



## PROJECT INTERIM REPORT

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## 1. Work progress and achievements during the period

### 1.1 Work Package 1: Project Management

Regarding Work Package 1 reference is made to section 2 “Project Management” following the individual work package descriptions.

### 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

Use cases and scenarios have been further refined for the different cancer domains of the project that is lead by USAAR. In addition, the requirements for enhancing hypermodels beyond the domain of cancer were discussed extensively within the consortium and deliverable D2.3 will be submitted with a short delay. All clinical partners continued to collect data from the different cancer domains, including clinical data, imaging data, and molecular data. UPENN worked on the deregulation

associated with signalling of EGFR family receptors that 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 UPENN's study of EGFR mutations and signalling can be extended to domains beyond cancer. USAAR continued discussions about lines of interaction with the *p-medicine* environment.

### Summary of details for each task

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

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, Requirements for enhancing hypermodels beyond the domain of cancer.

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. ICCS contributed to the preparation of deliverable D2.3 from the modelling perspective. Such domains that will be included in the deliverable are: retina angiogenesis in diabetes, angiogenesis in embryology, cell cycling in wound healing, extension of molecular networks and pathways to all other medical domains, biomechanics in musculoskeletal system diseases etc.

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.

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. They show here that their results shed molecular-level insight into the various mechanisms governing such transforming mutations at the level of kinase activity and are remarkably consistent with experimental observations. In particular, their computational predictions matched experimental measures of kinase activity with over 85% accuracy in the mutations investigated from neuroblastoma patients.

USAAR and other clinical partners enhanced the requirements from the clinical perspective.

#### **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 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 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 functioning for the upload of data to the CHIC platform these data will be shared with all other partners. This will happen before the next consortium meeting in 2015.

### 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.
- 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 UPENN 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. UPENN 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**

Due to a heavy workload the contribution to deliverable D2.3 from the modelling perspectives is planned to be completed by the end of M20. The submission of the D2.3 has been slightly delayed (M18) and an extension has been requested with the approval of the WP leader and the CHIC coordinator. We do not expect any 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 (total)	Actual PM M13-M18
1-ICCS	2.00	0.40	0.30
3-USAAR	25.00	7.00	n/a
7-FORTH	3.00	1.00	1.00
9-UPENN	5.00	1.00	0.17
13-CUSTODIX	1.00	0.25	0.00
14-PHILIPS	4.00	2.00	0.14
<b>Total</b>	<b>40.00</b>	<b>11.65</b>	

### 1.3 Work Package 3: Clinical and Translational Science Scenarios

#### Main objectives of this WP

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

#### Active tasks in this reporting period:

- Task 3.1, Wilms tumor (M1-48)
- Task 3.2, Glioblastoma multiforme (M1-48)
- Task 3.3, Non-small cell lung cancer (M1-48)
- Task 3.4, Applying the CHIC infrastructure to other cancer types (M12-36)

#### Summary of progress achieved towards objectives

In Task 3.1, exploitation of Wilms tumor patients' multiscale data was carried out by ICCS. Preparatory work regarding micro-RNA data is to be provided by ICCS. Major work was done by USAAR after defining the data that will be used in the nephroblastoma to start collecting them and in addition to render tumour volumes of nephroblastoma. ObTiMA is used for data collection. New functionalities are needed for ObTiMA that are currently being programmed by IT people from USAAR.

In Task 3.2, ICCS defined the specific multiscale data to be used by the glioblastoma multiforme multiscale models to be developed. At KULeuven, major work was done in collecting data that will be used in the glioblastoma multiforme scenario. Construction of CRFs and usage of a data management system is extensively explored and preparation/construction is still ongoing. ObTiMA is used for data collection. Close interaction with ICCS modellers was also continued.

In task 3.3, ICCS carried out 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. And collection of data from patients with Non-Small-Lung-Cell Cancer (NSCLC) has begun. UPENN published a number of papers related to WP3. These publications are listed in the publications table in this document.

In task 3.4, The data collection from patients undergoing prostatectomy at UNITO was closed in May 2014. Checking these data was completed in September 2014. Data on anamnesis, biopsy, pathology, surgical and medical therapies, follow-up are recorded in the UNITO database.

#### Summary of details for each task

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

- **ICCS:** Exploitation of Wilms tumor patients' multiscale data is in progress. Preparatory work for the provision of micro-RNA data are under way. Continuous interactions of ICCS with USAAR.
- **USAAR:** Within the SIOP Renal Tumor Study Group a new clinical trial is further developed. 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 will take 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**

- **ICCS:** 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.
- **USAAR:** Together with KU Leuven it was discussed how they can collect their data with ObTiMA. For that purpose new functionalities are needed for ObTiMA that are under programming by IT people from USAAR.
- **KU LEUVEN:** The HGG-2010 clinical trial will serve as the data source of glioblastoma multiforme data. An extra application for sharing the data in the CHIC consortium was approved on April 7<sup>th</sup>, 2014. The CHIC Data Provider Agreement was signed on May 23<sup>th</sup> 2014.
- Different data management systems for storing and sharing of the glioblastoma multiforme data were explored extensively. FileMaker was studied locally but did not satisfy us for practical reasons, nor other CHIC partners 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 and sharing of the glioblastoma multiforme data. Discussions and meetings with USAAR partners were held to learn to work with ObTiMA. These interactions are still ongoing for preparing and constructing the appropriate CRFs.
- An extra effort was done for collecting a big 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. Imaging data (DICOM format) are stored in the hospital's PACS system. Analysis of some immunotherapy related aspects (FACS acquisitions) was started and will provide extra data for sharing. Furthermore, patient material was collected for future biological research. Experimental research for future immune monitoring is still ongoing.
- Intense interaction with modellers from ICCS 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.

### **Task 3.3: Non-small cell lung cancer**

- **ICCS:** Exploitation of lung cancer patients' multiscale data is in progress. Continuous interactions of ICCS with USAAR.
- **USAAR:** Together with WP2 data for the Non-small cell lung cancer hypermodel was further elaborated. 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 are stored locally up to now until the legal and ethical framework is in place for CHIC and the user interface allows upload of the data.
- **UPENN:** 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)

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

- **ICCS:** ICCS is in contact with UNITO in order to adapt various models being developed primarily by UNITO to the CHIC framework. 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
- **USAAR:** A discussion started how ObTiMA can be used for data collection for other cancer types
- **UNITO:** Data collection of a total of 3538 patients from 13 clinical units (sending from 65 to 513 cases) with 188 fields per patient.
- Applications of the modelling activities from UNITO to lung cancer have been discussed with CHIC partners at the progress meeting in Leuven. Applications to the prostate cancer are in progress.
- **UPENN:** Cf. contribution of UPENN to task 3.3. and the publications mentioned in the publication table.

### **Summary of significant results**

#### **ICCS:**

- Exploitation of Wilms tumor and lung cancer patients’ multiscale data.
- Definition of the specific multiscale data to be provided for glioblastoma multiforme modelling.
- Continuous interaction of ICCS with the clinicians regarding the details of the provision, checking and usage of the multiscale data.

#### **USAAR:**

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

#### **KU LEUVEN:**

- Legal and ethical issues for sharing data in the framework are cleared.
- Consensus for using ObTiMA as the data management system for glioblastoma multiforme data. CRFs are being prepared.
- Source documents of the multiscale data are available.
- Continuous interaction with ICCS.

#### **UNITO:**

- Data collection on prostatectomized patients has been completed (Euraka1). Data collection on irradiated patients is almost completed.
- The clinical database is resident on the server 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.

#### **UPENN:**

- The results of the *in silico* profiling algorithm are helpful in the rational design of mutant-specific inhibitors and to rationalize the effect of mutation on inhibitor (crizotinib) sensitivity in a given cohort of patients in neuroblastoma and inhibitor sensitivity (erlotinib, gefitinib, and lapatinib) in non-small-cell lung cancer.



### 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 WP3			
Partner	Planned PM Total	Planned PM Period 2 (total)	Actual PM M13-M18
1-ICCS	2.00	0.50	0.35
3-USAAR	49.00	16.00	n/a
4-KULeuven	68.00	20.00	8.00
9-UPENN	2.00	0.50	0.17
11-UNITO	14.00	4.00	2.96
<b>Total</b>	<b>135.00</b>	<b>41.00</b>	

## 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.
- To clearly define who is entitled to do what with existing models and data sets from inside and outside the consortium. 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 whitepaper on these issues for the use of the European Commission and other political stakeholders will be produced. Specific focus will be on the amalgamation of models in the field.
- Being legal advisor for all not yet foreseen legal and ethical questions for all partners for the whole duration of the project.

### Active tasks in this reporting period:

- Task 4.3, Development of a data protection and copyright framework for CHIC (M1-42)

Work started early in the following task:

- 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” (M14-28)

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

The data protection and copyright framework has been developed and the first iteration has been completed. Deliverable D4.3.1 has been submitted in that respect. The framework includes the development of pseudonymisation and security framework for deploying data to the CHIC platform. In respect of the IPR, the clarification of the definition of joint and composite work in the context of CHIC as well as the draft of the MoU has been developed. Work is on-going for the second iteration towards the end of the project.

In task 4.4, research is being done 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 M9 relating the on-going reform in the area of data protection.

The partners’ involvement in this work package is as follows:

**LUH** contributed in the development of the data protection and copyright framework and Deliverable D4.3.1 submitted in that respect. Currently developing a whitepaper recommendation for amending the European legal framework on patients' and researchers' rights and duties in E-health related research.

**USAAR** contributed to the submission of D4.3.1 as well as how the pseudonymisation/anonymisation of data needed for the nephroblastoma and small lung cell cancer hypermodel were developed and refined. Feedback was also given to the IPR document.

**CUSTODIX** contributed to 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 joint and composite work in the context of CHIC as well as review of the Memorandum of Understanding (MoU).

**UPENN** contributed to the IPR development 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, potential IPR issues arising from the gap in the CA and GA have been investigated and a memorandum of understanding drafted to take care of the identified problems. Negotiation concerning the MOU is still on-going. Similarly, the data protection agreements are being concluded between the CDP and the partners. The data protection framework includes the development of a pseudonymisation and security framework for deploying data to the CHIC platform. As a result of this task, Deliverable D4.3.1 which show this first iteration has been submitted in M14. The final iteration will be done in M42.

#### **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.”**

The goal of this task is to develop a whitepaper recommendation relevant for the on-going reforms in terms of patients' and researchers' rights and duties in E-health related research. Initial research in this task has taken place and the task will be completed in M36.

### **Summary of significant results**

- The partners completed the first iteration of the data protection and copyright framework.
- Development of the IPR memorandum of understanding and circulation among the CHIC partners.

- The concluding phase of data protection agreements between the CDP and partners is currently in progress.

#### **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 (total)	Actual PM M13-M18
1-ICCS	2.00	0.60	0.45
3-USAAR	4.00	1.50	n/a
8-LUH	48.00	12.00	7.17
9-UPENN	2.00	0.50	0.17
13-Custodix	2.00	0.50	0.49
<b>Total</b>	<b>58.00</b>	<b>15.10</b>	

## **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 specific objectives for the period have been to identify the components, or building blocks/services, that make up the overall information system, and provide a plan, from which

interoperable sub-systems can be developed. In this context, the initial Reference Architecture has been established. While the implementation has started through the technical work packages, refinements to the Architecture are being made, based on more refined and elaborate specification as requirements are crystalized. Feedback from the developers and further requirements from the end users is being collected, in order to enhance and update the architecture.

Considering the security tools, the integration of the single-sign-on security mechanism into the model/tool repository and *in-silico* trial repository has been performed. 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.

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

Finally, all planned deliverables have been delivered.

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

#### **Task 5.1, Reference Architecture Definition.**

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. TEI-C and the Lead Architect (Dr Fay Misichroni, ICCS) have jointly coordinated the functioning of the Board. 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. It took the leading role in the implementation and integration of the architectural components. ICCS was active in the preparation of a plan (in terms of Gantt chart) regarding the time of availability of services to the clinicians. A draft version, based on the technological aspect, was prepared. The analysis of the basic science and legal information will follow.

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 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 specific 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 are 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 looked 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.

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

In the context of this task, we 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 contributed in the analysis the state of the art in cloud computing technologies.

The relevant deliverable *D5.3: Techniques to build the cloud infrastructure available to the community*, due on M24 is in preparation.

### **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” was delivered.
- A refined version of the CHIC reference architecture was 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.
- 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 is well under way.
- The final version of Deliverable “*D5.2: Security guidelines and initial version of security tools*” was produced, gone through internal evaluation and submitted.
- The private cloud infrastructure was developed and was put into production, providing data storage and computational resources to all of the technical partners of the consortium.

### **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 originally developer of the security part of VPH-HF. This change will be compensated in WP7 effort without any change in the total man months planned for CINECA and USFD.

The 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 by 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, instead of BED, and will need to increase its person months 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 neither affect the deliverables described in the DoW nor the already allocated budget.

Actions are in progress with the CHIC partners 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**

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

**Corrective actions**

Not applicable.

**Statement on the use of the resources**

Planned versus actual efforts in WP5			
Partner	Planned PM Total	Planned PM Period 2 (total)	Actual PM M13-M18
1-ICCS	3.00	0.80	0.69
5-BED	19.00	5.00	0.00
6-USFD	12.00	6.00	2.94
7-FORTH	10.00	8.50	2.50
12-UBERN	4.00	1.50	0.00
13-Custodix	12.00	3.50	2.41
14-Philips	15.00	7.00	0.00
16-CINECA	0.00	0.00	0.25
17-TEI-C	15.00	4.00	1.25
<b>Total</b>	<b>90.00</b>	<b>36.30</b>	<b>10.04</b>

**BED:** Due to the revision of several tasks, BED needed to reallocate their personnel resources. A redistribution was performed and 7 PM were moved from WP5 to WP9. BED's original planned effort for the second period was 10 PM. A complete overview of BED's revised PM efforts is included in the management section of this report.

**FORTH:** Due to the revision of several tasks, FORTH needed to reallocate their personnel resources, which resulted in an increase of PM in several work packages. A complete list of the revised PM planning is provided in the management section of this report.

## 1.6 Work Package 6: Cancer Models and Hypermodel Design

### Main objectives of this WP

Work package 6 aims at achieving the following targets:

- To develop new multiscale models or to extend and/or adapt already existing ones in order to spatiotemporally simulate the specific clinical trials and studies addressed by the CHIC project. To clinically adapt and partly validate them based on the data available by the clinical partners of the project.
- To "break down" already developed tumor models, so that models and computer codes of elementary biological processes (bio mechanisms) can be provided to the model repository to be developed. Elementary biological processes may include inter alia cell cycling (including e.g. the duration of the various phases of the cell cycle based on the molecular profile of the tumor and interactions among critical molecular entities), the probability of a tumor cell to undergo apoptosis following a particular treatment, such as the administration of a special chemotherapeutic drug or radiotherapy or a targeted therapy agent based on the molecular profile of the tumor (e.g. through the use of molecular networks), the angiogenesis process (e.g. a basic algorithm for creating new blood vessels from existing ones based on the local concentration of TAF) etc.
- To standardize the inputs, outputs and descriptions of such elementary process modules according to the hypermodelling (or integrated modeling) metalanguage to be developed by work package WP7 in collaboration with WP6. The set of parameters that could best describe and make widely usable each one of the elementary process models will have to be identified. In order to end up with

a reasonable and hopefully universally acceptable and easily usable description of the basic aspects of all multiscale cancer models (input/output parameters, modelling strategy, mathematical methods used etc.), all cancer modelers participating in the CHIC project will have to make suggestions so that a consensus will be finally reached.

d) For selected tumor types to fit together the standardized elementary tumor bioprocess modules that will have been produced during steps b and c, so as to end up with a modular “re-creation” of existing models referring to the specific cancer type. The resultant hypermodels will be numerically studied and at least partly experimentally and/or clinically adapted and validated using data available from literature and/or collected by collaborating experimentalists and/or clinicians. This step will serve as an initial demonstrator of the analysis and experimental and/or clinical adaptation and validation process applied to modular hypermodels.

e) To contribute to the creation of multi-modeler hypermodels (or integrated models) concerning various tumor types addressed by CHIC by utilizing standardized elementary process modules. The standardized elementary bioprocess models will have to be linked to elementary bioprocess models of complementary mechanisms developed by other modelers according to the model standardization to be achieved by WP7 in collaboration with WP6. Such multi-modeler models will undergo numerical analysis and at least partial clinical adaptation and validation using pertinent multiscale data to be provided by the CHIC clinical partners and/or mined from literature and/or provided by experimental or clinical collaborators of modelers. These hypermodels will serve as demonstrators of the implementation of the concept of hypermodelling in the cancer domain.

#### 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 tumor modeling (M1-36)
- Task 6.4, The clinical modeling paradigms of neuroblastoma, glioblastoma and lung cancer (M6-46)
- 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, ICCS proposed a lung cancer multi-modeller hypermodel which was adopted and is under implementation by all WP6 partners. The inputs, outputs and basic description of each hypomodel (component model) have been crystalized by the partners involved. 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 possible their linking and re-writing in the context of hypermodelling. FORTH is developing a sub-cellular model that describes the aberrant metabolism of cancer cells at genome scale incorporating gene expression data, a hybrid discrete-continuous tumour growth model for studying the emergence, selection and evolution of tumour clones that interact with each other and their microenvironment, 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 and a metabolic model focusing on lung cancer, in order to contribute to the lung cancer hypermodel. UOXF have participated in modelling discussions regarding the interaction of ICCS tumour growth and response to treatment components, the UBERN biomechanics component model and an angiogenesis and vascular tumour component being developed at UOXF. Suitable interactions between these component models for the lung cancer clinical case have been identified and discussed with all modelling partners. Detailed testing and comparison of both discrete and continuum angiogenesis and vascular tumour models are on-going.

In Task 6.2, a clear way of linking subcellular multiscale models with cellular and super cellular models has been established as a result of UPENN and ICCS interaction. 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. A subcellular model for intracellular trafficking that is predictive (the first of its kind) is under development. Tumour markers with high specificity against prostate cancer which can be identified in tissues available after surgical resection and/or biopsy (e.g. TMPRSS2-ERG) have been investigated by UNITO. FORTH is developing a sub-cellular model that describes the aberrant metabolism of cancer cells at genome scale incorporating gene expression data as well as a hybrid discrete-continuous tumour growth model for studying the emergence, selection and evolution of tumour clones that interact with each other and their microenvironment.

In Task 6.3, ICCS, in collaboration with UBERN, has made concrete suggestions regarding the integration of biomechanics modelling into discrete-entity discrete-event multiscale cancer modelling. At UBERN, a meshing tool is available to automatically construct FE meshed from segmented images. Integration of the FE solver with cellular bio-model and adaptation of workflow to integrated patient-specific geometries into the bio-model simulations is taking place. The first conceptual design to integrate infiltration of the cell in the healthy tissue devise has been developed.

In Task 6.4, the clinical modelling paradigms of CHIC have been carefully investigated by UNITO in order to find similarities and differences with respect to prostate cancer and to share knowledge with the other researchers within CHIC. In SubTask 6.4.a, extensive *in silico* experimentation, analyses and explorations using the available nephroblastoma data were carried out by ICCS. Extensive discussions took place between ICCS and USAAR as well as preplanning regarding the use of micro-RNA data. In SubTask 6.4.b, a mechanistic model of the response of GBM to immunotherapy treatment is under development by ICCS in close interaction with KUL. In SubTask 6.4.c, advanced numerical checking and exploration of an ICCS-developed model of non-small cell lung cancer response to treatment has been carried out. FORTH is developing a metabolic model focusing on lung cancer to contribute to the lung cancer hypermodel. Lung cancer response to gemcitabine and cisplatin has been modelled by UNITO by the two-population model described in Task 6.2. All modelling partners of WP6 are performing adaptations to their lung cancer component models in order to construct the lung cancer hypermodel of Task 6.1

In Task 6.5, UOXF is developing discrete and continuum models of vascular tumour growth. Detailed testing and comparison of the models is underway. In addition validation of the models is on-going. Modifications to the UOXF code 'Chaste' which includes already existing colorectal cancer and angiogenesis models are also underway to allow the use of XML type input data. There is interaction of ICCS with UOXF in order to ensure compatibility of the colon cancer model development with the CHIC framework.

In Task 6.6, UNITO's data collection from the Urological and Radiotherapy departments in Regione Piemonte is almost completed and 3538 complete follow-up pertaining to prostatectomized patients are available for model validation. Concerning the radiotherapy cohort, around 3500 cases with complete follow-up will be available. There is interaction between ICCS and UNITO in order to ensure compatibility of the colon cancer model development with the CHIC framework.

### **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 super cellular 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 (ICCS, UPENN, FORTH, UOXF, UBERN, UNITO). The architecture of this hypermodel was developed by ICCS which also coordinates its implementation. See also the following tasks for the description of WP6 partners' component models.

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

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 it possible their linking and re-writing in the context of hypermodelling. Previous work underlines the dependence of the cancer growth on the age of the tumour, the different clones that compose the tumour mass, the percentage of each clone with respect to the total cancer mass and the mutation rate between clones.

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.
- A hybrid discrete-continuous tumour growth model describing cells as discrete variables and the tumour microenvironment as continuous variable. The model is appropriate for studying the emergence, selection and evolution of tumour clones that interact with each other and their microenvironment. In general, these approaches are computationally demanding and thus mainly applied to small systems.
- 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 1<sup>st</sup> and the 2<sup>nd</sup> WP6 Cancer Modeller's Meetings that took place at Oxford and Heraklion, respectively, there was an additional need to implement a metabolic model focusing on lung cancer, in order to contribute to the lung cancer hypermodel. **FORTH** has taken up this additional task and the related work is in progress.

Suitable interactions between angiogenesis and vascular tumour component models are being developed at UOXF and ICCS tumour growth and response to treatment and UBERN biomechanics components have been identified. The vascular tumour component has spatial cell concentrations as inputs, which can be provided by the ICCS component and supplies a spatial vessel density. For the lung cancer clinical case the interaction between the UBERN mechanical component and UOXF vascular tumour is indirect. Pressures from the UBERN component influence cell proliferation direction in the ICCS model, which in turn influences vessel distribution in the UOXF model. More direct interactions between biomechanics and vascular tumour components for other cases are being discussed by UOXF and UBERN.

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

In the context of molecular modelling 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 has been presented at UPENN. These results shed molecular-level insight into the various mechanisms governing such transforming mutations at the level of kinase activity and are remarkably consistent with experimental observations. The current study on ALK with suitable validation is expected to 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.

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 modelling platform for predictively analysing the role played by the external cell environment on intracellular trafficking in mammalian cells.

Tumour markers with high specificity against prostate cancer which can be identified in tissues available after surgical resection and/or biopsy (e.g. TMPRSS2-ERG) have been investigated by UNITO. Collaboration with Fondazione Edo Tempia, Biella (TO), on genetic biomarkers could start in the next months. In prostate cancer at least two cells 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.

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.

A clear way of linking subcellular UPENN multiscale models with cellular and super cellular models has been established under the lead and guidance of ICCS.

### **Task 6.3, Biomechanics enhanced tumour modelling**

To ensure an automatic application of the biomechanical model within the CHIC project, a robust automatic tool must be provided to build the FE meshed from segmented images. A software tool previously developed has been adapted for the CHIC project by UBERN. The voxel based meshing tool provides the meshing functionalities requested for the project and has been tested on brain and lung images.

The coupling between the biomechanical simulation 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.

An initial workflow has been designed 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.

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.

### **Task 6.4, The clinical modelling paradigms of nephroblastoma, glioblastoma and lung cancer**

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 have taken place using the available nephroblastoma data by ICCS. Extensive discussions and preplanning regarding the use of micro-RNA data by the nephroblastoma hypermodel Oncosimulator were carried out.

#### ***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 KULeuven. Intensive interaction of ICCS with the involved multidisciplinary clinical team of KULeuven took pace.

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

Advanced numerical checking and exploration of an ICCS-developed model of non-small cell lung cancer response to treatment was carried out. This model serves as the basis component of the multi-modeller hypermodel developed in task 6.1. FORTH is developing a metabolic model focusing on lung cancer to contribute to the lung cancer hypermodel. Lung cancer response to gemcitabine and cisplatin has been modelled by UNITO by the two-population model described in Task 6.2. All

modelling partners of WP6 are performing adaptations to their lung cancer component models in order to construct the lung cancer hypermodel of Task 6.1

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

Discrete and continuum models of vascular tumour growth are under development at UOXF. Detailed testing and comparison of the models is underway. In addition, validation of the models is on-going based on the use of vascular tumour imaging data in mice with collaborators in the Dept. of Oncology, UOXF. Modifications were made to the UOXF code 'Chaste' which includes already existing colorectal cancer and angiogenesis models are also underway to allow the use of XML type input data. This will facilitate the integration of models developed in Chaste with the Hypermodelling framework.

Interaction took place between ICCS and UOXF in order to ensure compatibility of the colon cancer model development with the CHIC framework.

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

At UNITO, data collection from the Urological and Radiotherapy departments in Regione Piemonte is almost completed and 3538 complete follow-up pertaining to prostatectomized patients are available for model validation. Concerning the radiotherapy cohort, around 3500 cases with complete follow-up will be available. The development of the 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 insertion of a stochastic part in the models is under investigation. The UNITO model is based on the following hypotheses: a) after surgery, tumour regrows according to the gompertzian law, b) the parameters of the gompertzian function strictly depend on the age of the tumour, c) although the age of the tumour is unknown, patients can be divided into subgroups using Gleason Score and stage (pT) and eventually other clinical information, d) there are two types of cells in prostate cancer: one Androgen Dependent (prevailing) and one Androgen Independent. This difference becomes important during therapy, especially for hormone therapy. UNITO plans to create a different (hypo-) model for each subgroup of patients to simulate the regrowth of cancer and eventually the response to therapy, using a two population model.

Interaction took place between ICCS and UNITO in order to ensure compatibility of the colon cancer model development with the CHIC framework.

### **Summary of significant results**

Lung cancer multi-modeller hypermodel were delineated and are under implementation. The inputs, outputs and basic description of each hypomodel (component model) have been crystalized. Several component models are under development by all WP6 partners.

Extensive *in silico* experimentation, analyses and explorations were carried out using the available nephroblastoma data by ICCS. A mechanistic model of the response of GBM to immunotherapy treatment is under development. An ICCS-developed model of non-small cell lung cancer response to treatment is undergoing advanced numerical checking and exploration. An automatic meshing tool was finalized by UBERN. Multi-scale coupling between the biomechanical and cellular bio-model were integrated into a single package. The initial design of the workflow to integrate cellular infiltration at the macroscopic scale was developed. UNITO models (tumour growth with and without mutation, with and without treatment) have been successfully applied in different contexts. Discrete and continuum models of vascular tumour growth are under development by UOXF. Detailed testing and comparison of the models is underway. In addition validation of the models is on-going. Modifications were made to the UOXF code 'Chaste' which includes already existing colorectal cancer and angiogenesis models are also underway to allow the use of XML type input data. 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. A subcellular model for intracellular trafficking that is predictive (the first of its kind) is under development.

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

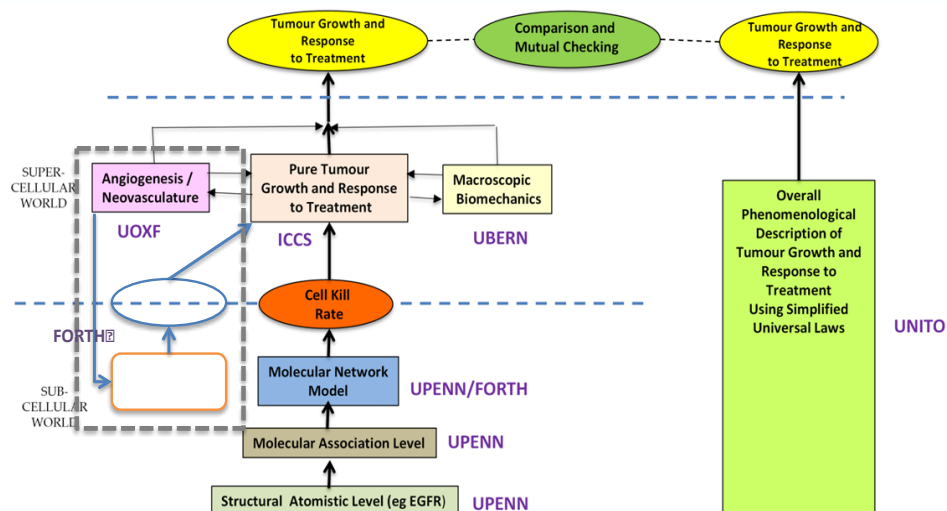
Additional work, not initially foreseen in the CHIC Technical Annex has been undertaken by **FORTH** in task 6.1. The extra work will be performed with FORTH resources and will not have any impact on other tasks and the overall planning. After the Modelers' meeting that took place at Oxford and Heraklion, ICCS proposed an outline of the master topology (fig. 1) of the lung cancer indicating the following additional needs:

- to implement a metabolic model focusing on Lung, in order to be part of the Lung cancer case hypermodel.
- to link the additional model with the angiogenic neovasculature hypomodel.
- to link the additional model with the pure tumor growth hypomodel.

FORTH has taken up these additional tasks (fig. 1 – gray box outline) and the related work is in progress. Hence, we need to reflect this additional workload in the DoW in order to be able to declare and claim the corresponding PM effort.



**Figure 1:** An outline of the current version of the master topology of the lung cancer multi-modeller hypermodel and its envisaged clinically adapted, validated and optimized version.



**CHIC WP6 MASTER TOPOLOGY OF THE LUNG CANCER  
MULTI-MODELLER HYPERMODEL**

17-18 June 2014

CHIC WP6 2nd HYPERMODELLING  
WORKSHOP HERAKLION, CRETE

3

### 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 WP6			
Partner	Planned PM Total	Planned PM Period 2 (total)	Actual PM M13-M18
1-ICCS	44.00	10.50	6.56
7-FORTH	9.00	7.50	5.00
9-UPENN	61.00	15.00	15.67
10-UOXF	46.00	15.16	5.77
11-UNITO	14.00	4.00	1.98
12-UBERN	20.00	8.00	1.90
14-Philips	1.00	0.00	0.00
<b>Total</b>	<b>195.00</b>	<b>60.16</b>	<b>36.88</b>

**FORTH:** Due to the revision of several tasks, FORTH needed to reallocate their personnel resources, which resulted in an increase of PM in several work packages. A complete list of the revised PM planning is provided in the management section of this report.

## 1.7 Work Package 7: Hypermodelling infrastructure

### Main objectives of this WP

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

### Active task in this reporting period:

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

### Summary of progress achieved towards objectives

All partners in WP7 contributed to deliverable D7.1, and participated in the discussion on the minimum metadata schema for model and data that should be required for the publication of a resource.

USFD deployed a small set of test models on the first installation of the hypermodelling execution environment. They have also undertaken an analysis of the refactoring of the generic stub that may be required due to changes in the hypermodelling execution environment. USFD also deployed the template wrapper on a local installation of the alpha version of the hypermodelling framework. They have implemented the hypomodels described in T7.1 on both the local hypermodelling execution environment, as well as the FORTH installation. USFD also developed and deployed a VPH-HF installer. Jointly with CINECA, they have carried out an analysis of the CHIC specific requirements for this execution environment and have developed a plan for the necessary implementation of the new version.

CINECA worked primarily on the VPH-HF release, testing with two preliminary hypermodels, and revising the architectural components to drive the future releases.

FORTH has driven the drafting of 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.



ICCS participated in most technical discussions, reviewed the metadata schema in relation to existing ones, and provided a model for testing purposes, including documentation. They also consolidated and finalised D7.1.

BED released the initial version of the tagging service; the underlying metadata schema will need to be finalised according to the decision from the consortium. Also more user tests are needed. They also released the first version of the Hot Maps service; they need to consolidate the system by introducing the mapping between biological process and genomes. Also, the system will have to run in batch and back-end processing mode to allow for large-scale knowledge collection.

UCL carried out the first implementation and testing of the HOT Maps knowledge management effort. In this initial collaboration with Bedfordshire and Saarland, they carried out the text mining of cancer literature for nephroblastoma as a means to link cancer mechanism knowledge to annotations of CHIC elementary process models. We have used gene name mentions in text as surrogate markers for Gene Ontology biological process terms that are mapped to Cancer Hallmark categories.

USAAR was not active in WP7 during this reporting period.

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

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

USFD have deployed 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 lung cancer “black-box” hypomodels designed to mimic the likely set of actual CHIC hypomodel and their interactions as defined by WP6. These were also installed on the hypermodelling execution platforms hosted by USFD, as well as FORTH and CINECA. USFD staff attended a WP6 workshop hosted by FORTH on defining the initial set of hypomodels for implementation in June 2014.

#### **Task 7.2, Metamodels annotation**

All partners active in WP7 participated in the discussion relating to the metadata schema for CHIC models and data. UCL carried out the first implementation and testing of the HOT Maps knowledge management effort. In this initial collaboration with BED, and in close collaboration with the clinical experts at USAAR and KUL, we carry out the text mining of cancer literature for nephroblastoma as a means to link cancer mechanism knowledge to annotations of CHIC elementary process models. We have used gene name mentions in text as surrogate markers for Gene Ontology biological process terms that are mapped to Cancer Hallmark categories. BED has released the initial interactive version of the HotMap services online. More work will need to be carried out along the direction of finding mappings between genomes and biological process. Also, we will convert the text mining from an interactive system as it is now, into a batch processing process, which will support large-scale knowledge collection within Pubmed from backend. BED also has completed the initial version and 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 has been developed. The work has used an initial metadata schema proposed by CINECA, which will be updated upon the finalisation of the schema.

#### **Task 7.3, Hypermodels execution**

All partners active in WP7 contributed to the definition of hypermodelling specifications which ICCS finalized 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 CHIC Review meeting. After this first deployment a revision of the VPH-HF components took place so to make sure that all the CHIC needs would be satisfied. 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, which will be implemented in the next VPH-HF releases. CINECA has also completed a first release of the VPH-HF components and of the client application HyperModelMonitor.

BED has started to look into the designing of the metadata component of VPH-HF, in which BED is the service provider and CINECA is the user. The designing of the component should include the metadata schema and a few other functionalities. We will define which functionalities this component should have, and then based on this we will define the APIs that will be exposed to the other modules. When this is done the design should also include two decisions: one on the format we will use to store the metadata in VPH-HF and one on the technology we will use to develop this component.

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 of WP10 developed by FORTH and therefore we are focusing our efforts on the specification of the interactions between the editor and the hypermodelling execution framework.

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

Task 7.5 a VPH-HF installer was developed for and successfully used on the platform specified by FORTH. Documentation of this version of the VPH-HF has been created. Jointly with CINECA, USFD undertook a detailed review of the existing framework in terms of the needs of the CHIC project and have accordingly come up with a detailed 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 and BED, USFD have agreed a plan for developing and implementing this architecture in line with the planned completion of *D7.2 - First Release Hypermodelling framework deployed on test nodes* at PM24. We are currently undertaking an analysis of the refactoring of the generic stub that is required by the architectural changes. CINECA installed into the FORTH infrastructure the first VPH-HF release. In order to make a relevant test, ICCS hypomodels were installed also on the machine. USFD provided a hypermodel composed of the ICCS hypomodels which was executed with the VPH-HF technology from the HyperModelMonitor interface. The platform was working as expected and the VPH-HF installation will be kept up to date with the new software releases. Based also on these preliminary tests, FORTH in collaboration with partners CINECA and USFD initiated the design of the final 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.

#### **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.

Task 7.3: Successful deployment and demonstration of first exemplar hypermodel.

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**

Due to the planned revision of the VPH-HF hypermodelling execution platform, refactoring of the generic stub is required. This refactoring is not anticipated to cause any significant issues with the development or deployment of the hypermodelling environment, particularly as it was always planned to revise the definition of the generic stub throughout the course of the project.

Hot Map is a new initiative, not originally planned, with great potential in CHIC. The idea emerged only during the running of the project. This involves a significant amount of effort in web and text mining and BED will need to commit additional resources into this, which will lead to the increase of the personnel months spent on WP7.

#### **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 WP7			
Partner	Planned PM Total	Planned PM Period 2 (total)	Actual PM M13-M18
1-ICCS	6.00	1.50	1.00
3-USAAR	4.00	1.00	n/a
5-BED	19.00	12.00	2.00
6-USFD	128.00	35.00	17.00
7-FORTH	6.00	2.50	1.00
15-UCL	24.00	7.00	0.60
16-CINECA	42.00	14.00	8.92
<b>Total</b>	<b>229.00</b>	<b>73.00</b>	

**BED:** Due to the revision of several tasks, BED needed to reallocate their personnel resources. A redistribution was performed and 7 PM were moved from WP5 to WP7. BED's original planned effort for the second period was 8 PM. A complete overview of BED's revised PM efforts is included in the management section of this report.

**FORTH:** Due to the revision of several tasks and human resources management, FORTH needed to reallocate their personnel resources, which resulted in an increase of PM in several work packages. A complete list of the revised PM planning is provided in the management section of this report.

## **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 8.2.c, Resource annotations
  - SubTask 8.2.d, Global metadata search engine

Work started early in the following task:

- Task 8.3, Integration with the security and the legal/ethical framework (M10-48)

#### Summary of progress achieved towards objective

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. Moreover, the design of the back-end of the model/tool repository has been completed. ICCS, FORTH and PHILIPS collaborated closely in order to define and design the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repository. In Subtask 8.1.b UBERN has completed the initial deployment of the clinical data repository on the CHIC cloud infrastructure. Additionally, the first version of the REST services of the aforementioned repository has been extended with more functionality. A first version of the external timeline tool developed by BED has been integrated into the clinical data repository interface. In SubTask 8.1.c ICCS finalized the information model to be used in *in silico* trial repository and the technologies to be used in its development. ICCS also designed the back-end of the *in silico* trial repository. In Task 8.2 USAAR participated in the iterative process to optimize the semantic metadata management. In Subtask 8.2.a ICCS tested 3 distinct solutions for the distributed RDF repository. In Subtask 8.2.b ICCS studied the possible enrichment of the reasoning part of the knowledge base with additional rule-based reasoners. In Subtask 8.2.d ICCS studied existing federated SPARQL query engines (approaches and implementations) and tested some of them. In Task 8.3, ICCS continued to collaborate closely 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). CUSTODIX has collaborated with UBERN for the integration of CHIC clinical data repository with the first version of the CHIC data protection framework.

#### Summary of details for each task

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

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

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. The technologies to be used in the development of the model/tool repository have been selected.

The design of the back-end of the model/tool repository has been completed and its specifications will be included in the corresponding sections of the deliverable “D8.1: Design of the CHIC repositories”.

ICCS, FORTH and PHILIPS collaborated closely in order to define and design the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repository (advanced phase). This was a joint effort between WP8 and WP10.

#### ***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.

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

ICCS finalized the information model to be used for the *in silico* trial repository, according to the requirement analysis performed the first year of the project. The technologies to be used in the development of the *in silico* trial repository have been selected.

The design of the back-end of the *in silico* trial repository has been completed and its specifications will be included in the corresponding sections of the deliverable “D8.1: Design of the CHIC repositories”.

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

USAAR participated in the iterative process to optimize the semantic metadata management. Discussion with p-medicine project is continued in order to collaborate in the area of semantic interoperability. The ‘HOT Maps’ efforts continued and are 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.

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

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

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

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**

ICCS continued to collaborate closely 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).

CUSTODIX and UBERN are collaborating closely for the integration of CHIC clinical data repository with the first version of the CHIC data protection framework.

### **Summary of significant results**

The information model and the technologies for the model/tool repository and the *in silico* trial repository are finalized. The partners designed the back-end of the model/tool repository and the *in silico* trial repository. Advanced phase of the definition of the interoperable interfaces for retrieving

model and hypermodel descriptions from the model/tool repository. Three different solutions were tested for the distributed RDF repository. Second phase of the integration of the single-sign-on security mechanism into the model/tool and the *in silico* trial repositories. Initial integration of the clinical data repository with the CHIC cloud infrastructure was completed. Initial integration of external timeline tool developed by BED into the data repository interface was carried out. REST services of the clinical data repository were extended with more functionality. A review of the way in which the p-medicine project is dealing with semantic interoperability is underway. 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 submission of the deliverable "D8.1: Design of the CHIC repositories" has been originally postponed due to unforeseen workload at the partner in charge. After the CHIC review meeting (3 Sep 2014) and the very valuable comments that we have received from the reviewers concerning the data representation (both clinical data and models) the consortium decided to wait for the official review report in order to understand more precisely their suggestions. In the meantime there was a draft version of the deliverable circulated among the involved partners, and therefore the postponement has not caused any delays on other tasks as described in the DoW.

The reviewers' suggestions were incorporated into the deliverable. The final outcome of this procedure was finalized during the progress and technical meetings of 15-17 October 2014 in Leuven. The decisions taken in the aforementioned meetings were incorporated into this deliverable as well. The deliverable "D8.1: Design of the CHIC repositories" was submitted at the end of November. The PO was informed about this delay.

### **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 (total)	Actual PM M13-M18
1-ICCS	14.00	3.50	2.10
3-USAAR	3.00	1.00	n/a
7-FORTH	6.00	1.50	1.00
9-UPENN	3.00	0.00	0.00
12-UBERN	15.00	6.00	3.50
13-Custodix	3.00	1.00	0.54
14-Philips	7.00	2.00	0.00
15-UCL	48.00	15.00	0.60
<b>Total</b>	<b>99.00</b>	<b>30.00</b>	

## **1.9 Work Package 9: Image Processing and Visualization**

### **Main objectives of this WP**

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

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

#### Active tasks in this reporting period:

- Task 9.2, Scalable visualization techniques (M3-18)
- Task 9.3, Uncertainty data visualization (M9-24)
- Task 9.5, A general image processing development toolkit (M6-18)
- Task 9.6, Image registration tools (M3-36)
- Task 9.7, Multimodal and longitudinal brain tumor image analysis (M9-46)
- Task 9.8, A software platform for the Assessment of Tumor Treatment Response (M8-42)

Work started early in the following task:

- Task 9.4, Visualization toolkit for the model/data repository (M13-46)

#### Summary of progress achieved towards objectives

Overall this WP is making good progress towards the objectives. There are numerous outputs from many partners. Interactions with other WPs are also taking place, with some of the visualization components integrated into WP8 data repository. BED has been focusing on the work of scalable (timeline) and uncertainty (3D volume) visualization, and nephroblastoma image segmentation. FORTH has taken up the additional task to integrate most of the technologies into the DrEye platform, towards the objective of providing a general image processing development toolkit (relative to Task 9.5). In addition, the initial work in Task 9.8, led by FORTH, regarding several biomarkers that will be tested as model input parameters has shown promising results and will be published in the next few months. At UBern, the I/O for Doctor eye plug-in architecture is being studied through tutorials prepared by the developers. A first complete registration pipeline has been developed and testing on medical images performed. Also, feature extraction and learning approaches using supervised approaches have been implemented; initial tests performed. At ICCS, discussions concerning the expectations primarily of WP6 (basic science) from WP9 regarding both image processing and visualization tools and services. USAAR has modelled the model/data repository regarding its usability. Most of the partners in WP9 have significantly contributed to the evaluation activities in the project.

#### Summary of details for each task

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

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

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

BED developed a 3D volume rendering software CCGVIS, which will visualise the uncertainty of tumour growth from the cancer modelling.

##### **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. At USAAR the model/data repository was evaluated regarding usability and feedback given.

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

After the unanimous decision of the consortium, FORTH has taken up 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 the DrEye 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. BED has been working on a super-pixel approach for nephroblastoma 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.

**Task 9.6, Image registration tools**

A first complete registration pipeline has been developed and testing on medical images performed at UBERN. The main components of the monomodal and multimodal registration metric for monomodal and multimodal image registration have been initially implemented. Registration metric using point-wise mutual information, image resampling, optimization routines was implemented. First testing on medical images has been conducted.

**Task 9.7, Multimodal and longitudinal brain tumor image analysis**

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

**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). 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.

**Summary of significant results**

At BED, both the timeline and CCGVIS have been internally tested by some of the partners. FORTH has taken up the additional task to integrate most of the technologies into the DrEye platform. Initial work in Task 9.5 has shown promising results and will be published in the next few months. At UBERN, the first full implementation of monomodal and multimodal registration routines using point-wise mutual information metric was undertaken. UBERN implemented the identification of building components necessary to integrate registration and multimodal brain tumor segmentation, and feature extraction and supervised learning using random forests for brain tumor segmentation.

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

FORTH has taken up 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 (total)	Actual PM M13-M18
1-ICCS	3.00	0.80	0.45
3-USAAR	15.00	5.00	n/a
5-BED	36.00	10.50	10.00
7-FORTH	20.00	8.50	8.00
12-UBERN	12.00	3.00	3.30
17-TEI-C	1.00	1.00	1.00
<b>Total</b>	<b>87.00</b>	<b>28.80</b>	

**FORTH:** Due to the revision of several tasks, FORTH needed to reallocate their personnel resources, which resulted in an increase of PM in several work packages. A complete list of the revised PM planning is provided in the management section of this report.

## **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)

Other active tasks in this reporting period:

- 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

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.

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.

### **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. Details are provided in the subchapter on deviations from Annex I.

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

PHILIPS collaborated with partners ICCS and FORTH in order to define the interoperable interfaces for retrieving model and hypermodel descriptions from the model/tool repository (advanced phase).

#### **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 has analysed the double encryption scheme in place in PhysiomeSpace and a clear plan for update and integration with the CHIC platform in conjunction with CUSTODIX work in WP5 has been defined so as to achieve MS25.

#### **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.

### **Summary of significant results**

- Task 10.2: Definition of the programmatic interfaces for accessing the model repositories.
- Task 10.3: Implementation of the CHIC Data Upload tool for the secure uploading of sensitive patient data to the CHIC platform. Analysis of the current PhysiomeSpace encryption services.
- Task 10.4: Initial design of the CHIC Hypermodelling Editor

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

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. Additional person month efforts will be necessary. This task was initially planned to finish on M8, providing the fully functioning CHIC portal. Task 10.1 is an integration activity which collectively depends on the input of all technical WPs, as well as the end user requirements from the non-technical WPs. By M8, on which this task was initially planned to finish, almost no deliverables and no technical implementation had been scheduled to be ready and delivered from any WP. The majority of the necessary input from other WPs was planned and started to be delivered after M8. FORTH did the best it could be feasible

with the available input by M8 and continues supporting this task till today, despite the fact that this task has finished. FORTH is willing to provide this extra effort within the already available budget; however, in order to continue supporting this task and provide the CHIC portal, we need to make appropriate amendment to the DoW and extend this task until the end of the project.

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

Not applicable.

**Corrective actions**

Task T10.1 was initially planned to finish in M8 and FORTH, who leads this task, continues supporting this task with own resources. Due to the integration activities performed on this task and the fact that the necessary input from the rest of the technical work packages will be available much later during the implementation course of the project, the CHIC consortium has agreed to extend this task until 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 need to increase its person months in Task 10.1 in order to integrate, maintain and potentially extend the CHIC Portal in line with the evolving project requirements. This change will neither affect the deliverables described in the DoW nor the already allocated budget. A revised list of PM efforts is provided in the management section of this report.

**Statement on the use of the resources**

Planned versus actual efforts in WP10			
Partner	Planned PM Total	Planned PM Period 2 (total)	Actual PM M13-M18
1-ICCS	7.00	1.80	1.10
3-USAAR	7.00	2.00	n/a
7-FORTH	21.00	8.00	9.00
12-UBERN	3.00	1.00	0.10
14-Philips	18.00	2.50	0.14
16-CINECA	8.00	3.50	1.25
<b>Total</b>	<b>64.00</b>	<b>18.80</b>	

**FORTH:** continuous integration work has to be performed at the CHIC Portal, a task which, according to the CHIC DoW has already ended in M08. Therefore, additional PM had to be allocated to WP10. FORTH revised their PM effort table to accommodate the necessary adaptation of task durations. The revised PM effort table is available in the management section of this report.

## **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:

- Task 11.2, Coordinate evaluation activities by partners (M6-18)

Work started early in the following task:

- Task 11.3, Clinical adaptation of the CHIC infrastructure as a whole (M12-48)

#### Summary of progress achieved towards objectives

Together with all partners of WP11, USAAR continued to consolidate evaluation and validation criteria for enhancing the clinical adaptation of hypermodels. Evaluation and validation criteria from other EU projects (p-medicine and EURECA) were taken into consideration by preparing evaluation sheets for the first evaluation workshop round which was prepared with the help of all CHIC partners and which took place during the CHIC progress meeting in Leuven from 15-17 October 2014. The workshop was successfully concluded. Evaluation sheets of the participants were analyzed and were reported D11.2 (Report on the first evaluation workshop round) by USAAR. ICCS contributed to the coordination of the evaluation activities during the whole reported period and subsequently on several physical meeting occasions as well as through electronic correspondence. Initial discussions 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. Hypermodels 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. All partners of WP11 were involved in this activity. UPENN in addition is developing a

comprehensive double-blind validation strategy to validate the predictions of molecular models on the activation status of a given clinical mutation in genes relevant to targeted therapy.

### **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) is started and nearly finalized under the responsibility of USAAR. The first evaluation workshop was successfully held as described above. Results will be reported in D11.2. All partners, specifically ICCS, USAAR, BED and FORTH did participate in the organization of the first round of evaluation tests of CHIC components, which took place in the 3rd Process meeting in Leuven. FORTH provided cloud resources and technical support in order to set up an online and remotely accessible test bed, 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.

The CHIC Upload Tool has been provided with the corresponding end user guide for the evaluation workshop in preparation for Deliverable 11.2. End user guides for DrEye, BraTumIA, CCGVis and the Timeline and clinical data repository were provided as well by FORTH, BED and UBERN.

All partners took part in the evaluation of the following tools: DrEye, BraTumIA, CCGVis, Timeline and clinical data repository, Upload Tool.

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

Initial 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.

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.

UPENN has devised a double-blind validation protocol for assessing the accuracy of their predictive algorithm by computing ROC (receiver operating characteristic) curve. The prediction of the activation status is based on the results of text mining, evolutionary analysis of the protein sequence, and based on specific interactions (hydrogen bonds etc.) in the dynamics simulations. The double-blind comparison validates these predictions with in vitro and cellular assays of kinase activation in different mutants.

### **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 was successful.

Results of the first evaluation workshop will be provided in D11.2

UPENN presents a computational modelling and simulation approach to delineate molecular-level mechanisms of activation of protein receptor tyrosine kinases and describes clinical implications of mutations in the Anaplastic Lymphoma Kinase (ALK) receptor tyrosine kinase in paediatric neuroblastoma. They show here that their results shed molecular-level insight into the various mechanisms governing such transforming mutations at the level of kinase activity and are remarkably consistent with experimental observations. In particular, their computational predictions matched experimental measures of kinase activity with over 85% accuracy in the mutations investigated from neuroblastoma patients.

### 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 (total)	Actual PM M13-M18
1-ICCS	7.00	1.50	0.90
3-USAAR	25.00	7.00	n/a
5-BED	8.00	2.00	0.00
7-FORTH	3.00	0.50	0.21
9-UPENN	5.00	1.00	0.17
11-UNITO	20.00	6.00	2.98
12-UBERN	3.00	1.00	0.00
13-PHILIPS	3.00	0.00	0.00
<b>Total</b>	<b>74.00</b>	<b>19.00</b>	

## 1.12 Work Package 12: Dissemination and Exploitation

### Main objectives of this WP

The objectives of this work package are the following:

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

### Active task in this reporting period:

- Task 12.1, Dissemination activities (M1-48)
  - SubTask 12.1.a, Strategic Dissemination Planning
  - SubTask 12.1.b, Web presence
  - SubTask 12.1.c, Newsletter
  - SubTask 12.1.d, Dissemination kit
  - SubTask 12.1.e, Conferences, Exhibitions, Workshops
  - SubTask 12.1.f, Scientific and Technical Papers Publications
  - SubTask 12.1.g, Interfacing with other projects

- Task 12.2, Exploitation and IPR issues (M1-48)
- Task 12.3, Training activities

### **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. 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. 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.

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.

### **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. Eurice are currently enhancing the website with a feature for the clinicians to access demo versions of the CHIC tools to try out and evaluate.



In association to the activities of Task 12.3, ICCS prepared the 6th 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/>). ICCS was a major contributor of the annual 2014 CHIC newsletter; ICCS 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 M13-18 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.
- Presentation of the CHIC project in the 7<sup>th</sup> World Congress on Biomechanics, Boston US, 6-11 July 2014 (invited talk).
- 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).
- USAAR: active participation 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.
- 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.
- For this reporting period, UPENN listed a total of 8 dissemination activities of CHIC supported research, among them invited lectures/talks, conference presentations and activities directed at media publicity.

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 submitted for peer-reviewed journal publication the following manuscript:

1. Georgios Stamatakis and Stavroula Giatili, "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", submitted to the journal Bulletin of Mathematical Biology.

Five articles, to which ICCS and various other CHIC partners contributed, were submitted for peer-reviewing to the 6<sup>th</sup> IARWISOCI- The CHIC Project Workshop, 3-4 Nov, Athens, Greece. These articles are listed in the table on dissemination activities and publications in this report.

Eleven other papers, including those by partners FORTH, UNITO and UPENN were published in scientific journals and conference proceedings. A detailed overview of these 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.
- CINECA had interactions with the VPH-Share project on some architectural components of the hypermodelling framework.

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

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: Discussion with p-medicine continued 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.
- ICCS has initiated a discussion among a number of CHIC partners, including CINECA, PHILIPS, USAAR, KUL, USFD, regarding the multi-directional exploitation of the expected project outcome. This includes clinical, industrial, research, academic teaching, and legal/legislation exploitation channels.
- 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, NTUA, by the CHIC coordinator G.Stamatakis. 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 exploitative activities undertaken within the reporting period include several public lectures delivered by Prof N. Forgó, which are listed in the table on workshops and conferences further below in this report.

#### **Task 12.3: Training activities**

ICCS undertook the organization of the 6<sup>th</sup> 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 will be informed about the achievements of the CHIC project and the latest achievements of *in silico* oncology and its extension to *in silico* medicine.

First steps were made regarding the organization of the first CHIC Summer School, which is to take place in September 2015. The current location of choice is the Leibniz Center for Informatics at Schloss Dagstuhl in Wadern, Germany, where the p-medicine Summer School was also held in 2013. A formal request written by Eurice and USAAR was sent to Schloss Dagstuhl for evaluation.

### **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.

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 has started and exploitation activities have also started with preparatory work from different partners.

Training activities, part of the WP, have also started.

### **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. 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. 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 newsletter and focus on the more crucial technical deliverables. As stated above, the delay does not have any impact on WP12.

### **Corrective actions**

Not applicable.

### **Statement on the use of the resources**

<b>Planned versus actual efforts in WP12</b>			
<b>Partner</b>	<b>Planned PM Total</b>	<b>Planned PM Period 2 (total)</b>	<b>Actual PM M13-M18</b>
1-ICCS	8.00	2.80	2.21
2-Eurice	12.00	3.00	1.85
3-USAAR	3.00	1.00	n/a
5-BED	6.00	2.00	0.00
6-USFD	6.00	2.00	0.80
7-FORTH	6.00	1.00	1.00
8-LUH	6.00	1.00	0.21
9-UPENN	6.00	1.50	0.17
10-UOXF	6.00	2.00	0.00
11-UNITO	6.00	1.00	0.49
12-UBERN	5.00	1.00	0.00
13-Custodix	6.00	1.50	0.15

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14-Philips	6.00	0.50	0.16
15-UCL	2.00	0.50	0.00
16-CINECA	6.00	1.00	0.56
17-TEI-C	1.00	0.00	0.00
<b>Total</b>	<b>91.00</b>	<b>21.80</b>	

## 2. 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-M18:

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).

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** of CHIC will be held in Turin on 26-28 March 2015. The meeting will last for two days and will be accompanied by a special database workshop also organized by CHIC partner UNITO.

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 Coordinator and 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.

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

No serious problems have occurred during M13-18.

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. Of the CHIC consortium, partners BED and FORTH 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.

#### **Changes in the consortium**

None.

#### **List of project meetings, dates and venues during M13-M18**

<b>Title</b>	<b>Date</b>	<b>Venue</b>	<b>Local organizer</b>
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

\*) these meetings took place outside the reporting period.

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.

#### Change of person months:

Due to the revision of several tasks, partners BED and FORTH needed to revise their person months 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 project management team asked BED and FORTH to prepare a revised PM effort table for the 4 project periods.



Partner 5 BED	Planned					Revised				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP1 Project Management					0,00					0,00
WP2 User Needs and Requirements					0,00					0,00
WP3 Clinical and Fundamental Science Scenarios					0,00					0,00
WP4 Legal and Ethical Framework					0,00					0,00
WP5 IT Architecture	5,00	10,00	4,00	0,00	19,00	5,00	5,00	0,00	0,00	10,00
WP6 Models and Hypermodel Design					0,00					0,00
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
WP8 Model and Data Repositories					0,00					0,00
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
WP10 Integrated Platform					0,00					0,00
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
<b>Total</b>	<b>14,00</b>	<b>32,50</b>	<b>26,50</b>	<b>15,00</b>	<b>88,00</b>	<b>14,00</b>	<b>31,50</b>	<b>27,50</b>	<b>15,00</b>	<b>88,00</b>

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
<b>Total</b>	<b>21,50</b>	<b>22,50</b>	<b>24,00</b>	<b>18,00</b>	<b>86,00</b>	<b>60,79</b>	<b>41,00</b>	<b>36,50</b>	<b>25,50</b>	<b>163,79</b>

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.

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.

### **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. If a delay was expected, the consortium partners informed the coordinator as well as the project management partner Eurice who then immediately informed the

EC project officer about the delay and the reasons for the delay. However, the delayed deliverables did not have any significant impact on the overall progress in CHIC, so no contingency measures had to be put in place.

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

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. 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 have also decided to enable access to some of the CHIC tools via the 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. As the project continues over the next 2.5 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 M13-18
1-ICCS	8.00	2.00	1.00
2-Eurice	38.00	9.50	5.15
6-USFD	4.00	1.80	2.32
7-FORTH	2.00	0.50	0.21
10-UOXF	2.00	0.30	0.30
16-CINECA	1.00	0.20	0.10
<b>Total</b>	<b>55.00</b>	<b>14.30</b>	<b>9.08</b>

## 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
Towards the mathematical principles of the natural philosophy of living matter: In Silico Oncology/ In Silico Medicine	Workshop	ICCS	6 <sup>th</sup> IARWISOCI –The CHIC Project Workshop*)	Athens, Greece	3-4 November 2014
Computational Horizons in Cancer: Developing Meta- and Hyper-Multiscale Models and Repositories for In-Silico Oncology – A Brief Technical Outline of the project	Workshop	ICCS, USAAR, KULeuven, BED, USFD, FORTH, LUH, UPENN, UOXF, UNITO, UBERN, Custodix, PHILIPS, UCL, CINECA, TEI-C	6 <sup>th</sup> IARWISOCI –The CHIC Project Workshop*)	Athens, Greece	3-4 November 2014
A Modular Semantic Infrastructure Layout for the Management of Hypermodel-Pertinent Metadata in the Context of In Silico Oncology	Workshop	ICCS	6 <sup>th</sup> IARWISOCI –The CHIC Project Workshop*)	Athens, Greece	3-4 November 2014
Modelling Glioblastoma Growth and Inhomogeneous Tumour Invasion with Explicitly Numerically Treated Neumann Boundary Conditions	Workshop	ICCS	6 <sup>th</sup> IARWISOCI –The CHIC Project Workshop*)	Athens, Greece	3-4 November 2014
A Brownian Motion Based Mathematical Analysis as a Potential Basis for Modelling the Extent of Infiltration of Glioma Cells into the Surrounding Normal Brain Tissue	Workshop	ICCS	6 <sup>th</sup> IARWISOCI –The CHIC Project Workshop*)	Athens, Greece	3-4 November 2014
Legal and ethical aspects of in silico based medicine	Workshop	LUH	6 <sup>th</sup> IARWISOCI –The CHIC Project Workshop*)	Athens, Greece	3-4 November 2014

Title	Type	Main leader/Participants	Event	Venue	Date
IPR issues in multiscale modelling	Workshop	LUH	6 <sup>th</sup> IARWISOCI –The CHIC Project Workshop*)	Athens, Greece	3-4 November 2014
Keynote lecture on Data Protection Reform	Conference	LUH	Leopoldina Symposium „Keimbahnmutationen bei krebskranken Kindern“	Freiburg, Germany	26 September 2014
The Importance of Data Sharing and Data Protection'	Conference	LUH	SIOPE-ENCCA conference 2014	Brussels, Belgium	18 September 2014
Multiscale modelling of cancer (workshop session)	Conference	ICCS	VPH2014	Trondheim, Norway	11 September 2014
In silico Neuro-Oncology: Simulating glioma growth and inhomogeneous invasion under explicitly treated Neumann boundary conditions	Conference	ICCS	VPH2014	Trondheim, Norway	11 September 2014
A Generalized Model of Tumor Growth and Response to Treatment using the PUN approach (poster)	Conference	UNITO	VPH2014	Trondheim, Norway	11 September 2014
The VPH Hypermodelling Framework for cancer research	Conference	USFD, CINECA	VPH2014	Trondheim, Norway	11 September 2014
A Two-Clones Model of Tumor Growth and its Response to Treatment	Conference	UNITO	MPDS14 Conference	Turin, Italy	29 August 2014
Nomination to Best Msc thesis work – Automatic Multimodal Brain Tumor Segmentation	Conference	UBERN	SSBE 2014 Annual Meeting	Zurich, Switzerland	27-28 August 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 August 2014

Title	Type	Main leader/Participants	Event	Venue	Date
Patient-specific Semi-supervised Learning for Postoperative Brain Tumor Segmentation	Summer School	UBERN	Medical Imaging Summer School (MISS) 2014	Favignana, Italy	28 July - 01 August 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 July 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 July 2014
Computational Challenges in Multiscale Modelling	Conference (Podium discussion)	USFD	7th World Congress of Biomechanics	Boston, MA, USA	6-11 July 2014
ApiNATOMY: The Generation of Interactive CircuitBoard Views of Complex Physiology Knowledge	Conference	UCL	4 <sup>th</sup> International Conference on Complex Systems and Applications (ICCSA 2014)	Le Havre, France	23-26 June 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 June 2014
Piedmont multicenter retrospective study on operated prostate cancer: first report	Congress/Conference	UNITO	24 <sup>th</sup> Annual Meeting of the Italian Society of Uro-Oncology (SIUro)	Bologna, Italy	22-24 June 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 June 2014
IT Challenges for innovative Clinical Trials	Workshop	USAAR	IT workshop on tools/services for clinical trials	Düsseldorf, Germany	26-27 May 2014

Title	Type	Main leader/Participants	Event	Venue	Date
Participation in Training School	Workshop	UNITO	ESTRO School of Radiotherapy and Oncology: Basic Clinical Radiobiology	Istanbul, Turkey	25-29 May 2014
Data Protection reform	Invited Lecture	LUH	Datenschutzforum	Berlin, Germany	15 May 2014
Computational medicine: Current and Future prospects	Conference	FORTH	eHealth Forum 2014	Athens, Greece	12-14 May 2014
Participation in training event	Workshop	CINECA, USFD	VPHHF development training	Bologna, Italy	11-16 May 2014
Presentation of the CHIC project on a special leaflet	Showcase event	USFD	Insigneo Institute first anniversary showcase event <sup>1</sup>	Sheffield, UK	08 May 2014
Poster presentation of CHIC	Showcase event	USFD	Insigneo Institute first anniversary showcase event	Sheffield, UK	08 May 2014
Presentation of the CHIC project	Workshop	USFD	Collaborations Workshop 2014 (CW14) - software in your reproducible research	Oxford, UK	26 April 2014
Data protection issues in ehealth projects	Conference	LUH	EHR4CR First European Hospital Conference	Brussels, Belgium	9 April 2014

\*) These events took place outside the reporting period.

### Press activities and other media

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

<sup>1</sup> 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.

Title	Type	Main leader	Reference	Date
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 Multiscale Modeling Consortium of the Inter Agency Modeling Group	Video	UPENN	<a href="https://www.youtube.com/watch?v=ttNG86de3ps">https://www.youtube.com/watch?v=ttNG86de3ps</a>	2014
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



## Publications

Title	Contact person	Involved Institutions	Reference	Category	Publication date	Co-Authors	Status
Integrative functional assessment of ALK mutations for therapeutic stratification in neuroblastoma	Ravi Radhakrishnan	UPENN	Cancer Cell	Peer-reviewed publication	n.d.	Weiser D, Bressler S, Huwe PJ, Lemmon MA, Mosse Y	Submitted
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
Computational Horizons in Cancer: Developing Meta- and Hyper-Multiscale Models and Repositories for In-Silico Oncology – A Brief Technical Outline of the project	Georgios Stamatakis	ICCS	IEEE Proceedings of the 6 <sup>th</sup> International Advanced Research Workshop on In-Silico Oncology and Cancer Investigations	Conference proceedings	n.d.	Dionysiou D, Misichroni F, Graf N, Van Gool S, Bohle R, Dong F, Viceconti M, Marias K, Sakkalis V, Forgo N, Radhakrishnan R, Byrne H, Guiot C, Buechler P, Neri E, Bucur A, de Bono B, Testi D, Tsiknakis M	In press

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	Conference proceedings	n.d.	Radhakrishnan R.	In press
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 multicenter 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, Porpogia F, Muto G, Guiot C	Published
Mesoscale computational methods for membrane bilayer remodeling by curvature inducing proteins	Ravi Radhakrishnan	UPENN	Physics Reports 543 DOI: 10.1016/j.physrep.2014.05.001	Peer-reviewed publication	2014	Ramakrishnan N, Sunil Kumar PB	
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
Exploring the competition between proliferative and invasive cancer phenotypes in a continuous spatial model	Kostas Marias	FORTH	PLoS One 8 (8)	Peer-reviewed publication	8 August 2014	Tzamali E, Grekas G, Sakkalis V	Published (Open Access)
High-throughput mutagenesis reveals functional determinants for DNA targeting by Activation-Induced Cytidine Deaminase	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)

Computational Delineation of Tyrosyl-Substrate Recognition and Catalytic Landscapes in the Epidermal Growth Factor Receptor Tyrosine Kinase Domain	Ravi Radhakrishnan	UPENN	Molecular Biosystems, DOI: 10.1039/C3MB70620F	Peer-reviewed publication	July 2014	Liu Y	Published
Enabling multiscale modeling in systems medicine	Georgios Stamatakis	ICCS, UOXF	Genome Medicine 6: 21	Peer-reviewed publication	2014	Volkenhauer 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 modelling with information technology in the in silico oncology context	Georgios Stamatakis	ICCS, TEI-C, FORTH, USAAR	IEEE J. Biomed Health Inform. doi: 10.1109/JBHI.2013.2284276	Peer-reviewed publication	May 2014	Dionysiou D, Lunzer A, Belleman R, Kolokotroni E, Georgiadi E, Erdt M, Pukacki J, Rüping S, Giatili S, Donofrio A, Sfakianakis S, Marias K, Desmedt C, Tsiknakis M, Graf N	Published

### 3. Deliverables and milestones tables

#### 3.1 Deliverables

The deliverables due in this reporting period are highlighted in light blue.

No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due delivery date from Annex I	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	<p>FORTH, the partner leading this deliverable, informed the coordinator that a one-month extension would be necessary, a request to which the coordinator agreed and which was passed on to the EC project officer.</p> <p>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.</p>
D2.2	Scenario based user needs and requirements	2	3-USAAR	R	PU	30.11.2013	Yes	13.01.2014	Due to the missing contributions of a crucial partner, the deliverable was delayed.
D2.3	Requirements for enhancing hypermodels beyond the domain of cancer	2	14-PHILIPS	R	CO	30.09.2014	Yes	02.12.2014	<p>An extension of the original deadline (M18) was requested because the partners responsible for the deliverable agreed to go beyond the mentioned atomic/granular models, thereby showing common ways in reusing models in other domains. Therefore, further information from</p>

No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due delivery date from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
									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 legal requirements for	4	8-LUH	R	PU	31.12.2013	Yes	06.01.2014	

No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due delivery date from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
	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	
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. The final version of D5.1.1 was submitted to the EC on 13 June 2014.
D5.1.2	The final CHIC technical architecture (including the security tools	5	7-FORTH	R	RE	30.09.2016	No		

No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due delivery date from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
	and cloud infrastructure)								
D5.2	Security guidelines and initial version of security tools	5	13-CUSTODIX	R	CO	30.09.2014	Yes	01.10.2014	
D5.3	Techniques to build the cloud infrastructure available to the community	5	5-BED	R	PU	31.03.2015	No		
D6.1	Cancer hypomodelling and hypermodelling strategies and initial component models	6	1-ICCS	R	CO	30.09.2013	Yes	22.10.2013	D6.1 is a very extensive report and is expected to serve as the initial scientific basis for the entire project. The coordinator firmly believes that the quality, the extent and the depth of the document will have an important impact on most of the subsequent CHIC work and deliverables. Therefore, D6.1 should be of the highest quality possible and an extension of the deadline for submission proved to be necessary.
D6.2	CHIC cancer component models: initial tested versions	6	1-ICCS	R	CO	30.11.2014	No	22 December 2014	This deliverable was postponed by about 3 weeks due to its complex and multidisciplinary nature. 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 and	6	1-ICCS	R	CO	31.01.2017	No		



No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due delivery date from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
	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	No		
D7.3	Hypermodels annotation services	7	15-UCL	P	RE	31.03.2016	No		
D7.4	Final Hypermodelling framework deployed on test node	7	16-CINECA	O	RE	31.08.2016	No		
D8.1	Design of the CHIC repositories	8	1-ICCS	R	CO	31.07.2014	Yes	20.11.2014	The submission of deliverable 'D8.1: Design of the CHIC repositories' 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 representation (both

No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due delivery date from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
									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	No		
D8.3	Implementation of the interfaces of the CHIC repositories	8	15-UCL	R	PU	30.09.2015	No		
D8.4	Report on the final system	8	1-ICCS	R	PU	30.09.2016	No		
D9.1	User requirements for the visualization toolkit and image analysis toolkits	9	5-BED	R	PU	30.09.2013	Yes	01.10.2013	
D9.2	A model and data visualization toolkit	9	5-BED	P	RE	31.01.2017	No		
D9.3	A multimodal and longitudinal brain tumor image analysis tool	9	12-UBERN	P	RE	31.01.2017	No		
D9.4	The tumor response	9	7-FORTH	P	RE	31.03.2016	No		

No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due delivery date from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
	quantitative platform								
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	No		
D10.4	The Physiomics enabled storage on public clouds	10	7-FORTH	R	CO	31.03.2016	No		
D10.5	The CHIC integrale Plattform	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.
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 extension of the original deadline was that the CHIC consortium met for a first round of evaluations of the CHIC tools in mid-

No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due delivery date from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
									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	31.03.2015	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	No		
D12.4	Draft Plan for the Use and Dissemination of Foreground	12	16-CINECA	R	CO	31.03.2016	No		
D12.5	Final Plan for the Use and Dissemination of Foreground	12	16-CINECA	R	CO	31.03.2017	No		
D12.6	Periodic Newsletters	12	2-EURICE	R	PU	31.03.2014 31.03.2015 31.03.2016 31.03.2017	Yes	30.10.2014	The first issue of the periodic newsletter was unfortunately delayed but several months. The delay was caused by a massive and unscheduled workload at the participating partner institutions (e.g. review meeting preparations for CHIC partner projects, periodic reports and

No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due delivery date from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
									other contractual obligations). The bi-monthly newsletters were largely unaffected by this delay and have been issued as planned during M13-M18.

### 3.2 Milestones

Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I did/mm/ivy	Achieved Yes/No	Actual/ Forecast achievement data did/mm/ivy	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	The 1 <sup>st</sup> progress meeting of CHIC was held at FORTH, Heraklion, Greece, from 17-18 October 2013
MS3	User needs and Requirements are defined	2	3-USAAR	30.11.2013	Yes		
MS4	Hypermodels are accepted by users	2	3-USAAR	30.09.2016	No		
MS5	Scenarios and data from nephroblastoma, GBM and NSCLC	3	4-KULEUVEN	31.03.2015	No		

Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I did/mm/ivy	Achieved Yes/No	Actual/ Forecast achievement data did/mm/ivy	Comments
	are available						
MS6	Exploitation of the CHIC infrastructure by further cancer typest	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	No		
MS13	Availability of hypermodels for all clinic. scenarios compliant w. the	6	1-ICCS	31.07.2016	No		

Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I did/mm/ivy	Achieved Yes/No	Actual/ Forecast achievement data did/mm/ivy	Comments
	guidelines to be prov. by WP7						
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		
MS17	Hypermodel editor, development and execution application ready	7	7-FORTH	31.03.2016	No		
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	No		



Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I did/mm/ivy	Achieved Yes/No	Actual/ Forecast achievement data did/mm/ivy	Comments
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	No		
MS25	The CHIC Orchestration Platform and Encrypted Data Services	10	7-FORTH	31.03.2015	No		
MS26	Public cloud Deployment	10	7-FORTH	31.03.2016	No		
MS27	Evaluation and validation criteria for clinical adaptation are ready	11	3-USAAR	31.03.2014	No		
MS28	First evaluation Workshop	11	3-USAAR	30.09.2014	Yes	01.12.2014	D11.2 available
MS29	Second evaluation Workshop	11	3-USAAR	31.03.2016	No		
MS30	Internal collaborative area and external website	12	2-EURICE	30.06.2013	Yes	28.06.2013	Website is online and operational: <a href="http://www.chic-vph.eu">www.chic-vph.eu</a>
MS31	First CHIC summer School	12	3-USAAR	30.09.2014	No	September 2015	The Project Management Team informed the PO, Mr Jaakko Aarnio, that MS31 and MS32 would have to be turned around. The First CHIC Summer School is to take place in September

Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I did/mm/ivy	Achieved Yes/No	Actual/ Forecast achievement data did/mm/ivy	Comments
							2015.
MS32	CHIC workshop	12	1-ICCS	30.09.2015	Yes	3.-4.11.2014	6 <sup>th</sup> IARWISOCI Workshop – The CHIC Workshop took place in Athens, Greece. The Project Management Team informed the PO, Mr Jaakko Aarnio, that MS31 and MS32 would have to be turned around. The First CHIC Summer School is to take place in September 2015.
MS33	Second CHIC summer school	12	3-USAAR	30.09.2016	No		

## 4. Explanation of the use of the resources

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

### 4.1 Budget Overview

Cost Budget Follow-up Table							
Contract n°	600841	Project acronym		CHIC	CHIC		
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)			Percentage spent	Remaining Budget (EUR)
			Period 1	Interim Period	Total	Total/ Budget	
			M1-M12	M13-M18			
ICCS	Total Person-month	106,00	30,27	17,11	47,38	29%	58,62
	Personnel	636.000,00	117.446,00	66.442,08	183.888,08	18%	452.111,92
	Other direct costs	227.000,00	22.114,00	17.165,58	39.279,58	10%	187.720,42
	Subcontracting	6.000,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	517.800,00	83.734,00	50.164,60	133.898,60	16%	383.901,40
	Total Costs	1.386.800,00	223.294,00	133.772,26	357.066,26	16%	1.029.733,74
Eurice	Total Person-month	50,00	12,88	6,99	19,87	26%	30,13
	Personnel	324.500,00	65.313,00	36.080,55	101.393,55	20%	223.106,45
	Other direct costs	39.173,00	5.314,00	2.342,77	7.656,77	14%	31.516,23
	Subcontracting	6.000,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	275.825,00	39.978,00	22.774,04	62.752,04	14%	213.072,96
	Total Costs	645.498,00	110.605,00	61.197,36	171.802,36	17%	473.695,64
USAAR	Total Person-month	135,00	11,29		11,29	8%	123,71
	Personnel	725.498,00	64.750,00	87.280,79	152.030,79	9%	573.467,21
	Other direct costs	326.764,00	18.692,00	23.140,14	41.832,14	6%	284.931,86
	Subcontracting	5.682,00	0,00	0,00	0,00	0%	5.682,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	631.357,00	50.065,00	66.252,56	116.317,56	8%	515.039,44
	Total Costs	1.689.301,00	133.507,00	176.673,49	310.180,49	8%	1.379.120,51
KULeuven	Total Person-month	68,00	8,50		8,50	13%	59,50
	Personnel	340.000,00	41.421,00		41.421,00	12%	298.579,00
	Other direct costs	167.500,00	9.090,00		9.090,00	5%	158.410,00
	Subcontracting	2.000,00	0,00		0,00	0%	2.000,00
	Adjustments		0,00		0,00	0%	0,00
	Indirect costs	304.500,00	30.306,00		30.306,00	10%	274.194,00
	Total Costs	814.000,00	80.817,00		80.817,00	10%	733.183,00
BED	Total Person-month	88,00	14,00	12,00	26,00	16%	62,00
	Personnel	484.000,00	52.323,00	43.600,00	95.923,00	11%	388.077,00
	Other direct costs	49.000,00	6.988,00	400,00	7.388,00	14%	41.612,00
	Subcontracting	5.000,00	0,00	0,00	0,00	0%	5.000,00
	Adjustments		0,00	0,00	0,00	0%	0,00
	Indirect costs	319.800,00	35.586,00	26.400,00	61.986,00	11%	257.814,00
	Total Costs	857.800,00	94.897,00	70.400,00	94.897,00	11%	762.903,00

Due to many parallel  
periodic reports,  
KULeuven cannot provide  
financial detail for this  
internal interim report.

Cost Budget Follow-up Table							
Contract n°	270089	Project acronym	CHIC				
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)			Percentage spent	Remaining Budget (EUR)
			Period 1	Interim Period	Total	Total/ Budget	
			M1-M6	M13-M18			
USFD	Revised number of PM	154,40	32,81	23,00	55,81	21%	98,59
	Personnel	679.296,00	115.475,00	89.001,97	204.476,97	17%	474.819,03
	Other direct costs	78.001,00	12.986,00	19.917,69	32.903,69	17%	45.097,31
	Subcontracting	4.000,00	0,00	0,00	0,00	0%	4.000,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	454.378,00	77.076,00	65.351,80	142.427,80	17%	311.950,20
	Total Costs	1.215.675,00	205.537,00	174.271,46	205.537,00	17%	1.010.138,00
FORTH	Total Person-month	86,00	60,79	28,91	89,70	71%	-3,70
	Revised number of PM	163,79	60,79	28,91	89,70	37%	74,09
	Personnel	412.800,00	105.586,00	57.867,00	163.453,00	26%	249.347,00
	Other direct costs	110.170,00	17.911,00	29.597,03	47.508,03	16%	62.661,97
	Subcontracting	6.000,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	359.136,00	87.636,00	44.557,59	132.193,59	24%	226.942,41
	Total Costs	888.106,00	211.133,00	132.021,62	211.133,00	24%	676.973,00
LUH	Total Person-month	54,00	16,07	7,38	23,45	30%	30,55
	Personnel	350.622,00	72.235,00	35.553,39	107.788,39	21%	242.833,61
	Other direct costs	28.000,00	2.795,00	502,04	3.297,04	10%	24.702,96
	Subcontracting	3.000,00	0,00	0,00	0,00	0%	3.000,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	227.173,00	45.018,00	21.940,46	66.958,46	20%	160.214,54
	Total Costs	608.793,00	120.048,00	57.995,89	178.043,89	20%	430.749,11
UPENN	Total Person-month	84,00	21,00	16,55	37,55	25%	46,45
	Personnel	391.564,00	72.110,00	60.194,27	132.304,27	18%	259.259,73
	Other direct costs	63.501,00	24.241,00	3.816,68	28.057,68	38%	35.443,32
	Subcontracting	5.000,00	0,00	0,00	0,00	0%	5.000,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	282.140,00	59.738,00	39.686,79	99.424,79	21%	182.715,21
	Total Costs	742.204,00	156.089,00	103.697,74	156.089,00	21%	586.115,00
UOXF	Total Person-month	54,00	1,47	6,06	7,53	3%	46,47
	Personnel	289.077,00	6.217,00	25.325,93	31.542,93	2%	257.534,07
	Other direct costs	59.184,00	735,00	1.054,76	1.789,76	1%	57.394,24
	Subcontracting	3.902,00	0,00	0,00	0,00	0%	3.902,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	208.956,00	4.171,00	15.828,41	19.999,41	2%	188.956,59
	Total Costs	561.119,00	11.123,00	42.209,10	53.332,10	2%	507.786,90
UNITO	Total Person-month	54,00	9,59	8,42	18,01	18%	35,99
	Personnel	270.000,00	35.978,00	41.505,51	77.483,51	13%	192.516,49
	Other direct costs	100.000,00	3.227,00	7.352,45	10.579,45	3%	89.420,55
	Subcontracting	5.000,00	0,00	0,00	0,00	0%	5.000,00
	Adjustments		0,00	0,00	0,00	0%	0,00
	Indirect costs	222.000,00	23.522,00	29.298,58	52.820,58	11%	169.179,42
	Total Costs	597.000,00	62.727,00	78.156,54	140.883,54	11%	456.116,46

Cost Budget Follow-up Table							
Contract n°	270089	Project acronym	CHIC				
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)			Percentage spent	Remaining Budget (EUR)
			Period 1	Interim Period	Total	Total/ Budget	
			M1-M6	M13-M18			
UBERN	Total Person-month	62,00	11,20	8,72	19,92	18%	42,08
	Personnel	465.000,00	71.512,00	68.686,00	140.198,00	15%	324.802,00
	Other direct costs	60.000,00	10.972,00	7.137,72	18.109,72	18%	41.890,28
	Subcontracting	4.000,00	0,00	0,00	0,00	0%	4.000,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	315.000,00	49.490,00	45.494,23	94.984,23	16%	220.015,77
	Total Costs	844.000,00	131.974,00	121.317,95	253.291,95	16%	590.708,05
CUSTODIX	Total Person-month	24,00	2,37	3,59	5,96	10%	18,04
	Personnel	180.000,00	12.227,00	17.862,59	30.089,59	7%	149.910,41
	Other direct costs	33.000,00	1.790,00	0,00	1.790,00	5%	31.210,00
	Subcontracting	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	90.000,00	6.777,00	6.609,16	13.386,16	8%	76.613,84
	Total Costs	303.000,00	20.794,00	24.471,75	45.265,75	7%	257.734,25
PHILIPS	Total Person-month	54,00	1,20	0,34	1,54	2%	52,46
	Personnel	398.466,00	11.276,00	3.070,00	14.346,00	3%	384.120,00
	Other direct costs	25.000,00	0,00	0,00	0,00	0%	25.000,00
	Subcontracting	3.000,00	0,00	0,00	0,00	0%	3.000,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	592.650,00	19.418,00	8.155,00	27.573,00	3%	565.077,00
	Total Costs	1.019.116,00	30.694,00	11.225,00	41.919,00	3%	977.197,00
UCL	Total Person-month	74,00	6,65	1,20	7,85	9%	66,15
	Personnel	497.978,00	39.837,00	7.350,81	47.187,81	8%	450.790,19
	Other direct costs	161.000,00	4.214,00	1.957,62	6.171,62	3%	154.828,38
	Subcontracting	6.000,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	395.386,00	26.430,00	5.585,06	32.015,06	7%	363.370,94
	Total Costs	1.060.364,00	70.481,00	14.893,49	85.374,49	7%	974.989,51
CINECA	Total Person-month	57,00	15,95	11,08	27,03	28%	29,97
	Personnel	228.000,00	56.196,00	33.176,40	89.372,40	25%	138.627,60
	Other direct costs	54.408,00	5.258,00	1.182,98	6.440,98	10%	47.967,02
	Subcontracting	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	313.899,00	92.025,00	20.615,63	112.640,63	29%	201.258,37
	Total Costs	596.307,00	153.479,00	54.975,01	208.454,01	26%	387.852,99
TEI-C	Total Person-month	17,00	3,96	2,25	6,21	23%	10,79
	Personnel	37.400,00	10.527,00	6.967,39	17.494,39	28%	19.905,61
	Other direct costs	11.900,00	4.065,00	4.008,83	8.073,83	34%	3.826,17
	Subcontracting	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	29.580,00	8.755,00	6.585,73	15.340,73	30%	14.239,27
	Total Costs	78.880,00	23.347,00	17.561,95	40.908,95	30%	37.971,05
Total	Total Person-month	1.145,00	260,00	153,60	413,60	23%	731,40
	Personnel	6.710.201,00	950.429,00	526.241,81	1.543.112,89	14%	5.167.088,11
	Other direct costs	1.593.601,00	150.392,00	79.270,57	246.828,15	9%	1.346.772,85
	Subcontracting	64.584,00	0,00	65.351,80	0,00	0%	64.584,00
	Adjustments	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	5.539.580,00	739.725,00	409.047,08	1.148.772,08	13%	4.390.807,92
	Total Costs	13.907.963,00	1.840.546,00	964.394,86	2.458.322,30	13%	11.449.640,70

The total number of PM before FORTH's increase in PM was 1067.

## 4.2 Budget Explanations

Explanation of the use of resources for				ICCS		
Contract n°	600841	Project acronym	CHIC			
Work Package		Item description	Amount in €		Explanations	
all WPs		Personnel	66.442,08		Salary of senior scientists, PhD students, assistants and junior researchers for a total of 17.11 PM	
WP6, WP8, WP12		Travel	11.760,05		Travel to: WP6 Cancer Modellers' meeting in Oxford, UK; WP6 Cancer Modellers' Meeting in Heraklion, Greece; CHIC review meeting, Brussels, Belgium; VPH 2014 Conference in Trondheim, Norway; 7th World Congress of Biomechanics, Boston, USA	
WP6		Consumables	21,54		Computer consumables	
		Equipment				
		Subcontracting				
WP12		Other	5.383,99		Publication fees and journals' bank fees, registration fees for conferences	
Total Direct Costs			83.607,66			
		INDIRECT COSTS	50.164,60			

Explanation of the use of resources for				EURICE		
Contract n°	600841	Project acronym	CHIC			
Work Package		Item description	Amount in €		Explanations	
WP1, WP12		Personnel	36.080,55		Salaries of project officers, communication officers, project manager, IT support staff for a total of 6.99 PM	
WP1		Travel	521,65		CHIC review meeting, Brussels, Belgium	
		Consumables				
		Equipment				
		Subcontracting				
WP1, WP12		Other	1.821,12		Shipping costs, meeting organisation, dissemination material	
Total Direct Costs			38.423,32			
		INDIRECT COSTS	23.947,29			

Explanation of the use of resources for			USAAR			
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP2, WP3, WP4, WP7, WP11	Personnel	87.280,79		Salaries for 7 employees		
	Travel					
	Consumables	23.140,14				
	Equipment					
	Subcontracting					
	Other					
Total Direct Costs		110.420,93				
INDIRECT COSTS		66.252,56				

Explanation of the use of resources for			KULeuven		
Contract n°	600841	Project acronym	CHIC		
Work Package	Item description	Amount in €		Explanations	
	Personnel				
<div>KULeuven informed the Project Management Team that, due to several periodic reports due at the same time as the CHIC interim report, the financial administration does not have the resources to provide any figures for this reporting period.</div>					
	Subcontracting				
	Other				
Total Direct Costs					
	INDIRECT COSTS				

Explanation of the use of resources for			BED			
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP5, WP7, WP9, WP11, WP12	Personnel	43.600,00		salaries of 4 scientists for a total of 12 PM (approximate figures)		
	Travel	400,00		Travel and accommodation costs of 2 people for the CHIC review meeting, Brussels, 2-3 September 2014		
	Consumables					
	Equipment					
	Subcontracting					
	Other					
Total Direct Costs		44.000,00				
INDIRECT COSTS		26.400,00				

Explanation of the use of resources for				USFD		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €	Explanations			
WP1, WP5, WP7, WP12	Personnel	89.001,97	Salaries of senior scientists, scientists, PhD student and administrative staff for a total of 23 PM			
WP7	Travel	7.082,66	Travel to CHIC review meeting, Brussels, Belgium; VPH 2014 Conference, Trondheim, Norway; WP6 Cancer Modellers' Workshop, Oxford, UK; WP6 Cancer Modellers' Workshop, Heraklion, Greece; CHIC bilateral meeting, Bologna, Italy			
	Consumables	0,00				
WP7	Equipment	12.815,61	Computer consumables (USB keys, Blu Ray discs, Dual Xenon Server system)			
	Subcontracting					
WP7	Other	19,42	Shipping costs			
<b>Total Direct Costs</b>		<b>108.919,66</b>				
<b>INDIRECT COSTS</b>		<b>65.351,80</b>				

Explanation of the use of resources for				FORTH		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €	Explanations			
WP2, WP5, WP6, WP7, WP8, WP9, WP10, WP11	Personnel	30.849,47	Salaries of Senior scientists, scientist, technicians, medical doctor for a total of 28,91 PM			
WP1, WP6, WP9, WP10	Travel	7.350,11	Travels to WP6 Cancer Modellers' Meeting, Oxford, UK; CHIC review meeting, Brussels, Belgium; Summer School on Biology in Cyber Space, Dresden, Germany			
WP10	Consumables	19.557,00	procurement of extra software tools and licenses for Matlab			
	Equipment					
	Subcontracting					
WP6, WP12	Other	2.689,92	Publication fees, hospitality expenses for WP6 Cancer Modellers' Meeting in Heraklion, Greece			
<b>Total Direct Costs</b>		<b>60.446,50</b>				
<b>INDIRECT COSTS</b>		<b>44.557,59</b>				



Explanation of the use of resources for				LUH		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP4	Personnel	35.553,39		Salaries of a professor, a student assistant and research associates for a total of 7.38 PM		
WP4	Travel	502,04		Travel to WP6 Cancer Modellers' Meeting, Heraklion, Greece; CHIC progress meeting, Luton, UK		
	Consumables					
	Equipment					
	Subcontracting					
	Other					
Total Direct Costs		36.055,43				
INDIRECT COSTS		21.940,46				

Explanation of the use of resources for				UPENN		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP2, WP3, WP4, WP6, WP8, WP11, WP12	Personnel	60.194,27		Salaries of senior scientists, scientist and PhD students at a total of 16,55 PM		
WP6	Travel	2.008,14		CHIC progress meeting, Luton, UK, 18-22 February 2014; WP6 Modeller's Meeting, Oxford, UK, 10-11 April 2014; Northeast Bioengineering, Boston, MA, 25-27 April 2014; ASCD-IFCB Conference, Philadelphia, PA, 6-10 December 2014		
	Consumables					
	Equipment					
	Subcontracting					
WP6	Other	1.808,54		Publication fees and computer cluster maintenance fees		
Total Direct Costs		64.010,95				
INDIRECT COSTS		39.686,79				

Explanation of the use of resources for			UOXF		
Contract n°	600841	Project acronym	CHIC		
Work Package	Item description	Amount in €	Explanations		
WP1, WP6	Personnel	25.325,93	Salaries of senior scientist and assistant for a total of 6.06 PM		
WP6	Travel	1.054,76	Travel to CHIC progress meeting, Luton, UK; WP6 Cancer Modellers' Meeting, Heraklion, Crete		
	Consumables				
	Equipment				
	Subcontracting				
	Other				
<b>Total Direct Costs</b>		<b>26.380,69</b>			
<b>INDIRECT COSTS</b>		<b>15.828,41</b>			

Explanation of the use of resources for			UNITO		
Contract n°	600841	Project acronym	CHIC		
Work Package	Item description	Amount in €	Explanations		
WP3, WP6, WP11, WP12	Personnel	41.505,51	Salaries of 8 researchers for a total of 8.42 PM		
WP3, WP11, WP12	Travel	4.540,25	Travel to WP6 Cancer Modellers' Workshop, Oxford, UK; Siuro Congress, Bologna, Italy; 2 trips for clinical data collection (Milano, Italy, and Biella, Italy); International Conference on Biomedical and Health Informatics, Valencia, Spain; Estro School "Basic Clinical Radiobiology", Istanbul, Turkey		
WP3	Consumables	2.785,20	Physion, medication containers and current generator		
WP3	Equipment	131,75	Depreciation of Libreria Cortina hardware (total costs: 948,66; 36 months total depreciation)		
	Subcontracting				
	Other				
<b>Total Direct Costs</b>		<b>48.962,71</b>			
<b>INDIRECT COSTS</b>		<b>29.298,58</b>			

Explanation of the use of resources for				UBERN		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP6, WP8, WP9, WP10	Personnel	68.686,00		Salaries of senior scientists, administration staff and assistant for a total of 8.72 PM		
WP8, WP9	Travel	6.640,70		Travels to CHIC progress meeting, Luton, UK; WP6 Modellers' Meeting, Heraklion, Greece; CHIC review meeting, Brussels, Belgium; MICCAI 2014 Conference, Boston, USA; EMBC 2014 Conference, Chicago, USA; MISS Summer School, Favignana, Italy; SSBE Meeting, Zürich, Switzerland		
WP8	Consumables	497,02		License SQL license server for CHIC cloud		
	Equipment					
	Subcontracting					
	Other					
Total Direct Costs		75.823,72				
INDIRECT COSTS		45.494,23				

Explanation of the use of resources for				CUSTODIX		
Contract n°	600841	Project acronym	CHIC			
Work Package	XXX	Item description	Amount in €		Explanations	
WP4, WP5, WP8, WP12		Personnel	17.862,59		Salaries of 2 senior scientists for a total of 3.59 PM	
		Travel	0,00			
		Consumables				
		Equipment				
		Subcontracting				
		Other				
Total Direct Costs			17.862,59			
INDIRECT COSTS			6.609,16			

Explanation of the use of resources for				PHILIPS		
Contract n°	600841	Project acronym	CHIC			
Work Package		Item description	Amount in €		Explanations	
WP5, WP12		Personnel	3.070,00		Salaries of researcher for a total of 0.34 PM	
		Travel	0,00			
		Consumables	0,00			
		Equipment	0,00			
		Subcontracting				
		Other				
Total Direct Costs			3.070,00			
INDIRECT COSTS			8.155,00			

Explanation of the use of resources for				UCL		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP7, WP8	Personnel	7.350,81		Salaries of 2 senior scientists for a total of 1.20 PM		
WP6, WP7	Travel	1.957,62		Travels to VPH 2014 Conference, Trondheim, Norway; ICCSA 2014 Conference, Le Havre, France		
	Consumables	0,00				
	Equipment	0,00				
	Subcontracting					
	Other					
<b>Total Direct Costs</b>		<b>9.308,43</b>				
		<b>INDIRECT COSTS</b>		<b>5.585,06</b>		

Explanation of the use of resources for				CINECA		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP1, WP5, WP7, WP10, WP12	Personnel	33.176,40		Salaries of 3 employees for a total of 11.08 PM		
WP1	Travel	1.182,98		Travel to CHIC review meeting, Brussels, Belgium		
	Consumables	0,00				
	Equipment	0,00				
	Subcontracting					
	Other					
<b>Total Direct Costs</b>		<b>34.359,38</b>				
		<b>INDIRECT COSTS</b>		<b>20.615,63</b>		

Explanation of the use of resources for			TEI-C		
Contract n°	600841	Project acronym	CHIC		
Work Package	Item description	Amount in €	Explanations		
WP5, WP9	Personnel	6.967,39	Salaries of senior scientist and PhD student for a total of 2.25 PM		
WP5	Travel	1.386,33	Travel to CHIC review meeting, Brussels, Belgium		
	Consumables	0,00			
WP5	Equipment	2.622,50	Depreciation of 2 computers		
	Subcontracting				
	Other				
Total Direct Costs		10.976,22			
INDIRECT COSTS		6.585,73			

### **4.3 Planned versus actual efforts**

A list of planned versus actual efforts is included in each WP description. It has to be noted, however, that the planned efforts are made for the whole period, i.e. M13-M24. Therefore, deviations between planned and actual efforts after until M18 are expected.

Moreover, due to the reallocation of PM efforts by partners FORTH and BED, the distribution of planned PM for the whole project has been revised by both partners. Tables which specify the reallocation of PM efforts are provided in the Management section of this report. Since FORTH increased their total number of PM efforts, the total number of planned PM efforts in the project has increased as well. The budget overview table in this report includes the new amount of total PM in the project.