of the resources

Planned versus actual efforts in WP5			
Partner	Planned PM Total	Planned PM Period 2	Actual PM Period 2
1-ICCS	3.00	1.00*)	1.50
5-BED	19.00	5.00**)	4.00
6-USFD	6.00 (revised)	4.00	3.71
7-FORTH	28.00***)	8.50	8.50
12-UBERN	4.00	1.50	1.00
13-Custodix	12.00	3.50	3.76
14-Philips	15.00	7.00	1.00

16-CINECA	6.00 (new)	6.00	6.00
17-TEI-C	15.00	4.00	2.70
<b>Total</b>	<b>108.00</b>	<b>45.50</b>	<b>32.17</b>

\*) New PM effort planning after an internal revision of efforts at ICCS. The revision was performed as the future work in the remaining 2 periods of CHIC became clearer.

\*\*) New planned PM efforts resulting from a revision by BED which was carried out after the 2<sup>nd</sup> CHIC review.

\*\*\*)) New planned PM efforts resulting from a revision by FORTH which was carried out after the 2<sup>nd</sup> CHIC review. The new PM effort table was sent to the EC on 11 December 2014. The CHIC partners are currently working towards an amendment to incorporate these changes in the CHIC DoW.

The image analysis and processing involves works that were not foreseen (e.g. the segmentation of healthy organs) and hence leads to higher number of personnel months than expected at BED in WP9. At the same time, BED's activities in WP5 were reduced, which balances the overspending in WP9.

At Philips, the Actual PM in Period 2 is less than the 7PM planned due to staff shortage. More human resources have already been allocated to the CHIC project which will resolve the problem. There was no impact on other tasks and regarding the planning, Philips is committed to deliver in a timely manner.

## 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, the modelling partners are revisiting their developed or under development hypomodels in order to enable their linking and re-writing in the context of hypermodelling. ICCS proposed a lung cancer multi-modeller hypermodel which was adopted by all WP6 partners and is under implementation. The inputs, outputs and basic description of each hypomodel (component model)

have been crystalized by the partners involved. The hypomodels already developed by UNITO (e.g. radiotherapy and chemotherapy models) have been revisited in order to make them linkable to other models and re-writable in the context of hypermodelling. UOXF participated in discussions for linking the UOXF vascular component with a continuum cell growth component being developed at FORTH and the UOXF vascular component with the ICCS's model for tumour growth and response to treatment. UOXF developed new components of vasculature growth with a focus on being able to interact with the ICCS tumour growth component model and provided the source code for the vascular component. A model of chemical transport was developed to help link the vasculature and tumour growth components. UOXF has also started to collaborate with oncologists performing intravital multiphoton imaging of tumours in mice and plans to use these data to validate elements of the angiogenesis models. A range of approaches for modelling discrete vessels in continua is under development by UOXF. The Development and extension of hybrid and continuum (PDE) models of angiogenesis is also done by UOXF as well as of a pipeline that can be used to determine which experiments to perform in order to maximally constrain parameters in mathematical models of angiogenesis and reduce the uncertainty in predictions generated from angiogenesis models.

FORTH is developing 3 different models (sub-cellular model, hybrid discrete-continuous tumor growth model and tissue-level model). FORTH are also currently developing an additional metabolic model focusing on lung cancer.

In Task 6.2, a clear way of linking subcellular multiscale models with cellular and supercellular models has been established and concrete examples have been provided. 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 also developed by UPENN. In addition, a subcellular model for intracellular trafficking that is predictive (the first of its kind) is being developed. UNITO in collaboration with Fondazione Edo Tempia, Biella (TO) is studying the relationship between some particular genes (e.g. ESE3/EHF, ERG, ESE1/ELF3, KLK3) and the good/bad response of prostate tumours to hormone therapy.

ICCS and UBERN have made concrete suggestions regarding the integration of biomechanics modelling into discrete-entity discrete-event multiscale cancer modelling. The fused pure tumour evolution and biomechanics model has been under adaptation in order to include the ICCS angiogenesis component. A meshing tool is available by UBERN to automatically construct FE meshes from segmented images. A validated UBERN FE solver is integrated with the cellular bio-model (ICCS) and the simulation workflow has been adapted to allow simulation on patient-specific geometries. Parameter settings of the bio-mechanics component of this "Coupled Simulator" can be specified through an xml-based configuration file. A strategy for validation of the mechanical model has been devised by UBERN. A first conceptual design has been developed by UBERN to integrate infiltration of cancer cells into surrounding healthy tissue. UOXF is in collaboration with UBERN regarding the development and experimental validation of a glioma model with vasculature.

In Task 6.4, 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. Extensive *in silico* experimentation, analyses and explorations using the available nephroblastoma data were done by ICCS. Extensive discussions and preplanning regarding the use of micro-RNA data were carried out as well as the development of an alternative clinical adaptation methodology making more extensive use of histological data.

A mechanistic model of the response of GBM to immunotherapy treatment is under development by ICCS in close interaction with KU Leuven. An alternative mathematical approach to the phenomenon of GBM invasion to surrounding tissues based on the Brownian motion is developed. The "Coupled Simulator" of UBERN/ICCS has been tested by UBERN on cases of glioma patients.

ICCS has been performing advanced numerical checking and exploration of an ICCS-developed model of non-small cell lung cancer response to treatment. They have also developed the algorithmic fusion of the ICCS pure tumour evolution hypomodel with an ICCS angiogenesis hypomodel. The “Coupled Simulator” of UBERN/ICCS has been tested by UBERN on cases of lung cancer patients. Lung cancer response to gemcitabine and cisplatin has been modelled by the UNITO two-population model described in Task 6.2

In Task 6.5 UOXF and ICCS adapted certain cell division and migration algorithmic approaches to the generic solid tumour growth modelling.

In Task 6.6, ICCS collaborated with UNITO in order to ensure compatibility of the prostate cancer model development with the CHIC framework. Data collection from the Urological and Radiotherapy departments in Regione Piemonte has been completed and 3538 follow-up pertaining to prostatectomized patients are available for UNITO model validation. As far as the radiotherapy cohort is concerned, 3500 complete follow-up are available. UNITO is performing preliminary statistical studies on the above data in order to define stratification criteria based on meaningful and clinically significant parameters. The UNITO hypermodel which connects the tissue level (tumour 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.

### Summary of details for each task

#### **Task 6.1, Cancer hypomodelling and hypermodelling strategies and elementary models**

A multi-modeller hypermodel concerning lung cancer and addressing crucial molecular, cellular and supercellular aspects of tumour growth and response to treatment for the paradigm of non-small cell lung cancer has been delineated and adopted by all WP6 partners. This hypermodel is to serve as the basis for several hypermodels dealing with different types of solid tumour growth and treatment response following pertinent changes and adaptations. This fundamental hypermodel is under implementation by all involved WP6 partners. The architecture of this hypermodel was developed by ICCS which also coordinates its implementation.

The inputs, outputs and basic description of each hypomodel (component model) have been crystalized by the partners involved.

During the second semester, the core hypermodelling strategies have been refined in order to allow compatibility of the hypomodels developed by the different research groups. All modelling partners are revisiting their developed or under development hypomodels.

FORTH is developing:

1. A sub-cellular model that describes the aberrant metabolism of cancer cells at genome scale incorporating gene expression data into well-developed constrained-based methods such as the Flux Balance Analysis method.

Special effort has been dedicated to identify a list of dysregulated metabolism proteins in Non-small cell lung cancer (NSCLC) and provide the linking interface between the subcellular metabolic model and the Angiogenesis/ Neovasculature model in closed loop design.

2. A hybrid discrete-continuous tumor growth model describing cells as discrete variables and the tumour microenvironment as continuous variables is appropriate for studying the emergence, selection and evolution of clones in tumours as they interact with each other and their microenvironment. In general, these approaches are computationally demanding and thus mainly applied to small systems.

3. A tissue-level model that describes the spatiotemporal evolution of tumour growth and its microenvironment in a deterministic and continuous manner using a system of coupled, partial differential equations of reaction-diffusion-haptotaxis type. The model has been also extended to

account for polyclonal cell populations and describe the coexistence of proliferative and invasive phenotypes as both types play an important role in tumour progression, invasion and metastasis.

After the Modelers' meeting that took place at Oxford and Heraklion there was an additional need to implement a metabolic model focusing on lung cancer, in order to be part of the lung cancer case hypermodel demonstrator. FORTH has undertaken this additional task and the related work is in progress.

The hypomodels already developed by UNITO and pertaining to the CHIC project (e.g. radiotherapy and chemotherapy models) have been revisited in order to make them linkable to other models and re-writable in the context of hypermodelling.

A new component models of vasculature growth was developed by UOXF with a focus on being able to interact with the ICCS tumour growth component model. A model of chemical transport was developed to help link the vasculature and tumour growth components.

An addition was made to UOXF's CHASTE software of functionality for modelling vasculature and angiogenesis. CHASTE is open source software developed primarily at UOXF. At present it has functionality for discrete cell based modelling and ODE and PDE system solving. The addition of a vasculature modelling ability to CHASTE will facilitate the development of sophisticated vasculature and tissue growth hypomodels for use in CHIC. The addition of this functionality is still in progress but will be made available to CHIC modelling partners and the wider community once complete.

There was a collaboration with biologists at the Dept. of Oncology, UOXF who are performing intravital imaging of vascular tumour development and treatment in mice. New software has been developed for the extraction of vessel network data from 3-D multiphoton images. It is planned to use this software to analyse imaging data generated by the biologists to validate the vasculature and angiogenesis models. In the longer term, this software will be included within CHASTE and made available to modelling partners when complete.

UOXF has developed a range of approaches for modelling discrete vessels in continua by UOXF. Approaches for modelling species transport from vessels are being developed using high resolution finite element methods, finite difference methods and greens function methods. These methods will be compared for suitability in modelling the vasculature at different size scales. The different solvers will be made available as part of CHASTE and can be used to construct both vasculature and cell-based hypomodels. Moreover, UOXF is involved in the development and extension of hybrid and continuum (PDE) models of angiogenesis by UOXF, with a focus on tip-cell ECM interactions, the response of the evolving vasculature to VEGF and FGF, two angiogenic growth factors, and their cross-talk as well as the development of a pipeline that can be used to determine which experiments to perform in order to maximally constrain parameters in mathematical models of angiogenesis and reduce the uncertainty in predictions generated from angiogenesis models.

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 by UPENN.

### **Task 6.2, Subcellular cancer modelling**

A clear way of linking subcellular multiscale models with cellular and supercellular models has been established under the lead and guidance of ICCS. Concrete examples have been produced in collaboration with UPENN.

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 by UPENN.

In addition, a subcellular model for intracellular trafficking that is predictive (the first of its kind) is being developed by UPENN.



FORTH is developing a sub-cellular model that describes the aberrant metabolism of cancer cells at genome scale incorporating gene expression data into well-developed constrained-based methods such as the Flux Balance Analysis method. Special effort has been dedicated to identify a list of dysregulated metabolism proteins in Non-small cell lung cancer (NSCLC) and provide the linking interface between the subcellular metabolic model and the Angiogenesis/ Neovasculature model in closed loop design.

UNITO in collaboration with Fondazione Edo Tempia, Biella (TO) is studying the relationship between some particular genes (e.g. ESE3/EHF, ERG, ESE1/ELF3, KLK3) and the good/bad response of prostate tumours to hormone therapy. At least two cell populations, responsive and resistant to hormonal therapy have been detected. The model takes into account their interplay assuming that mutations and different response to therapies can occur.

UPENN presented 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 pediatric neuroblastoma. The 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 with suitable validation will transform our 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.

UPENN engaged in Multiscale Modelling of Trafficking: Receptor trafficking from the cell membrane and in the organelles is often deregulated in cancer cells in order to achieve a proliferative or migratory cell phenotype. 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.

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 modelling**

In the first semester, ICCS in collaboration with UBERN has made concrete suggestions regarding the integration of biomechanics modelling into discrete-entity discrete-event multiscale cancer modelling in order to refine the tumour shape prediction. Specific implementation advances have taken place.

In the second semester, the fused ICCS pure tumour evolution and UBERN biomechanics model has been under adaptation in order to include the ICCS angiogenesis component.

Automatic application of the UBERN biomechanical model within the CHIC project requires a robust tool that builds models of patient anatomy from segmented images. A previously developed, voxel-based meshing tool has been adapted for this purpose. It provides basic meshing functionalities required for the project and has been tested on brain and lung images. Further development is being undertaken to improve automation and results of the model-building workflow.

The coupling between the biomechanical simulator and the cellular bio-model has been refined. One of the new feature concerns the initial shape of the tumour, which can now be defined based on patient-specific images in the cellular simulator. This geometric information is now directly transferred to the biomechanical model for the macroscopic simulations. Furthermore, a

configuration mechanism for the biomechanics component has been implemented to improve user interaction. Parameters can now be set through an xml file which is parsed at simulator runtime.

Validation of the hypomodel-simulator plays a crucial role. This includes validation of model assumptions and parameters for the UBERN biomechanics model: body-site specific cancer & healthy tissue properties, and boundary conditions in patient-specific anatomy. A strategy has been devised for validating these assumptions in the biomechanics model and for validating the interaction of the biomechanics with a cell-simulator. UBERN is currently seeking suitable imaging data to be able to proceed with model validation.

An initial workflow has also been designed by UBERN to include the infiltration of tumour cells in the healthy tissue with the biomechanical mass effect. The infiltration will be modelled as a diffusion-reaction and the equations will be solved on the same mesh as the biomechanical model, using the finite element method. Sequential coupling between the two solvers will be implemented.

#### **Task 6.4, The clinical modelling 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.

Multiscale Modelling by UPENN: Among the members of the ErbB/HER family of receptor tyrosine kinases, the deregulation of the EGFR/ErbB1/HER1, HER2/ErbB2, and HER3/ErbB3 kinases is associated with many types of human cancer, while the HER4/ErbB4 kinase has recently been shown to play an anti-carcinogenic role in certain tumours, including mammary carcinomas. UPENN developed molecular as well as network models of the HER4/ErbB4 activation and signalling in order to elucidate molecular mechanisms of activation in the wild type kinase and to help rationalize the effects of the clinically identified HER4 somatic mutants on the cell phenotype.

##### ***SubTask 6.4.a, The nephroblastoma paradigm***

Extensive *in silico* experimentation, analyses and explorations using the available nephroblastoma data were done by ICCS. Extensive discussions and preplanning regarding the use of micro-RNA data by the nephroblastoma hypermodel Oncosimulator were carried out. An alternative clinical adaptation methodology making more extensive use of histological data was developed.

##### ***SubTask 6.4.b, The glioblastoma paradigm***

A mechanistic model of the response of GBM to immunotherapy treatment is under development by ICCS in close interaction with KU Leuven. Intensive interaction between ICCS and the involved multidisciplinary clinical team of KU Leuven took place.

An alternative mathematical approach to the phenomenon of GBM invasion to surrounding tissues based on the Brownian motion has been developed.

At UBERN, a model-building workflow and simulator have been tested on example cases of glioma cancer. Further quantitative validation is needed

##### ***SubTask 6.4.c, The lung cancer paradigm***

ICCS performed advanced numerical checking and exploration of an ICCS-developed model of non-small cell lung cancer response to treatment. This model serves as the basis component of the multi-modeller hypermodel developed in task 6.1. Moreover, ICCS developed the algorithmic fusion of the ICCS pure tumour evolution hypomodel with an ICCS angiogenesis hypomodel.

UBERN's model-building workflow and simulator have been tested on example cases of lung cancer. Further quantitative validation is needed

FORTH is developing a sub-cellular model that describes the aberrant metabolism of cancer cells at genome scale incorporating gene expression data into well-developed constrained-based methods

such as the Flux Balance Analysis method. Special effort has been dedicated to identify a list of dysregulated metabolism proteins in Non-small cell lung cancer (NSCLC) and provide the linking interface between the subcellular metabolic model and the Angiogenesis/ Neovasculature model in closed loop design. After the Modelers' meeting that took place at Oxford and Heraklion there was an additional need to implement a metabolic model focusing on lung cancer, in order to be part of the lung cancer case hypermodel demonstrator. FORTH has undertaken this additional task and the related work is in progress.

Lung cancer response to gemcitabine and cisplatin has been modelled by the UNITO two-population model described in Task 6.2

UOXF has developed a new component model of vasculature growth with a focus on being able to interact with the ICCS tumour growth component model. This required the development of new models and software to best fit the lung cancer hypermodel plan. A model of chemical transport was developed to help link the vasculature and tumour growth components. Model details were provided in the CHIC D6.2 report and source code has been made available to modelling partners.

#### **Task 6.5, The colon cancer modelling paradigm**

UOXF and ICCS adapted certain cell division and migration algorithmic approaches to the generic solid tumour growth modelling.

#### **Task 6.6, The prostate cancer modelling paradigm**

There was interaction of ICCS with UNITO in order to ensure compatibility of the prostate cancer model development with the CHIC framework.

Data collection from the Urological and Radiotherapy departments in Regione Piemonte has been completed and 3538 follow-up pertaining to prostatectomized patients are available for model validation. As far as the radiotherapy cohort is concerned, 3500 complete follow-up are available. UNITO is performing the preliminary statistical studies on the above data in order to define stratification criteria based on meaningful and clinically significant parameters, e.g. clusters formed by patients who underwent adjuvant hormone therapy vs. patients who did not seem to show different probability for secondary cancer recurrence.

The UNITO hypermodel which connects the tissue level (tumour 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. The model can estimate tumour growth parameters by PSA values; these parameters could stratify very well different types of patients, in particular those with a low or high probability of a second relapse. UNITO is formulating different (hypo-) models for each subgroup of patients to simulate regrowth of cancer and eventually therapy, using a two population model.

#### **Summary of significant results**

Lung cancer multi-modeller hypermodel delineated and under implementation.

Extensive *in silico* experimentation, analyses and explorations using the available nephroblastoma data by ICCS.

A mechanistic model of the response of GBM to immunotherapy treatment is under development by ICCS in close interaction with KU Leuven. Development of an alternative mathematical approach to the phenomenon of GBM invasion to surrounding tissues based on the Brownian motion.

Advanced numerical checking and exploration of the **ICCS** model of non-small cell lung cancer response to treatment was performed.

The automatic meshing tool is available. Multi-scale coupling was done between the UBERN biomechanical and ICCS cellular bio-model integrated into a single configurable package. Code,

documentation and tested examples (glioma, lung cancer) are available at [https://bitbucket.org/istb\\_iccs/eu-chic-team](https://bitbucket.org/istb_iccs/eu-chic-team). A model validation strategy was devised. The “Coupled Simulator” of UBERN/ICCS has been tested by UBERN on cases of lung cancer patients.

The fused ICCS pure tumour evolution and UBERN biomechanics model has been under adaptation by ICCS in order to include the ICCS angiogenesis component.

UNITO successfully applied their models (tumour growth with and without mutation, with and without treatment) in different contexts: breast cancer *in vitro* and *in vivo* (mice), prostate cancer in human patients, lung cancer in human patients. Lung cancer response to gemcitabine and cisplatin has been modelled by the UNITO two-population model.

Prostate cancer data collection has been completed. Preliminary studies are underway by UNITO.

UOXF developed new components of vasculature growth with a focus on being able to interact with the ICCS tumour growth component model. An addition was made to Oxford’s CHASTE software of functionality for modelling vasculature and angiogenesis. A range of approaches for modelling discrete vessels in continua is under development by UOXF. Development and extension of hybrid and continuum (PDE) models of angiogenesis. Development of a pipeline that can be used to determine which experiments to perform in order to maximally constrain parameters in mathematical models of angiogenesis and reduce the uncertainty in predictions generated from angiogenesis models.

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 by UPENN.

Several models are under development by FORTH.

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

Additional work, not initially foreseen in the CHIC Technical Annex has been undertaken by FORTH. This work will be performed with FORTH resources and will not have any impact on other tasks and the overall 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

See above.

#### Corrective actions

Not applicable.

#### Statement on the use of the resources

Planned versus actual efforts in WP6			
Partner	Planned PM Total	Planned PM Period 2	Actual PM Period 2
1-ICCS	44.00	12.00*)	13.04
7-FORTH	25.61**)	7.50	11.80
9-UPENN	61.00	15.00	24.00
10-UOXF	46.00	15.16	19.57
11-UNITO	14.00	4.00	4.00
12-UBERN	20.00	8.00	4.50
14-Philips	1.00	0.00	0.00

<b>Total</b>	<b>211.61</b>	<b>61.66</b>	<b>76.91</b>
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\*) New PM effort planning after an internal revision of efforts at ICCS. The revision was performed as the future work in the remaining 2 periods of CHIC became clearer.

\*\*) New planned PM efforts resulting from a revision by FORTH which was carried out after the 2<sup>nd</sup> CHIC review. The new PM effort table was sent to the EC on 11 December 2014. The CHIC partners are currently working towards an amendment to incorporate these changes in the CHIC DoW.

At FORTH, extra effort was needed for the standardization of the exchange interface between the model parameters. This is a purely technical work that involves mostly junior staff implementing interfaces compliant with the proposed CHIC workflow alternatives.

Regarding planned PM versus actual PM, UPENN provide justification in two steps. (a) Overall, the actual PM for PENN will show an increase to 27 PM per year in comparison to Planned PM of 21. Please note that this increase will not result in an increase in budget and the actual costs per year will remain the same. The reason for this increase is a field specific: the original plan was to have a computer scientist at the postdoctoral research associate level devote 50% effort in developing hyper models for WP6 but also touching upon other WPs, especially WP11. Due to the economy, (computer scientists at the postdoctorate level have a large supply of jobs in the industry and hence are not pursuing Postdoctoral positions in academia), UPENN decided to hire a Research Associate from Biochemistry and Biophysics (who has a degree/minor in computer science and hence, the required skills) and utilize 100% of their effort in the above WP in order to ensure smooth functioning of the tasks and meeting of the milestones. (b) It can be noticed that year 2 is unique because the actual PM is greater than the average of 27 PM resulting from the revision. The actual PM in the 2<sup>nd</sup> reporting period was 32.5. In addition to the 27 PM UPENN needed to utilize the expertise of the research associate Peter Huwe for 3PM and postdoctoral research associate David Slochower for 2.5 PM, which accounts for the added 5.5 PM over 27 PM bringing the total to 32.5 PM. The Justification for Peter Huwe's efforts (additional 3 PM) is that he worked on the algorithm/hypermodel which served the first test scenario for clinical validation. The validation was completed in the prestigious Cancer Cell article published in 2014. However, prior to publication of the article, the reviewers and editors stipulated for us to conduct several tests which the publication was contingent on. These tests were unanticipated and we had to avail of additional efforts from Dr. Huwe. The publication is central to CHIC because it not only validates the hyper model at the international stage in the Oncology community given the stature of the Journal Cancer Cell, but UPENN's data agreement clearly states that the data will be made available to CHIC consortium members upon publication. The remaining 2.5 PM for David Slochower was to integrate multiple layers of data beyond genomics. In WP6 and other WPs, UPENN's role is to integrate molecular data and the planned tasks are primarily on protein level data. But our research has led us to believe that even beyond protein data, lipid data and chemical data (because many targeted drugs are neither proteins nor lipids but small molecular weight chemicals), we had to slightly revise our platform. We have demonstrated that this exercise was successful through the Physical Chemistry Chemical Physics article published by Slochower and Radhakrishnan in 2015 which is described in our progress report.

The problem of UBERN to hire a suitable co-worker on the project mentioned in the last report has been solved. However, the effect of the delayed hiring affected 3 months in the present reporting period, which explains the deviation compared to the plan.

## 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)

Work has started early in the following task:

- Task 7.4, Metahypermodels annotation (M25-48)

### Summary of progress achieved towards objectives

During the second year WP7 developed mostly as planned. The partners re-factored the original VPH-HF technology developed in the VPHOP project to fit the needs of CHIC. The resulting software has a much simpler structure; the hypomodels now need to be wrapped only in the workflow execution manager (WEM), which largely simplifies the usage. All models so far provided by WP6 have been successfully wrapped in the new VPH-HF architecture.

All WP7 partners contributed to the definition of the minimum annotation set required by the VPH-HF to recognise semantically four types of resources: data objects, data sets (collections of data objects), hypomodels, and hypermodels. A Generic URI Schema was agreed for each of these resources, and encoded in a JSON template document. All wrapped hypomodels and all test input sets are currently being annotated with this minimum annotation set, enabling the development of the semantic layer. Additional services allow the free tags annotation, or the annotation based on the available ontologies.

The VPH-HF technology was designed to execute hypermodels whose topology could be described as a Directed Acyclic Graphs (DAG). De facto recent extensions make possible to manage a number of other workflow topologies, including conditional branches, loops, etc. Still, it is not possible to execute hypermodels that include strongly coupled hypomodels, which need to exchange messages while they execute in parallel. However, as the CHIC hypermodels were further developed it became evident that in some cases this limitation was too severe. The problem is complex: the limitation to DAG topologies ensures an efficient execution of re-usable components, something anything more general would struggle to provide. An attempt to extend our current workflow execution manager (Taverna) to deal with strongly coupled hypermodels was successful, but made evident that this would break the fundamental design of Taverna, producing a number of side effects. We are currently experimenting with an alternative workflow execution manager, called MUSCLE, developed as part of the MAPPER project, and also distributed with a permissive open source license. As we think Taverna remains considerably more efficient than MUSCLE, the idea would to keep both WEM, with the Director that at run time invokes one of the other depending on the topology of the hypermodel to be executed.

While Task 7.4 will start only at M25, preliminary activities were conducted to explore multiple alternatives. We will start soon the development of a metamodeling language to describe hypermodels, based on the semantic representation of the resources described above, that the VPH-HF Director module will down-lift into a concrete hypemodelling workflow, that will be then



executed. The specifications of the interactions between the hypermodelling editor and the hypermodelling execution framework are being discussed and drafted.

As the VPH-HF and all related technologies are developed, the software is tested on two test beds (one in Bologna, one in Sheffield), and then replicated at each release on the production environment in Crete. The first release of the hypermodelling framework deployed on test nodes (described in D7.2), is now being replicated in production, and will be demonstrated at the second review meeting.

Partner USFD contributed to the re-factoring of the VPH-HF software, and wrapped all models provided by WP6 partners. USFD coordinated the discussion on the minimum annotation set, and captured it into a JSON template. Last USFD is currently exploring the extension of VPH-HF to strongly coupled models.

Partner CINECA contributed to the refactoring of VPH-HF and the relative revision of the component model generic stub. They also participated in the discussion on the minimum annotation set, proposing an initial version and produced the first release of the VPH-HF that is now being installed on the production nodes at FORTH.

Partner ICCS collaborated with partner USFD in the wrapping of their models, and in the discussions on the minimum annotation set and on the generalisation of VPH-HF to strongly coupled models.

Partner BED participated in the discussion on the minimum annotation set and updated its free tagging service to integrated with the new annotation schema.

Partner UCL participated in the discussion on the minimum annotation set, providing details on how this would integrate with the general semantic annotation infrastructure they are developing for the rest of the project. They deployed on the production node the Hypermodels ontology annotation services, and the relative ontology search service.

Partner FORTH contributed to the revision of the component model generic stub, and has been leading the discussion on the specifications of the interactions between the editor and the hypermodelling execution framework. Design of the hosting platform for the hypermodelling infrastructure has been initiated based on input from WP8 and other WP7 tasks.

### Summary of details for each task

#### **Task 7.1, Models execution**

USFD deployed on the VPH-HF a set of exemplar hypomodels relating to breast cancer and its chemotherapeutic treatment provided by ICCS. These were installed and successfully run on both the local USFD hypermodelling installation and the primary CHIC installation hosted by FORTH. We have also locally developed a set of Matlab-based generic cancer “black-box” hypomodels designed to mimic the likely set of actual CHIC hypomodel and their interactions as defined by WP6 on the hypermodelling execution platforms hosted by USFD, FORTH and CINECA. We have wrapped and executed the hypomodels supplied by WP6 partners forming core components of the first CHIC exemplar hypermodel. USFD staff attended a number of WP6 workshops focussed on defining the initial set of hypomodels and associated relation models. We contributed to the refactoring of VPH-HF, and we are currently exploring the execution of strongly coupled hypermodels.

CINECA contributed to the refactoring of VPH-HF, its deployment on the production node, and the refinement of previous version of the Component Model Generic Stub developed during the first year of the Project activity.

ICCS participated in related discussions in its capacity as the project’s coordinator.

### Task 7.2, Metamodels annotation

USFD led the discussion on the minimum annotation set for modelling resources. We have circulated a revised version of the proposed metadata schema for agreement by other partners, and captured the final version in a JSON template. The set is inspired by the EBI MIRIAM Standard, and by the resources annotation set used in PhysiomeSpace and more recently in the VPH-Share infrastructure, but it includes various elements that are specific of computational oncology.

UCL has set up the necessary infrastructure, which is now running smoothly on a CHIC server. Now that the minimum annotation set for modelling resource is established, and all modelling resources are being annotated, in the coming months UCL expects to proceed with consolidation of tags into first ontology revision. UCL has set up ontology search services, including the development of original new technologies and querying methods. For example, UCL developed so-called “UCL Syntax”, an improvement of Manchester Syntax, to remove the intermediary step of looking up ontology term IRIs separately while constructing a composite class expression to search for. This included cutting-edge work & research on problems involving ambiguities, especially in the case when distinct reference ontologies contain competing classes with the same plain-text label. In the coming year UCL hopes to develop cutting-edge technology to facilitate searches over units-of-measure ontologies.

Together with all partners active in WP7, CINECA participated in the discussion relating to the metadata schema for CHIC models and data. CINECA proposed a first version of the metadata schema for resource annotations needed for the execution in VPH-HF; the draft schema derives from that used in PhysiomeSpace and VPH-Share projects. CINECA worked with USFD to collect feedbacks and suggestions from the other partners and finalise the version with which the annotation and other services could be completed. Future updates of the schema might take place in future to comply with the project needs.

BED has released the tagging services such as: view all/individual tags, view tags grouped by resource URI or grouped by user. Tagging user interface (client), which allows users three main functions: add tags, view tags and view community tags.

### Task 7.3, Hypermodels execution

Partner USFD: test workflows consisting of the two sets of orchestrated exemplar hypomodels described in T7.1 above were constructed and successfully executed on both the USFD and FORTH hypermodelling execution environment installations on the alpha v0.1 version of the hypermodelling framework. A demonstration was successfully run in the CHIC Review meeting.

Partner CINECA: contributed to the implementation of hypermodelling specifications, described in in the deliverable “D7.1 Hypermodelling specifications”. ICCS provided to partners USFD and CINECA, for testing purposes, a complete hypermodel, consisting of three hypomodels: a pharmacokinetics model, a pharmacodynamics model and a response to therapy model. Additionally, detailed documentation concerning the way the aforementioned hypomodels are joined together from the technical and basic science aspects were provided. In conjunction with Task 7.5 VPH-HF has been deployed both on a USFD server and on the FORTH cloud environment. Test workflows consisting of the two sets of orchestrated exemplar hypomodels described in T7.1 above were constructed by USFD and CINECA, and successfully executed on both the USFD and FORTH hypermodelling execution environment installations. A demonstration was successfully run in the first CHIC Review meeting. After this first deployment, CINECA has established a revision of some of the VPH-HF components in order to satisfy all the CHIC needs. This, together with an analysis on the integration with the CHIC services under development in other WPs, led to a refactoring plan for some of the VPH-HF components. The first release of the VPH hypermodelling framework, which included the Director, Storage Management Service, Metadata Repository, Authentication and Workflow Management Service components, was delivered on time and described in details together with the APIs to be

used by other CHIC tools in D7.2. The VPH-HF has been deployed successfully on the CINECA and USFD test node for testing purposes. Test workflows were successfully executed on both the USFD and CINECA test node.

Partner ICCS provided to partners USFD and CINECA, for testing purposes, a complete hypermodel, consisting of three hypomodels: a pharmacokinetics model, a pharmacodynamics model and a response to therapy model for breast cancer. Additionally, detailed documentation concerning the way the aforementioned hypomodels were joined together from the technical and basic science aspects was provided. ICCS refined the hypermodelling specifications gathered by developers of WP7 components and finalized the deliverable “D7.1 Hypermodelling specifications”. ICCS participated in discussions and provided explanations concerning the execution of hypermodels that require a dynamic exchange of information between them during their execution (strongly coupled hypermodels). A fused ICCS-UBERN model was provided for this purpose. In this context, ICCS directed during the Turin plenary meeting (March 2015) the discussion regarding two important decisions on WP7. First, a hypermodel dynamic execution functionality was agreed on, and second, a number of simplistic atomic hypomodels will be developed in order to demonstrate the hypomodel-independent orchestrated execution.

Partner FORTH participated in the discussions with partners CINECA and USFD with respect to the execution of the hypermodels. These hypermodels will be designed in the hypermodelling editor FORTH is developing as part of WP10 and therefore we are focusing our efforts on the specification of the interactions between the editor and the hypermodelling execution framework.

#### **Task 7.4, Metahypermodels annotation**

Task 7.4 will formally start on M25, but some preparatory activities were already conducted during this second year.

Partner USFD has initiated discussion relating to possible hypermodelling mark-up languages.

Partner UCL: Hypermodels annotation services have been made available in the form of UCL’s “RDFStore”, a template system which transforms SPARQL queries into user-friendly forms, and accompanying APIs for integration into other members’ projects. UCL has worked with, and will continue to work with, other CHIC partners to improve these services. UCL has developed the OWLKB API to facilitate creation of so-called “composite terms”, allowing modellers to use existing ontology terms to create new custom terms. (For example, if an ontology has terms for “blood” and “aorta” but not for “blood of the aorta”, OWLKB can be used to obtain a semantically-meaningful term for the latter.) This API was further enhanced with UCL’s “UCL Syntax” to cut out unnecessary intermediate ontology searching steps.

#### **Task 7.5, Hypermodelling infrastructure**

Partner USFD: a VPH-HF installer was developed for and successfully used on the platform specified by FORTH. Documentation of the alpha v0.1 version of the VPH-HF has been created. Jointly with CINECA, we have undertaken a detailed review of the existing framework in terms of the needs of the CHIC project and have accordingly come up with a revised description of a revised hypermodelling architecture optimised for CHIC, which involves the integration of widely used components such as the Taverna work flow engine. Along with partners CINECA we have participated in implementing this architecture (alpha version 0.2) in line with the planned completion of D7.2 - First Release Hypermodelling framework deployed on test nodes at PM24 (a two month delay has been requested).

Partner CINECA: An installer of the VPH-HF version released before the architecture refactoring was developed by CINECA and successfully used on the platform specified by FORTH. CINECA installed into the FORTH infrastructure this release version of the VPH-HF. Documentation of this version of

the VPH-HF has been created. The first release of the VPH-HF after the architecture refactoring will be deployed on the FORTH machine at the beginning of the third year of the project activity.

Partner ICCS participated in the deployment of all hypermodels on the production node.

Partner FORTH in collaboration with partners CINECA and USFD initiated the design of the hypermodelling infrastructure. The hypermodelling infrastructure will provide a hosting environment for the execution of the component (hypo) models and this task will continue based on the input gathered from the WP8 and the other tasks of WP7, which will provide the model repositories, and the annotation of the models. Partner UCL has taken care to provide all its contributions in the form of well-documented APIs hosted on CHIC servers, in order to facilitate Task 7.5.

### Summary of significant results

Task 7.1 – Deployment of exemplar set of hypomodels supplied by project partners and development of black box hypomodels representative of initial test set as agreed by WP6. Deployment of set of hypomodels supplied by WP6 which constitute first CHIC exemplar lung cancer model. Revision of generic stub.

Task 7.2 – Consolidation of the first version of the metadata schema used to annotate data and resources to be used in the VPH-HF. An initial version of folksonomy tagging service has been achieved in WP7.

Task 7.3 – Successful implementation and deployment of the first release of the revised VPH-HF and demonstration of test workflows on CINECA and USFD test node. Provision of models and hypermodels for testing purposes, and their wrapping and annotation.

Task 7.5 – Development of software for the easy deployment of alpha version of hypermodelling environment on a remote machine. Agreement of revised architecture for the beta version of this framework, optimised for the needs of the CHIC project.

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

The deadline of D7.2 has been postponed of two months with respect to the contractual one. The delay was managed, and did not affect any other activity in the project.

In BED, there are a number of issues that may lead to the increase of the personnel month spending with WP7, including the work of the metadata repository and the investigation of the HotMap.

### 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 reason for the delay of deliverable D7.2 is related to the fact that there is an on-going discussion on how the orchestration of strongly coupled hypermodels has to be managed by the VPH-HF. This could have an impact on the architectural design of some components of the VPH-HF. Several solutions have been proposed and analysed to understand which is the best for the CHIC needs.

### Corrective actions

Not applicable.

### Statement on the use of the resources

Planned versus actual efforts in WP7			
Partner	Planned PM Total	Planned PM Period 2	Actual PM Period 2
1-ICCS	6.00	1.60*)	2.40
3-USAAR	4.00	1.00	0.01

5-BED	19.00	12.00**)	11.00
6-USFD	134	37.00	34.19
7-FORTH	7.50***)	2.50	2.50
15-UCL	24.00	7.00	6.11
16-CINECA	42.00	8.00	11.81
<b>Total</b>	<b>236.50</b>	<b>65.10</b>	<b>68.02</b>

\*) New PM effort planning after an internal revision of efforts at ICCS. The revision was performed as the future work in the remaining 2 periods of CHIC became clearer.

\*\*) New planned PM efforts resulting from a revision by BED which was carried out after the 2<sup>nd</sup> CHIC review.

\*\*\*) New planned PM efforts resulting from a revision by FORTH which was carried out after the 2<sup>nd</sup> CHIC review. The new PM effort table was sent to the EC on 11 December 2014. The CHIC partners are currently working towards an amendment to incorporate these changes in the CHIC DoW.

At USAAR it has been agreed that USAAR will need to work in this project at the end of the project, as USAAR's task is to evaluate hypermodels, not setting them up. Evaluation is only possible at the end of the project. This has no negative influence on the WP.

## 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

Joint discussions between WP8 and WP10 for the definition and design of interoperable interfaces for the repositories were carried out. Moreover, iterative discussions were held on how to develop the repositories in a way that meets clinical needs. In addition the way to upload data to the data repository was discussed and optimized in an iterative way with all stakeholders. The web-based user interface was evaluated and feedback given in an iterative way for usability issues. In SubTask 8.1.a, ICCS finalized the information model to be used in the model/tool repository and the technologies to be used in its development. ICCS designed the back-end of the model/tool repository and collaborated with partner PHILIPS in order to define the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repository (advanced phase). During the second semester, ICCS installed all the necessary components into the CHIC's private cloud in order to deploy the model/tool repository, developed the model/tool mysql database according to the descriptions of deliverable D8.1 and developed the model layer for the model/tool repository.

UBERN completed the initial integration of the data repository with the CHIC cloud infrastructure. A first version of the external timeline tool developed by BED has been integrated into the data repository interface. The first version of the REST services has been extended with more functionality in line with the defined milestones. Support for additional data formats to store medical image and clinical study datasets has been added to fulfil the requirements of the clinicians.

ICCS finalized the information model to be used in *in silico* trial repository and the technologies to be used in its development. ICCS designed the back-end of the *in silico* trial repository. During the second semester, ICCS installed all the necessary components into the CHIC's private cloud in order to deploy the *in silico* trial repository, developed the *in silico* trial mysql database according to the descriptions of deliverable D8.1 and developed the model layer for the *in silico* trial repository

USAAR discussion with p-medicine continued on how to collaborate in the area of semantic interoperability. The 'HOT Maps' efforts were continued. ICCS tested 3 distinct solutions for the distributed RDF repository. ICCS studied the possible enrichment of the reasoning part of the knowledge base with additional rule-based reasoners. UCL has developed OWLKB, a realtime API to take advantage of cutting-edge semantic edge reasoning capability, designed for seamless integration into other partners' projects. UCL has investigated potential ontologies for usage in CHIC and selected a set of reference ontologies; UCL has developed cutting-edge technology to deal with the problem of ambiguous terms and the "RDFStore" system and accompanying API designed for seamless integration into other partners' projects. UBERN made initial efforts to integrate the RICORDO framework within the upload workflow to simplify the annotation process of the data providers.

UBERN and CUSTODIX completed the integration of the data repository within the first version of the CHIC data protection framework. ICCS had a close collaboration with partner CUSTODIX in order to integrate the single-sign-on security mechanism into the model/tool repository and the *in silico* trial repository (second phase).

### Summary of details for each task

#### **Task 8.1, Development of repositories**

FORTH participated in the joint discussions between WP8 and WP10 for the definition and design of interoperable interfaces for the repositories. UCL has taken care to provide all its contributions in the form of well-documented APIs hosted on CHIC servers, in order to ease the usage of semantic metadata wherever it is needed in the main data repositories. USAAR participated in iterative



discussions on how to develop the repositories in a way that meets clinical needs. In addition, the way to upload data to the data repository was discussed and optimized in an iterative way with all stakeholders. The web-based user interface was evaluated and feedback given in an iterative way for usability issues. A meeting dealing with data upload was held in Homburg in December 2014. Personnel effort for these tasks was claimed under WP2 as USAAR's work in both WP2 and WP8 is connected.

#### ***SubTask 8.1.a, Development of the model/tool repository***

During the 1<sup>st</sup> semester, ICCS finalized the information model to be used in the model/tool repository, according to the requirement analysis performed in the first year of the project as well as the selection of the technologies to be used in the development of the model/tool repository.

ICCS designed the back-end of the model/tool repository and prepared the corresponding sections of the deliverable D8.1: "Design of the CHIC repositories". ICCS collaborated with partner PHILIPS in order to define the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repository (advanced phase).

During the 2<sup>nd</sup> semester, ICCS integrated all contributions for deliverable D8.1 into its final version. ICCS installed all the necessary components (database servers, application servers, web framework, drivers, libraries) into the virtual machine provided by FORTH in order to deploy the model repository on CHIC's private cloud. Moreover, they created the mysql database for the model/tool repository according to the description of the deliverable D8.1. ICCS also developed the model layer (abstraction layer for structuring and manipulating the data) for the model/tool repository.

#### ***SubTask 8.1.b, Development of the data repository***

The development environment previously provided by UBERN has been deployed to the CHIC cloud infrastructure. The final upload workflow including the upload tool, the Trusted Third Party and the data repository has been successfully demonstrated during the annual review in Brussels.

A first version of the external timeline tool developed by BED has been integrated into the data repository interface. The timeline tool itself leverages the functionalities provided by the data repository REST services. All objects can be displayed within the graphical environment and the datasets can be directly downloaded from the timeline interface.

The first version of the REST services has been extended with more functionality. The technical implementation of the authentication mechanism for the REST service has been integrated and is based on SAML token. The REST endpoints to organize the personal internal folder structure and to set permissions of objects and folders have been implemented. All the services and endpoints of the service have been documented and are available online.

The file formats such as DICOM (Digital Imaging and Communications in Medicine), MetaImage, Analyze, Niftii, and HDF5 (Hierarchical Data Format) have been extended by the multi-slice DICOM and CDISC ODM (Clinical Data Interchange Standards Consortium - Operational Data Model). The first file format is used to store medical images and the latter for clinical study datasets.

#### ***SubTask 8.1.c, Development of the in silico trial repository***

During the 1<sup>st</sup> semester, ICCS finalized the information model to be used the *in silico* trial repository, according to the requirement analysis performed the first year of the project as well as the selection of the technologies to be used in the development of the *in silico* trial repository. ICCS designed of the back-end of the *in silico* trial repository and prepared the corresponding sections of the deliverable "D8.1: Design of the CHIC repositories".

During the 2<sup>nd</sup> semester, ICCS installed all the necessary components(database servers, application servers, web framework, drivers, libraries) into the virtual machine provided by FORTH in order to deploy the *in silico* trial repository on CHIC's private cloud. ICCS created the mysql database for the *in silico* trial repository according to the description of the deliverable D8.1. They also developed the

model layer (abstraction layer for structuring and manipulating the data) for the *in silico* trial repository

### **Task 8.2, Infrastructure for Semantic Metadata Management**

USAAR: discussion with p-medicine continued on how to collaborate in the area of semantic interoperability. The 'HOT Maps' efforts were continued and were further developed in an iterative process with input from all clinical partners. This work is led by UCL.

#### ***Subtask 8.2.a, RDF storage solution for semantic metadata***

ICCS tested 3 distinct solutions for the distributed RDF repository. UCL has carefully evaluated available triple-store databases to determine the database (Virtuoso) most appropriate for CHIC. UCL has developed a software interface, in the form of its "RDFStore" API, which allows creation of user-friendly templates from SPARQL queries (the idea being that a SPARQL expert would craft a template once, and end-users would then be able to use that template indefinitely, without SPARQL knowledge); this API has been designed and documented so as to facilitate seamless incorporation into other partners' projects.

#### ***Subtask 8.2.b, A core knowledge base to support semantic querying of metadata***

UCL has developed OWLKB, a realtime API to take advantage of cutting-edge semantic edge reasoning capability, designed for seamless integration into other partners' projects. OWLKB allows expression and querying of complex ontology terms using its "composite terms" innovation (for example, if the ontology has terms for "blood" and "aorta", but not for "blood in the aorta", OWLKB provides API commands to generate a semantically-meaningful term for "blood in the aorta" from the two existing terms). UCL has investigated potential ontologies for usage in CHIC and selected a set of reference ontologies; a key problem here is the problem of ambiguous terms, when distinct reference ontologies offer competing terms with the same plaintext label: UCL has developed cutting-edge technology to deal with this problem (via a system of configurable relative ontology priorities). In the coming year it remains to formalize a workflow for systematic maintenance of the reference ontologies.

ICCS studied the possible enrichment of the reasoning part of the knowledge base with additional rule-based reasoners.

#### ***Subtask 8.2.c, Resource annotations***

UCL has developed the "RDFStore" system and accompanying API, which facilitates manipulation of annotations via a templating system, designed for seamless integration into other partners' projects. In the coming year, UCL expects to augment this with a bulk-loading solution, for the case when metadata needs to be added to the database in bulk. The RDFStore API includes a simple GUI (whose intended purpose is to help guide other CHIC partners in integrating the API into their own projects, more so than to be directly accessed by end-users). This is in addition to the related OWLKB demo GUI (with similar intended purpose) which allows users to construct complex ontological concepts for annotations, to search for specific ontological terms, to view parts of ontological trees.

In order to integrate the RICORDO framework within the upload workflow a close collaboration between UCL and UBERN has been established. The goal was to streamline the interfaces providing the functionalities needed to simplify the annotation process performed by the data providers. Those interfaces include the search for available ontologies, ontology terms and ontology predicates. Based on the returned results the semantically correct triples can be built and finally stored in the triple store. In order to update/overwrite existing triples an interface providing this functionality has been requested.

### **Subtask 8.2.d, Global metadata search engine**

UCL has developed the “RDFStore” system, and accompanying API, to facilitate search over RDF repositories via a templating system (the idea is that a SPARQL-expect can create a template one time, and that template can then be used by end-users indefinitely, without requiring the end-users to have knowledge of SPARQL). The RDFStore API is designed for seamless integration into any of the web-based CHIC interfaces where it is needed.

ICCS studied existing federated SPARQL query engines (approaches and implementations) and tested some of them.

### **Task 8.3, Integration with the security and the legal/ethical framework**

Ongoing integration of the CHIC data repository with the CHIC data protection framework is taking place between UBERN and CUSTODIX.

UCL has outlined (during the Homburg discussions) the security considerations relevant to UCL’s APIs. Specifically, the APIs have been designed for compatibility with a firewall-based security situation, in which a firewall prevents the public from directly accessing the APIs, and instead, the APIs are accessed by other CHIC partners’ projects (which are allowed through said firewall). This setup has the benefit of avoiding duplication of authentication efforts, thereby also reducing the surface area where possible authentication errors could occur.

ICCS had a close collaboration with partner CUSTODIX in order to integrate the single-sign-on security mechanism into the model/tool repository and the *in silico* trial repository (second phase).

### **Summary of significant results**

Finalization of the information model and the technologies for the model/tool and the *in silico* trial repositories.

Design of the back-end of the model/tool and the *in silico* trial repositories.

Advanced phase of the definition of the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repository.

Development of components of the back-end of the model/tool and *in silico* trial repositories and deployment on CHIC’s private cloud.

Second phase of the integration of the single-sign-on security mechanism into the model/tool and the *in silico* trial repositories.

Integration of the data repository with the first version of the CHIC data protection framework completed.

First integration of external timeline tool developed by BED into the data repository interface completed.

First integration of external timeline tool developed by BED into the data repository interface. REST services extended with more functionality in line with the defined milestones. Support for clinical study datasets. Initial integration with RICORDO framework started.

Evaluation of available triple-store databases to determine the database (Virtuoso) most appropriate for CHIC completed. Development of a software interface, in the form of its “RDFStore” API, which allows creation of user-friendly templates from SPARQL queries.

Development of OWLKB. Selection of a set of reference ontologies for CHIC. Development of cutting-edge technology to deal with the problem of ambiguous terms.

Development of the “RDFStore” system and accompanying API.

The way in which p-medicine is dealing with semantic interoperability was reviewed and discussed within the project. Collaboration and discussions are ongoing. 'HOT Maps' of tumour-specific hallmark knowledge is under further development.

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

The Deliverable 'D8.1: Design of the CHIC repositories' (originally due M16) was submitted on 21 November 2014.

The PO was informed for this delay. The submission was initially postponed due to unforeseen workload at the partner in charge. After the CHIC review meeting (3 September 2014) and the valuable comments that were received from the reviewers concerning data representation (both for clinical data and models), a decision was taken to wait for the official review report in order to precisely clarify the suggestions of the reviewers and address them within the deliverable. The final outcome of this procedure was finalized on the upcoming progress and technical meetings held on 15-17 October 2014 in Leuven. Integration issues were one of the main topics of the meetings and the decisions taken in the aforementioned meetings were also integrated in this deliverable. In the meantime there draft versions of the deliverable had been circulated among the involved partners, so the postponement has not caused any delay in the work described in the DoW.

The PO has been also informed for a delay in Deliverable D8.2 "Prototype implementation of the CHIC repositories" (due M24). The submission of the deliverable has been postponed for about one month due to the heavy workload at ICCS following recent personell changes.

This delay will have no impact on other tasks.

#### 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 2	Actual PM Period 2
1-ICCS	14.00	4.50*)	6.60
3-USAAR	3.00	1.00	0.00
7-FORTH	6.50**)	1.50	1.50
9-UPENN	3.00	0.00	0.00
12-UBERN	15.00	6.00	6.40
13-Custodix	3.00	1.00	0.58
14-Philips	7.00	2.00	1.00
15-UCL	48.00	15.00	7.20
<b>Total</b>	<b>99.50</b>	<b>31.00</b>	<b>23.28</b>

\*) New PM effort planning after an internal revision of efforts at ICCS. The revision was performed as the future work in the remaining 2 periods of CHIC became clearer.

\*\*) New planned PM efforts resulting from a revision by FORTH which was carried out after the 2<sup>nd</sup> CHIC review. The new PM effort table was sent to the EC on 11 December 2014. The CHIC partners are currently working towards an amendment to incorporate these changes in the CHIC DoW.

Various technical developments and related difficulties ICCS had to deal with have proved to need increased participation by less senior staff than originally planned. In addition, due to recent staff changes the PMs of the second period were further increased.

At USAAR it has been agreed that USAAR will work in this work package at the end of the project, as USAAR's task is to evaluate hypermodels, not setting them up. Evaluation is only possible at the end of the project. This has no negative influence on the WP. Personnel effort for these tasks was claimed under WP2 as the work in both WPs is connected.

UCL's WP8 effort reflects the momentum of the annotation effort at a whole-project level. The CHIC annotation effort took longer than expected to gain momentum and, because of this, UCL's WP8 effort to manage the annotations produced had to be temporarily reduced, given the lower workload. We anticipate that UCL will spend more effort in WP8 in the next period as annotation creation increases and more metadata-related services come online.

## 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:

- T9.2, Scalable visualization techniques (M3-18)
- T9.3, Uncertainty data visualization (M9-24)
- T9.4, Visualization toolkit for the model/data repository (M13-46)
- T9.5, A general image processing development toolkit (M6-18)
- T9.6, Image registration tools (M3-36)
- T9.7, Multimodal and longitudinal brain tumor image and analysis (M9-46)
- T9.8, A software platform for the Assessment of Tumor Treatment Response (M8-42)

### Summary of progress achieved towards objectives

Overall this WP is making good progress towards the objectives. Discussions concerning the expectations primarily of WP6 (basic science) from WP9 regarding both image processing and visualization tools and services. ICCS proposed that the provision of web services by visualization and image analysis toolkits in order to be used by other CHIC components (hypermodelling execution framework, (hypo)models, etc).

There are numerous outputs from many partners. A Doctor eye plug-in for multimodal brain tumor image segmentation has been developed, a first complete registration pipeline has been developed and testing on medical images performed, a fully automatic multimodal MRI brain tumor segmentation software has been developed. The ktrans DCE-MRI biomarker has been tested providing promising results and this work has been accepted for publication in the Cancer informatics journal. Various visualization components have been developed. An integrated architecture has

started to emerge under the general framework of Dr Eye. Preparatory tasks have been performed in order to enable all partners to use the DrEye tool as the single integrated imaging platform of CHIC. For this purpose, documentation, API and other material have been provided through a dedicated repository. Interactions with other WPs are also taking place, with some of the visualization components integrated into WP8 data repository. Many tools from WP9 were evaluated by the partners within the consortium in the Leuven workshop.

### Summary of details for each task

#### **Task 9.2 Scalable visualization**

BED has looked into scalable visualization techniques to allow the visualization of clinical data along a scalable timeline.

#### **Task 9.3 Uncertainty data visualization**

BED has developed a 3D volume rendering software CCGVIS, which can visualise the uncertainty and time varying information in volumetric data, which can be useful for the visualization of growing tumour with uncertainty.

At USAAR, a tool for automatic tumor rendering for nephroblastoma and glioblastoma is being developed. This work was done together with work in Task 9.5 and will continue in task 9.4.

#### **Task 9.4: Visualization toolkit for the model/data repository**

The timeline visualization has been embedded and tested under the clinical data repository from WP8.

Also, BED has been working on the volumetric visualization using iso-surfaces, as well as the volume visualization of time-varying data.

At USAAR, the model/data repository was evaluated regarding usability and feedback was given. More than 20 patients with nephroblastoma and MRI images at diagnosis and after preoperative chemotherapy were rendered and tumor volume calculated as well as histograms of signal intensities analysed.

#### **Task 9.5 A general image processing development toolkit**

After the unanimous decision of the consortium, FORTH has undertaken the additional task to integrate most of the technologies into the DrEye platform that has been initially developed for the ContraCancrum project. This has created an internal integration task that will develop a one-stop-shop solution for clinical users within the context of WP9 and will include sophisticated registration, segmentation, visualization and therapy response assessment tools. FORTH will provide technical support for Doctor's Eye platform with updated manuals, apis, developer's forum and other means, and also will provide a plugin warehouse to host the available to the consortium plugins

FORTH created, provides and maintains an FTP repository for the gathering of the imaging tools which will be bundled all together in the integrated imaging toolkit of WP9, which will be based on the DrEye platform. Once all the tools will have been available to the FTP repository, FORTH will test and then will assemble all the imaging tools into a single package for distribution to the partners.

FORTH has also provided access to the plugin API of DrEye and has compiled instructional material regarding the development of integrated tools in to the Dr Eye platform. All of the material among with simple examples has been uploaded in the FTP repository for the imaging tools.

After consultations with relevant stakeholders, arose the need for interconnection and communication of the imaging platform with other services of the project. In that context FORTH started the development of additional functionalities to the imaging platform.



In this period support to export from the platform to MetalImage format has been added to the platform, while support for communicating with PACS systems is in advanced implementation phase.

BED has been investigating on a number of novel approaches for neuroblastoma image segmentation. The results have been tested on the initial (small) set of testing images. More tests will be needed when more datasets are available.

At UBERN the I/O to expand the functionality of the suite in a modular and flexible manner is being studied through tutorials and live demos prepared from Dr Eyes developers. A plug-in for the general-purpose software DrEye has been developed for the specific task of multimodal MRI brain tumor segmentation.

#### **Task 9.6: Image registration tools**

At UBERN a first complete registration pipeline has been developed and testing on medical images performed. The main components of the monomodal and multimodal registration metric for monomodal and multimodal image registration have been implemented. Registration metric using point-wise mutual information, image resampling, optimization routines have been implemented. First testing on medical images has been conducted. An approach for non-uniform prior regularization has been tested on brain tumor images.

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

At UBERN feature extraction and learning approaches using supervised approaches have been implemented; initial tests performed. Routines for feature extraction, supervised learning using random forests has been implemented for brain tumor tissues and sub-compartments.

A software tool has been developed to perform automatic brain tumor segmentation from multimodal MRI, called BraTumIA for Brain Tumor Image Analysis, and made available at <http://www.nitrc.org/projects/bratumia>. The approach relies on supervised learning and a conditional random field regularization component. A full characterization of the tumor tissue types is provided along with sub-volumes. The output has been used as biomarker to link to survivability in GBM patients and as input for neuronavigation. First steps towards longitudinal brain tumor analysis have been conducted for high and low grade gliomas.

#### **Task 9.8: Multimodal and longitudinal brain tumor image analysis**

This task, led by FORTH, began much earlier than anticipated due to the fact that several biomarkers will be also tested as model input parameters in the hope that they will improve the simulation prediction result. Initial work has shown promising results and will be published in the next few months.

Also, this task started developing comparison mechanisms for DrEye in order for the user to be able to confront predictions to actual outcome based on statistical measures (DrCompare functionalities).

The ktrans DCE-MRI biomarker has been tested as model input parameters and the results indicate that there is a potential to improve the simulation prediction result. This work has been accepted for publication in the Cancer informatics journal. The main work for this task has started which will include comparison mechanisms within the DrEye integrative platform of WP9 in order for the user to be able to confront predictions to actual outcome based on statistical measures (DrCompare functionalities). The user will also be able to compare sequential MRI data sets from either raw MRI images, or biomarkers derived from post-processed DCE-MRI data (such as ktrans maps) or DW-MRI data (e.g. ADC maps) in order to be able to assess response to therapy which can serve as golden truth for the simulation validation experiments.

In addition, ICCS has contributed to discussions concerning the expectations primarily of WP6 (basic science) from WP9 regarding both image processing and visualization tools and services. ICCS in a

more general sense has tried to ensure compatibility of the work performed in WP9 with the overarching CHIC hypermodelling principles.

ICCS proposed the provision of web services by visualization and image analysis toolkits in order to be used by other CHIC components (hypermodelling execution framework, (hypo)models, e.t.c).

ICCS collaborated with FORTH to develop, as a part of the DrEyer toolkit, software for the preprocessing of the imaging datasets used as the ICCS's Oncosimulator's input. This software will also serve the need to visualize the area of interest in various timepoints throughout a simulation.

### **Summary of significant results**

All the partners have been working on the definition of the basic science expectations from WP9, development of software for the preprocessing of imaging datasets according to the needs of the ICCS Oncosimulator.

In BED, Both the timeline and CCGVIS have been tested internally by some of the partners.

FORTH has uptaken the additional task to integrate most of the technologies into the DrEye platform. Initial work in Task 9.5 has shown promising results. Preparatory tasks have been performed in order to enable all partners to use the DrEye tool as the single integrated imaging platform of CHIC. For this purpose, documentation, API and other material have been provided through a dedicated repository.

The ktrans DCE-MRI biomarker has been tested providing promising results and this work has been accepted for publication in the Cancer informatics journal.

At UBERN, full implementation of monomodal and multimodal registration routines using point-wise mutual information metric was carried out. Leverages use of multimodal MRI for data analysis. A fully operative plug-in for DrEye software to perform automatic segmentation of brain tumor from multimodal MRI was developed. Enabling translational research of modern medical image analysis techniques to the medical community. Automatic segmentation approach performing amongst the best three best approaches in the international brain tumor segmentation competition. Automated tumor volumetry leverages design of biomarkers for patient survivability and neuro-navigation. There is high potential to improve status quo in current RANO criteria for tumor assessment.

At USAAR, the model/data repository was evaluated regarding usability and feedback was given. The development of a tool for automatic rendering of tumor volume in glioblastoma and nephroblastoma was started. This will be integrated into DrEye.

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

FORTH has uptaken the additional task to integrate most of the technologies into the DrEye platform, towards the objective of providing a general image processing development toolkit. This work will be performed with FORTH resources without any need for additional resources or impact to other tasks.

### **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 2	Actual PM Period 2
1-ICCS	3.00	0.90*)	1.10
3-USAAR	15.00	5.00	4.04
5-BED	36.00	10.50	19.80
7-FORTH	43.29**)	8.50	12.00
12-UBERN	12.00	3.00	6.10
17-TEI-C	1.00	1.00	1.00
<b>Total</b>	<b>110.29</b>	<b>28.90</b>	<b>44.04</b>

\*) New PM effort planning after an internal revision of efforts at ICCS. The revision was performed as the future work in the remaining 2 periods of CHIC became clearer.

\*) New planned PM efforts resulting from a revision by FORTH which was carried out after the 2<sup>nd</sup> CHIC review. The new PM effort table was sent to the EC on 11 December 2014. The CHIC partners are currently working towards an amendment to incorporate these changes in the CHIC DoW.

During period 2, work on longitudinal glioma tumor segmentation was intensified at UBERN following novel findings regarding image analysis of post-operative images. As a result, a total of 6.10 PM was allocated during this period. For period 3 and 4, work on WP11 will take place, which in turn will balance the efforts.

The image analysis and processing involves works that were not foreseen (e.g. the segmentation of healthy organs) and hence leads to higher number of personnel months than expected at BED in WP9. At the same time, BED's activities in WP5 were reduced, which balances the overspending in WP9.

At FORTH, the additional effort was needed for the additional task to integrate all WP9 technologies in the DoctorEye platform.

## 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 10.2, 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)

Work continues in the following task:

- Task 10.1, Portal (M1-8)

### **Summary of progress achieved towards objectives**

The models repositories of WP8 enriched with the semantic annotations and the hypermodelling descriptions defined in WP7 and WP6 should be wrapped by standardized and interoperable programmatic interfaces so that they can be accessed by the other CHIC components in an architecturally compliant way. Philips, in collaboration with ICCS and FORTH, defined these interfaces and prepared Deliverable 10.2, “Design of the orchestration platform, related components and interfaces”.

FORTH, collaborating with CUSTODIX, developed the CHIC Data Upload Tool. This is the tool targeting the “data ingestion” scenario in CHIC, i.e., the workflow for the secure (privacy preserving through pseudonymization) and easy publishing of patient data in the CHIC infrastructure. Furthermore, in conjunction with the activities of WP5 (on the security aspects) and of WP7 on the hypermodelling execution environment, CINECA has analysed the double encryption scheme in place in PhysiomeSpace and developed a module in the hypermodelling infrastructure to encrypt and decrypt data according to the AES-CBC algorithm.

The Hypermodelling editor is the tool used by computational researchers, system biology experts, and other domain users for building hypermodels. An initial requirement analysis and design for its user interface and functionalities have been made and the editor has been successfully demonstrated in the recent CHIC progress review. In view of the CHIC hypomodeling paradigm, an approach for loose coupling between model components has to be developed. This requires interfaces to be defined for communication among hypomodels and among hypomodels and CHIC infrastructure. The so called “CoupledSimulator” has been chosen as representative example on which inter-hypomodel dependencies will be explored.

### **Summary of details for each task**

#### **Task 10.1, Portal**

FORTH continues and leads the integration work for the CHIC Portal, although according to the initial planning in the CHIC Technical Annex the Task 10.1 has officially finished.

#### **Task 10.2, Interoperable interfaces for retrieving model and hypermodel descriptions from the corresponding repositories**

PHILIPS, taking under consideration the different needs for information among the different components and use cases, and the structure of the underlying repositories, collaborated with partners ICCS and FORTH in order to define the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repository and the Insilico trial repository.

#### **Task 10.3, Data Management and Computational infrastructure**

FORTH developed the Data Upload tool as the end user application for the clinicians and data curators to pseudonymise and upload clinical data and images to the CHIC platform. ICCS has provided the specifications for the virtual machine that will host the model/tool repository and the in silico trial repository. CINECA starting from the analysis of the double encryption scheme in place in PhysiomeSpace developed a module inside the VPH-HF framework that encrypts and decrypts data according to the AES-CBC algorithm. The passphrase is encrypted using the RSA-public key algorithm and stored on the security layer provided by CUSTODIX. All details have been described in

Deliverable 10.3. It has to be noted that there is a mistake/typo in the current DoW regarding the leadership of D10.3. The correct lead of this deliverable is CINECA, not CUSTODIX.

#### **Task 10.4, Data and hypermodel orchestration**

FORTH started the design of the CHIC Hypermodelling Editor in Task 10.4, with the majority of the work focused on the definition of the interactions with the hypermodelling execution framework of WP7, as well as the integration with the CHIC security framework. ICCS collaborated closely with FORTH about the interaction of the model/tool repository and the in silico trial repository with the hypermodelling editor.

The need for supporting the “strong-coupling” of the hypomodels in which the models dynamically exchange information during their execution has been identified. ICCS, UBERN, FORTH, and representatives of WP7 have analysed the requirements and explored the options. In preparation of interface development, the “Coupled Simulator” has been packaged with data examples to allow profiling by WP7 with regard to inter-hypomodel dependencies and execution performance. Further discussions between UBERN, ICCS, (and BED) took place in preparation and follow-up of the analysis of this simulator.

#### **Summary of significant results**

The programmatic interfaces for accessing the model repositories were defined. The interfaces will be implemented and used not only by the internal components of the CHIC platform but will enable interoperability with external research organizations.

The CHIC Data Upload tool for the secure uploading of sensitive patient data to the CHIC platform was implemented. Further development of the current PhysiomeSpace encryption services with state of art encryption algorithms.

The initial design of the CHIC Hypermodelling Editor is available, as are preliminary integration results and exploration for supporting “strongly-coupled” models.

#### **Deviations from Annex I and their impact on other tasks as well as on available resources and planning<sup>1</sup>**

The deliverable D10.3 has been slightly delivered (one week) due to Easter holidays. This will not have impact on other tasks and resources in WP10. Moreover, the lead beneficiary of D10.3 is CINECA, not CUSTODIX. This is a mistake in the DoW, as CUSTODIX are not partner in WP10. This mistake will be corrected when an amendment is carried out.

#### **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 2	Actual PM Period 2
1-ICCS	7.00	1.90*)	2.40
3-USAAR	7.00	2.00	0.00
7-FORTH	36.79**)	8.00	8.00
12-UBERN	3.00	1.00	0.40

14-Philips	18.00	2.50	2.20
16-CINECA	8.00	3.50	3.43
<b>Total</b>	<b>79.79</b>	<b>17.90</b>	<b>16.43</b>

\*) New PM effort planning after an internal revision of efforts at ICCS. The revision was performed as the future work in the remaining 2 periods of CHIC became clearer.

\*\*) New planned PM efforts resulting from a revision by FORTH which was carried out after the 2<sup>nd</sup> CHIC review. The new PM effort table was sent to the EC on 11 December 2014. The CHIC partners are currently working towards an amendment to incorporate these changes in the CHIC DoW.

At USAAR it has been agreed that USAAR will need to work in this work package predominantly at the end of the project, as USAAR's task is to evaluate hypermodels, not setting them up. Evaluation is only possible at the end of the project. This has no negative influence on the WP.

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

#### **Summary of progress achieved towards objectives**

The first evaluation workshop (evaluation of DrEye, BraTumIA, CCGVis, Timeline and clinical data repository, upload tool) taking place during the consortium meeting in Leuven from 15 – 17 of October was prepared with the help of all partners. The workshop ran successfully. Evaluation sheets of the participants were analysed and are reported in D11.2. During the whole reporting period deliverable D11.2 was written, evaluation sheets were developed according the criteria defined in D11.1. Deliverable D11.2 was submitted. Results of the 1<sup>st</sup> evaluation workshop were discussed and will be used to optimize the corresponding tools.

Available clinical data on prostatectomized (EUREKA1 database) or radically radio-treated (EUREKA2 database) patients are provided by UNITO and are under investigation following two approaches:

- statistical analysis (bottom-up) in order to stratify data according to meaningful and clinically significant parameters;
- mathematical modelling (up-down) of prostate tumor growth and parameter values validation on the clinical scenarios defined by the above statistical results.

Initial discussions were started on the use of the first multi-modeller hypermodel concerning lung cancer for providing the first complete (basic and technology) example for the fine-tuning of the CHIC infrastructure based on the corresponding multiscale clinical data. This discussion was mainly carried out by ICCS and USAAR with the participation of modellers and IT-people. Hypomodels describing the interplay between cell populations, which can exhibit mutations and differential response to therapies, are ready for implementation in the lung-cancer hypermodel provided by UNITO in cooperation with USAAR and other partners. UNITO also finalized the database structure for the validation of the prostate cancer model. Discussions on the use of the first multi-modeller hypermodel concerning lung cancer for providing the first complete (basic and technology) example for the fine-tuning of the CHIC infrastructure based on the corresponding multiscale clinical data was initiated and continuously maintained by ICCS. Clinical adaptation of the CHIC infrastructure as a whole was carried out by UBERN. The software BraTumIA is being developed as a plug-in to the Doctor Eye software suite, which will enable its incorporation into the complete CHIC infrastructure

#### **Summary of details for each task**

##### **Task 11.2, Coordinate evaluation activities by partners**

Writing of D11.2, “Report on the first evaluation workshop round” was finalized under the responsibility of USAAR and was submitted in time. The first evaluation workshop was successfully held as described above. All partners, specifically ICCS, USAAR, BED and FORTH participated in the

organization of the first round of evaluation tests of CHIC components, which took place during the 3rd Process meeting in Leuven. FORTH provided cloud resources and technical support in order to set up an online and remotely accessible testbed, hosted into cloud based Virtual Machines, for evaluating tools provided by other partners. This tool evaluation “sandbox” was also used during the evaluation workshop held in parallel to the Progress Meeting at Leuven. All partners took part in the evaluation of the following tools: DrEye, BraTumIA, CCGVis, Timeline and clinical data repository, Upload Tool and contributed to the results of the evaluation which are presented in D11.2.

The CHIC Upload Tool has been provided with the corresponding end user guide for the evaluation workshop. End user guides for DrEye, BraTumIA, CCGVis and the Timeline and clinical data repository were provided as well by FORTH, BED and UBERN. The clinical aspects regarding adaptability and clinical integration have been analysed for software BraTumIA by UBERN.

Statistical models were developed by UNITO. In more detail, they contain the formulation of hypo-models integrating clinical (age, pre-treatment PSA, clinical Staging, bioptic Gleason Score, percentage of positive cores at biopsy), pathologic (pathologic Staging, surgical margins) or therapeutic factors (adjuvant radiotherapy, RT dose, adjuvant androgen depriving therapy).

Mathematical models were also formulated by UNITO. They include the formulation of hypo-models describing the interplay between cell populations which can exhibit mutations and differential response to therapies are ready for implementation in the lung cancer and prostate cancer hyper-models (e.g. hormone sensitive versus hormone resistant cells); in addition, the database structure for the validation of prostate cancer model is ready.

The database structure is available and partners in WP11 are ready to share it and to find a common ontology with the other groups. A SW allowing multiple choices by the user and running models with different parameters values (various types of cancer) is also prepared.

### **Task 11.3, Clinical adaptation of the CHIC infrastructure as a whole**

Initial discussions have been initiated by ICCS on the use of the first multi-modeller hypermodel concerning lung cancer for providing the first complete (basic and technology) example for the fine-tuning of the CHIC infrastructure based on the corresponding multiscale clinical data.

The first approach of the clinical adaptation of the CHIC infrastructure as a whole was discussed in depth with all partners, mainly ICCS. Corresponding data for the different types of the oncosimulator are prepared for usage to validate these different oncosimulators in the environment of the CHIC platform.

UNITO made the database structure available for prostate cancer and they are ready to share it and to find a common ontology with the other groups. UNITO is creating also a program to allow users to run different models with different parameters (different types of cancer) based on their choices.

The work of UPENN is described in WP3.

### **Summary of significant results**

Work in task 11.2 started in an iterative way and the evaluation process will continue throughout the whole lifetime of the project. The collaboration within the consortium is excellent. The organization of the first round of evaluation tests of CHIC components was carried out mainly by ICCS, FORTH, BED and USAAR.

Cloud resources have been used for the evaluation activities of CHIC, proving to be an additional and valuable tool for the objectives of WP11. With the technical knowledge earned through this process it is expected that it will also be used in the future for such activities with even better results.

Definition of the first multi-modeller hypermodel for lung cancer as a first complete example for the fine-tuning of the CHIC infrastructure based on the corresponding multiscale clinical data.

A first version of BraTumIA as a DrEye Plugin was developed.

**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 WP11			
Partner	Planned PM Total	Planned PM Period 2	Actual PM Period 2
1-ICCS	7.00	1.50	1.90
3-USAAR	25.00	7.00	2.36
5-BED	8.00	2.00	0.00
7-FORTH	3.07	1.00	1.00
9-UPENN	5.00	1.00	3.00
11-UNITO	20.00	6.00	5.67
12-UBERN	3.00	1.00	0.10
13-PHILIPS	3.00	0.00	0.00
<b>Total</b>	<b>74.07</b>	<b>19.50</b>	<b>14.03</b>

At USAAR, the underspending of PM in WP11 is due to the fact that more resources were needed to fulfil the work in WP3. Moreover, in the course of the project it became apparent that much more work has to be done in the last 2 years of CHIC. The underspending now is without influence on the outcome of WP11.

Regarding planned PM versus actual PM, UPENN provide justification in two steps. (a) Overall, the actual PM for PENN will show an increase to 27 PM per year in comparison to Planned PM of 21. Please note that this increase will not result in an increase in budget and the actual costs per year will remain the same. The reason for this increase is a field specific: the original plan was to have a computer scientist at the postdoctoral research associate level devote 50% effort in developing hyper models for WP6 but also touching upon other WPs, especially WP11. Due to the economy, (computer scientists at the postdoctorate level have a large supply of jobs in the industry and hence are not pursuing Postdoctoral positions in academia), UPENN decided to hire a Research Associate from Biochemistry and Biophysics (who has a degree/minor in computer science and hence, the required skills) and utilize 100% of their effort in the above WP in order to ensure smooth functioning of the tasks and meeting of the milestones. (b) It can be noticed that year 2 is unique because the actual PM is greater than the average of 27 PM resulting from the revision. The actual PM in the 2<sup>nd</sup> reporting period was 32.5. In addition to the 27 PM UPENN needed to utilize the expertise of the research associate Peter Huwe for 3PM and postdoctoral research associate David Slochower for 2.5 PM, which accounts for the added 5.5 PM over 27 PM bringing the total to 32.5 PM. The Justification for Peter Huwe's efforts (additional 3 PM) is that he worked on the algorithm/hypermodel which served the first test scenario for clinical validation. The validation was

completed in the prestigious Cancer Cell article published in 2014. However, prior to publication of the article, the reviewers and editors stipulated for us to conduct several tests which the publication was contingent on. These tests were unanticipated and we had to avail of additional efforts from Dr. Huwe. The publication is central to CHIC because it not only validates the hyper model at the international stage in the Oncology community given the stature of the Journal Cancer Cell, but UPENN's data agreement clearly states that the data will be made available to CHIC consortium members upon publication. The remaining 2.5 PM for David Slochower was to integrate multiple layers of data beyond genomics. In WP6 and other WPs, UPENN's role is to integrate molecular data and the planned tasks are primarily on protein level data. But our research has led us to believe that even beyond protein data, lipid data and chemical data (because many targeted drugs are neither proteins nor lipids but small molecular weight chemicals), we had to slightly revise our platform. We have demonstrated that this exercise was successful through the Physical Chemistry Chemical Physics article published by Slochower and Radhakrishnan in 2015 which is described in our progress report.

During period 2, work on longitudinal glioma tumor segmentation was intensified at UBERN following novel findings regarding image analysis of post-operative images. As a result, a total of 6.10 PM was allocated during this period to WP6. For period 3 and 4, work on WP11 will take place, which in turn will balance the efforts.

## 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:

- T12.1, Dissemination activities (M1-48)
- T12.2, Exploitation and IPR issues (M1-48)
- T12.3, Training activities (M12-48)

### Summary of progress achieved towards objectives

In Task 12.1, with continuous input from Eurice and, whenever necessary, from other CHIC partners, CINECA took care of the writing and distribution of the electronic bi-monthly newsletter. Eurice contributed regularly to the bi-monthly CHIC newsletter as well. CINECA has also been monitoring the statistics on the newsletter reading and subscriptions so to take actions if necessary. EURICE was main editor and published, albeit with a larger delay, the first annual CHIC newsletter, available for download on the CHIC public website (<http://chic-vph.eu/highlights/details/article/1st-annual-chic-newsletter/>). The newsletter contains contribution from ICCS, CINECA, and KU Leuven. Moreover, EURICE continuously updates the project website with the latest news from the CHIC partners. In February 2015, Eurice began working on the 2nd annual newsletter. The dissemination activities actively went on from the previous period. A formal reporting of the dissemination events will be presented in more detail in the respective tables in this report, but we can already mention poster

presentation given by Dr Daniele Tartarini and Dr Kewei Duan at the Insigneo Showcase 2014, oral presentations about CHIC given by Dr Daniele Tartarini at the VPH2014 Conference in Trondheim, Norway as well as various publications, conference and other talks by several CHIC partners (ICCS, FORTH, UPENN, UNITO, LUH) in the context of the project. CINECA continued their interaction with the p-medicine, MyHealthAvatar, DrTherapat projects by ICCS and with VPH-Share. UNITO organized the CHIC 4th Progress Meeting in Torino (Neuroscience Department, March 26-27th, 2015 and the FPO-IRCCS Cancer Center of Candiolo organized the EUREKA studies meeting in Candiolo Cancer Center (Aula Cappa, March 28th, 2015) as satellite event to the 4th CHIC Progress Meeting. Regarding to EUREKA studies, a collaboration with the Epidemiology Division of University of Torino (Prof. Merletti and Prof. Ciccone) to exploit EUREKA-1 and EUREKA-2 data (comparison between surgery and radiotherapy cohorts, studies on personalized follow-up) has also been established.

In Task 12.2, CINECA monitored the outputs from WP4 on the memorandum of understanding to capture indication for the future exploitation planning. ICCS contributed to the discussions on the CHIC project exploitation. A new post-graduate course entitled “Multi-scale Cancer Modelling and In Silico Medicine” has been created and is being taught in the autumn-winter semester 2014 in the School of Electrical and Computer Engineering, National Technical University of Athens, by the CHIC coordinator G.Stamatakis. LUH carried out a number of exploitative activities. These include presentations at various conferences. FORTH has engaged into important discussions with the legal partners of the project in order to expedite the IPR agreement and most importantly contribute to the understanding of the project as a whole from the exploitation perspective.

Task 12.3, ICCS organized the 6<sup>th</sup> IARWISOCI - The CHIC Project Workshop, 3-4 Nov, 2014, Athens, Greece. Post-graduate students registered to attend the 6<sup>th</sup> IARWISOCI - The CHIC Project Workshop, 3-4 Nov, 2014, Athens, Greece. They were informed about the achievements of the CHIC project and the latest achievements of *in silico* oncology and its extension to *in silico* medicine. Organization of the CHIC Summer School 2015 has commenced.

### Summary of details for each task

#### **Task 12.1: Dissemination activities**

##### ***Subtask 12.1a: Strategic Dissemination Planning***

CINECA continuously keeps monitoring the dissemination activities so to adapt the dissemination planning according to the needs. This is done in particular with contribution from Eurice and ICCS.

##### ***Subtask 12.1b: Web presence***

Eurice continued to collect information from the CHIC partners regarding (participation in) conferences, workshops, noteworthy achievements, news from partner projects and other news from within the CHIC consortium. The efficient communication structures put in place at the beginning of the project as well as the close collaboration within the whole consortium are huge assets when it comes to regularly disseminating CHIC news and highlights. Eurice also upgraded the download section of the website, which now features the public deliverables of the first year of the project, the CHIC flyer, a general presentation about the CHIC project as well as the first annual newsletter, published on 31 October 2014. Moreover, the list of publications has been updated. Open access papers can be directly accessed via the CHIC website. Together with the CHIC developers, Eurice is currently setting up free access to test-versions of the CHIC tools and services via the CHIC public website. Eurice is currently enhancing the website with a feature for the clinicians to access demo versions of the CHIC tools to try out and evaluate. UBERN developed a dedicated website to disseminate the software BraTumIA to the scientific community, which provides information regarding institution and usage of the software. Since last May over 150 download requests have been processed. In association to the activities of Task 12.3, ICCS prepared the 6<sup>th</sup> IARWISOCI – The CHIC Project Workshop website (<http://6th-iarwisoci.iccs.ntua.gr/>).

### **Subtask 12.1c: Newsletter**

CINECA took care to the main writing and distribution of the electronic bi-monthly newsletters. Eurice continued to support CINECA in putting together the bi-monthly CHIC newsletter. Eurice provided information about relevant conferences and workshops in the field of computational medicine, cancer modelling, etc., and contributed small teaser texts, especially for the section concerning news from the CHIC project. CINECA has been also monitoring the statistics on the newsletter reading and subscriptions so to take actions if necessary.

Eurice is also responsible for the regular publication of the annual newsletters, which are to provide a more detailed insight into the CHIC project and consortium. Due to a very heavy workload not only at Eurice but also at other partner institutions, the first newsletter, to be published at the end of M12, was delayed. The newsletter was finally published on 31 October 2014 and is available for download on the CHIC website (<http://chic-vph.eu/highlights/details/article/1st-annual-chic-newsletter/>). The 2nd issue of the annual CHIC newsletter is in preparation. Eurice and CINECA drafted an outline of contributions to this second issue, which will be more substantial than the first issue. Contributions are being collected from the CHIC partners ICCS, USAAR, USFD, UBERN, BED, CINECA as well as from members of the external advisory board and the newsletter is expected to be published in M26 or M27. ICCS was a major contributor of the annual 2014 CHIC newsletter; they contributed two articles, one introducing the CHIC project and the second one outlining the emerging scientific domains of *in silico* oncology and *in silico* medicine.

### **Subtask 12.1e: Conferences, Exhibitions, Workshops**

A list of the events and contributions from the different partners for M13-24 includes (among other things):

- Eurice provided assistance to the coordinator, ICCS, in the organization of the 6<sup>th</sup> IARWISOCI Workshop, which was at the same time the first of two larger CHIC workshops. USAAR actively participated in the Workshop.
- ICCS presented the CHIC project at the 7<sup>th</sup> World Congress on Biomechanics, Boston US, 6-11 July 2014 (invited talk).
- ICCS gives an introductory talk to the 6<sup>th</sup> IARWISOCI- The CHIC Project Workshop, 3-4 Nov, Athens, Greece by G.Stamatakis: "Towards the mathematical principles of the natural philosophy of living matter: In Silico Oncology/ In Silico Medicine".
- The CHIC coordinator (G. Stamatakis, ICCS) was invited to the workshop entitled "Prostate Carcinoma: Reports from EUREKA Studies (CHIC studies)" that took place in Turin, Mar 28, 2015 in the IRCC-FPO Istituto Scientifico di Candiolo. He presented the CHIC project and the broader philosophy of *in silico* oncology and intensely interacted with the about 40 participating clinicians regarding the clinical acceptance of hypermodels.
- The Work Package Leader of Dissemination (Simone Bnà, CINECA) was invited to the workshop entitled "Prostate Carcinoma: Reports from EUREKA Studies (CHIC studies)" that took place in Turin, Mar 28, 2015 in the IRCC-FPO Istituto Scientifico di Candiolo. He gave a general presentation of the CHIC project.
- Eurice started organizing the CHIC Summer School, to be held from 7-9 September 2015 at Schloss Dagstuhl in Germany. Eurice co-organizes the three-day event with USAAR, who is the scientific leader of the workshop. Eurice will be responsible for the managerial details around this workshop, among other things the set-up of a dedicated Summer School website, accessible via the CHIC public website, the design of a Summer School logo and corresponding promotion/dissemination material, the technical and logistic aspects of the registration process and the rest of the meeting organization. The event is laid out for a maximum of 30 participants. The call for papers is expected to be published at the Summer School website in mid-May.
- K. Duan and D. Tartarini presented poster describing CHIC Project with the focus on Hypermodelling Infrastructure at the Insigneo Showcase 2014 on the 07/05/2014. The focus of



the Showcase was on the impact achieved through collaboration with industrial and clinical partners. The event was attended by high profile guests including key representatives from industry, the health and research sector, and important funding bodies. Additionally, the leaflets describing Project CHIC were disseminated during this event.

- Oral Presentations about the CHIC Hypermodelling Framework in Cancer Research developed in WP7 was given on the 11/09/2014 by Dr Daniele Tartarini at the VPH2014 Conference in Trondheim, Norway. It was focused on the CHIC technological framework that through the CHIC Portal will allow the clinicians to investigate the clinical questions related to cancer disease and personal patients' data. Researchers will be allowed to create hypermodel workflows involving datasets and models from repositories and execute them on the CHIC Hypermodelling Framework.
- CUSTODIX prepared and submitted a paper for the CHIC Workshop (3-4 November) and the EICAR conference (17-18 November). The CHIC Workshop and EICAR conference have also been attended to present the papers.
- USAAR active participated in an IT workshop on tools/services for clinical trials that was organized by ECRIN at the 26-27 May 2014 in Düsseldorf. Moreover, a talk was given at SIB/SystemsX.ch Summer School, June 22-27, 2014 in the Swiss Alps, Hotel Victoria in Kandersteg. This was a combined effort of p-medicine and CHIC.
- In the past year, UCL presented the RICORDO infrastructure and its CHIC applications to mathematical modellers in pharmaceutical companies at the DDMoRE meetings in Hoofddorp (The Netherlands) on separate occasions: once in March 2015 and once in September/October 2014.
- UNITO: Ilaria Stura presented a talk at MPDE14 Conference at University of Turin, Italy. She also presented an e-poster at the VPH 2014 Conference in Trondheim, Norway. UNITO hosted the CHIC 4<sup>th</sup> Progress Meeting in Torino in March 2015. FPO-IRCCS Cancer Center of Candiolo organized the EUREKA studies meeting in Candiolo Cancer Center (Aula Cappa, March 28th, 2015) as satellite event to the 4th CHIC Progress Meeting. For this reporting period, UNITO listed 9 dissemination activities, among abstracts and meeting presentations, and 7 full papers.
- For this reporting period, UPENN listed a total of 32 dissemination activities of CHIC supported research, among them invited lectures/talks, conference presentations and activities directed at media publicity.
- LUH listed a total of 13 dissemination activities undertaken within the reporting period including several public lectures delivered by Prof. N. Forgó.

A detailed description of these dissemination and publication activities is provided in the respective tables in this report.

#### ***SubTask 12.1.f: Scientific & Technical Papers Publications***

ICCS published an article in the Journal of Biomedical and Health Informatics and submitted for peer-reviewed journal publication two manuscripts, which are currently under revision. Four articles, in which ICCS contributed, were accepted after peer-reviewing to the 6th IARWISOCI- The CHIC Project Workshop, 3-4 Nov, Athens, Greece and were published in the open access version of the workshop's proceedings (available at <http://6th-iarwisoci.iccs.ntua.gr/>). The articles have also been published - following the standard IEEE review process- in the IEEE Xplore Digital Library (<http://ieeexplore.ieee.org/xpl/mostRecentIssue.jsp?punumber=7024236>). The Institute of Electrical and Electronics Engineers (IEEE), Engineering in Medicine and Biology Society (EMBS) co-sponsored the workshop. An editorial article is also included in the open access version of the 6th IARWISOCI proceedings. These articles are listed in the table of dissemination activities and publications of this report.

FORTH, UNITO and UPENN listed 20 publications in scientific journals and conference proceedings. UNITO also edited a supplement number of "Minerva Urologica and Nefrologica" journal, Impact

Factor 0,7 (Editors: Caterina Guiot & Domenico Gabriele, publisher: Edizioni Minerva Medica) entitled “Prostate Carcinoma: reports from EUREKA studies (CHIC project)”. A detailed overview of all the publications is provided in the table on dissemination activities and publication in this report.

#### ***SubTask 12.1.g: Interfacing with other projects***

- ICCS has had continuous interaction with the following projects: p-medicine, MyHealthAvatar, DrTherapat, AVICENNA.
- CINECA had interactions with the VPH-Share project on some architectural components of the hypermodelling framework.

#### **Task 12.2: Exploitation and IPR issues**

With support and input from the CHIC consortium who provided information via an innovation questionnaire, CINECA drafted D12.3, the Preliminary Plan for the Use and Dissemination of Foreground, which features an update of the dissemination strategy, the CHIC IPR Management Strategy (especially with regard to the specifically drafted CHIC MoU) an exploitation overview and first exploitation plans of some of the CHIC partners. The deliverable was submitted with a slight delay on 30 April 2015. The preliminary PUDF will have two regular updates, one after each remaining project period (month 36 and month 48).

Different activities preparatory to the next exploitation plan definition took place in this reporting period:

- CINECA monitored the outputs from WP4 on the memorandum of understanding to capture indication for the future exploitation planning.
- USAAR continued the discussion with p-medicine about sustainability issues. 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 addition USAAR reviewed a first draft of the IPR Memorandum of Understanding.
- ICCS has initiated a discussion among a number of CHIC partners, including CINECA, PHILIPS, USAAR, KULeuven, USFD, regarding the multi-directional exploitation of the expected project outcome. This includes clinical, industrial, research, academic teaching, and legal/legislation exploitation channels. An extensive collaboration with WP4 has ensured the addressing of all major potential issues regarding intellectual rights and other legal and ethical aspects of the joint endeavour.
- A new post-graduate course entitled “Multi-scale Cancer Modelling and In Silico Medicine” has been created and was taught in the autumn-winter semester 2014/2015 in the School of Electrical and Computer Engineering, NTUA, by the CHIC coordinator G.Stamatakis. The course was enthusiastically received by post-graduate students. This course has extensively exploited the outcome aspects of the up to now outcome of the CHIC project as well as of other research projects funded by the EUROPEAN Commission (<http://www.vph-institute.org/news/new-postgraduate-subject-on-multiscale-cancer-modelling-and-in-silico-medicine-mscm-ism.html>).
- FORTH has engaged in important discussions with the legal partners of the project also involving FORTH’s lawyers in order to expedite the IPR agreement and most importantly contribute to the understanding of the project as a whole from the exploitation perspective.
- LUH listed 13 exploitative activities undertaken within the reporting period including several public lectures delivered by Prof N. Forgó and publication of two peer-reviewed articles based on contributions to the 6th IARWISOCI, one on Legal and Ethical Aspects of In Silico Medicine, and the other on Intellectual Property Rights Issues in Multiscale Cancer Modeling. These are listed in the table on workshops and conferences further below in this report.
- The IPR framework has been studied by UBERN in regard to the dissemination of the software BraTumIA.

### Task 12.3: Training activities

ICCS undertook the organization of the 6th IARWISOCI-The CHIC Project Workshop (<http://6th-iarwisoci.iccs.ntua.gr/>), which took place on Nov 3-4, 2014, Athens, Greece. Following a targeted process of informing academic entities in Greece about the workshop, a considerable number of post-graduate students have registered to attend the workshop. They were informed about the achievements of the CHIC project and the latest achievements of *in silico* oncology and its extension to *in silico* medicine.

The CHIC coordinator (G. Stamatakis, ICCS) was invited in the workshop entitled "Prostate Carcinoma: Reports from EUREKA Studies (CHIC studies)" that took place in Turin, Mar 28, 2015 in the IRCC-FPO Istituto Scientifico di Candiolo. This constituted a major training activity since G. Stamatakis presented the CHIC project and intensely interacted with the about 40 participating clinicians regarding the clinical acceptance of hypermodels.

The preparations of the CHIC Summer School to be held in 2015 have started. The event will be organized by USAAR and Eurice. This Summer School will take place in Schloss Dagstuhl, Germany between 6 and 9 September 2015, where the p-medicine Summer School was also held in 2013. A dedicated Summer School website featuring information on the content and on organizational issues around the workshop has been set up by Eurice ([www.chic-vph.eu/summer-school/](http://www.chic-vph.eu/summer-school/)). A registration process was defined by USAAR, ICCS and Eurice and the registration process is currently running. The CHIC work package leaders will help evaluate the abstracts which are sent in with the applications. About 20-30 participants are expected at the workshop. Eurice and many other CHIC partners are actively engaged in the dissemination of the event in the larger VPH community.

Clinicians from the consortium and from Inselspital are being trained on the use of the software BraTumIA. A command-line version has been transferred to colleagues at Harvard Medical School and to UCLA for batch analysis. BraTumIA highlighted by the NIRC.org website as a compatible tool for the TCIA database from the NIH.

### Summary of significant results

The project website is up to date, regular dissemination of news and highlights via the CHIC newsletters is ongoing and effective. The 2nd annual newsletter is currently in the making.

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, is actively ongoing.

A discussion about sustainability and maintenance issues of the CHIC project via the proposed Study Trial and Research Institute that is part of the maintenance program of p-medicine has started and exploitation activities have also started with preparatory work from different partners. Further discussions are needed and must be integrated into the exploitation planning report of CHIC. A first version of the Preliminary Plan for the Use and Dissemination of Foreground (PUDF) was submitted to the EC.

Training activities, most notably the CHIC Summer School 2015, have also started or are currently being organized.

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

D12.6, the first issue of the Periodic Newsletter, was published on 31 October 2014, i.e. with a 7 months delay and D12.3, Preliminary Plan for the Use and Dissemination of Foreground (PUDF), has been delivered with a slight delay of about 4 weeks. However, this will not have any impact on the tasks and resources in WP12. The second issue of the periodic newsletter will be published on time.

### 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

As mentioned in the first Periodic Report of the CHIC project, partner Eurice faced a huge workload in most of 2014 and 2015. Other CHIC partners reported to have similar problems. Given the fact that the bi-monthly newsletters were published regularly, the partners decided to postpone the CHIC newsletters and focus on the more crucial technical deliverables. As stated above, the delays do not have any impact on WP12.

### Corrective actions

Not applicable.

### Statement on the use of the resources

Planned versus actual efforts in WP12			
Partner	Planned PM Total	Planned PM Period 2	Actual PM Period 2
1-ICCS	8.00	2.80	3.97
2-Eurice	12.00	3.00	
3-USAAR	3.00	1.00	0.05
5-BED	6.00	2.00	0.00
6-USFD	7.00	2.00	1.53
7-FORTH	6.00	2.00	1.06
8-LUH	6.00	1.00	0.49
9-UPENN	6.00	1.50	2.00
10-UOXF	6.00	2.00	0.00
11-UNITO	6.00	1.00	2.00
12-UBERN	5.00	1.00	0.40
13-Custodix	6.00	1.50	1.11
14-Philips	6.00	0.50	0.00
15-UCL	2.00	0.50	0.00
16-CINECA	6.00	1.00	2.03
17-TEI-C	1.00	0.00	0.00
<b>Total</b>	<b>92.00</b>	<b>22.80</b>	

### 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
Prostate carcinoma: reports from Eureka studies (CHIC project)	Conference	UNITO, CINECA, ICCS, USAAR	Prostate carcinoma: reports from Eureka studies congress. Oral presentations made by Simone Bnà (CINECA), Georgios Stamatakis (ICCS), Norbert Graf (USAAR), Domenico Gabriele, Caterina Guiot and Ilaria Stura (UNITO)	Candiolo, Turin, Italy	28.03.2015
Is there still a role for computed tomography and bone scintigraphy in prostate cancer staging? An analysis from the Eureka-1 database	Conference	UNITO	EAU 2015 International Meeting	Madrid, Spain	20.-24.03.2015
Data Protection and Clinical Data in Pediatric Research and Treatment	Video lecture	LUH	International Childhood Cancer Awareness Day Event in the European Parliament		03.02.2015
Data Protection and Data Security: A Lawyer's View on Personal Clinical Information	Winter School	LUH	Fourth Winter School Ethics and Neuroscience, Bernstein Center for Computational Neuroscience Berlin, Berlin School of Mind and Brain	Berlin	23.02.2015
Rechtsfragen der personalisierten Medizin	Invited lecture	LUH	Paul Fritzsche Stiftung, Universität des Saarlands	Homburg	29.01.2015
Predicting the Effects of Clinically	Meeting	UPENN	ASCB Annual Meeting	Philadelphia PA	2015

Observed Kinase Mutations using Molecular Modeling and Machine Learning Algorithms					
Dendritic cell therapy in brain cancer	Conference	KU Leuven	Presentation by Prof. Van Gool at the “VII congresso nacional associacao portuguesa neuro oncologia” organised by Associacao portuguesa neuro oncologia	Lisbon, Portugal	21.11.2014
Providing a Network of Trust in Processing Health Data for Research	Conference	CUSTODIX	23rd EICAR ANNUAL CONFERENCE Trust and Transparency in IT Security	Frankfurt, Germany	18.11.2014
Providing a Network of Trust in Processing Health Data for Research	Conference	LUH	23 <sup>rd</sup> EICAR Annual Conference	Frankfurt	17-18.11.2014
In Silico Medicine: The Paradigm of In Silico Oncology	Workshop	ICCS	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
Legal and ethical aspects of in silico based medicine	Workshop	LUH	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
IPR issues in multiscale modelling	Workshop	LUH	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
A two population Model of Cancer growth with fixed Carrying capacity	Conference	UNITO	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
Dendritic Cell Vaccination for Glioblastoma Multiforme	Conference	KU Leuven	Skype-presentation by Prof. Van Gool to the 6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation (IARWISOCI) - The CHIC Project Workshop	Athens, Greece	04.11.2014
Incorporating Data Protection in In Silico Research: A case of CHIC (publication)	Conference	CUSTODIX	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation	Athens, Greece	03.11.2014



Keynote lecture on Data Protection Reform	Conference	LUH	Leopoldina Symposium „Keimbahnmutationen bei krebskranken Kindern“	Freiburg, Germany	26.09.2014
The Importance of Data Sharing and Data Protection'	Conference	LUH	SIOPE-ENCCA conference 2014	Brussels, Belgium	18.09.2014
Multiscale modelling of cancer (workshop session)	Conference	ICCS	VPH2014	Trondheim, Norway	11.09.2014
In silico Neuro-Oncology: Simulating glioma growth and inhomogeneous invasion under explicitly treated Neumann boundary conditions	Conference	ICCS	VPH2014	Trondheim, Norway	11.09.2014
A Generalized Model of Tumor Growth and Response to Treatment using the PUN approach (poster)	Conference	UNITO	VPH2014	Trondheim, Norway	11.09.2014
The VPH Hypermodelling Framework for cancer research	Conference	USFD, CINECA	VPH2014	Trondheim, Norway	11.09.2014
A Two-Clones Model of Tumor Growth and its Response to Treatment	Conference	UNITO	MPDS14 Conference	Turin, Italy	29.08.2014
Nomination to Best Msc thesis work – Automatic Multimodal Brain Tumor Segmentation	Conference	UBERN	SSBE 2014 Annual Meeting	Zurich, Switzerland	27.-28.08.2014
Cancer cell patterns emerging from agent based movement (poster presentation)	Summer School	FORTH	Spatiotemporal modelling and simulation of biology systems: Biology in Cyber Space	Dresden, Germany	02.-09.08.2014
Patient-specific Semi-supervised Learning for Postoperative Brain Tumor Segmentation	Summer School	UBERN	Medical Imaging Summer School (MISS) 2014	Favignana, Italy	28.07. – 01.08. 2014

What is the role of in silico modelling and simulation to help translate pre-clinical data into the design of human clinical trials	Invited Lectures	UPENN	Tumor Models Summit, Boston 2014	Boston, MA, USA	22.-24.07.2014
Invited lecture: What is the role of in silico modelling and simulation to help translate pre-clinical data into the design of human clinical trials	Conference	UPENN	Tumor Models Summit	Boston, MA, USA	21. - 23.07.2014
In Silico Oncology: A generic platform for clinically driven and oriented cancer hypermodeling. The Hypermodel Based Oncosimulator	Conference	ICCS	7th World Congress of Biomechanics	Boston, MA, USA	6.-11.07.2014
Computational Challenges in Multiscale Modelling	Conference (Podium discussion)	USFD	7th World Congress of Biomechanics	Boston, MA, USA	6.-11.07.2014
Immunotherapy for relapsed malignant glioma in children	Conference	KU Leuven	Presentation by Prof. Van Gool at the ISPNO conference at Singapore	Singapor	28.06.2014
ApiNATOMY: The Generation of Interactive CircuitBoard Views of Complex Physiology Knowledge	Conference	UCL	4th International Conference on Complex Systems and Applications (ICCSA 2014)	Le Havre, France	23.-26.06.2014
Data modeling and simulations. Do they pave the way to personalized medicine?	Workshop	USAAR	SIB/Systems X.ch Summer School	Kandersteg, Switzerland	22.-27.06.2014
Piedmont multicenter retrospective study on operated prostate cancer: first report	Congress/conference	UNITO	24th Annual Meeting of the Italian Society of Uro-Oncology (SIUro)	Bologna, Italy	22.-24.06.2014
Immunotherapy for malignant glioma: preclinical research and clinical experience	Conference	KU Leuven	Presentation by Prof. Van Gool at the "Internal lab meeting seeking for collaboration on oncolytic virus research" organised by Prof. Alan Melcher, Medical Oncology, at Leeds, UK	Leeds, UK	16.06.2014

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.-4.06.2014
Immunotherapy for malignant glioma: preclinical research and clinical research	Conference	KU Leuven	Presentation by Prof. Van Gool at the 30th National Congress of Neurosurgery, organised by the Portuguese Neurosurgical Society by Dr. Miguel Casimiro, at Lisbon, Portugal	Lisbon, Portugal	30.05.2014
IT Challenges for innovative Clinical Trials	Workshop	USAAR	IT workshop on tools/services for clinical trials	Düsseldorf, Germany	26.-27.05.2014
Participation in Training School	Workshop	UNITO	ESTRO School of Radiotherapy and Oncology: Basic Clinical Radiobiology	Istanbul, Turkey	25.-29.05.2014
Data Protection reform	Invited Lecture	LUH	Datenschutzforum	Berlin, Germany	15.05.2014
Computational medicine: Current and Future prospects	Conference	FORTH	eHealth Forum 2014	Athens, Greece	12.-14.05.2014
Participation in training event	Workshop	CINECA, USFD	VPHF development training	Bologna, Italy	11.-16.05.2014
Immunotherapy for malignant glioma: preclinical research and clinical research	Conference	KU Leuven	Presentation by Prof. Van Gool at the conference "Oncobiology - genes and tumoral microenvironment" at the Medical Sciences Faculty, Nova University, organised by Prof. José Luis Passos Coelho and Prof. Doutora Ana Felix, at Lisbon, Portugal	Lisbon, Portugal	09.05.2014
Presentation of the CHIC project on a special leaflet	Showcase event	USFD	Insigneo Institute first anniversary showcase event1	Sheffield, UK	08.05.2014

Poster presentation of CHIC	Showcase event	USFD	Insigneo Institute first anniversary showcase event1	Sheffield, UK	08.05.2014
Presentation of the CHIC project	Workshop	USFD	Collaborations Workshop 2014 (CW14) - software in your reproducible research	Oxford, UK	26.04.2014
Immunotherapy for children and adults with malignant glioma: the Leuven experience	Conference	KU Leuven	Presentation by Prof. Van Gool at the Johannes Wesling Klinikum Minden, 23th GPHO Arbeitstagung Experimentelle Neuroonkologie, organised by Prof. Bernhard Erdlenbruch, at Minden, Germany	Minden, Germany	26.04.2014
Data protection issues in ehealth projects	Conference	LUH	EHR4CR First European Hospital Conference	Brussels, Belgium	09.04.2014
n.d.	Invited Lectures	UPENN	Department of Chemical and Biomolecular Engineering, State University of New York Buffalo,	Buffalo NY	2014

## Press activities

Title	Type	Main leader	Reference	Date
CHIC project featured in The Parliament Magazine	Online article	ICCS	Link: <a href="http://www.vph-institute.org/news/chic-project-featured-in-the-parliament-magazine.html">http://www.vph-institute.org/news/chic-project-featured-in-the-parliament-magazine.html</a>	05 May 2014
Computational Horizons in Cancer	Newspaper/Magazine Article	ICCS	Link to an online issue of The Parliament Magazine, Issue 389: <a href="http://viewer.zmags.com/publication/6eced2e8#/6eced2e8/36">http://viewer.zmags.com/publication/6eced2e8#/6eced2e8/36</a>	28 April 2014
Grantee presentation to the	Video	UPENN	<a href="https://www.youtube.com/watch?v=ttNG86de3ps">https://www.youtube.com/watch?v=ttNG86de3ps</a>	2014

Multiscale Modeling Consortium of the Inter Agency Modeling Group				
Video introducing Physics Reports article in the author's own words	Video	UPENN	<a href="http://audioslides.elsevier.com/getvideo.aspx?doi=10.1016/j.physrep.2014.05.001">http://audioslides.elsevier.com/getvideo.aspx?doi=10.1016/j.physrep.2014.05.001</a>	2014
Article in Physical Review E featured in the journal's kaleidoscope section	Online article	UPENN	<a href="http://journals.aps.org/pre/kaleidoscope/pre/90/2/022717">http://journals.aps.org/pre/kaleidoscope/pre/90/2/022717</a>	2014
Coverage in Science Daily: Classification of gene mutations in a children's cancer may point to improved treatments	Coverage in Science Daily News	UPENN	link: <a href="http://www.sciencedaily.com/releases/2014/11/141110123457.htm">http://www.sciencedaily.com/releases/2014/11/141110123457.htm</a>	2014

## Publications M13-M24

Title of Publication	Contact Person	Involved Institutions	Reference	Category	Publication Date	Co-Authors	Status
Legal and Ethical Aspects of In Silico Medicine	Iheanyi Nwankwo	LUH	2014 6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation. DOI: 10.1109/IARWISOCI.2014.7034647	Peer-reviewed publication	10.03.2015	Marc Stauch, Alan Dahi, and Nikolaus Forgo	Published
Intellectual Property Rights Issues in Multiscale Cancer Modeling	Iryna Lishchuk	LUH	2014 6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation	Peer-reviewed publication	10.03.2015	Marc Stauch and Nikolaus Forgo	Published
EUREKA-1 database: an epidemiological analysis	Domenico Gabriele	UNITO	Minerva Urol Nefrol 2015; 67 (Suppl. 1 to No. 1): 9-15	Peer-reviewed publication	2015	GABRIELE D, PORPIGLIA F, MUTO G, GONTERO P, TERRONE C, ANNOSCIA S, RANDONE D, BENVENUTI S,	Published

						ARENA G, STURA I & GUIOT C	
Gleason Score and other variables	Domenico Gabriele	UNITO	Minerva Urol Nefrol 2015; 67 (Suppl. 1 to No. 1): 21-26	Peer-reviewed publication	2015	GABRIELE D, ODERDA M, GONTERO P, MUTO G, COLLURA D, ANNOSCIA S, ARENA G, BOLLITO E, STURA I, GUIOT C & GABRIELE P	Published
The current role of CT and bone scintigraphy in prostate cancer staging	Domenico Gabriele	UNITO	Minerva Urol Nefrol 2015; 67 (Suppl. 1 to No. 1): 39-42	Peer-reviewed publication	2015	ODERDA M, GABRIELE D, COLLURA D, STURA I, FIORITO C, PORPIGLIA F, TERRONE C, ZACCHERO M, GUIOT C & GABRIELE P	Published
Report from the study EUREKA-2 on prostate cancer patients treated by radical radiotherapy: first data analysis	Domenico Gabriele	UNITO	Minerva Urol Nefrol 2015; 67 (Suppl. 1 to No. 1): 47-55	Peer-reviewed publication	2015	GABRIELE D, GARIBALDI M, MARRA AM, JERECZEK-FOSSA B, KRENGLI M, TESSA M, BONA C, FERRAZZA P,	Published



						BALCET V, RUO REDDA MG, MORO G & GABRIELE P	
Do radiotherapy techniques impact the outcome?	E. Garibaldi	UNITO	Minerva Urol Nefrol 2015; 67 (Suppl. 1 to No. 1): 63-75	Peer-reviewed publication	2015	GARIBALDI E, DELMASTRO E & GABRIELE P	Published
Modeling prostate cancer within CHIC	Ilaria Stura	UNITO	Minerva Urol Nefrol 2015; 67 (Suppl. 1 to No. 1): 97-98	Peer-reviewed publication	2015	STURA I, GABRIELE D & GUIOT C	Published
A multicenter retrospective study on irradiated prostate cancer: preliminary report	Domenico Gabriele	UNITO	Abstract in Anticancer research 2014 : 34	Peer-reviewed publication	2014	Gabriele P, Ruo Redda MG, Garibaldi M, Cattari G, Garibaldi E, Guiot C	Published
Piedmont multi center retrospective study on operated prostate cancer: first report	Domenico Gabriele	UNITO	Abstract in Anticancer research 2014 : 34	Peer-reviewed publication	2014	Gontero P, Terrone C, Porpoglia F, Muto G, Guiot C	Published
Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology - a Brief Technical Outline of the Project.	G.Stamatakis	BED, CINECA, CUSTODIX, FORTH, ICCS, KU Leuven, LUH, PHILIPS, TEI-C, UBERN, UCL,	Proc. 2014 6th Int. Adv. Res. Workshop on In Silico Oncology and Cancer Investigation - The CHIC Project Workshop (IARWISOCI) (open-access version)	Conference proceedings	01.02.2015	G.Stamatakis, D. Dionysiou, F. Misichroni, N. Graf, S. van Gool, R. Bohle, F. Dong, M. Viceconti, K. Marias, V. Sakkalis, N. Forgo, R. Radhakrishnan	Published

		UNITO, UOXF, UPENN, USAAR, USFD				, H. Byrne, C. Guiot, P. Buechler, E. Neri, A. Bucur, B. de Bono, D. Testi, M. Tsiknakis	
A Model of Tumor Growth Coupling a Cellular Biomodel with Biomechanical Simulations	Farhad Rikhtegar	ICCS-UBERN	In Silico Oncology and Cancer Investigation (IARWISOCI), 2014 6th International Advanced Research Workshop on	Conference proceedings	4/11/2014	Eleni Kolokotroni, Georgios Stamatakis and Philippe Buchler	Published
Incorporating Data Protection in In Silico Research: A case of CHIC	Elias Neri	CUSTODIX	2014 6 th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation, DOI: 10.1109/IARWISOCI.2014.7034643	Peer-reviewed publication	10.03.2015	Wouter Dhaeze	Published
Computational Delineation of Tyrosyl-Substrate Recognition and Catalytic Landscapes by the Epidermal Growth Factor Receptor Tyrosine Kinase Domain	Yingting Liu	UPENN	Molecular Biosystems doi: <a href="http://dx.doi.org/10.1039/c3mb70620f">http://dx.doi.org/10.1039/c3mb70620f</a>	Peer-reviewed publication	28.04.2014	Ravi Radhakrishnan	Published
Mesoscale computational methods for membrane bilayer remodelling by curvature inducing proteins	N. Ramakrishnan	UPENN	Physics Reports 543, DOI: 10.1016/j.physrep.2014.05.001	Peer-reviewed publication	28.04.2014	P. B. Sunil Kumar, Ravi Radhakrishnan	Published
Integrative functional assessment of ALK mutations for therapeutic stratification in neuroblastoma	Ravi Radhakrishnan	UPENN	Cancer Cell	Peer-reviewed publication	n.d.	D. Weiser, S. Bressler, P. J. Huwe, R. Radhakrishnan , M. A.	Submitted

						Lemmon, Y. Mosse	
In silico profiling of activating mutations in cancer	Ravi Radhakrishnan	UPENN	Integrative Biology	Peer-reviewed publication	n.d.	Jordan E	Submitted
An Explicit Numerical Treatment of the Three-Dimensional Boundary Conditions Imposed by the Skull on an Inhomogeneous Diffusion-Reaction Tri-scale Model of Glioblastoma Multiforme Tumour Growth and Invasion into the Brain. Clinical Validation Considerations.	Georgios Stamatakis	ICCS	Bulletin of Mathematical Biology	Peer-reviewed publication	n.d.	Giatili S	Submitted
Multiscale Computational Models in Physical Systems Biology of Intracellular Trafficking	Ravi Radhakrishnan	UPENN	IET Syst. Biol. 8 (5)	Peer-reviewed publication	October 2014	Tourdot RW, Bradley RP, Ramakrishnan M	Published
Defining the Free Energy Landscape of Curvature Inducing Proteins on Membrane Bilayers	Ravi Radhakrishnan	UPENN	Phys. Rev. E 90, 022717	Peer-reviewed publication	25 August 2014	Tourdot RW, Ramakrishnan M	Published
High-throughput mutagenesis reveals functional determinants for DNA targeting by Activation-Induced Cytidine	Ravi Radhakrishnan	UPENN	Nucleic Acids Research 42 (15)	Peer-reviewed publication	26 July 2014	Gajula KS, Huwe PJ, Mo CY, Crawford DJ, Stiver JT, Kohli RM	Published (Open Access)
Machine learning predictions of cancer driver mutations	E. Joe Jordan	UPENN	IEEE Proceedings of the 6 <sup>th</sup> International Advanced Research Workshop on In-Silico Oncology and Cancer investigation, pp1-4. DOI: 10.1109/IARWISOCI.2014.7034632	Conference proceedings	2014	Radhakrishnan R.	In press
Physical chemistry and membrane properties of two	D. R. Slochower	UPENN	Physical Chemistry Chemical Physics (A Royal Society of Chemistry Journal). DOI:	Peer-reviewed publication	2015	R. Radhakrishnan	In press

phosphatidylinositol bisphosphate isomers			10.1039/c5cp00862j			P. A. Janmey	
Exploring the competition between proliferative and invasive cancer phenotypes in a continuous spatial model	Kostas Marias	FORTH	PLoS One 8 (8)	Peer-reviewed publication	08/08/2014	Tzamali E, Grekas G, Sakkalis V	Published (Open Access)
Enabling multiscale modeling in systems medicine	Georgios Stamatakis	ICCS, UOXF	Genome Medicine 6:21	Peer-reviewed publication	2014	Wolkenhauer O, Auffray C, Brass O, Clairambault J, Deutsch A, Drasdo D, Gervasio F, Preziosi L, Byrne H, et al.	Published
The Technologically Integrated Oncosimulator: Combining Multiscale Cancer Modeling with Information Technology in the In Silico Oncology Context	G. Stamatakis	FORTH, ICCS, TEI-C, USAAR	IEEE J. Biomed Health Inform. doi: 10.1109/JBHI.2013.2284276	Peer-reviewed publication	01/05/2014	Dionysiou D, Lunzer A, Bellemann R, Kolokotroni E, Georgiadi E, Erdt M, Pukacki J, Rueping S, Giatili S, Donofrio A, Sfakianakis S, Marias K, Desmedt C, Tsiknakis M, Graf N.	Published

## 2. Deliverables and milestones tables

### 2.1 Deliverables

Deliverables submitted in the 2<sup>nd</sup> period are highlighted in light blue. Deliverables of the 1<sup>st</sup> period are highlighted in light grey.

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 was 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	2	14-PHILIPS	R	CO	30.09.2014		Yes	02.12.2014	An extension of the original deadline (M18) was requested because the partners responsible for the deliverable agreed to go

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
	the domain of cancer									beyond the mentioned atomic/granular models, thereby showing common ways in reusing models in other domains. Therefore, further information from modelers had to be gathered and incorporated into the deliverable.
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	4	8-LUH	R	PU	31.12.2013		Yes	06.01.2014	



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
	legal requirements for the sharing of data									
D4.3.1	Development of the data protection and copyright framework for CHIC first iteration	4	8-LUH	R	PU	31.05.2014		Yes	02.06.2014	May 31 and June 1, 2014, were weekend days, so the deliverable was sent to the EC on Monday, June 2, 2014.
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	13.06.2014	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.
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	5	13-CUSTODIX	R	CO	30.09.2014		Yes	01.10.2014 05.05.2015	A first version of D5.1 was submitted in 2014. However, an updated version of D5.2

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
	security tools									was produced after a second internal review and sent to the EC in May 2015. The updated version contains the following modifications: Updated security vocabular, updated integration tutorials, added audit Json schema
D5.3	Techniques to build the cloud infrastructure available to the community	5	5-BED	R	PU	31.03.2015		Yes	31.03.2015	
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		Yes	05.01.2015	This deliverable was postponed by about 3 weeks due to its complex and multidisciplinary nature as well as due to the Christmas break. The EC officer was informed accordingly.
D6.3	Initial standardized cancer hypermodels	6	1-ICCS	R	CO	31.05.2016		No		
D6.4	Clinical adaptation	6	1-ICCS	R	CO	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
	and partial validation of hypermodels									
D7.1	Hypermodelling Specifications	7	1-ICCS	R	PU	31.03.2014		Yes	02.07.2014	D7.1 could only be submitted after the 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.
D7.2	First Release Hypermodelling framework deployed on test nodes	7	16-CINECA	P	RE	31.03.2015		Yes	08.06.2015	The submission of this deliverable was postponed by 2 months and the EC was informed accordingly on 26 March 2015. The reason for this delay was an ongoing consensus process on the architectural design which had to be fully resolved before work on D7.2 could be started.
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		Yes	20.11.2014	The submission of this deliverable was postponed due to unforeseen workload at the partner in charge. After the CHIC review meeting held on the 3rd of September 2014 and the very valuable comments that we received from the reviewers during the review meeting concerning the data

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
										representation (both clinical data and models), the partners decided to wait for the official review report in order to understand more precisely the suggestions of the reviewers. In the meantime a draft version of the deliverable was circulated by email among the involved partners, so the postponement did not cause any delays on the work described in the DoW.
D8.2	Prototype implementation of the CHIC repositories	8	12-UBERN	O	CO	31.03.2015		Yes	04.05.2015	The deliverable was delayed by about 4 weeks. The request for a later submission results from the heavy workload at ICCS, one of the partners strongly involved in the writing of D8.2, that followed a recent change in staff.
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 longitudinal brain tumour image	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
	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		Yes	04.12.2014	An extension of the original deadline (M18) was requested because new needs related to the interfaces and the orchestration of the different components were identified during the Technical Meeting in Leuven and it was crucial to incorporate the necessary changes in the deliverable, having in mind the reviewers’ recommendation on paying special attention in models and components integration.
D10.3	The CHIC Encryption Services	10	13-CUSTODIX	O	CO	31.03.2015		Yes	07.04.2015	The deliverable was submitted directly after the Easter break.
D10.4	The PhysiomSpaceenabled 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 was postponed by 2 months. The EC was informed accordingly.
D11.2	Report on the first evaluation workshops round	11	3-USAAR	R	RE	30.09.2014		Yes	01.12.2014	The original submission date was 30 September 2014 (M18). However, the deliverable submission was extended by about two months. The reason for the

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
										extension of the original deadline was that the CHIC consortium met for a first round of evaluations of the CHIC tools in mid-October, during the CHIC Progress Meeting in Leuven, Belgium. The corresponding report, which is D11.2, was then written after this evaluation workshop.
D11.3	Report on the second evaluation Workshops round	11	3-USAAR	R	RE	31.03.2016		No		
D11.4	Validation of CHIC infrastructure as a whole	11	1-ICCS	R	RE	31.03.2017		No		
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		Yes	30.04.2015	Due to the slow feedback of some of the CHIC partners, the deliverable was delayed by about 4 weeks. The EC was informed accordingly.
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		No (2 <sup>nd</sup> issue)	19 June 2015	The second issue of the CHIC newsletter is delayed by about 6 weeks, as valuable contributions to its content are missing.

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
						31.03.2017				

## 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 15-17/10/2014 26-27/03/2015	1 <sup>st</sup> progress meeting of CHIC at FORTH, Heraklion, Greece, from 17-18 October 2013 2 <sup>nd</sup> progress meeting at BED, Luton, UK, from 20-21 February 2014 3 <sup>rd</sup> progress meeting at KU Leuven, Leuven, Belgium, from 15 to 17 October 2014 4 <sup>th</sup> progress meeting at UNITO, Turin, Italy, from 26-27 March 2015	
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	Yes	31/03/2015		



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
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	Yes	31/05/2014	D4.1, D4.2 and D4.3.1 are available.
MS9	Initial CHIC Architecture and security guidelines	5	7-FORTH	30.09.2014	Yes	01/10/2014	D5.1.1 and D5.2 are available.
MS10	Final version of the CHIC Architecture	5	7-FORTH	30.09.2016	No		
MS11	Initial component models available for all cancer modelling branches	6	1-ICCS	30.09.2013	Yes	22/10/2013	D6.1 is available
MS12	Rational, numerical and clinical experience based check of the component models complete	6	1-ICCS	30.11.2014	Yes	05/01/2015	D6.2 is available
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	Yes	02/07/2014	D7.1 is available
MS16	Folksonomy and Ontology annotation and search services deployed	7	5-BED	31.03.2015	No	End of May 2015	
MS17	Hypermodel editor, development and execution	7	7-FORTH	31.03.2016	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
	application ready						
MS18	Metahypermodels annotation completed	7	6-USFD	31.03.2017	No		
MS19	Design of the CHIC repositories completed	8	1-ICCS	31.07.2014	Yes	21/11/2014	D8.1 is available
MS20	Deployment of the CHIC repositories	8	15-UCL	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	Yes	31.03.2015	Visual analytics techniques were verified by technical experiments on the data used within the project.
MS23	Image segmentation & registration techniques	9	12-UBERN	30.09.2014	Yes	30.09.2014	Image segmentation and registration techniques were verified by technical experiments on the data used in the project.
MS24	Initial version of the tumor response quantitative platform	9	7-FORTH	31.03.2015	Yes	31.03.2015	Testing results of the initial version of the platform are available.
MS25	The CHIC Orchestration Platform and Encrypted Data Services	10	7-FORTH	31.03.2015	Yes	31.03.2015	D10.1, D10.2 and D10.3 are available.
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	Yes	17.-18.10.2014	The first evaluation workshop was held during the CHIC progress meeting at KU Leuven.
MS29	Second evaluation Workshop	11	3-USAAR	31.03.2016	No		
MS30	Internal collaborative area and	12	2-EURICE	30.06.2013	Yes	28.06.2013	Website is online and operational:

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
	external website						<a href="http://www.chic-vph.eu">www.chic-vph.eu</a>
MS31	First CHIC summer School	12	3-USAAR	30.09.2014 (now 30.09.2015)	No		The first CHIC training workshop was held in the context of the 6 <sup>th</sup> IARWISOCI workshop in Athens from 3-4 November 2014. Therefore, the consortium will switch MS31 and MS32, as a dedicated CHIC Summer School will take place from 7-9 September 2015.
MS32	CHIC workshop	12	1-ICCS	30.09.2015 (now 30.09.2014)	Yes		The first CHIC training workshop was held in the context of the 6 <sup>th</sup> IARWISOCI workshop in Athens from 3-4 November 2014. Therefore, the consortium will switch MS31 and MS32, as a dedicated CHIC Summer School will take place from 7-9 September 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)

The following achievements were made during M13-M24:

The **2<sup>nd</sup> CHIC review** (after M12) took place with a bit of a delay on 3 September 2014. The day before, the work package leaders and several other CHIC partners met in Brussels to prepare for the review by putting together a common project presentation.

At the review meeting itself, the coordinator, Research Professor Dr Georgios Stamatakis (ICCS) gave an overview of the progress achieved in the first year of the project, before members of the CHIC consortium presented concisely various aspects of the project such as the clinical, technological as well as legal and ethical requirements, hypermodeling design, IT Architecture, hypermodeling infrastructures, image processing, etc. Moreover, the CHIC integrated platform, Security Framework and hypermodelling demonstrations were presented. We are happy to announce that the assessment included in the Review Report was very positive. The reviewers see the project on track and consider the goals of the 1st year achieved. CHIC is advised to focus more attention on exploitation and IPR issues. As stated in the WP4 report above, IP issues are dealt with thoroughly by LUH and the rest of the consortium. Following further recommendations from the CHIC reviewers, the partners have been developing a gantt chart illustrating the availability of services and tools to the clinicians and have also prepared a glossary of terms for reference. The 2nd Review Meeting will be held after the 2nd Periodic Report (M24).

The CHIC consortium members agreed with the CHIC PO at the European Commission to schedule the **3<sup>rd</sup> CHIC review** (after M24) on 8 July 2015. The CHIC partners agreed to the proposed reviewers and to Brussels as the location for the review. Eurice is organizing a preparation meeting, which will take place the day before the official review also in Brussels.

A **3rd Progress Meeting (MS2)** was held on 16-17 October 2014 at KULeuven in Leuven, Belgium where the work done since the first Periodic Report was presented and the work anticipated for the upcoming months was discussed. A special focus lay on the recommendations from the annual CHIC review and on the discussion of a work plan/schedule to meet the recommendations. Special attention was also paid to the IPR issues. A dedicated **technical meeting** was held at KULeuven on 15 October 2014. Its purpose was to carefully assess the recommendations made by the reviewers of the CHIC project and to develop a detailed action plan in response to these recommendations. Moreover, technical aspects such as tool integration, security framework and tool/components development were discussed. 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.

The **4<sup>th</sup> progress meeting (MS2)** of CHIC was held in Turin on 26-27 March 2015. The CHIC partners presented their work of the past six months and discussed obstacles, solutions and options within the work packages. A special focus of the meeting lay in the preparation of the 3<sup>rd</sup> CHIC review meeting which is to take place in July 2015. The CHIC members identified various demonstrators to

be presented at this review. These include a clinical demonstrator (clinical data and pseudonymization workflow), an integrated lung cancer multi-modeller hypermodel as well as a demonstration of the overall technological workflow. A draft agenda for the review meeting was developed by Eurice with support from all CHIC partners. The meeting minutes as well as the presentations of the meetings were stored on the CHIC intranet ProjectAngel as usual. The meeting was accompanied by an optional database workshop also organized by CHIC partner UNITO.

The **5<sup>th</sup> progress meeting** is currently being organized. The original idea was to hold the meeting at CHIC's transatlantic partner institution UPENN. However, given the fact that travel costs will be much higher than for a meeting within Europe, the CHIC coordinator, supported by Eurice, is currently negotiating the place and modalities of this meeting with the EC project officer Mr. Jaakko Aarnio. Independent of its final location, the meeting is scheduled for late October 2015.

In terms of **financial monitoring**, the CHIC consortium received their first periodic payment from the EC after the successful conclusion of the annual review meeting. However, due to budgetary constraints, the EC informed the Project Management Team that the first periodic payment would be delayed.

Moreover, the amount of payment to be expected from the EC was at first reduced for almost all CHIC partners. Since the reasons for the reductions as well as the calculation method underlying the reductions were not clear, the Project Management Team asked the EC for clarification. As the review report from the CHIC review on 3 September 2014 had been sent to the CHIC coordinator by then, the EC performed a reassessment of the cost claims and accepted almost all cost originally claimed. The CHIC partners were informed accordingly by the Project Management Team that their share of the overall requested funding would be transferred by the coordinator as soon as possible. The payment was then transferred by ICCS according to the following table:

Project Number: 600841				Project Title: CHIC					
Participant Nr	Participant Short name	Fund. %	Total Costs	Requested EU Contribution	% of Total EU Contribution	Pre-financing	Cost Claims 1st report	1st Periodic Payment	Cost Claims 2nd report
1	ICCS	60.0	1.386.800 €	1.128.800 €	10,67%	395.080,00 €	177.447,00 €	175.194,00 €	
2	EURICE	85.0	645.498 €	645.498 €	6,10%	225.924,30 €	110.605,00 €	110.605,00 €	
3	USAAR	60.0	1.689.301 €	1.282.996 €	12,12%	449.048,60 €	100.130,00 €	100.130,00 €	
4	KULeuven	60.0	814.000 €	625.000 €	5,91%	218.750,00 €	60.612,00 €	60.612,00 €	
5	BED	60.0	857.800 €	659.800 €	6,24%	230.930,00 €	71.172,00 €	71.172,00 €	
6	USFD	60.0	1.215.675 €	941.825 €	8,90%	329.638,75 €	158.387,00 €	158.315,00 €	
7	FORTH	87.0	888.106 €	688.031 €	6,50%	240.810,85 €	159.592,00 €	159.592,00 €	
8	LUH	60.0	608.794 €	474.928 €	4,49%	166.224,80 €	90.036,00 €	90.036,00 €	
9	UPENN	62.0	742.206 €	573.282 €	5,42%	200.648,70 €	120.883,00 €	120.883,00 €	
10	UOXF	60.0	561.120 €	446.591 €	4,22%	156.306,85 €	10.363,00 €	10.363,00 €	
11	UNITO	60.0	597.000 €	462.998 €	4,38%	162.049,30 €	49.597,00 €	49.597,00 €	
12	UBERN	60.0	844.000 €	651.000 €	6,15%	227.850,00 €	98.980,00 €	98.980,00 €	
13	CUSTODIX	50.0	303.000 €	245.375 €	2,32%	85.881,25 €	15.595,00 €	15.595,00 €	
14	PHILIPS	149.0	1.019.116 €	566.120 €	5,35%	198.142,00 €	16.671,00 €	16.671,00 €	
15	UCL	60.0	1.060.364 €	804.156 €	7,60%	281.454,60 €	53.154,00 €	53.154,00 €	
16	CINECA	20.0	596.307 €	325.560 €	3,08%	113.946,00 €	125.530,00 €	125.530,00 €	
17	TEI-C	60.0	78.880 €	60.040 €	0,57%	21.014,00 €	17.510,00 €	16.794,00 €	
			13.907.967 €	10.582.000 €	100,00%	3.703.700,00 €	1.436.264,00 €	1.433.223,00 €	

General financial monitoring is done throughout the project by Eurice. A table providing an overview of the current financial status of the project is provided in this report.

Regarding **contractual management**, the management team closely followed the development and signing process of the CHIC Memorandum of Understanding which was drafted and negotiated by CHIC partner LUH. The final signed CHIC MoU will be an addition to the CHIC Consortium Agreement and will be made available to all CHIC partners via the CHIC intranet.

Given the fact that several modifications had to be made to the original CHIC DoW, the CHIC Consortium is currently preparing for an **amendment**, which will be officially requested by the CHIC coordinator after the submission of the 2<sup>nd</sup> periodic report. This decision was taken in order not to cause any delays in the reporting schedule (see also the section below).

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

No serious problems have occurred during M13-24.

However, it has to be noted that several modifications were made to the original CHIC DoW. These changes mainly concern the addition of subtasks and task prolongations in work packages 5, 6 and 10, but also the contributions of CHIC partners to work packages in which they weren't originally involved. Of the CHIC consortium, partners BED, FORTH, USFD and CINECA are affected by these changes. Detailed descriptions of the content of these changes are provided in the work package reports in this document. A revision of PM planning is provided in the subsection on project status and planning in this management report. A request for an amendment to the CHIC DoW is being prepared.

### Changes in the consortium

None.

### List of project meetings, dates and venues during M13-M24

Title	Date	Venue	Local organizer/participants
WP9 Preparation telco*)	18.05.2015	Skype, Phone	ICCS, USAAR, BED, FORTH, UBERN, TEI-C
Skype meeting about data for biomechanical validation study*)	07.05.2015	Skype	KULeuven, UBERN
Skype meeting about Study Events in ObTiMA*)	29.04.2015	Skype	KULeuven, USAAR
Skype meeting about data sharing*)	21.04.2015	Skype	KULeuven, Custodix
Clinical Database Workshop	28.03.2015	Turin, Italy	UNITO
4 <sup>th</sup> Progress Meeting	26.-27.03.2015	Turin, Italy	UNITO
Bi-weekly telco focused on technical issues	12.03.2015	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
Bi-weekly telco focused on technical issues	12.02.2015 and 26.02.2015	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
Linkage of biomechanics and vascularization model	26.01.2015	Skype, Phone	UBERN, UOXF

Bi-weekly telco focused on technical issues	15.01.2015 and 29.01.2015	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
Telco concerning decoupling of CoupledSimulator	17.12.2014	Skype, Phone	UBERN, ICCS, USFD
Workgroup meeting: Clinical Data Upload	11.-12.12.2014	Homburg, Germany	USAAR, UBERN, ICCS, UCL, FORTH, Custodix, LUH
Telco concerning decoupling of CoupledSimulator	10.12.2014	Skype, Phone	UBERN, ICCS
Linkage of biomechanics and vascularization model	25.11.2014	Skype, Phone	UBERN, UOXF
Bi-weekly telco focused on technical issues	13.11.2014 and 18.12.2014	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
WP6 Modellers' Meeting	05.11.2014	Athens, Greece	ICCS
3 <sup>rd</sup> Progress Meeting	16.-17.10.2014	Leuven, Belgium	KULeuven
CHIC Technical Meeting	15.10.2014	Leuven, Belgium	KULeuven
Meeting concerning Glioblastoma data	13-14.10.2014	Leuven, Belgium	ICCS, KULeuven
Bi-weekly telco focused on technical issues	25.09.2014	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
Bi-lateral Skype call	25.09.2014	Skype	UBERN, UCL
2 <sup>nd</sup> CHIC review meeting	03.09.2014	Brussels, Belgium	EC
Review preparation meeting	02.09.2014	Brussels, Belgium	Eurice, ICCS, BED
Bi-weekly telco focused on technical issues	21.08.2014 and 28.08.2014	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
Bi-lateral Skype call	21.08.2014	Skype	UBERN, Custodix
Bi-weekly telco focused on technical issues	10.07.2014 and 24. 07.2014	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4



Skype meeting concerning Glioblastoma data	30.06.2014	Skype	KULeuven, ICCS
Skype meeting about HOT maps	30.06.2014	Skype	KULeuven, UCL
Bi-weekly telco focused on technical issues	26.06.2014	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
ObTiMA meeting II	23.06.2014	Leuven, Belgium	KULeuven, USAAR
WP6 Cancer Modellers' Meeting	17.-18.06.2014	Heraklion, Crete, Greece	FORTH
Bi-weekly telco focused on technical issues	12.06.2014	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
Bi-lateral Skype call	26.05.2014	Skype	UBERN, Custodix
Bi-weekly telco focused on technical issues	22.05.2014	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
Bi-weekly telco focused on technical issues	08.05.2014	Skype	ICCS, various CHIC partners, mainly from WPs 5, 7, 8, 9, 10 and 4
ObTiMA meeting	17.04.2014	Homburg, Germany	KULeuven, USAAR
WP6 Hypermodelling Meeting	10.-11.04.2014	Oxford, United Kingdom	UOXF
Skype meeting about HOT maps	10.04.2014	Skype	KULeuven, UCL, USAAR, ICCS

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.

However, deviations from the original work plan occurred and are described in the following paragraphs. Given the extent and nature of these deviations, the CHIC partners are currently preparing for an official amendment to the CHIC DoW which will be requested after the submission of the 2<sup>nd</sup> Periodic Report.

### Change of person months:

With the second year of the CHIC project now finished, ICCS performed a reassessment of their PM effort planning. This revision was due to a more concrete and detailed picture of the future work in the project. Moreover, after the revision, ICCS reported that it is more or less certain that ICCS's total PMs will be larger than initially estimated, but that ICCS will remain within the same budget. This is because various technical developments and related difficulties ICCS had to deal with have proved to need increased participation by less senior staff than originally planned. In addition, due to recent staff changes the PMs of the second period were further increased. The updated PM effort plan is as follows (changes are highlighted in yellow):

Partner 1 ICCS	Planned					Revision after year 2				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP1 Project Management	2,00	2,00	2,00	2,00	8,00	2,00	2,00	2,00	2,00	8,00
WP2 User Needs and Requirements	1,00	0,40	0,40	0,20	2,00	1,00	0,60	0,30	0,10	2,00
WP3 Clinical and Fundamental Science Scenarios	0,50	0,50	0,50	0,50	2,00	0,50	0,70	0,40	0,40	2,00
WP4 Legal and Ethical Framework	0,70	0,60	0,50	0,20	2,00	0,70	0,70	0,40	0,20	2,00
WP5 IT Architecture	0,80	0,80	0,80	0,60	3,00	0,80	1,00	0,70	0,50	3,00
WP6 Models and Hypermodel Design	13,00	10,50	10,50	10,00	44,00	13,00	12,00	10,00	9,00	44,00
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	1,50	1,50	1,50	1,50	6,00	1,50	1,60	1,60	1,30	6,00
WP8 Model and Data Repositories	4,00	3,50	3,50	3,00	14,00	4,00	4,50	3,50	2,00	14,00
WP9 Image Processing and Visualization	0,70	0,80	0,80	0,70	3,00	0,70	0,90	0,90	0,50	3,00
WP10 Integrated Platform	1,80	1,80	1,80	1,60	7,00	1,80	1,90	1,90	1,40	7,00
WP11 Clinical Adaption and Validation	1,00	1,50	2,20	2,30	7,00	1,00	1,50	2,20	2,30	7,00
WP12 Dissemination and Exploitation	1,60	2,80	1,80	1,80	8,00	1,60	2,80	1,80	1,80	8,00
<b>Total</b>	<b>28,60</b>	<b>26,70</b>	<b>26,30</b>	<b>24,40</b>	<b>106,00</b>	<b>28,60</b>	<b>30,20</b>	<b>25,70</b>	<b>21,50</b>	<b>106,00</b>

Due to the revision of several tasks, partners BED and FORTH needed to revise their person month efforts in various work packages. These revisions do not have any impact on the requested funding. For BED, the total number of PM remains unchanged. FORTH had to allocate additional PM efforts in WP5, Task 5.3, WP6, Task 6.1 and WP10, Task 10.1. Details about why these additional PM efforts are needed and how they were and will be used are provided in the respective work package reports in this document. However, FORTH will remain within the budget set out at the beginning of the project. A detailed explanation on recruitment issues at FORTH, as requested by the reviewers during the CHIC review in September 2014, has been prepared for justification of the additional personnel efforts. FORTH has prepared a mitigation plan (see table and explanation below) concerning the planned PMs, that includes also the extra work that has been taken up, with totally 163.79 PMs for the whole project.

The Management Team asked BED and FORTH to prepare a revised PM effort table for the 4 project periods.

Partner 5 BED	Planned					Revision after year 1				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP5 IT Architecture	5,00	10,00	4,00	0,00	19,00	5,00	5,00	0,00	0,00	10,00
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	4,00	8,00	7,00	0,00	19,00	4,00	12,00	12,00	0,00	28,00
WP9 Image Processing and Visualization	5,00	10,50	10,50	10,00	36,00	5,00	10,50	10,50	10,00	36,00
WP11 Clinical Adaptation and Validation	0,00	2,00	3,00	3,00	8,00	0,00	2,00	3,00	3,00	8,00
WP12 Dissemination and Exploitation	0,00	2,00	2,00	2,00	6,00	0,00	2,00	2,00	2,00	6,00
Total	14,00	32,50	26,50	15,00	88,00	14,00	31,50	27,50	15,00	88,00

Partner 7 FORTH	Planned					Revised				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP1 Project Management	0,50	0,50	0,50	0,50	2,00	0,53	0,50	0,50	0,50	2,03
WP2 User Needs and Requirements	1,00	1,00	1,00		3,00	2,00	1,00	1,00	1,00	5,00
WP3 Clinical and Fundamental Science Scenarios					0,00					0,00
WP4 Legal and Ethical Framework					0,00					0,00
WP5 IT Architecture	3,00	3,00	3,00	1,00	10,00	9,00	8,50	6,50	4,00	28,00
WP6 Models and Hypermodel Design	2,50	2,50	2,50	1,50	9,00	7,61	7,50	6,50	4,00	25,61
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	1,50	1,50	1,50	1,50	6,00	2,00	2,50	1,50	1,50	7,50
WP8 Model and Data Repositories	1,50	1,50	1,50	1,50	6,00	2,00	1,50	2,00	1,00	6,50
WP9 Image Processing and Visualization	5,00	5,00	5,00	5,00	20,00	19,79	8,50	8,50	6,50	43,29
WP10 Integrated Platform	5,00	6,00	6,00	4,00	21,00	17,29	8,00	7,50	4,00	36,79
WP11 Clinical Adaptation and Validation	0,50	0,50	1,00	1,00	3,00	0,57	1,00	0,50	1,00	3,07
WP12 Dissemination and Exploitation	1,00	1,00	2,00	2,00	6,00		2,00	2,00	2,00	6,00
Total	21,50	22,50	24,00	18,00	86,00	60,79	41,00	36,50	25,50	163,79

It has to be noted that, before estimating the revised plan, **FORTH** has implemented a mitigation/change plan in the human resources involved in the project after the recommendations of the first year review. This plan includes the reduction of the use of lower rate personnel (e.g. postgraduate students) and the strongest involvement of senior personnel. The expected result of this new resource plan is also reflected by the gradual PM decrease from period 1 to period 4 despite the additional tasks/work assigned to FORTH.

Due to rearrangement of responsibilities in task 5.2, **USFD** and **CINECA** also modified their PM effort planning in this reporting period. The efforts in Task 5.2 originally planned to be allocated on USFD were shared between USFD and CINECA as CINECA was the original developer of the security part of VPH-HF. In order to better reflect how the software development tasks are distributed between partners USFD and CINECA, it was agreed to swap 6 PM between the two partners and between WP5 and WP7. As a result of this adjustment the effort of partner USFD is reduced of 6pm in WP5, and increased 6 pm in WP7. Symmetrically, the effort of partner CINECA is reduced of 6pm in WP7 and increased of 6pm in WP5. This means that CINECA, contrary to the CHIC DoW, is now a partner in WP5. The overall amount of PM efforts hasn't changed for both partners.

It has to be noted, however, that, contrary to the original plan, USFD already performed a revision of PM efforts after the first year of CHIC, without any effect on the overall funding. 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.

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 planned 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.

The following tables present an overview of the revisions of PM planning for both USFD and CINECA:

Partner 6 USFD	Revision after year 1					Revision after year 2				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP1 Project Management	2,00	1,80	1,80	1,80	7,40	2,00	1,80	1,80	1,80	7,40
WP5 IT Architecture	0,00	6,00	4,00	2,00	12,00	0,00	4,00	1,00	1,00	6,00
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	30,00	39,00	39,00	20,00	128	30,00	37,00	34,00	33,00	134,00
WP12 Dissemination and Exploitation	0,60	2,00	2,20	2,20	7,00	0,60	2,00	2,20	2,20	7,00
Total	32,60	48,80	47,00	26,00	154,40	32,60	44,80	39,00	38,00	154,40

Partner 16 CINECA	Planned					Revised				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP1 Project Management	0,40	0,20	0,20	0,20	1,00	0,40	0,20	0,20	0,20	1,00
WP5 IT Architecture					0,00		6,00			6,00
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	12,00	14,00	12,00	4,00	42,00	12,00	8,00	12,00	4,00	36,00
WP10 Integrated Platform	1,00	3,50	3,50	0,00	8,00	1,00	3,50	3,50	0,00	8,00
WP11 Clinical Adaptation and Validation					0,00					0,00
WP12 Dissemination and Exploitation	2,00	1,00	1,00	2,00	6,00	2,00	1,00	1,00	2,00	6,00
Total	15,40	18,70	16,70	6,20	57,00	15,40	18,70	16,70	6,20	57,00

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 financial resources originally planned.

Partner **UPENN** also revised their PM effort planning for the rest of the CHIC project. Overall, the actual PM for PENN will show an increase to 27 PM per year in comparison to Planned PM of 21. This increase will not result in an increase in budget and the actual costs per year will remain the same. The reason for this increase is field specific: the original plan was to have a computer scientist at the postdoctoral research associate level devote 50% effort in developing hyper models for WP6 but also touching upon other WPs, especially WP11. Due to the economy, (computer scientists at the postdoctorate level have a large supply of Jobs in the industry and hence are not pursuing Postdoctoral positions in academia), UPENN decided to hire a Research Associate from Biochemistry and Biophysics (who has a degree/minor in computer science and hence, the required skills) and utilize 100% of their effort in the above WPs in order to ensure smooth functioning of the tasks and meeting of the milestones. UPENN are happy to report that this has been very successful and they have met all of their goals in a timely manner. However, this change has resulted in the number of actual PM going to 27 (=12+12+3) in comparison to the planned PM of 21 (=12+6+3). The increase in 6 PM is exactly as noted above. This increase will be reflected in Periods 2, 3, and Period 4 (which on average is expected to show 27 PM instead of 21 PM). But UPENN confirms that due to field specific salaries (Computer Science versus Biochemistry) the costs are not altered. Moreover, there is no

compromise on skill or quality and UPENN have the best skill level to complete the tasks. An updated PM effort table is currently in the making and will be provided with the next report. However, in year 2 of the CHIC project, UPENN had to increase their PM efforts even more. In addition to the 27 PM (=12 for Ghosh + 12 for Jordan + 3 for Radhakrishnan), which are explained above, UPENN needed to utilize the expertise of the research associate Peter Huwe for 3PM and postdoctoral research associate David Slochower for 2.5 PM, which accounts for the added 5.5 PM over 27 PM bringing the total to 32.5 PM.

### Impact of possible deviations from the planned milestones and deliverables

During the reporting period in question, most deliverables and milestones have been submitted or achieved as foreseen in Annex I or only with a smaller delay. These delays occurred mainly because some of the reviewers' recommendations from the CHIC review in September 2014 had to be incorporated in the deliverables or because internal discussions about one or more aspects of a deliverable were ongoing. 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.

The 2<sup>nd</sup> year of CHIC also saw changes in leadership of two deliverables:

Contrary to the CHIC DoW, it was agreed that **FORTH** would lead **D5.3**, "Techniques to build the cloud infrastructure available to the community" (M24), as the lead of task 5.3 also went to FORTH. The EC project officer was informed of this change upon submission of D5.3.

Moreover, because of a typo in the DoW, D10.3, "The CHIC Encryption Services" (M24), Custodix was originally set as leader of this deliverable. However, Custodix are not partner in WP10. This mistake was noticed when Eurice informed Custodix about the timeline for the preparation and submission of D10.3, a workflow which runs automatically about 6 weeks before a deliverable is due. It was agreed among the WP10 members that the correct leader of D10.3 was **CINECA**, who then prepared and submitted D10.3.

### Any changes to the legal status of any of the beneficiaries

There are no changes to the legal status for any of the CHIC beneficiaries. The consortium remains as it was at the beginning of the CHIC project.

### Ongoing development of the Project website

The CHIC website registers a continuously increasing number of visitors. Eurice keeps the website updated 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. The CHIC newsletters, both bi-monthly and annual, can be downloaded from the website and a subscription plug-in has been installed. 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. The CHIC consortium members all contribute regularly to the website with their updates and news-items. 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. The CHIC partners are also currently preparing access to some of the CHIC tools via the official website. This way, clinicians can test and familiarize themselves with the CHIC tools and services. Access to the tools will be implemented within the coming weeks.

The official website of the CHIC Summer School is also hosted on the public CHIC website (<http://chic-vph.eu/summer-school/>). An electronic registration process via the Summer School website has been put in place.

As the project continues over the next 2 years, the website will be constantly revised and updated to reflect the project's progress and meet the consortium's requirements. More information about the current status of the project website can be found in the WP12 report above as well as on the CHIC website at [www.chic-vph.eu](http://www.chic-vph.eu).

The features of the website are described 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 2 (total)	Actual PM M13-24
1-ICCS	8.00	2.00	1.71
2-Eurice	38.00	9.50	
6-USFD	4.00	1.80	2.71
7-FORTH	2.00	0.50	0.27
10-UOXF	2.00	0.30	0.72
16-CINECA	1.00	0.20	0.22
<b>Total</b>	<b>55.00</b>	<b>14.30</b>	<b>9.08</b>

## 4. Explanation of the use of the resources

The costs presented in this periodic report are an overview of total amounts. Details are provided in the Explanation on the Use of Resources which is entered electronically in the NEF tool when completing Form C.

### 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.