



PROJECT PERIODIC REPORT

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Publishable Summary

I. Summary of the project context and objectives

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

II. Description of the work performed during the 2nd year of the project's implementation and the main results achieved

Overall progress of the project implementation

The project has fully achieved the targets foreseen for the third year of its implementation with rather minor adjustments. Special emphasis has been put on *the clinical relevance* of the entire endeavour as a response to the reviewers' suggestions. In the following subsections important indicative progress and result examples from all workpackages are provided. A more comprehensive and detailed listing of the achievements is provided in the third annual project periodic report.

Work Package 1 (WP1): Project Management

Representative achievements that were made during M25-M36 include the following:

The **3rd CHIC review** (after M24) took place on July 8, 2015. Focus on the demonstration of the clinical relevance of the project in the subsequent review was the main suggestion made by the reviewers. A **5th Progress Meeting (MS2)** was held on 21-23 October 2015 at CINECA in Bologna, Italy. Norbert Graf was appointed Assistant Clinical Coordinator whereas a Clinical Advisory Committee was

established. The **4th CHIC review** took place on January 29, 2016. Its outcome was *excellent progress*. The **6th Progress Meeting (MS2)** of CHIC was held on 21-23 March 2016 at the University of Bern, Switzerland. Several **telephone and Skype conferences** took place in order to discuss and strategically plan the following steps of the project. The **2nd Progress Report** was successfully finalized and submitted. Within the usual regular and close collaboration between ICCS and Eurice, **scientific and contractual management** of CHIC was implemented effectively and according to plan. ICCS has been in regular contact with the project officer regarding several administrative issues such as the agreement on the review meeting dates, and the organization of a CHIC workshop in the context of the International Conference and Exhibition on Pediatric Oncology, to take place in Toronto, Canada on August 11-13, 2016. Moreover, ICCS has been scientifically coordinating the entire project through a series of communication procedures such as emailing, regular teleconferencing and Skype-conferencing. Decisions at the consortium level have been reached through electronic voting or preference stating platforms such as Doodle. The CHIC consortium has prepared an amended version of Annex 1 to the CHIC Grant Agreement.

Work Package 2 (WP2): User Needs and Requirements

Collection of clinical, imaging and molecular data has continued. The clinical relevance of the project has been further elaborated. All partners of CHIC have contributed to the requirements analysis for enhancing hypermodels beyond the domain of cancer. Scenarios and use cases have been further developed by the clinical partners and in close interaction with all non-clinical ones. Scenarios have been further dissected into granular modules. Interaction and collaboration with the p-medicine and MyHealthAvatar projects have continued. A new document (D2.5) summarizing the efforts concerning the clinical relevance of the project for the different cancer types (glioblastoma, nephroblastoma, non-small cell lung cancer and prostate cancer) addressed by CHIC has been written and submitted. A decision to organize a CHIC workshop within the framework of the International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics to take place in Toronto, Canada on August 11-13, 2016 has been taken. A nephroblastoma demonstrator was shown in the conference of Renal Tumor Biology that took place in Toronto on April 2-3, 2016.

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

Feedback to the clinical partners regarding the exploitability of provided data has been provided by the cancer modelling partners. The latter have also contributed to the crystallization of the hypermodelling scenarios. Additional data to be used in the hypermodels of nephroblastoma, non-small cell lung cancer and glioblastoma have been collected. The ontology-based clinical trial management system ObTiMA has been further developed for the specific needs of CHIC. The source documents and MRI images at the University of Leuven have been updated (twice during this reporting period). The data sets have been securely uploaded on the CHIC platform. A translational research protocol regarding glioblastoma has been approved by the University Hospital of Leuven. New glioblastoma data are being collected. Several adaptations of the models have been made in order to facilitate the exploitation of the actual multiscale clinical data.

Work Package 4 (WP4): Legal and Ethical Framework

The CHIC data protection framework has been deployed. Ongoing de-identification of various CHIC datasets such as nephroblastoma data (ODM XML, mirna and DICOM) and glioblastoma data (ODM XML and DICOM), and the validated data have been made ready for data sharing. An intellectual property rights (IPR) memorandum of understanding has been completed and signed. Research on the whitepaper has been conducted and published as scheduled in M36.

Work Package 5 (WP5): IT Architecture

Several important results for the successful implementation of the project were produced. In The CHIC private cloud infrastructure has been redesigned for productive use and is now fully functional. The uninterruptable provision of the private cloud infrastructure has been seen as a significant result.

The CRAF (Clinically Relevant Application Framework) component has been introduced and is being further developed. The CHIC security framework has been made available. It has been deployed and integrated with all of the CHIC repositories, services and tools. In parallel, the extension of the CHIC security framework to support SAML delegation tokens has also been an important achievement. An initial integration between the data repository and the auditing system of the CHIC security framework has been performed. VPH-HF alpha v0.2 including security tools and services has been successfully deployed on the CHIC production node.

Work Package (WP6): Cancer Models and Hypermodel Design

Integrated multimodeller hypermodels have been developed using the ICCS Oncosimulator as their basis. Hypomodels (component models) developed by other modelling partners have been appropriately integrated. They address biomechanics, angiogenesis, metabolism and molecular interactions in significant detail. An additional phenomenological model has also been developed in order to provide initial gross estimates of tumour response to treatment. Hypermodels address nephroblastoma, lung cancer, glioblastoma and prostate. In parallel with mechanistic hypermodels, machine learning models have been being developed in order to address clinical questions for which the available data types are not sufficient for the development of mechanistic hypermodels. Clinical relevance has served as the driving force for the development and the adaptation of the hypermodels. Mechanistic hypermodels can run under the MUSCLE hypomodel coupling library. Early comparisons of the hypermodel predictions with biological reality and clinical experience support their potential to serve as clinical decision support systems in the future.

Work Package 7 (WP7): Hypermodelling infrastructure

The alpha version of the VPH-HF, as inherited from the VPH-OP project has been successfully refactored in order to meet the needs of CHIC. This framework has been deployed and tested on both test and production nodes and integrated with the CHIC authentication system. The VPH-HF is now fully integrated into the rest of the CHIC IT infrastructure. All hypomodels and hypermodels supplied by the modelling partners so far have been successfully deployed and executed within VPH-HF. A minimum annotation set for resources has been agreed. A URI schema has also been agreed and formally captured in a JSON document. Automated workflow wrapper generation, automated deployment and testing of models uploaded to the model repository have been implemented. Deliverable D7.3 consolidates the semantic annotation services and related technologies driving production and consumption of metadata in the hypermodelling editor, the model and the data repositories.

Work Package 8 (WP8): Model and Data Repositories

The prototype and the web services for the model/tool and *in silico* trial repositories have been developed. The *in silico* trial repository has been moved to another virtual machine in the CHIC private cloud and it has been totally split from the model and the tool repository. The clinical data repository now supports genetic/molecular and histopathology datasets. The REST services have been extended with more functionality and the repository has migrated from *database first* to *code first* development approach. The semantics infrastructure has been developed in such a way as to refine the hypo/hypermodel metadata schema, to create applications that leverage the schema, to provide annotation (RDF) store and ontology DB Knowledge Base through RICORDO and to link RICORDO metadata management web services with the hypermodelling editor. In parallel the clinical data repository has been integrated with the RICORDO framework in a preliminary way. Work has been done on the ontology annotation tool. Most of the aforementioned advances have been documented in deliverables D8.2 and D8.3.

Work Package 9 (WP9): Image Processing and Visualization

Clinical evaluation of longitudinal tumour volumetry has been completed. Results demonstrate the feasibility of automated longitudinal volumetry in clinics. Clinicians have evaluated the performance

of different approaches on imaging data sets. A wide range of imaging features with respect to their discriminative potential for nephroblastoma response to preoperative chemotherapy have been analysed. A semi-automatic method for the segmentation of nephroblastoma is under development. The method has already been evaluated on 20 hand-labelled t2 sequences annotated by 2 human experts. The fully automatic method for brain tumour segmentation is evaluated on 188 data sets with high-grade gliomas and 25 with low-grade gliomas from the BraTS14 database. Within a computation time of only three minutes, Dice scores that are comparable to state-of-the-art methods have been achieved. Multidimensional visualization for all demonstrator hypermodel predictions has been provided.

Work Package 10 (WP10): Integrated Platform

Documentation regarding the consumption of model/tool repository web services by the hypermodelling editor has been produced. The requirements and the design for supporting “strongly coupled” hypomodels have been finalized and the first version of the high level hypermodelling language used by the Hypermodelling Editor to describe hypermodels with “strongly coupled” hypomodels and to submit them to the hypermodelling execution framework has been made available. Work on the Data Upload tool and the Hypermodelling Editor continues. The need for having a “packaged” clinically relevant representation of the CHIC environment has led to the introduction of an additional component for the project, the Clinically Relevant Application Framework (“CRAF”) that is currently under further development. This suite of tools and end-user applications will provides a “one-stop” solution for accessing the results of CHIC for clinical research in the clinical domain.

Work Package 11 (WP11): Clinical Adaptation and Validation

Two evaluation workshops were successfully run by USAAR and are reported in D11.3. The CHIC infrastructure is clinically oriented and well recognized by the scientific and the clinical communities. The introduction of the CRAF architectural component constitutes important progress towards utilizing the CHIC platform in the clinical research domain. The first multi-modeller hypermodel for lung cancer has been utilized as a first complete example for the fine-tuning of the CHIC infrastructure based on the corresponding multiscale clinical data. The nephroblastoma hypermodel has served as another paradigm to the same end. The modelling work on glioblastoma has focused on the utilization of machine learning techniques. Data collection is ongoing. Clinical adaptation of the CHIC infrastructure for prostate cancer is ongoing by paying attention to the collection of data for the model validation.

Work Package 12 (WP12): Dissemination and Exploitation

The project website is up to date. Regular dissemination of news and highlights via the CHIC newsletters and web channels (web site and socials) is ongoing and effective. The 2nd and 3rd annual newsletters have been released. 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. As a result several dissemination items have been reported together with a large number of peer reviewed scientific papers and contributions to conference proceedings. The discussion about sustainability and maintenance of the CHIC project has continued and a plan is in place to reach agreement in the final exploitation paths by the next review. Contacts to people outside the consortium have been initiated. An agreement on a CHIC workshop at the International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics has been reached.

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

The major expected results of the project can be summarized as the implementation of its objectives outlined in section I. These include the development, the clinical adaptation and the partial clinical validation of a series of cancer models, hypermodels, technological tools, services and secure infrastructure. Regarding the impact of the project, CHIC is expected to have a major influence on the following sectors: **1. Fundamental Science** (quantitative decomposition of complex biological phenomena into elementary biomechanisms, mathematical and computational modelling of each biomechanism, virtual (re)synthesis of complex phenomena via hypermodelling) **2. Clinical Medicine** (conduction of virtual clinical experiments instead of eventually ethically forbidden real ones on the level of a single patient or a clinical trial) **3. Industry** (provision of models, hypermodels, technological infrastructure, tools and oncosimulators to be utilized for the development of patient individualized decision support and treatment planning systems and in silico clinical trial platforms. **4. Society** (expected achievement of increased life expectancy and improved quality of life through the conduction of experiments *in silico* aiming at the optimization of the treatment strategy in the patient individualized context, reduction of the experimental cost due to the partial replacement of costly *in vitro* and *in vivo* experiments by in silico experiments, conduction of virtual clinical experiments instead of real ones.). Within the third year of the implementation of the project several actions aiming at facilitating the exploitation of the project outcomes were taken. A discussion about sustainability and maintenance issues of the CHIC project via the proposed Study Trial and Research Centre (STaRC) that is part of the maintenance program of the p-medicine project has been initiated and exploitation related activities are progressing. Relevant discussions among all partners are ongoing. Training activities, most notably a CHIC workshop within the framework of the German School of Pediatric Oncology and Hematology that took place in Haus Schönblick am Söllereck (Oberallgäu) on January 9-13, 2016 and the upcoming International Conference on Pediatric Oncology and Clinical Pediatrics (Toronto August, 11-13, 2016) where a special CHIC workshop is being organized ensure the clinical dissemination and strengthen the clinical impact of the endeavour. (<http://pediatriconcology.conferenceseries.com/organizing-committee.php>)

IV. Address of the public website

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

1. Work progress and achievements during the period

1.1 Work Package 1: Project Management

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

1.2 Work Package 2: User Needs and Requirements

Use cases and scenarios are further refined for the different cancer domains of the project that is led by USAAR. Main work was done on specifying the clinical relevance of the project. For that purpose an additional deliverable D2.5 [Clinical relevance of the CHIC project – Describing the integrated workflows of the scenarios from a clinical perspective] was submitted before the last review. The subject was intensively discussed in several Skype conferences as well as on the 5th Progress Meeting in Bologna from 21st to 23rd of October 2015 and the 6th Progress Meeting in Bern from 21st to 23rd of March 2016.

USAAR continued discussions about interactions with the *p-medicine* environment and MyHealthAvatar.

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 addresses the needs for developing secure and consistent hypermodels together with the technological requirements (in conjunction with all other WPs) from a clinical application standpoint facilitating VPH research. The project takes 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 are changing during the evolution of the project the specification of user needs and requirements is 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 investigates 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 mark-up languages do exist that can be used for building hypermodels?

In this WP user requirements and specifications for the interaction with existing infrastructures are 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 needs to be addressed and solutions will be 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:

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

Summary of progress achieved towards objectives

Task 2.4: In task 2.4 USAAR is analysing the requirements to get acceptance of hypermodels. This is done in close cooperation with all partners and in close cooperation with WP11, as tools, models and hypermodels will only be used in the clinical setting and beyond the domain of cancer if they are validated. For that reason a questionnaire is developed to find ways of bringing models and hypermodels into clinical practice. With the developed questionnaire further answers are collected from patients and physicians. Possibilities for education and training in using hypermodels are analysed. Important requirements in this task are addressed on the legal side including mainly IP issues of composed hypermodels. In addition requirements for sustainability and maintenance of hypermodels are elaborated. All partners of the CHIC consortium are included in this work. Work is done in close collaboration with WP11 and WP12.

- ICCS did contribute in discussions and exploration to organize a CHIC workshop embedded within a major clinical conference and to the preparation of the nephroblastoma demonstrator shown by Prof. Graf during the conference of renal tumor biology that took place in Toronto on April 2-3, 2016.
- UPENN has implemented a machine learning approach for predicting the effect of clinical mutations on oncogene activation of signalling proteins using support vector machine framework, which is a machine learning method.
- UPENN has implemented an area-under-the-curve method for assessing the predictions of our mechanistic molecular models for predicting oncogene activation in kinases.
- UPENN has devised a double-blind validation protocol for assessing the accuracy of our predictive algorithm by computing ROC (receiver operating characteristic) curve. The prediction of the activation status is based on specific interactions (hydrogen bonds etc.) in the dynamics simulations. The double-blind comparison has been validated against a panel of ALK mutations in neuroblastoma and EGFR and ErbB2 mutations in lung cancer.

Summary of details for each task

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

The requirements for the validation 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 did take part in initial discussions on how to gain acceptance of hypermodels. To get acceptance of the hypermodels by patients and physicians contact to clinical partners outside of the CHIC consortium was initiated to recruit patients for testing and evaluating CHIC tools. Presenting the work performed in CHIC in clinical oriented conferences is further elaborated. USAAR and ICCS are organizing a CHIC workshop within the framework of the *“International Conference and Exhibition on*

Pediatric Oncology” to be held in Toronto, Canada on August 11-13, 2016. The Project Officer already approved the workshop. Five participants of CHIC will be demonstrating the work of CHIC at this conference. This activity was done together with WP12.

The most important requirement for the validation of models and hypermodels are the availability of data. In this reporting period all clinical partners continued with the collection of data for the different cancer domains. As the legal and ethical framework is in place and the user interface is functioning for the upload of data to the CHIC platform these data can be shared to all other partners. This was achieved before the consortium meeting in Bologna in October 2015. ICCS has also contributed to the preparation of the nephroblastoma demonstrator shown by Prof. Graf during the conference of renal tumor biology that took place in Toronto on April 2-3, 2016.

Summary of significant results

- We continued to collect clinical, imaging and molecular data. Now more than 1.000 imaging data of patients with nephroblastoma are anonymized and 100 nephroblastoma tumours are annotated and ready for upload to the CDR. The clinical relevance was further elaborated. 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 MyHealthAvatar.
- The clinical relevance of the project is discussed and elaborated by all partners of CHIC in an iterative process. A new document (D2.5) is written and submitted that summarizes efforts concerning clinical relevance of the project for the different diseases [Glioblastoma, nephroblastoma, Non-small cell lung cancer and prostate cancer] enrolled in CHIC. The impact on the CHIC infrastructure is manifold and now much more clinically oriented.
- Decision to organize a CHIC workshop within the International Conference and Exhibition on Paediatric Oncology, to take place in Toronto, Canada on August 11-13, 2016.
- Contribution of ICCS to the preparation of the nephroblastoma demonstrator shown by Prof. Graf during the conference of renal tumor biology that took place in Toronto on April 2-3, 2016.
- Double-blind validation: UPENN’s computational predictions matched experimental measures of kinase activity as well as experimental measures of cell transformation with over 85% accuracy in the mutations investigated from 1500 patients, and with a significance (p-value) of 0.07..

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

There are no deviations from Annex I during this reporting period.

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 3	Actual PM Period 3
1-ICCS	3.20	0.70	0.70
3-USAAR	25.00	7.00	2.94*
7-FORTH	5.00	1.00	1.11
9-UPENN	5.00	1.50	1.00
13-CUSTODIX	1.00	0.25	0.26
14-PHILIPS	4.00	1.50	1.10
Total	43.20	11.95	7.11

*) As there was the request for demonstrating the clinical relevance of the project a lot of additional work was to be done in the different scenarios within WP3. Part of this work was also strongly related to WP2 but could only be allocated to one WP. So WP3 is overspent and WP2 underspent.

1.3 Work Package 3: Clinical and Translational Science Scenarios

Main objectives of this WP

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

Active tasks in this reporting period:

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

Summary of progress achieved towards objectives

Task 3.1: Wilms tumor (M1-M48)

ICCS:

An assessment of the exploitability of the nephroblastoma data took place and pertinent feedback was provided to the clinical providers.

Contribution to the discussion concerning the project's clinical relevance.

Contribution to the crystallization of the nephroblastoma multimodeller hypermodelling scenarios.

USAAR:

Major work was done in providing the data that will be used in the nephroblastoma scenario. ObTiMA is used for data collection. Data are anonymized and uploaded to the CHIC repository and can be used by developers of the hypermodel.

Together with WP2 the hypermodel for nephroblastoma was further defined and clinical relevance addressed.

UPENN:

A hybrid network modelling framework was built, combining mechanistic deterministic network modelling and Boolean modelling of mitogenic signalling pathways and DNA damage and cell cycle pathways.

Task 3.2: Glioblastoma multiforme (M1-M48)**ICCS:**

Provision of feedback to the clinicians.

Contribution to the discussion concerning the project's clinical relevance.

Contribution to the crystallization of the glioblastoma hypermodelling scenarios.

USAAR:

Providing support for the use and further development of ObTiMA.

KU LEUVEN:

The availability of data and images were kept up to date, ongoing issues in ObTiMA were solved and data from ObTiMA were transferred to the CDP, de-identified and uploaded to the CHIC platform. Based on insights from the clinical trial which serves as the input for CHIC, further experimental research was prepared and started to provide additional data.

Interaction with the modellers was intensified by their reporting on the processing of the provided data.

Also, the clinical relevance of the CHIC project to the glioblastoma scenario was described in D2.5 and the clinical scenario and data were reported in D3.1.

Task 3.3: Non-small cell lung cancer (M1-M48)**ICCS:**

Provision of feedback to the clinicians.

Contribution to the discussion concerning the project's clinical relevance.

Contribution to the crystallization of the non-small cell lung cancer multimodeller hypermodelling scenarios.

USAAR:

Major work was done in providing the data that will be used in the non-small cell lung cancer scenario. ObTiMA is used for data collection. Data are anonymized and uploaded to the CHIC repository and can be used by developers of the hypermodel.

Together with WP2 the hypermodel for non-small cell lung cancer was further defined and clinical relevance addressed.

UPENN:

Cfr. Task 3.1

Task 3.4: Applying the CHIC infrastructure to other Cancer types (M12-36)

ICCS:

Contacts with UNITO in order to adapt various models being developed by UNITO to the CHIC framework.

Supporting the alignment of the prostate cancer models with the CHIC approach.

UNITO:

As far as the modelling activity is concerned, the EUREKA-2 based nomogram (Candiolo nomogram) has been completed, and the EUREKA-1's one is in progress.

Moreover, the application of the West model to predict the timing of prostate cancer recurrence following radical prostatectomy has been completed, while that referred to radical radiotherapy is in progress.

Also the application of the Gompertz model using innovative data treatment techniques has been submitted to Mathematics and Computer Simulations.

Further developments are in progress aiming at making available to patients and urologists a number of tools for predicting prostate cancer relapse probability.

The research activity about Prostate Cancer has been finalized and reported in the deliverable D3.2 'Report on scenarios and data from other cancer types for usage by the CHIC infrastructure' due at M36. In D3.2 the clinical data collection from EUREKA1 and EUREKA2 studies have been described.

Summary of details for each task

Task 3.1: Wilms tumor

ICCS:

Provision of feedback to the clinicians concerning a special set of micro-RNA data. Continuous interactions of ICCS with USAAR.

Contribution to the discussion concerning the project's clinical relevance and the clinical context adjustment of the basic science and technological components of the project for the nephroblastoma branch.

Contribution to the crystallization of the nephroblastoma multimodeller hypermodelling scenarios.

USAAR:

The UMBRELLA trial for kidney tumours, that is chaired by Norbert Graf (Task Leader) is still under development. This trial will use ObTiMA as the data management system. Corresponding CRFs are further developed.

Imaging data (DICOM) are collected from patients with nephroblastoma at the time of diagnosis and after 4 weeks of preoperative chemotherapy. Part of these DICOM data are post-processed by rendering the tumor using DoctorEye. A doctoral thesis is building a tool for automatic annotation of Wilms Tumor. This tool is under validation in a feedback loop with the developer.

The availability, accessibility and completeness of the nephroblastoma data were examined and new data are locally stored and uploaded to the CHIC repository as well.

UPENN:

Using the hybrid network modelling framework described above, a hypermodel framework has been implemented to integrate the miRNA data from Wilms tumor patients and predict the response to chemotherapy.

Task 3.2: Glioblastoma multiforme (M1-M48)

ICCS:

Provision of feedback to the clinicians.

Contribution to the discussion concerning the project's clinical relevance and the clinical context adjustment of the basic science and technological components of the project for the glioblastoma branch.

Contribution to the crystallization of the glioblastoma hypermodelling scenarios.

USAAR:

Perfect collaboration with KU Leuven on setting up and performing the data management with ObTiMA and the subsequent export. This comprised the installation of the software, support in creating the data definitions and CRFs, troubleshooting during the period of data entering and export to the consortium (through Custodix).

During each of these steps, iterative feedback was given by KU Leuven and incorporated into the ongoing development of ObTiMA, such as fixing reported issues, implementing new functionalities according the users' particular needs together with improvements to the overall usability of the software.

By working together with the respective partners, like UBERN, Custodix and ICCS, great care was also taken to interface and integrate both ObTiMA itself and the collected/exported data with the rest of the CHIC platform, such as enabling a straightforward import of ObTiMA data into the global data repository.

KU LEUVEN:

The HGG-2010 trial serves as the data source for the glioblastoma scenario for task 3.2. All material and information of the enrolled patients are stored at UZ Leuven as source documents with a continuous follow-up and an update of the local files every 6 months. During this reporting period the data and images were updated twice at UZ Leuven.

In a previous reporting period 82 patients' data sets were entered in ObTiMA but due to technical issues the export of these data sets failed and therefore they were no longer complete/accurate when exporting became possible during the current reporting period. Therefore the data sets in ObTiMA were updated based on the UZ Leuven source documents and at the same time previously missing data types (especially radiological parameters) were provided in ObTiMA.

MRI images, from which information was provided in the data sets in ObTiMA, were downloaded from the hospital's PACS system and pseudonymized/anonymized for sharing. Interaction with the partners from UBERN took place to discuss the purpose for using the images.

The pending problem of exporting the data from ObTiMA was solved. Other problems in the data management system were reported to the developers from USAAR during the continuous interaction. Study events and other features were integrated in the database of the GBM study.

The 82 patients' data sets were exported as pseudonymized data and transferred to Custodix via an sftp together with a descriptive explanation of the included parameters. The CDP determined the safety and sensitivity of the data and after de-identification the data were uploaded to the CHIC platform. The images were also transferred but not uploaded yet.

Interaction with other partners took place during this entire period, especially with USAAR for discussing the issues in ObTiMA, with Custodix for sharing the data and with ICCS for discussing the processing of the data. The latter learned the modellers to focus on more clinical significant parameters and learned the data provider that the complex data transfer is not flawless yet. Re-evaluation of the input and transfer had to be done after these discussions and is still ongoing.

Based on insights from the HGG-2010 trial, new experimental questions arose and a translational research protocol was designed for which ethical approval is obtained. All preparations on this research on pathological and biochemical samples were done and all experimental work is started in the meanwhile. Data from immune monitoring are being collected.

The clinical relevance of the CHIC project to the glioblastoma scenario was described in an additional deliverable ("D2.5 Clinical relevance to the CHIC project – Describing the integrated workflows of the scenarios from a clinical perspective"), which was provided by the assistant clinical coordinator. It sketched the expectations and considerations from the viewpoint of the clinical partners.

The clinical scenario and data from defined glioblastoma multiforme patients was reported thoroughly in deliverable D3.1 as a report of milestone MS5 ("Scenarios and data from nephroblastoma, glioblastoma multiforme and non-small cell lung cancer are available"). For the glioblastoma scenario theoretical background, the clinical problem, the clinical practice at UZ Leuven (thus the trial outline) and the generated data, including their source, storage and description, were provided in this deliverable.

Task 3.3: Non small cell lung cancer (M1-M48)

ICCS:

Continuous interactions with USAAR concerning the exploitability of the lung cancer data.

Provision of feedback to the clinicians.

Contribution to the discussion concerning the project's clinical relevance and the clinical context adjustment of the basic science and technological components of the project for the lung cancer branch.

Contribution to the crystallization of the non-small cell lung cancer multimodeller hypermodelling scenarios.

USAAR:

Together with WP2 data for the Non-small cell lung cancer hypermodel were further continuously collected. This includes clinical data, pathology data and molecular data (EGFR, KRAS, BRAF and

EML4-ALK). All clinical data are stored locally in ObTiMA. Imaging data are provided to Custodix for anonymization. Clinical and miRNA data are uploaded to Custodix. The clinical relevance of the corresponding hypermodel was further elaborated in an iterative process with all partners.

UPENN:

Using the hybrid network modelling framework described above, a framework has been implemented to predict the effect of clinical mutations in kinases on radiotherapy and targeted therapy in lung cancer.

Task 3.4: Applying the CHIC infrastructure to other Cancer types (M12-M36)

ICCS:

Contacts with UNITO in order to adapt various models being developed by UNITO to the CHIC framework, in particular regarding the multiscaleness of prostate models.

The idea is to align the prostate model as much as possible to the overarching principles of the CHIC project.

ICCS supported the alignment of the prostate cancer models with the CHIC approach.

UNITO:

■ Database update

Four centers have sent updates of their data for the EUREKA studies, consisting of follow-up data and seminal vesicles irradiation data. Also new centers have sent additional data from new cases for the EUREKA studies. New centers are joining the studies, which brings the total number of hospitals involved to 20.

Our final goal is to enhance our total data collection from the present 7314 patients with a 5-year median follow-up to 9000 patients with a median follow-up of at least 7 years (and to collect additional information, such as seminal vesicles irradiation data, pre-RT PSA lists and longer biochemical follow-up).

■ Modeling activity

Applications to lung cancer have been discussed with CHIC partners, applications to nephroblastoma will be discussed and applications to prostate cancer are in progress (see below and dissemination).

Association studies on prognostic factors

Four papers were written about association studies between the pathological variables collected and clinical outcomes. Data analysis were mainly performed using analysis of variance and chi-2 tests.

Two papers focus on the prognostic significance of lymphadenectomy extension (according to the number of lymph nodes resected), and the association between peri-neural and vascular invasion and oncologic outcomes, respectively. Two additional papers show the additional information provided by tertiary Gleason Score, and propose a simpler modified Gleason Score summing up primary and worst Gleason grades, respectively.

Statistical modeling

Three papers were written about statistical modeling applied to prostate cancer. Univariate and multivariate regression statistics (mainly logistic, because our outcomes are usually dichotomous) were applied together with Cox Proportional Hazard regression model for time-dependent variables, and log-rank tests to compare Kaplan-Meier survival curves.

One paper highlights the independent prognostic value of the percentage of positive prostate biopsies to predict biochemical outcome following radiation therapy.

Another article shows the poor value of CT and bone scintigraphy in the staging of EUREKA-1 surgical cohort.

A research proposes a new nomogram, called “Candiolo classifier”, for predicting recurrence after external beam radiotherapy for prostate cancer. It includes five pre-treatment parameters (i.e. PSA, Gleason Score, stage, percentage of positive biopsy cores and age) and overcomes D’amico risk classification in internal validation.

Mathematical modeling

A paper was written about mathematical modeling applied to prostate cancer. In this paper two main models of cancer growth were applied: Gompertzian model and West model (the latter being a more complex growth model with a stressed sigmoid shape due to time and/or tumor size dependent growth spurts driven by tumor biology, host characteristics and their reciprocal physio-pathological inter-dependence).

This paper (sent to Cancer Research, under review) shows a prediction mathematical tool based on West tumor growth law for predicting the timing of recurrence after Radical Prostatectomy. Another paper (sent to Mathematics and Computer Simulations, under review) shows a prediction mathematical tool based on Gompertz tumor growth law for predicting the timing of recurrence after Radical Prostatectomy.

Summary of significant results

ICCS:

Provision of feedback to the clinical partners regarding the exploitability of provided data or data to be provided.

Contribution to the crystallization of all the hypermodelling scenarios.

USAAR:

Data for usage in the hypermodels of nephroblastoma and Non-small cell lung cancer are defined and collected. The collection of data is ongoing. ObTiMA is further developed for the needs of CHIC.

KU LEUVEN:

The source documents and MRI images at UZ Leuven were updated (twice during this reporting period).

The 82 patients’ data sets were updated in and exported from ObTiMA.

The export from ObTiMA and the anonymised MRI images were transferred to the CDP via a secure link to approve sharing.

The data sets were uploaded to the CHIC platform.

ObTiMA as a data management system was evaluated continuously.

Continuous interaction with the partners in the dataflow chain and GBM modellers tackled problems and increased each other’s understanding.

A translational research protocol was approved by UZ Leuven. Experiments have started and new data are being collected.

The clinical relevance of the CHIC project to the glioblastoma scenario was described in D2.5

The clinical scenario and data from defined glioblastoma multiforme patients was reported in D3.1

UPENN:

A hybrid network modelling framework was built, combining mechanistic deterministic network modelling and Boolean modelling of mitogenic signalling pathways and DNA damage and cell cycle pathways. The models consist of MAPK, PI3K/Akt, P53, cell cycle growth and arrest, radiation and chemotherapy induced genotoxic stresses. Based on local, global sensitivity analysis, as well as network flows, the individual patient characteristics can be projected in the model and the response to chemotherapy, radiotherapy and targeted therapy can be predicted.

UNITO:

The first phase of data collection in EUREKA-1 and EUREKA-2 has been completed.

The local clinical database will be shared with other CHIC members according to the signed agreements.

Mathematical and statistical models are in progress. In particular the algorithm estimating the timing to recurrence based on the West and Gompertz law has been completed and submitted for publication.

These methods are aimed to be provided to clinicians/patients: for the clinicians to use them in clinical practice and as a tool, downloadable on the mobile phone, to be used and tested by patients and clinicians (in collaboration with BED).

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

ICCS:

Some delays in the provision of certain datasets occurred. Their impact to the completion of the foreseen tasks up to now appears to be rather minimal.

KU Leuven:

Deliverable 3.1 was not submitted in due time because of missing contributions.

KU Leuven re-allocated some budget upon request from the consortium to help to handling the additional workload for other partners.

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 3	Actual PM Period 3
1-ICCS	2.60	0.40	0.40
3-USAAR	49.00	14.00	26.78*
4-KULeuven	68.00	20.00	22.00**
9-UPENN	3.00	0.50	0.00
11-UNITO	14.00	4.00	3.82
Total	136.60	38.90	53.00

*) As there was the request for demonstrating the clinical relevance of the project a lot of additional work was to be done in the different scenarios within WP3. Part of this work was also strongly related to WP2 but could only be allocated to one WP. So WP3 is overspent and WP2 underspent.

**) KU Leuven: Due to the start of the translational research extra effort was done to speed up the extra work during this reporting period.

1.4 Work Package 4: Legal and Ethical Framework

Main objectives of this WP

This work package has five objectives:

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

Active tasks in this reporting period:

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

Summary of progress achieved towards objectives

The ethical and legal framework for data protection and copyright protection is in the second phase of its iteration. With respect to data protection, an initial version of the framework (including pseudonymisation & security) has been developed and deployed (both on the development as the production infrastructure). Some retrospective data from USAAR have been processed, checked and made available to the researchers under the framework. More data are being processed as they are made available by the providers. Plans are also underway to integrate some personal data into a separate database as and when required for the validation phase of the tools.

During the period under review, the IPR Memorandum requested by the reviewers was completed and signed by all partners.

Research was carried out to develop a Whitepaper and make recommendations to the European Commission and other stakeholders on ways of improving the European legal framework on patients’ and researchers’ rights and duties in E-health related research. The Deliverable (D4.4) that contained this was written and submitted on schedule in M36, and took account of the latest developments in the EU legislative process, leading up to the enactment of the new General Data Protection Regulation (due to replace Directive 95/46/EC in 2018).

Summary of details for each task

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

LUH led the task of setting up the data protection framework and have contributed in making sure that available retrospective data provided by partner have undergone the second layer of protection and processed according to the data protection framework set up in the first iteration. This includes a mechanism for releases of data from the clinical partners to the project to be checked and approved by the independent Center of Data Protection (CDP). The framework is now ready to process more data as they come in. CUSTODIX contributed in the deployment of the CHIC production data protection framework, and is also engaged in the ongoing de-identification of various CHIC datasets such as Nephroblastoma data (ODM XML, MiRNA and DICOM) and Glioblastoma data (ODM XML an DICOM and an update to the lung cancer dataset. USAAR contributed in the iterative process and contributed from a clinical perspective so that the framework will fit into the clinical needs. Regarding the envisaged validation phase where personal data may be needed, there is plan to adjust the framework so that a dedicated data repository for clinicians will be created with necessary controls mechanisms. ICCS continuously provided feedback to the legal and ethical task regarding all major aspects of the project which were of increased legal and ethical importance.

With respect to the IP aspect, all partners reached a consensus and the Memorandum of Understanding requested by the reviewers was prepared by LUH and has been signed by all partners.

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 whitepaper on the European legal framework on patients’ and researchers’ rights and duties in e-health-related research will make recommendations to the European Commission and other political stakeholders on the ongoing reforms in the European legal framework in this area. Particular attention has been paid to the data protection and privacy aspect they relate to patients and researchers, which are subject to current legal reform (in the form of the new General Data Protection Regulation, which is expected to become law in 2018), as well as the medical device regime for certifying medical devices, such as the clinical decision support tools in CHIC. The report also considered IPR aspects, and the desirability of reforms in that area, with special focus on the complexities created by the amalgamation of in silico models in relation to computer-assisted medical research. The whitepaper was submitted on time (as Deliverable D4.4) in M36.

Summary of significant results

The deployment of the CHIC production data protection framework. Ongoing de-identification of various CHIC datasets such as Nephroblastoma data (ODM XML, mirna and DICOM) and Glioblastoma data (ODM XML and DICOM), and the validated data have been made ready for data sharing

IPR Memorandum completed and signed

Research on the whitepaper conducted and publication as scheduled in M36

Summary on actions taken to meet the recommendations from the 4th CHIC review

WP4 is advising on the legal implications of approaches for demonstrating the clinical relevance of the hypermodels, and is ready to take care of the issues arising from the chosen approach. If the need arises for personal data to be processed, the workpackage is also dealing with IPR issues, including arising from collaboration that occurred with the related MyHealthAvatar project. Discussions already underway regarding the legal aspects of exploitation, including the ongoing clinical testing and certification of the in silico models as decision support tools.

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

Person months in tasks 4.3 and 4.4 overspend, which arose from additional legal research and drafting requirements, including for IPR memorandum of understanding and whitepaper, and with respect to maintaining the CDP. A detailed explanation has been/will be included in the justification separately presented by LUH and Custodix to EC via the CHIC project office.

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 3	Actual PM Period 3
1-ICCS	2.00	0.40	0.40
3-USAAR	4.00	1.50	0.00
8-LUH	48.00	12.00	16.17*
9-UPENN	2.50	0.50	0.50
13-Custodix	7.00	3.00	5.70
Total	63.50	17.40	22.77

*) The legal research and analysis underlying the WP4 whitepaper/deliverable D4.4, as well as on IP matters, proved particularly complex due to the unstable legislative situation in the EU. In this respect account needed to be (and was) taken of the changing regulatory landscape for data protection law (resulting from the enactment of the General Data Protection Regulation to replace the present EU Directive), as well as ongoing legal reforms in the IP and medical devices areas.

1.5 Work Package 5: IT Architecture

Main objectives of this WP

- The definition of the reference architecture for subsequent implementation and integration along with repetitive refinement and improvements cycles.
- The definition of appropriate interfaces among the modules to enable interoperability.
- Identification, analysis and selection of relevant existing standards with an impact on the system developed.
- Making sure that the legal and ethical restrictions defined in WP4 are met by the system through the definition and implementation of the appropriate policies and security mechanisms.
- Comparative analysis of the design of a private cloud infrastructure to support data processing, it's by utilizing resources within individual institutions.

Active tasks in this reporting period:

- Task 5.1, Reference Architecture (M1-42)
- Task 5.2, Security tools and services (M1-46)
- Task 5.3, Private cloud infrastructure (M1-48)

Summary of progress achieved towards objectives

The Review report of the second annual review of the project identifies that there is good overall progress in the work of WP5. In more detail it states that the CHIC technical architecture has been defined covering functionality, information, deployment and security views. Security guidelines and updates of the initial version of security tools has been produced (D5.2) and techniques to build the cloud infrastructure, available to the community (D5.3) has also been produced. In parallel the reviewers report that the decision of the project (and WP5) to abandon the plans to convert to a public cloud was an excellent one. Nevertheless, it also states that there are deficiencies relating to

the fact that a) the reference architecture has not been documented and b) the interplay between the IT architecture and the clinical models is not yet made explicit. An overall recommendation relates to the need to achieve better integration of the various platform elements, which – partly – relates to the work in WP5.

WP5 has taken full notice of these remarks and recommendations. During the third year it has focused, through regular skype meetings and participation into the planned consortia and technical meetings, on refining aspects of defined CHIC architecture and through appropriate and informed technical decisions to ease the overall integration challenge.

In more detail the work done during the reporting period relates to:

Task 5.1, Reference Architecture

All partners were involved in the effort to refine the reference architecture of the CHIC infrastructure, focusing specifically on the required functionality for clinicians to re-identify their patients, so that personalized clinical decisions can be taken, once the CHIC hypermodels are executed. WP5 also focused on the production of an updated version of D5.1.1 (The initial CHIC Technical Architecture), in an attempt to respond to the specific review comment, i.e. to better document the CHIC the reference architecture. New architectural components were also defined, implemented and integrated into the overall architecture as a result of the overall effort of the Consortium focusing on the clinical adaptation of the CHIC platform.

Task 5.2, Security tools and services

The CHIC security framework has been deployed and integrated with the data upload services and the data repositories. The main emphasis of the work during this period was on supporting the seamless integration of platform components and, in the process, on studying of issues that may affect final architectural specifications. In specific, supporting the integration between the data repository within the CHIC security framework has been extended in terms of authentication and authorization, and the model/tool and in silico trial repositories APIs (web services) were extended to make use of the CHIC brokered authentication mechanism. Significant efforts were made to incorporate the auditing system of the CHIC security framework in the data repository. The VPHHF was deployed and tested, with security tools and services integrated, on the production node of CHIC.

Task 5.3, Private cloud infrastructure

The CHIC private cloud infrastructure has been implemented and is fully functional, in line with the objectives of Task 5.1.

This task, based on the experience with the prototypes and the feedback from WP10, is responsible for implementing the spiral process of the architectural refinement and improvements. During the reporting period all partners have contributed to the production of deliverable D5.3. In specific Custodix has been involved in providing contributions to the refinement of the CHIC reference architecture with regards to the provision of functionality for clinicians to re-identify their patients. ICCS interacted with partner FORTH with regard to the creation and configuration of one virtual machine for the in silico trial repository and one virtual machine for the WP6 common virtual machine. Both partners worked on the firewall configuration of the virtual machine which hosts the in silico trial repository.

Summary of details for each task

Task 5.1, Reference Architecture

TEI-C and FORTH participate in all the Architectural Board activities, such as meetings and Skype telcos, gathering feedback in order to update and enhance the initial Reference Architecture definition. Equally TEI-C and FORTH participate and contribute in all the CHIC activities where feedback from the Reference Architecture perspective is needed, in order to coordinate the implementation and integration of the architecture.

All partners are involved in the refinement of reference architecture of the CHIC infrastructure with regards to the provision of functionality for clinicians to re-identify their patients. All partners are also involved in the production of an updated version of D5.1.1 (The initial CHIC Technical Architecture), in an attempt to respond to the specific review comment, i.e. to better document the CHIC the reference architecture. Deliverable D5.1.2 (Deployment models of the CHIC technical architecture and its private cloud) is in preparation.

In addition, a new architectural component called “Clinical Research Application Framework” (CRAF) was introduced into the architectural framework, for the clinical adaptation of the CHIC platform. This is a “disrupting” activity, since it requires a) the adaptation of the whole architecture for the clinical setting, b) handling of patients that are not fully anonymized and c) managing patient data access based on the users (clinicians) identifiers.

In parallel CUSTODIX, in conjunction with WP4, has further developed the data protection (security) framework and coordinated its deployment within the CHIC production environment. The CHIC security framework, which includes user management, authentication, authorisation and auditing, has been deployed and integrated with all of the CHIC components and services such as the pseudonymisation services (TTP, PIMS), repositories (data repository, model repository and in silico trial repository) and the model execution framework. To support the evolution of clinical scenarios developed and the use of personal data, additional security measures are currently in design and development such as multi factored authenticated, patient oriented auditing and a central authorisation policy based endpoint. Finally, a CHIC SSL proxy has been setup to handle all incoming SSL connections to the CHIC platform.

Task 5.2, Security tools and services

The technical implementation of the authentication mechanism for the REST service has been extended to support SAML delegation tokens. Those are required for some advanced SAML use cases which involve a single logical transaction that spans one or more intermediate clients or servers. A common example includes a SAML-enabled web site acting on behalf of a logged-in user while accessing additional SAML-enabled web services. Generalizing this example, a number of intermediaries might be transited before the final point of access. If a SAML assertion is used as a security token to authenticate and authorize such access, it is important that the identity and order of intermediaries, if any, be expressed within the token in some fashion.

The data repository has been prepared to incorporate the auditing system of the CHIC security framework. The goal is to produce high quality information on events with potential hazardous security risks. For this purpose, the audit data model called XDASv2 has been selected. At the heart of the model is the XDASv2Event object. This object contains an id and might contain a reference to another event. It also contains the main actors of an event: the initiator, the target and the observer of the event, along with the action undertaken, and a term indicating the severity of the event.

Partners also interacted regularly in order to resolve the technical challenges for the model/tool and in silico trial repositories web services to make use of the CHIC brokered authentication mechanism. ICCS provided the entity id, the SAML metadata, the domain name and the internal IP of the

model/tool and in silico trial repositories, in order for partner CUSTODIX to configure accordingly the CHIC proxy and the CHIC identity provider. The model and in silico trial repositories now accept http requests that are coming either from the CHIC cloud or from the CHIC proxy server.

The CHIC pseudonymisation services have been updated to better handle ODM XML data. PIMS has been deployed and integrated with CHIC to support patient de-identification and re-identification in the clinical scenario. Contrary to the research scenario where de-identification is only allowed with manual intervention of the CDP.

The refactored VPHHF (version alpha 0.2) has been deployed and tested with security tools and services integrated on the production node at FORTH. USFD ensured all the communications among VPH-HF components and other partner's components were managed complying with the security framework. Feedback was provided to partners CINECA and CUSTODIX, mainly regarding the mutual authentication between components in VPH-HF and between VPHHF and the other services provided by partners.

Since task T5.2 has been completed, security patches and further integration with components will, from now on, be performed under T5.1 and WP8.

Task 5.3, Private cloud infrastructure

In the context of this task, the WP5 partners have a) investigated the applicability of open source TEI-C and FORTH continue to support the productive cloud infrastructure, providing resources and technical support to the consortium. In parallel a process for the continuous gathering of feedback and additional requirements from the end users of the cloud infrastructure has been put in place, in order to enhance and upgrade the infrastructure as necessary.

The data processing and visualisation requirements conducted in WP9 as well as the use cases conducted in WP2 will be taken into account when managing the resource allocation (e.g. storage, compute power). Furthermore, we are planning to expose the data processing and visualisation algorithms within CHIC into reusable REST/SOAP web services in this community cloud.

The consortium has begun studying licensing issues and legal issues in such a private cloud computing environment. The work will be reported in future deliverable.

One problem that WP5 faces is the fact that whilst Task T5.3 is officially ending on M27, the relevant decision not to port the CHIC infrastructure on a public cloud, necessitates that this task needs to continue until the end of the project.

Relevant decisions need to be taken in the context of the planned contract amendment of the project.

Summary of significant results

The CHIC private cloud infrastructure has been redesigned for productive use and is now fully functional. The uninterruptable provision of the private cloud infrastructure is seen as a significant result. The CRAF component has been introduced and is being further developed.

The CHIC security framework is available, deployed and integrated with all of the CHIC repositories, services and tools. In parallel, the extension of CHIC security framework to support SAML delegation tokens has also been an important achievement.

An initial integration between the data repository and the auditing system of the CHIC security framework has been performed. VPH-HF alpha v0.2 including security tools and services successfully deployed on the CHIC production node

Summary on actions taken to meet the recommendations from the 3rd CHIC review

The main recommendations from the 3rd CHIC review that relate to WP5 are:

a) the reference architecture has not been documented and b) the interplay between the IT architecture and the clinical models is not yet made explicit. In parallel an overall recommendation relates to the need to achieve better integration of the various platform elements, which – partly – relates to the work in WP5.

In relation to these recommendations WP5 and the Consortium as a whole has taken specific actions. These relate to:

- i) All partners in WP5 are involved in the production of an updated version of D5.1.1 (The initial CHIC Technical Architecture), in an attempt to respond to the specific review comment, i.e. to better document the CHIC the reference architecture. Finally, efforts have been taken to further refine the reference architecture of the CHIC infrastructure with regards to the provision of functionality for clinicians to re-identify their patients.
- ii) The integration of architectural elements, under the coordination of the Integration Manager, is currently taking place with emphasis on providing clinically relevant functionality. In this process the interplay of architectural components and models will become much more apparent.

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

Task 5.3 was scheduled in the Technical Annex to finish on M27 and to be 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 the CHIC private cloud, offered, managed and extended by partner FORTH, will be available to the end of the project.

This decision implies that additional effort will be required by partners TEI-C and FORTH, who are responsible for the design, implementation, extension and optimization of the private cloud infrastructure. The above development was not foreseen in the Technical Annex and has an impact on the available resources and planning. The CHIC consortium has decided that FORTH will act as the Task leader for T5.3 and will need to increase its personnel month in Task 5.3 in order to run, maintain and potentially extend the CHIC private cloud in line with the evolving project requirements. Actions are in progress with the CHIC partners and the management team for an amendment of the Technical Annex in order to reflect and alleviate this change of planning.

This decision has an impact also in WP10 and milestone MS26. The CHIC Technical Annex initially planned that after the end of task T5.3, WP10 would lead the integration activities to deploy the CHIC platform in a public cloud and would be documented in D10.4 (The PhysiomSpace-enabled storage on public clouds). With the extension of task T5.3, this integration activity by WP10 and the corresponding deliverable is not applicable.

Additional tasks, including additional documents (internal or external): yes

Deliverable D5.1.2 "Deployment models of the CHIC technical architecture and its private cloud" has been introduced as a new deliverable in the amendment of the Technical Annex. Also task T5.3 has been extended to the end of the project, taking into consideration the key decision not to port the CHIC platform in a public cloud infrastructure, based on specific legal analysis and recommendations.

Budget changes necessary: 1 yes

As described above, budget changes are necessary. The budget changes have been handled and fully justified in the context of the last contract amendment.

Deviation from planned person month efforts? Yes

There are no major deviations from the planned efforts, apart from the fact that some of the partners, although active and contributing to the work of WP5, are not claiming significant efforts during this reporting period. As a result of the extension of Task 5.3 until the end of the project and the additional effort needed from FORTH, which was not originally planned in the Technical Annex, an increase in the planned person month effort has been documented in the amendment of the Technical Annex.

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

All critical objectives have been achieved in time.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP5			
Partner	Planned PM Total	Planned PM Period 3	Actual PM Period 3
1-ICCS	3.40	0.70	0.70
5-BED	10.00	0.00	0.00
6-USFD	6.00	1.26	1.79
7-FORTH	29.00	6.50	7.50
12-UBERN	4.00	1.00	1.00
13-Custodix	19.00	7.00	8.61
14-Philips	15.00	5.00	11.90*
16-CINECA	6.00	0.00	0.00
17-TEI-C	21.00	6.00	5.03
Total	113.40	27.46	36.53

*) First focused on the definition of uniform interfaces for linking the various CHIC repositories. Next, Philips has proposed an architecture enabling the integration of models as external services with the jBPM workflow framework to link to the clinical processes and data. In the last reporting period Philips has also investigated architectural approaches for the integration with clinical care environments based on widely-used healthcare standards.

1.6 Work Package 6: Cancer Models and Hypermodel Design

Main objectives of this WP

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

Active tasks in this reporting period:

- Task 6.1, Cancer hypomodelling and hypermodelling strategies and elementary models (M1-39)
- Task 6.2, Subcellular cancer modeling (M1-39)
- Task 6.3, Biomechanics enhanced tumour modeling (M1-36)
- Task 6.4, The clinical modeling paradigms of nephroblastoma, glioblastoma and lung cancer (M6-46)
 - SubTask 6.4.a: The nephroblastoma paradigm
 - SubTask 6.4.b: The glioblastoma paradigm
 - SubTask 6.4.c: The lung cancer paradigm
- Task 6.5, The colon cancer modeling paradigm (M6-46)

Summary of progress achieved towards objectives

Task 6.1, Cancer hypomodelling and hypermodelling strategies and elementary models

ICCS:

For each paradigmatic tumour type a palette of hypermodels is under development depending on the degree of detail that is required for a particular aspect of the biological phenomenon.

A first version of the lung cancer hypermodel was presented and demonstrated during the 3rd CHIC review.

A number of toy hypomodels have been developed and presented during the 3rd CHIC review.

A paradigmatic hypomodelling and hypermodelling strategy including elementary models has been demonstrated during the 4th CHIC review.

Special emphasis was put on the clinical relevance.

UOXF:

- Previously developed ODE model of vascular growth and PDE model of nutrient delivery has been uploaded to the model repository and successfully executed with ICCS, UBERN and FORTH models.
- A new ODE based hypomodel of vascular growth based on the model of Hahnfeldt has been developed, with source code made available to USFD. It is the basis of discussions on the development of surrogate modelling tools by USFD.

- A range of models of oxygen transport and delivery from networks of discrete blood vessels have been developed and compared, based on experimental images of vascular structures. Source code is to be made available.
- Proposed common virtual machine (CVM) for integrated model development and testing. This has been adopted by modelling partners and is being used for on-going integration testing. Took part in model integration and debugging with WP6 and WP7 partners on the CVM prior to January 2016 review demonstration.

UBERN:

- The coupled Biomechanical-OncoSimulator has been decoupled into an independent hypo-model for biomechanical simulations (BMS).
- Standardised interfaces for configuration and data exchange between BMS and other hypomodels have been implemented.
- The hypo-model for biomechanical simulations has been extended to communicate with other CHIC hypo-models and to integrate into the hypermodeling workflow.
- The meshing tool has been improved to allow variable element sizes for different regions of interest, and a 'remeshing' mechanism has been introduced in BMS to allow simulation of large tumour induced deformations.

UPENN: (Tasks 6.1, 6.2, 6.4)

A molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations was established. As part of the task a multiscale method to combine the molecular studies with signalling network studies was developed.

A hybrid subcellular model for cell fate was implemented to include the effect of STAT signalling, radiation dosage, chemotherapeutic exposure, and miRNA profile-mediated signalling.

FORTH:

FORTH participated in all modelling coordination activities providing information needed in order to update and enhance the initial standardized cancer hypermodels.

FORTH continues the development of the following hypomodels:

- A sub-cellular model that describes the aberrant metabolism of cancer cells at genome scale incorporating gene expression data into well-developed constraint-based.
- A hybrid discrete-continuous tumor growth model incorporating discrete (detailed) angiogenesis information.
- A continuous tissue-level tumor growth model simulating cell populations and interactions with coarse angiogenesis information.

FORTH works towards implementing the linking interface between the subcellular metabolic model and the Angiogenesis/ Neovasculature model.

UNITO:

The hypomodels already developed by UNITO have been revisited in order to make them linkable to other models and re-writable in the context of hypermodelling.

The model takes into account both resistant and responsive to hormonal therapy cell populations. It also considers their interplay assuming that mutations and different response to therapies can occur.

Considering different types of growth, the growth parameters of the tumor and the kill rates of the drugs can be estimated.

Task 6.2, Subcellular cancer modeling

UPENN: (Tasks 6.1, 6.2, 6.4)

A molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations was established. As part of the task a multiscale method to combine the molecular studies with signalling network studies was developed.

A hybrid subcellular model for cell fate was implemented to include the effect of STAT signalling, radiation dosage, chemotherapeutic exposure, and miRNA profile-mediated signalling.

UOXF:

- Implemented within CHASTE (UOXF software for multiscale modeling) an oxygen-dependent model of the cell cycle (see: Owen et al, Cancer Research, 2011) and model extensions that account for contact inhibition.
- Implemented within CHASTE models of radiation-induced cell death

FORTH:

- Implementation of the lung cancer-specific metabolic model to meet the initially foreseen hypermodel demonstrator. Related work is currently validated.
- Development of a metabolic model specific to nephroblastoma (Wilm's tumour). This work is in progress.

ICCS:

Utilization of the provided molecular data by ICCS in order to specialize the linking procedure for particular hypermodels.

ICCS coordinated the linking of subcellular cancer models with cellular and supercellular cancer models for the development of multimodeller hypermodels.

Task 6.3: Biomechanics enhanced tumour modelling

UBERN:

- The meshing tool has been improved to allow variable element sizes for different regions of interest, and a 'remeshing' mechanism has been introduced in BMS to allow simulation of large tumour induced deformations.
- A new biomechanical model has been developed for simulating the combined effects of volumetric tumour growth and tissue infiltration.

ICCS:

In close collaboration with UBERN ICCS integrated the biomechanics hypomodel into the trunk hypomodel of pure tumour growth and response to treatment.

ICCS coordinated the linking of the biomechanics models with the main oncosimulator models for the development of multimodeller hypermodels.

FORTH:

FORTH participates in the discussions related to the needs of this task in order to effectively provide the spatial and tissue specific information needed to initialize the biomechanics model.

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

UPENN: (Tasks 6.1, 6.2, 6.4)

A molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations was established. As part of the task a multiscale method to combine the molecular studies with signalling network studies was developed.

A hybrid subcellular model for cell fate was implemented to include the effect of STAT signalling, radiation dosage, chemotherapeutic exposure, and miRNA profile-mediated signalling.

FORTH:

FORTH as part of the elementary modeling team closely attends and participates in the proposed clinical scenarios contributing in all three cancer types.

UBERN:

Body-site specific biomechanical parameters for the simulation of Nephroblastoma, Lung cancer and Glioblastoma cases have been identified from literature. Patient-specific anatomic information was obtained by segmenting suitable images obtained from the CHIC data repository for both Lung cancer and Nephroblastoma cases. The biomechanical simulator has been tested successfully as part of the CHIC hyper-modelling workflow for these scenarios.

Independent testing of the diffusion-enhanced biomechanical model for glioblastoma patients using information derived from publicly available anatomic atlases.

UNITO:

Careful investigation to find similarities and differences with respect to prostate cancer, in order to share knowledge.

SubTask 6.4.a: The nephroblastoma paradigm

ICCS:

Extensive transformation of a pre-existing ICCS simulation code of nephroblastoma growth and treatment response in order to serve as a trunk hypomodel for the nephroblastoma multi-modeler hypermodel.

Clinical adaptation studies.

Regarding the Wilms mechanistic model, ICCS has worked on extensive parametric and sensitivity studies, literature review of the kinetics data of nephroblastoma, clinical adaptation methodology, adaptation of the hypomodel to MUSCLE environment, etc.

A close interaction with WP5, WP6, WP7, WP9 and WP10 has taken place for the specification of the hypermodel's data requirements, the analysis of the available data, the definition of data preprocessing requirements, the finalization of the data flow with the other models, the definition of the interface with hypermodelling infrastructure, the implementation of model configuration through the infrastructure, etc.

UOXF:

The 'UOXF_Vasculature_Nephroblastoma' hypomodel was re-parameterized for glucose transport and consumption, rather than for oxygen as used in the lung cancer case, with outputs passed to the FORTH Metabolic model for nephroblastoma. This model is currently being used in the nephroblastoma demonstration hypermodel.

UOXF has also participated in discussions with several CHIC consortium members regarding

1. Linking the vascular component with a continuum cell growth component being developed at FORTH.
2. Linking the vascular component with ICCS's model for tumour growth and response to treatment.
3. The development and experimental validation of a glioma model with vasculature (with UBERN).
4. The execution of the vascular component and troubleshooting in its execution (with USFD).

In all cases, source code for the vascular component and instructions for use have been provided.

UBERN:

Parameterisation of the biomechanical simulator for the nephroblastoma scenario.

UNITO:

Modelling in these fields has been carefully investigated to find similarities and differences with respect to prostate cancer, in order to share knowledge with the other researchers within CHIC. In particular the nephroblastoma is investigated by macroscopical models based on the Universal Phenomenologies in order to study the effects of combined chemotherapies on cancer growth. The growth parameters and the kill rates were found in literature but in accordance with the values found independently by the other partners (UPENN model).

SubTask 6.4.b: The glioblastoma paradigm

ICCS:

Further refinements on a mechanistic model of the response of GBM to immunotherapy treatment.

An alternative mathematical approach to the phenomenon of GBM invasion to surrounding tissues based on the Brownian motion was developed and published.

Development of a model that estimates the estimation of anisotropic diffusion of glioma cells in normal brain tissue.

Development of a model for tumor growth in inhomogeneous and time varying chemical fields.

Evaluation of the data provided for the glioblastoma case.

Machine learning approaches to the clinical questions regarding response of glioma patients in treatment with radiotherapy, temozolomide chemotherapy and immunotherapy.

UBERN:

Parameterisation of the biomechanical simulator for the glioblastoma scenario.

SubTask 6.4.c: The lung cancer paradigm

ICCS:

Towards the construction of Lung Cancer Hypermodel ICCS has worked on the following:

- Decoupling of the initially coupled ICCS's tumor growth core algorithm with UBERN's biomechanics model.
- Definition of the data flow between the Oncosimulator and the Biomechanics, Vasculature and Metabolic models
- Adaptation to MUSCLE environment

Two running, muscle-enabled lung hypermodel scenarios have been successfully implemented:

Scenario1: Oncosimulator-Biomechanics models

Scenario2: Oncosimulator-Biomechanics-Metabolic-Dummy vasculature models

Extensive lung cancer growth and response to treatment literature survey and sensitivity analyses. A preliminary model adaptation study based on one clinical case.

Regarding the lung mechanistic model, ICCS has worked on extensive parametric and sensitivity studies, sensitivity analysis, study of the kinetics, clinical adaptation methodology, analysis and preprocessing of the clinical data, finalization of the data flow between the oncosimulator and the other hypomodels, fine tuning of the model, etc.

Furthermore, interaction with the technical work packages has taken place for the definition of the interface with the hypermodelling infrastructure, the definition of the required elements to be included in the user graphical interface, the semantic representation of the models, the visualization of simulation results, etc.

Regarding the lung statistical model, ICCS has worked on the outline of the state of the art on the statistical models, the development of a preliminary workflow and the provision of additional data through an extensive interaction with USAAR.

UBERN:

Parameterisation of the biomechanical simulator for the lung cancer scenario.

Task 6.5: The prostate cancer modelling paradigm

UNITO:

The development of a nomogram on prostatectomized cohort (EUREKA1 study) is in progress.

A correlation between the timing of relapse and the growth parameter (West model) has been successfully shown and validated on EUREKA1 data.

A new approach using a stochastic method in combination with RBF interpolation has been validated on EUREKA1 data (submitted) and the validation on EUREKA2 is in progress.

The hypermodel, which connects the tissue level (tumor growth according to PSA level) to the cellular level (response to therapies) to the subcellular level (prediction of the response according to the detected biomarkers level) is in progress.

ICCS:

Interaction of ICCS with UNITO in order to ensure compatibility of the colon cancer model development with the CHIC framework

ICCS supported the integration of the prostate cancer modelling paradigm into the CHIC modelling platform.

Summary of details for each task

Task 6.1, Cancer hypomodelling and hypermodelling strategies and elementary models

ICCS:

A multi-modeller hypermodel concerning lung cancer and addressing crucial molecular, cellular and supercellular aspects of tumour growth and response to treatment for the paradigm of non-small cell lung cancer has been delineated by ICCS and adopted by all WP6 partners. A first version of the hypermodel was presented and demonstrated during the 3rd CHIC review.

Refinement of the basic strategies for developing cancer hypomodels and hypermodels based on the accumulated experience before that period. For each paradigmatic tumour type a palette of hypermodels is under development depending on the degree of detail that is required for a particular aspect of the biological phenomenon. At least one hypermodel for each tumour type is to undertake systematic clinical adaptation and partial clinical validation.

A paradigmatic hypomodelling and hypermodelling strategy including elementary models has been demonstrated during the 4th CHIC review. Special emphasis was put on the clinical relevance.

FORTH:

FORTH participated in all modelling coordination activities providing information needed in order to update and enhance the initial standardized cancer hypermodels to be fully addressed in D6.3.

FORTH continues the development of the following hypomodels:

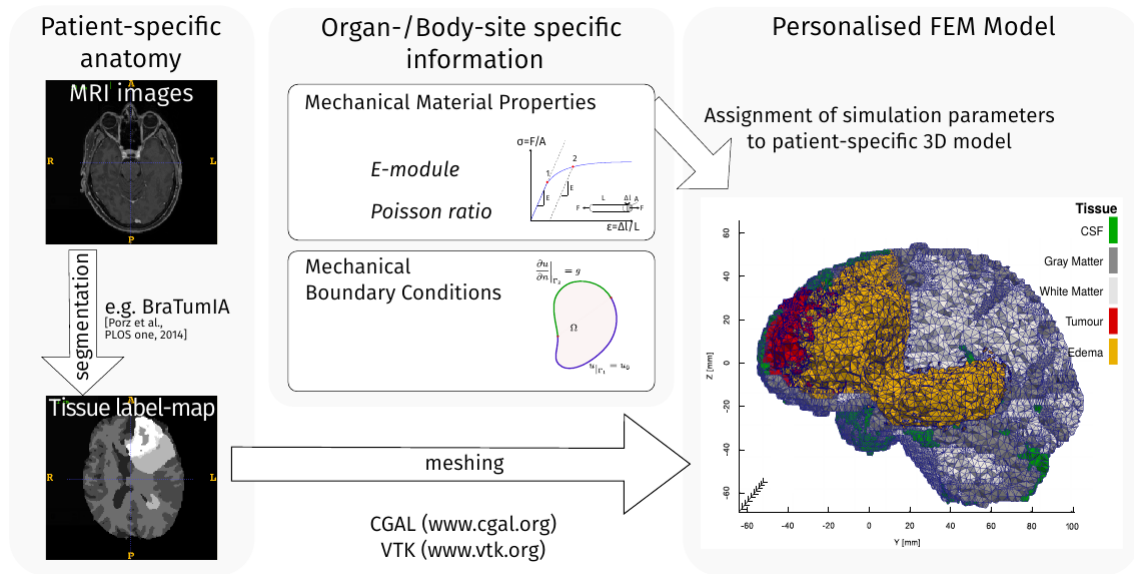
- A sub-cellular model that describes the aberrant metabolism of cancer cells at genome scale incorporating gene expression data into well-developed constraint-based methods such as the Flux Balance Analysis method, focusing on the lung cancer case (NSCLC).
- A hybrid discrete-continuous tumor growth model incorporating the discrete (detailed) angiogenesis information to be provided by UOXF.
- A continuous tissue-level tumor growth model simulating cell populations and interactions with the coarse angiogenesis information to be also provided by UOXF.

FORTH works towards implementing the linking interface between the subcellular metabolic model and the Angiogenesis/ Neovasculature model in a closed loop design.

UBERN:

UBERN has extended the biomechanical simulator (BMS) to for integration as hypo-model in CHIC hyper-model workflows:

- Personalised biomechanical predictions require a suitably configured computational model whose properties depend on characteristics of the individual patient (tumour and healthy tissue geometry), as well as on the organ/body-site (material parameters, boundary conditions). Manual creation of such models is complicated and not a viable approach the CHIC context. Therefore, a preprocessing pipeline has been implemented and integrated into BMS to allow automatic generation of personalized Finite-Element (FE) Models from patient-specific organ/tumour segmentation and body-site-specific parameters, Fig. 1.



- This personalised FE model is then initialized with a spatial tumour cell concentration map provided by the OncoSimulator hypo-model. From this concentration map, BMS computes the 'direction of least pressure' relative to each model element. This information is transferred to the OncoSimulator hypo-model and interpreted as the most likely direction of tumour expansion.

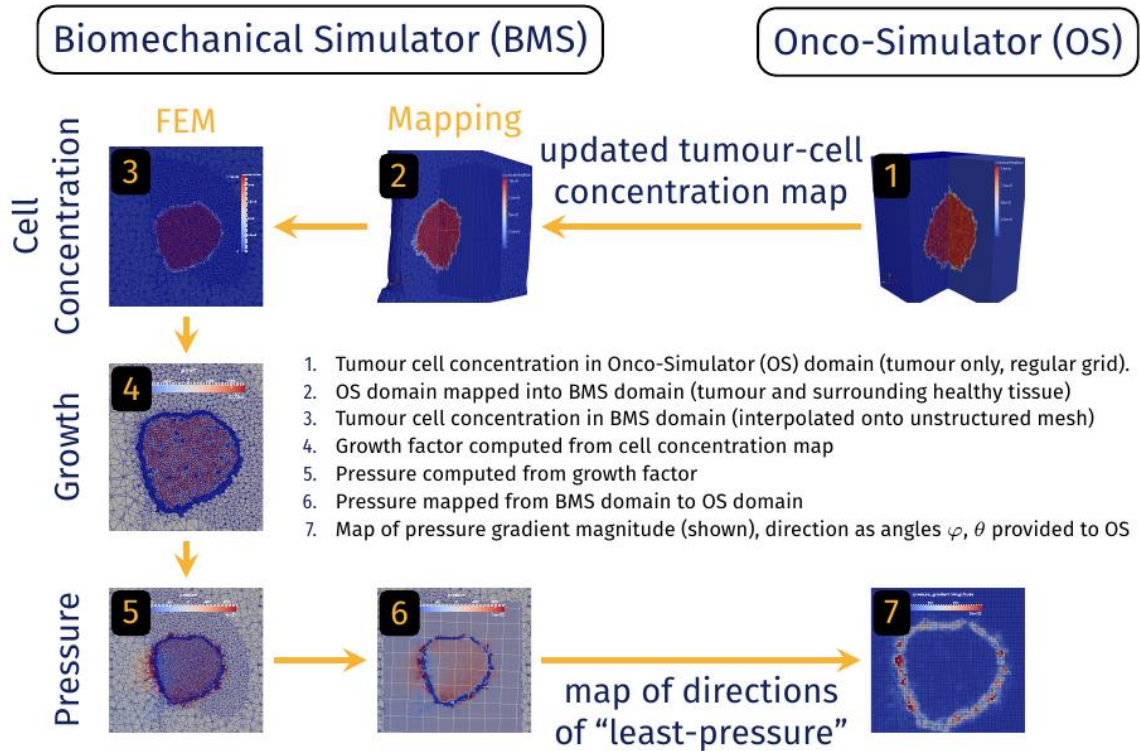


Fig. 2 illustrates the coupling between both hypo-models and details the computational steps involved.

UNITO:

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

The model takes into account both resistant and responsive to hormonal therapy cell populations. It also considers their interplay assuming that mutations and different response to therapies can occur. Considering different types of growth, moreover, the growth parameters of the tumor and the kill rates of the drugs can be estimated: this knowledge could support the prediction of the future behaviour of the cancer (time to relapse, severity and response to treatment).

UPENN: (Tasks 6.1, 6.2, 6.4)

A molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations was established. As part of the task a multiscale method to combine the molecular studies with signalling network studies was developed.

A hybrid subcellular model for cell fate was implemented to include the effect of STAT signalling, radiation dosage, chemotherapeutic exposure, and miRNA profile-mediated signalling.

The sub-cellular UPENN component is integrated as three distinct hyper-models (levels), which then get integrated with the multi-modeller hyper model through an integration layer. The integration layer serves as an interface between the three subcellular level models and the overall multi modeler hypermodel

UOXF:

- (Chic) Integration of the UOXF_Vasculature_Nephroblastoma model with the MUSCLE and VPHHF based execution environments. This required modifications to the build system for the Chaste software (www.cs.ox.ac.uk), allowing for the execution of Cell Based Chaste models from stand-alone archives and full run-time coupling with other codes. This allows rapid development of further, and more detailed, hypomodels using Chaste libraries in future. A Chaste user project with build modifications is available to partners.
- (Both) An ODE model for vascular tumour growth (see: Hahnfeldt et al, Cancer Research, 1999) has been implemented using Chaste. It will form the basis for surrogate modelling tool development in collaboration with USFD.
- (Chaste) A range of models of oxygen transport and delivery from discrete vessel networks has been developed. These models are being parameterized using high resolution imaging data of mouse vasculature (source: Muschel lab, Oncology, UOXF) and microfluidics based blood flow data (source: Alarcon lab, Centre De Recerca Matematica, Barcelona). The new software includes image segmentation of tubular structures, automated centreline extraction and finite element meshing, which can be made available to modelling partners.
- (Chaste) On- and off-lattice models of angiogenesis in 2D and 3D have been developed using CHASTE. These models account for discrete vessels, cells, blood flow, structural adaptation and chemical transport and are compatible with the MUSCLE and VPHHF execution environments (source code will be released in due course). A demo of the angiogenesis hypomodels has been developed and will be transferred to the CHIC model repository once it has been fully tested.
- Formal processes for the verification, validation and uncertainty quantification (VVUQ) of simple models of tumour growth have been established.

Task 6.2, Subcellular cancer modelling

UPENN: (Tasks 6.1, 6.2, 6.4)

A molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations was established. As part of the task a multiscale method to combine the molecular studies with signalling network studies was developed.

A hybrid subcellular model for cell fate was implemented to include the effect of STAT signalling, radiation dosage, chemotherapeutic exposure, and miRNA profile-mediated signalling.

- Layer 1 or Structural Atomistic Level: Molecular Model (based on molecular modeling and dynamics simulations)
- Layer 2 or Molecular Association Level: Machine Learning Algorithm (comprises of a machine learning and predictive algorithm for profiling benign and oncogenic mutations in signaling proteins)
- Layer 3 or Molecular Network Level: Network Model (establishes network models for EGFR signaling that are specific to each mutant.)

ICCS:

The molecular data provided within the reported period were utilized by ICCS in order to specialize the linking procedure for particular hypermodels.

ICCS coordinated the linking of subcellular cancer models with cellular and supercellular cancer models for the development of multimodeller hypermodels.

FORTH:

- FORTH devoted significant effort to implement the lung cancer-specific metabolic model to meet the initially foreseen hypermodel demonstrator. FORTH has undertaken this additional task (will be part of the amendment session) and the related work is currently validated.
- After careful consideration of the reviewer's comment, FORTH was assigned the extra task to develop a metabolic model specific to nephroblastoma (Wilm's tumour). This work is in progress.

UOXF:

- Implemented within CHASTE (UOXF software for multiscale modeling) an oxygen-dependent model of the cell cycle (see: Owen et al, Cancer Research, 2011) and model extensions that account for contact inhibition.
- Implemented within CHASTE models of radiation-induced cell death

Task 6.3, Biomechanics enhanced tumour modelling

UBERN:

An extension of the biomechanical model was developed for simulating growth characteristics of invasive tumours, such as Glioblastoma. This model combines simulation of the mass-effect caused by a growing solid tumour with a reaction-diffusion model, accounting for the tumour's invasive growth characteristics. An Abaqus (Simulia) implementation of this model is currently being evaluated in parametric studies.

Inclusion of this model into the BMS hypo-model requires the FE simulation back-end (currently FEBio) to be changed or an additional backend to be added. Thanks to the modular structure of BMS,

such extensions are possible without affecting the simulator's interfaces. FENICS has been identified as viable open source solution, and the model's implementation will be evaluated.

ICCS:

In close collaboration with UBERN ICCS integrated the biomechanics hypomodel into the trunk hypomodel of pure tumour growth and response to treatment. The resulting hypermodel was demonstrated during the 3rd CHIC review.

ICCS coordinated the linking of the biomechanics models with the main oncosimulator models for the development of multimodeller hypermodels.

FORTH:

FORTH participates in the discussions related to the needs of this task in order to effectively provide the spatial and tissue specific information needed to initialize the biomechanics model.

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

FORTH:

FORTH as part of the elementary modeling team closely attends and participates in the proposed clinical scenarios contributing in all three cancer types.

UBERN:

Body-site specific biomechanical parameters for the simulation of Nephroblastoma, Lung cancer and Glioblastoma cases have been identified from literature. Patient-specific anatomic information was obtained by segmenting suitable images obtained from the CHIC data repository for both Lung cancer and Nephroblastoma cases. The biomechanical simulator has been tested successfully as part of the CHIC hyper-modelling workflow for these scenarios.

The diffusion-enhanced biomechanical model for glioblastoma patients has been tested independently from other CHIC hypo-models using average patient geometries derived from publicly available anatomic atlases.

UNITO:

Careful investigation to find similarities and differences with respect to prostate cancer, in order to share knowledge. In particular the lung tumor and the nephroblastoma cases are investigated by macroscopical models based on the Universal Phenomenologies in order to investigate the effects of combined chemotherapies on cancer growth.

Lung cancer response to gemcitabine and cisplatin has been modelled by the two-population model described in Task 6.1. Nephroblastoma grows very fast, so a single population model (exponential or gompertzian) could be the best approximation In this case. The statistical analysis on the growth parameters could be useful but a larger amount of data is needed.

UPENN: (Tasks 6.1, 6.2, 6.4)

A molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations was established. As part of the task a multiscale method to combine the molecular studies with signalling network studies was developed.

A hybrid subcellular model for cell fate was implemented to include the effect of STAT signalling, radiation dosage, chemotherapeutic exposure, and miRNA profile-mediated signalling.

SubTask 6.4.a, The nephroblastoma paradigm

ICCS:

Extensive transformation of a pre-existing ICCS simulation code of nephroblastoma growth and treatment response in order to serve as a trunk hypomodel for the nephroblastoma multi-modeler hypermodel.

Clinical adaptation studies.

Wilms mechanistic hypomodel

Core modelling algorithms simulating tumor growth and response to combined chemotherapy of Dactinomycin and Vincristine were finalized.

Extensive parametric and sensitivity studies were conducted. Sensitivity analysis of the model using one-factor-at-a-time (OFAT) and two factors at a time approaches was performed.

Literature review of the kinetics data of nephroblastoma cancer was undertaken in order to exploit the narrowing of the applicable value range of Wilms Oncosimulator model parameters.

A clinical adaptation methodology was developed.

Adaptation of the hypomodel to MUSCLE environment has been implemented.

Release of the model binary as well as its full description (perspectives, input/output description, format, Units, reference value, etc.) on the Model Repository.

Release of the model binary on the common virtual machine

A close interaction with WP5, WP6, WP7, WP9 and WP10 has led to the following achievements:

- Specification of the hypermodel's data requirements
- Analysis of the available data
- Definition of data preprocessing requirements and implementation.
- Finalization of the data flow between the Oncosimulator and the Molecular, Biomechanics, Vasculature and Metabolic models was finalized.
- Resolving of incompatibility issues between models' input/output in terms of parameters' meaning.
- Implementation of hypermodel configuration on common virtual machine
- Contribution to model repository design in order to accommodate fully described models that can be integrated through the infrastructure.
- Release of Model input/output description (description, format, units, reference value etc.) on the Model Repository
- Definition of the interface with hypermodelling infrastructure (method of parsing of input parameters, format of parameters exchanged between models, etc.)
- Implementation of model configuration through the infrastructure
- Semantic representation of the models
- Definition of the required elements to be included in the user graphical interface
- Visualization of simulation results

- Preliminary model adaptation to two real clinical case provided within CHIC was implemented.
- A fine tuning of the model so as to get biological relevant and tumour specific simulation results after the hypermodel execution was achieved.
- A demo of the hypermodel was developed and presented at the 4th CHIC review.
- The execution of Wilms hypermodel was evaluated and results were included in deliverable D11.3.
- Muscle – integration issues have been resolved.

UOXF:

- The UOXF_Vasculature_Nephroblastoma model has been successfully executed with all necessary partner models as part of the nephroblastoma demonstrator. Current efforts are now focused on developing tests for coupled model stability (both in terms of software robustness to changes in input parameters and numerical) using the CVM.
- Development of new component models for vascular growth that can interact with the ICCS tumour growth component model. This required the development of new models and software to best fit the lung cancer hypermodel plan. A model of chemical transport was also developed to facilitate coupling of the vascular and tumour growth components. Model details were provided in the CHIC D6.2 report and source code has been made available to modelling partners.
- Incorporation into Oxford's CHASTE software of new functionality for modelling the vasculature, angiogenesis and radiotherapy is on-going. The addition of vascular modelling functionality into CHASTE will facilitate the development of sophisticated vascular and tissue growth hypomodels for use in CHIC.
- New software has been developed to extract vessel network data from 3-D multiphoton images. This software will be used to analyse imaging data generated in Professor Ruth Muschel's lab, in Oncology, Oxford, and, in the longer term, included within CHASTE and made available to CHIC partners.
- Development of a range of approaches for modelling discrete vessels in continua. Approaches for modelling species transport from vessels are being developed using high resolution finite element methods, finite difference methods and Greens function methods. The suitability of these methods for modelling the vasculature at different spatial scales will be assessed. The different solvers will be made available to CHIC members through CHASTE and used to construct vascular and cell-based hypomodels.
- Development of hybrid and continuum (PDE) models of angiogenesis, with a focus on tip-cell ECM interactions, and the impact of the angiogenic growth factors VEGF and FGF.
- Development of a pipeline that can be used to determine what experimental data is needed maximally to constrain parameters in mathematical models of angiogenesis and to reduce the uncertainty in their estimation.

UNITO:

Nephroblastoma grows very fast, so a single population model (exponential or gompertzian) is best approximation In this case. UNITO developed a model of growth and response to treatment considering the age of the patient, the time of the treatment and the initial tumor volume. The treatment protocol is considered standard.

An optional input parameter comes from molecular information (UPENN hypomodel): knowing the specific resistance to the chemotherapy, we can calibrate the prediction of the response to the treatment.

The statistical analysis on the growth parameters could be useful but a larger amount of data is needed.

UBERN:

Parameterisation of the biomechanical simulator for the nephroblastoma scenario.

SubTask 6.4.b, The glioblastoma paradigm

ICCS:

Further refinements on a mechanistic model of the response of GBM to immunotherapy treatment. Intensive interaction of ICCS with the involved multidisciplinary clinical team of KUL.

An alternative mathematical approach to the phenomenon of GBM invasion to surrounding tissues based on the Brownian motion was developed and published.

A model concerning the estimation of anisotropic diffusion of glioma cells in normal brain tissue has been developed. (Cancer Informatics Paper)

Another model for tumor growth in inhomogeneous and time varying chemical fields has also been created and implemented. (submitted paper in J of Th.Biology.)

The data provided for the glioblastoma case has been evaluated.

Missing values is still an important issue.

Machine learning approaches to the clinical questions regarding response of glioma patients in treatment with radiotherapy, temozolomide chemotherapy and immunotherapy.

Bayesian classifiers have been shown to be promising whereas decision trees have been shown not to be so promising

UBERN:

Parameterisation of the biomechanical simulator for the glioblastoma scenario.

SubTask 6.4.c, The lung cancer paradigm

ICCS:

ICCS refined the trunk hypomodel of pure tumour growth and response to treatment and made several necessary transformations in order to link it with the rest of the hypomodels with which it constitutes the multi-modeler lung hypermodel. A version of the latter was presented and demonstrated in the 3rd CHIC review meeting. Towards the construction of Lung Cancer Hypermodel ICCS has worked on the following:

- Decoupling of the initially coupled ICCS's tumor growth core algorithm with UBERN's biomechanics model.
- Definition of the data flow between the Oncosimulator and the Biomechanics, Vasculature and Metabolic models
- Adaptation to MUSCLE environment

Two running, muscle-enabled lung hypermodel scenarios have been successfully implemented:

Scenario1: Oncosimulator-Biomechanics models

Scenario2: Oncosimulator-Biomechanics-Metabolic-Dummy vasculature models

Extensive lung cancer growth and response to treatment literature survey and sensitivity analyses of the model have been performed. A preliminary model adaptation study based on one clinical case has been also performed.

A. Lung mechanistic hypermodel

Core modelling algorithms simulating tumor response to cisplatin-based doublet therapy (with vinorelbine, docetaxel and gemcitabine) in combination with radiotherapy were finalized.

Extensive parametric and sensitivity studies were conducted.

Sensitivity analysis of the model using one-factor-at-a-time (OFAT) and Latin Hypercube Sampling/Rank Correlation Coefficient (LHS/RCC) approaches was performed.

A study of the kinetics of non-small cell lung cancer: cell cycle duration, growth rate, growth fraction, necrosis, apoptotic index and stem cells fraction was undertaken.

Kinetic data were exploited for the narrowing of the LUNG cancer applicable value range of the model parameters.

A clinical adaptation methodology was developed.

A preliminary model adaptation to one real clinical case provided within CHIC was implemented.

Analysis and preprocessing of the clinical data provided was conducted.

The data flow between the Oncosimulator and the Molecular, Biomechanics, Vasculature and Metabolic models was finalized.

Incompatibility issues between models' input/output in terms of parameters' meaning were resolved.

A fine tuning of the model so as to obtain biologically relevant and tumour specific simulation results after the hypermodel execution was achieved.

B. Lung statistical model

An extensive interaction with USAAR for the provision of additional data took place.

The state of the art on the statistical models that can be recruited to answer whether a surgically treated lung cancer patient will relapse was outlined.

A preliminary workflow regarding missing value imputation, feature selection, model training and validation was developed.

C. Technological aspects

An adaptation of the model based on hypermodelling infrastructure specifications was achieved.

The model input/output description (description, format, units, reference value etc.) was released.

The model binary on common virtual machine was released.

The model information was uploaded on the model repository.

A close interaction with WP6, WP7, WP8, WP9 and WP10 partners has led to the following achievements:

- Finalization of communication scheme between the Oncosimulator and the Biomechanics, Vasculature and Metabolic models
- Definition of the interface with hypermodelling infrastructure (method of parsing of input parameters, format of parameters exchanged between models, etc.)
- Semantic representation of the models
- Definition of the required elements to be included in the user graphical interface
- Visualization of simulation results
- Muscle – integration issues have been resolved.

UBERN:

First tests towards the Lung Cancer hypomodelling scenario have been carried out by coupling BMS and the lung OncoSimulator (MUSCLE). Data exchange between both models is successful and the desired output variables can be obtained. As both simulators (BMS & OncoSimulator) operate on different domain discretization, results need to be interpolated frequently, potentially resulting in the introduction of numerical inaccuracies. Their impact on the final result must be evaluated further, and mitigation strategies need to be identified in collaboration between UBERN and ICCS.

Task 6.5, The prostate cancer modelling paradigm

UNITO:

The base of UNITO models is the following hypotheses:

- After surgery, tumor regrowth follows a Gompertzian or a West law
- Both Gompertz and West law can be re-written in order to study only one free parameter (the growth rate)
- The growth parameter is strictly related to the time to relapse
- There are (at least) two types of cells in prostate cancer: the Androgen Dependent (prevailing) and the Androgen Independent. This difference becomes important during therapy, especially when an adjuvant hormone therapy is prescribed just after the surgery

We can estimate tumor growth parameters by the PSA values; these parameters could stratify very well different types of patients, in particular those with a low or high probability of a relapse.

We are formulating different (hypo-) model for each subgroup of patients to simulate the regrowth of cancer and eventually the therapy, using a two populations model.

Considering only one population (the PSA value) and choosing a model (Gompertz or West law), we can estimate the growth parameter value for each patient. We found a strict correlation between the parameter value and the time to relapse. Interestingly, this correlation can be obtained also estimating the growth parameter by only the first 3-4 PSA values. Thus, after only nine months (3 PSA exams) our method can provide a first prevision of the timing to relapse.

ICCS:

Interaction of ICCS with UNITO in order to ensure compatibility of the colon cancer model development with the CHIC framework. The idea is to align the prostate model as much as possible to the overarching principles of the CHIC project.

ICCS supported the integration of the prostate cancer modelling paradigm into the CHIC modelling platform.

Summary of significant results

Integrated multimodeller hypermodels have been developed using the ICCS oncosimulator as their basis under the guidance and coordination of ICCS.

Clinical relevance has served as the driving force for the development and the adaptation of the hypermodels.

Mechanistic hypermodels can run under the Muscle hypomodel coupling library.

Early comparisons of the hypermodel predictions with biological reality and clinical experience support their potential to serve in the future as clinical decision support systems.

Publications (see WP12)

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 WP6			
Partner	Planned PM Total	Planned PM Period 3	Actual PM Period 3
1-ICCS	57.01	13.00	13.19
7-FORTH	28.61	6.50	6.50
9-UPENN	69.00	15.00	11.00*
10-UOXF	46.00	15.27	23.49**
11-UNITO	14.00	4.00	5.97
12-UBERN	20.00	8.00	7.60
14-Philips	1.00	1.00	1.00
Total	235.62	62.77	68.75

*) Underspending due to the following facts: the UPENN molecular model is subdivided into two categories (a) molecular dynamics and modeling; (b) network modeling. (b) had no changes in planned versus actual and Alokendra Ghosh, Joe Jordan, and Ravi Radhakrishnan worked on (b) for this period. In terms of (a) the nephroblastoma scenarios did not require molecular modeling and the lung cancer molecular modeling

scenarios were completed in period 2. (Note that in period 2, we had more emphasis on molecular modeling and a lot of the simulations were completed in period 2—these were analyzed in period 3 and will be further analyzed in period 4). So in terms of objectives and work completed, there is no change as the molecular modeling was ahead of schedule.

***) UOXF had an extra post doc during that period. This compensates for the delay in recruiting a post doc onto the project.

1.7 Work Package 7: Hypermodelling infrastructure

WP7's objective is the development of the hypermodelling infrastructure, intended as a set of services and technologies that make it possible to build and execute integrative models, formed by component models and relation models, coherent with the vision of VPH.

Partner USFD leads the workpackage.

Partners CINECA and USFD are primarily responsible for the development of the hypermodelling execution framework.

Partners UCL and BED are responsible for the semantic components of the hypermodelling infrastructure.

Partners FORTH, USFD, and ICCS are responsible for the wrapping of the existing models and of the deployment on the production cloud; partner FORTH is also in charge of the design of the tools to develop new hypermodels.

Partner USAAR has a small effort in WP7, primarily to ensure that what is developed reflects the clinical needs.

Main objectives of this WP

- Models execution: deployment of all component models, and wrapping with software layer that standardise their control and data flows, according to a Component Model Generic Stub template, which makes possible the orchestration of these models into hypermodels (task 7.1).
- Metamodels annotation: development of basic annotation and tags management services, to be used for the provision of i) folksonomy annotation and search services, and ii) ontology-base search services, including the definition of a models annotation ontology (Task 7.2).
- Hypermodels execution: development of the ICT hypermodelling infrastructure, intended as a set of services and technologies that make it possible to build and execute integrative models, formed by component models and relation models. This includes the definition of a high-level hypermodelling language and additional modelling services, to cope with the incompleteness of the inputs, and that to cope with strongly coupled models (Task 7.3).
- Metahypermodels annotation: using the models annotation ontology development of hypermodels annotation services. Explore the use of innovative technologies such as the use of linked data or semantic reasoning (Task 7.4).
- Hypermodelling infrastructure: deploy all hypermodelling technologies on a production private cloud where then can be used by the CHIC consortium to analyse patients' data (Task 7.5).

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 7.4, Metahypermodels annotation (M25-48)
- Task 7.5, Hypermodelling infrastructure (M7-42)

Summary of progress achieved towards objectives

Also in the third project year WP7 developed mostly as planned.

Task 7.1, Models execution, was completed as planned, at M27. Partner USFD, in collaboration with partner CINECA, completed a second extensive revision of the VPH-HF, which refactored a number of functionalities, and tested it extensively first using a set of simplified hypomodels provided by partner ICCS, and then on the full model implementations as they were made available. USFD, CINECA and FORTH finalised the specification for the Component Model Generic Stub; USFD wrapped all models made available by WP6 partners. FORTH re-factored the Cancer Metabolic (hypo)model as an executable artefact, in compliance with the requirements of the VPH-HF execution framework, and collaborated with USFD in the validation of interactions of this hypomodel within the hypermodel.

Task 7.2, MetaModels annotation, was also recently completed. USFD coordinated the discussion among all WP7 partners on the minimum metadata annotation set for resources started in the previous reporting period, and in collaboration with partner CINECA captured the agreed set in a JSON document, that was made available to partner UCL. In parallel, partner UCL developed the underlying multiscale anatomy annotation and topological framework for ApiNATOMY and RICORDO to handle the metadata for tumours in general and the nephroblastoma scenario in particular. They also evaluated and prototyped additional metadata dimensions embedded within the folksonomy approach also in connection with hypomodel descriptions provided by WP6. Partner BED maintained, which now will need to be integrated with WP8 and WP9 technologies, as part of WP8 activities. Partner ICCS reflected the work of this task in the in silico clinical trial repository, ensuring the necessary interoperability, and worked with partner UCL on the semantic of perspectives.

Task 7.3, HyperModels execution is running as planned. All basic functionalities are now deployed in production. The first release of the VPH hypermodelling framework, which included the Director, Storage Management Service, Metadata Repository, Authentication, Registry, Web User interface and Workflow Management Service components, was delivered on time and described in details together with the APIs to be used by other CHIC tools in deliverable D7.2 (submitted at the beginning of June and accepted by the European Commission). The VPH-HF has been deployed successfully on the CINECA and USFD test nodes for testing purposes and on the FORTH production instance. Using the release version of VPH-HF, USFD has produced demonstrations of hypermodelling scenarios supplied by WP6 – some based on a Directed Acyclic graph (DAG) workflow and some based more complex example involving iteratively coupled hypomodel execution. Last, the integration of the VPH-HF to all other relevant CHIC architectural components (clinical data repository, model repository, in-silico-trial repository, CRAF, authentication service) has been completed.

The definition of the high-level hypermodelling language is now completed. This was a complex process: first CINECA and USFD analysed multiple options, eventually focusing on the model description language provided by the two execution technologies used in VPH-HF: Taverna and MUSCLE. Taverna describes its models using the Taverna version 2 Workflows (T2flow) language;

MUSCLE called Multiscale Modelling Language. Both languages could in principle be used, and both would have required some extensions to support the features of the VPH-HF architecture. Initially, we concluded that the most elegant solution would have been the extension of the Multiscale Modelling Language (xMML) originally part of the MUSCLE software. This decision was also stated in some previous reports, where we described the analysis work done in this regard. However, as the project developed it became clear that in any case, as Taverna was the primary execution environment (which wraps MUSCLE), the T2flow syntax would have been used massively to store workflows, etc. while MML is certainly more elegant, partners CINECA, USFD and FORTH agreed that T2flow could be made equally expressive with just a few extensions. Thus, it has now been decided that hypomodels and hypermodels descriptions will be stored in the repositories, and passed between the hypermodelling editor, the repositories, and the VPH-HF as extended Taverna version 2 Workflows (xT2flow); the MML syntax will continue to be used within the MUSCLE sub-system.

Task 7.4, Metahypermodels annotation, is also running as planned. CINECA, USFD and FORTH, as part of the work on the modelling language, conducted an extensive analysis of process description languages, and of the extensions that would be required, if the MML was adopted. Partner UCL worked closely with the other partners to establish the web service solution to support semantics-based hypomodel integration in the hypermodelling editor. The primary demonstration of this work will be in support of the nephroblastoma scenario, also in connection with hypomodel descriptions provided by WP6. All partners contributed to the main WP7 deliverable for this reporting period, D7.3 - report on Hypermodels annotation services, that was submitted with only a minor delay.

Task 7.5, HyperModelling infrastructure is also running according to schedule. USFD complete the refactoring of the VPH-HF alpha v0.1 version, in order to support both DAG and strongly coupled models; this work, and its associated deliverable (D7.2 – First Release Hypermodelling Framework, now accepted by EC) originally planned for M24 was delayed a few months, and thus involved also this reporting period. CINECA, in collaboration with USFD and FORTH, developed a Vagrant script to deploy the VPH-HF framework with all the dependencies in a virtual machine and provides a portable working environment. Documentation of the code and of the APIs has been improved. The first release of the VPH-HF after the architecture refactoring (alpha v0.2) has been deployed in the FORTH machine. FORTH collaborated with USFD and the model providing partners for the execution of the two hypermodels that were demonstrated in the 4th Review meeting (January 2016) and had the overall supervision of the demos that were performed through the new “Clinical Research Application Framework” (CRAF) application. FORTH also maintains the hypermodelling infrastructure in the private cloud environment hosted in its premises.

Summary of details for each task

Task 7.1, Models execution (M1-M27)

- ICCS provided a number of reduced order hypomodels to USFD along with information about their execution.
- FORTH built and deployed the Cancer Metabolic (hypo)model as an executable artefact in compliance with the requirements of the VPH-HF execution framework. We also worked in close collaboration with the other modelling teams in order to check and validate the interactions of the metabolic model in the resulting hypermodels.
- CIN, USFD and FORTH completed the final version of the Component Model Generic Stub.
- USFD wrapped and exposed as components in the refactored version of the VPH-HF all hypomodels developed by WP6, and developed two hypermodels.

- Two exemplar hypermodelling scenarios were presented at the most recent review: one representing a generic reduced-order tumour model, and the other representing a lung cancer scenario. USFD worked closely with colleagues in WP6 to ensure that each of the constituent hypomodels was wrapped in either Taverna and MUSCLE (the workflow execution engines) and could be successfully executed within the refactored VPH-HF.

Task 7.2, Metamodels annotation (M7-M36)

- USFD led a discussion on the minimum metadata annotation set for resources that involved all WP7 partners; the result was captured in a JSON document. The set is inspired by the EBI MIRIAM Standard, and by the resources annotation set used in PhysiomeSpace and more recently in the VPH-Share infrastructure, but it includes various elements that are specific of computational oncology.
- UCL has been developing the underlying multiscale anatomy annotation and topological framework for ApiNATOMY and RICORDO to handle the metadata for tumours in general and the nephroblastoma scenario in particular.
- UCL also evaluated and worked on prototypes of additional metadata dimensions embedded within the folksonomy approach also in connection with hypomodel descriptions provided by WP6.
- BED has maintained the initial version of the tagging services that was developed in the previous stage, 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. The service will need to be integrated with WP8 and WP9.

Task 7.3, Hypermodels execution (M7-42)

- USFD led the refactoring the VPH-HF, following the analysis carried out in the previous reporting period in response to the need to support hypermodels that did not conform to the DAG topology. The refactored framework is focussed on a Director which can invoke either Taverna or MUSCLE as workflow engines depending on the topology of the hypermodelling scenario presented. All planned restructuring has been successfully implemented and the updated version successfully deployed on test and production nodes. Since deployment, USFD have also been involved in the configuration, testing and maintenance of the VPH-HF on both nodes, as well as the documentation of the refactored framework. The authentication of the production version of the VPH-HF has also been integrated into the Custodix CHIC authentication system (interface with WP5).
- CIN delivered, in collaboration with USFD, deployed on FORTH production node this refactored version of the VPH-HF.
- ICCS, in close collaboration with UBERN provided USFD with 2 strongly coupled hypomodels for testing purposes, which were wrapped and executed.
- Using the refactored version of VPH-HF USFD has produced two demonstrations of hypermodelling scenarios supplied by WP6 – one based on a Directed Acyclic graph (DAG) workflow and another more complex example involving iteratively coupled hypomodel execution.

- BED maintained a local resource metadata repository, which now will be integrated with the repositories developed in WP8 and WP9.
- FORTH, CIN, and USFD worked on the definition of the CHIC hypermodelling language. A number of process description language were considered and analysed, but in the end it was agreed that the best starting point is the Multiscale Modelling Language (xMML) developed as part of the MUSCLE multiscale models execution environment. An in depth analysis of the current version of xMML highlighted some shortcomings with respect to the needs of the CHIC project, especially in the handling of control structures such as iterations and conditional execution. Workgroup formed by experts of the CHIC consortium and of the original MUSCLE developers at the University of Amsterdam has been established, to formally approve a revised version of the xMML language that address these shortcomings, that represents the first version of the CHIC hypermodelling language. However, all partners involved have recently agreed to revise this decision and to select T2flow as template modelling language, instead of MML, on the basis of efficiency-over-elegance considerations.
- In collaboration with WP6, further models have been integrated in the execution environment: a nephroblastoma hypermodel and an equivalent phenomenological model, consisting of three and two hypomodels respectively connected using a DAG topology.
- In collaboration with WP6, a preliminary set of guidelines have been defined to organise the model metadata, files and input data in the Model Repository. These new rules have been taken into account in the Model Repository refactoring carried out by WP8.
- To simplify and make the process of integration of hypo/hypermodels into the VPH-HF reproducible, a Workflow-Wrapper-Compiler (WWF) has been created. This creates the workflow execution file required to run the model using information provided in the Model Repository.
- Development has started on the automated deployment of hypo/hypermodels, from the Model Repository, to the VPHHF execution environment. Steps have also been taken to organise each hypo/hypermodel's dependent software into isolated modules and a unit-test framework has been developed to test any new model uploaded into the Model Repository and its integration in the VPHHF execution layer.
- The Hypermodelling Editor that FORTH develops in WP10 will export the newly designed hypermodels in the CHIC hypermodelling language and therefore FORTH contributed to the definition of this language. We explored whether the xMML language and related infrastructure from the MUSCLE project can be adopted and some of their shortcomings were identified especially in the handling of control structures such as iterations and conditional execution.
- FORTH collaborated with USFD and the model providing partners for the execution of the two hypermodels that were demonstrated in the 4th Review meeting (January 2016) and had the overall supervision of the demos that were performed through the new "Clinical Research Application Framework" (CRAF) application.
- ICCS, CIN, USFD, FORTH completed deliverable "D7.2 first Release hypermodelling framework deployed on test nodes". The significant refactoring process for VPH-HF led to a two-month delay in the submission of D7.2. This Deliverable was submitted on 30th May 2015 and has since been accepted by the Commission.

Task 7.4, Metahypermodels annotation (M25-M48)

- All WP7 partners participated in regular teleconferences related to metahypermodels annotation.
- UCL worked closely with ICCS to establish the web-service solution to support semantics-based hypomodel integration in the hypermodelling editor, summarised in D7.3. The primary demonstration of this work will be in support of the nephroblastoma scenario.
- FORTH reflected the work developed here in the necessary support by the hypermodelling editor.

Task 7.5, Hypermodelling infrastructure (M7-42)

- CINECA developed a Vagrant script to deploy the VPH-HF framework with all the dependencies in a virtual machine and provides a portable working environment. Documentation of the code and of the APIs has been improved. The first release of the VPH-HF after the architecture refactoring has been deployed in the FORTH machine.
- FORTH production node now hosts VPH-HF refactored version, deployed by CIN and USFD. The new version is capable of executing also strongly coupled hypermodels through the MUSCLE sub-system.
- ICCS updated the model and tool repository web services according to the new requirements derived from the evolution of the hypermodelling infrastructure. Based on the aforementioned requirements, some more information like the universally unique identifiers of the models and their parameters, the relative path of the model's executable inside the compressed archive, etc., can now be exported through the new web services of the model repository.
- Based on the new requirements coming from the CHIC technical infrastructure, ICCS updated Wilms and Lung oncosimulators in order for them to be integrated into the hypermodelling infrastructure. The new versions of the aforementioned oncosimulators accept medical images in the form of metaimages (mhd), they compress the output raw files in a single archive, and input arguments are parsed with a flag.
- USFD, CINECA, and FORTH started in this period also scoping work related to the infrastructure functionality required for the caching of data, surrogate modelling and handling of incomplete inputs. It was decided that USFD will focus on the first two features, whereas the incomplete inputs handling will be initially implemented by FORTH as a CRAF functionality.

Summary of significant results

The alpha version of the VPH-HF, as inherited from the VPH-OP project has been successfully refactored in order to meet the needs of CHIC. This framework has been deployed and tested on both test and production nodes and integrated with the CHIC authentication system.

The VPH-HF is now fully integrated with the rest of the CHIC IT infrastructure.

All hypomodels and hypermodels supplied by WP6 partners so far have been successfully deployed and executed within VPH-HF.

A minimum annotation set for resources has been agreed. A URI schema has also been agreed and formally captured in a JSON document.

Automated workflow wrapper generation, automated deployment and testing of models uploaded to the model repository has been implemented.

Deliverable D7.3, submitted with two-weeks delay, consolidates the semantic annotation services and related technologies driving production and consumption of metadata in the hypermodelling editor, the model and data repositories (with partners UBERN, BED, USFD, FORTH, CINECA, ICCS).

The selection of the high-level hypermodelling language is completed.

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

D7.2 was submitted with a two-month delay, as a result of the need for significant refactoring of the VPH-HF to meet the needs of the CHIC modelling scenarios. This has been accepted and has not caused any further impact on other tasks or resources.

While the current focus is on the nephroblastoma scenario, the effort expended on this work suggests that significantly more effort will be needed in developing similar knowledge and metadata for the lung and glioblastoma scenarios. UCL, therefore, asks for permission to convert its own equipment/consumables budget into staffing budget to ensure a level of person-month resource commensurate with the scope of the work required.

After having identified MML as candidate high-level hypermodelling language, the consortium decided to adopt instead an extended version of T2flow, under efficiency-over-elegance considerations.

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 3	Actual PM Period 3
1-ICCS	7.20	1.70	1.70
3-USAAR	4.00	1.00	0.07
5-BED	28.00	12.00	0.27*
6-USFD	134.00	36.46	37.67
7-FORTH	10.00	1.50	3.00
15-UCL	36.00	12.00	6.99**
16-CINECA	36.00	12.00	9.94
Total	255.20	76.66	59.64

*) There have been limited activities in WP7 in the reporting period as compared to the prediction previously. The Hotmap initiative which was proposed at the beginning of the project (which involves text mining in the

ontology) didn't go ahead. The development of T7.2 (tagging service) and T7.3 (meta data repository) has been mainly completed in the first two years. Therefore we need a potential of moving resources from BED from WP7 to WP9.

**) Two developers on CHIC left UCL. There were some delays in recruiting (Dr Helvensteijn started in October, and Dr Kokash started very recently). UCL should be able to re-balance progress within the current project period.

1.8 Work Package 8: Model and Data Repositories

Main objectives of this WP

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

This involves the development of:

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

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

Active tasks in this reporting period:

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

Summary of progress achieved towards objectives

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

ICCS has developed the prototype and the web services for model/tool repository. Taking into account feedback from partners and in view of some new requirements, ICCS has slightly changed the model and tool repository schema and updated some of the web services. Furthermore, the user interface of the model and tool repository has been improved by using cutting edge front end technologies, like css3 and jquery library. Interactive dialogs have been incorporated into the web application, the font and the buttons are more appealing and the main page of the repository is more attractive. The page which is dedicated to the categorization of the model has been enriched with more functionalities and the model repository is now able to store and expose through the web services technical information of the models which is critical for their integration into the CHIC infrastructure. During the process of testing the integration of the model and tool repository, many bugs have been fixed. ICCS included most of the aforementioned advances in the Deliverables 8.2 and 8.3. Finally, all modelling partners (ICCS, UOXF, UBERN, UPENN, UNITO, FORTH) have populated the repository with some of their models.

SubTask 8.1.b, Development of the data repository

UBERN has extended the REST service with more functionality. Consequently, the authentication mechanism now supports SAML delegation tokens, and requests initiated by the search query builder are now supported. Furthermore, UBERN implemented a chunked upload REST endpoint in order for the client to be able to upload large files in small chunks and an endpoint which accepts a multitude of combinations consisting of nested groups, source types, logical operators, nested conditions, etc. The chunked upload REST endpoint has been documented in the Deliverable 8.3. The clinical data repository now supports additional data formats, such as the MIniML (MIAME Notation in Markup Language), the JPEG (Joint Photographic Experts Group) and the CSV (comma-separated values). UBERN has also changed the database development approach from database first to code first in order to make use of the code-based migrations feature. Consequently, the database schema of the clinical data repository can be automatically updated when the model changes, without losing any existing database objects.

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

ICCS has developed the prototype and the web services for the *in silico* trial repository. Taking into account feedback from partners and in view of some new requirements, ICCS has slightly changed the *in silico* trial repository schema and updated some of the web services. Furthermore, the user interface of the *in silico* trial repository has been updated in order for the user to be able to store the values of miscellaneous parameters of a particular experiment and to easily download the input or the output data of an experiment through a single page. Furthermore, the *in silico* trial repository has been updated so as to automatically create a universally unique identifier for a newly created experiment. This identifier can be exposed to the CHIC clients through the corresponding web services. ICCS has moved the *in silico* trial repository to another virtual machine in the CHIC private cloud and it has been totally split from the model and tool repository. Finally, ICCS has included most of the aforementioned changes in the Deliverables 8.2 and 8.3.

Task 8.2, Infrastructure for Semantic Metadata Management

UCL has developed the infrastructure, in co-ordination with stakeholders in the consortium so as to refine the hypo/hypermodel metadata schema, to create applications that leverage the schema, to provide annotation (RDF) store and ontology DB Knowledge Base through RICORDO, to link RICORDO

metadata management web services with the hypermodelling editor and to bridge radiological data with semantic metadata in models. The interface specification for the relevant repository components was reported in Deliverable 8.3. Since the hypermodelling editor is the “consumer” of the semantic metadata annotations for the models and the “producer” of the corresponding semantic annotations for the hypermodels, FORTH presented the details and the management of these semantic annotations from the Editor’s point of view. Furthermore partner ICCS provided feedback to partner UCL in order to develop some template-based SPARQL endpoints that will be used from the model repository for the storage of metadata. Partner UBERN has preliminary integrated the clinical data repository with the RICORDO framework in order to simplify the annotation process of the data providers and finalized the dynamic search query builder which enables to conduct sophisticated search queries on the data repository. Moreover, partner PHILIPS worked further on the ontology annotation tool, implementing the normalization algorithms for SNOMED-CT for the long normal form, for both focus concepts and attributes (including representation of groups of attributes).

Finally, partner USAAR continued the iterative process to define ‘HOT Maps’ of tumour-specific hallmark knowledge and evaluated, structured and optimized the data corpus for nephroblastoma and lung cancer data.

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

ICCS updated the model/tool and *in silico* trial repository web services, so as to make use of the CHIC brokered authentication mechanism. Furthermore ICCS has integrated the model/tool and *in silico* trial repositories into the CHIC security framework and the single sign on mechanism has been implemented for both of them. Partners ICCS and UBERN have set up the model, the clinical data and the *in silico* trial repositories so as to run behind a CHIC proxy in order for the client to use only secure connections (SSL) when interacting with the repositories. This is now possible with the installation of a trusted SSL certificate in the virtual machine which accommodates the CHIC proxy. Moreover, partner UBERN, in collaboration with partner CUSTODIX, has further integrated the clinical data repository with the CHIC data protection framework. Finally, partner USAAR has prepared data to conduct manual ground truth annotations and anonymization of nephroblastoma, and lung cancer data.

Summary of details for each task

Task 8.1, Development of repositories

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

ICCS:

The prototype for model/tool repository (frontend and backend) has been developed.

Model/tool’s repository web services have been developed.

ICCS has contributed in the preparation of deliverable “D8.2 Prototype implementation of the CHIC repositories”, by providing sections related to model/tool repository.

ICCS has contributed in the preparation of deliverable “D8.3 Implementation of the interfaces of the CHIC repositories”, by providing sections related to model/tool repository.

Taking into account feedback from partners and in view of some new requirements, model/tool schema has been slightly changed. These changes are included in deliverable “D8.3 Implementation of the interfaces of the CHIC repositories”.

Based on the requirements from wp7, a new web service named “getPackageByToolId” has been developed. This web service returns to the CHIC client the compressed package that contains the model’s executable along with the dependencies.

In order to facilitate the communication with the model repository, a new web service named “getToolByParameterId” has been developed. This service returns the descriptive information of a model to which the given parameter belongs.

During the process of testing the integration of the model/tool repository, many bugs of the model repository’s web services have been fixed.

The user interface of the model and tool repository has been improved by using cutting edge front end technologies, like css3 and jquery library. Interactive dialogs have been incorporated into the web application, the font and the buttons are more appealing, the main page of the repository is more attractive and the page which is dedicated to the categorization of the model has been enriched with more functionalities.

The model and tool repository is now able to store through the user interface and expose through the web services technical information of the models which is critical for their integration into the CHIC infrastructure. Such information is, for example, the relative path of the model executable inside the corresponding compressed archive.

FORTH:

The new CRAF architectural component for the execution of hypermodels in the clinical setting introduced some requirements for the model repository. ICCS and FORTH discussed about these new requirements and proper changes in the programming interface of the aforementioned repository were made.

Last but not least, all modelling partners (ICCS, UOXF, UBERN, UPENN, UNITO, FORTH) have populated the repository with some of their models.

SubTask 8.1.b, Development of the data repository

UBERN:

The REST service has been extended with more functionality. The technical implementation of the authentication mechanism for the REST service has been extended to support SAML delegation tokens.

The chunked upload REST endpoint has been implemented to upload large files in small chunks. All the services and endpoints of the service have been documented in Deliverable D8.3 and are available online.

The file formats such as DICOM (Digital Imaging and Communications in Medicine), MetaImage, Analyze, Niftii, HDF5 (Hierarchical Data Format), CDISC ODM (Clinical Data Interchange Standards Consortium - Operational Data Model) have been extended by the MINiML (MIAME Notation in Markup Language), JPEG (Joint Photographic Experts Group) and CSV (comma-separated values). The first file format is used to store genetic / molecular datasets and the others for histopathology datasets.

The REST service has been extended with more functionality. An endpoint to support requests initiated by the search query builder developed for task 8.2 has been added. This endpoint accepts a multitude of combinations consisting of nested groups, source types, logical operators, nested conditions, source fields, comparison operators and input values. Furthermore, the Open Data Protocol (OData) implementation has been extended. The filter system query option can now be applied to filter datasets based on the unique patient identifier/pseudonym.

The Microsoft ADO.NET Entity Framework is an Object/Relational Mapping (ORM) framework used by the data repository. It offers three different database development approaches called database first, model first and code first. The database first approach was previously used by the data repository and has now been replaced by the code first approach, in order to leverage the code-based migrations feature. This feature enables to automatically update the database schema, when the model changes without losing any existing data or other database objects. With code-based migration we will be able to meet new requirements faster.

ICCS:

ICCS has provided feedback to partner UBERN, in order for the clinical data repository to provide more sophisticated search functionalities.

USAAR:

USAAR provided clinical feedback regarding the structure of the CHIC clinical data repository and how data can be uploaded. The clinical data repository was evaluated in an iterative process with external clinicians and researchers during evaluation workshops in collaboration with WP11.

Subtask 8.1.c, Development of the in silico trial repository

ICCS:

The prototype for *in silico* trial repository (frontend and backend) has been developed.

In silico trial's repository web services have been developed.

ICCS has contributed in the preparation of Deliverable "D8.2 Prototype implementation of the CHIC repositories", by providing sections related to *in silico* trial repository.

ICCS has contributed in the preparation of Deliverable "D8.3 Implementation of the interfaces of the CHIC repositories", by providing sections related to *in silico* trial repository.

Taking into account feedback from partners, ICCS has changed the schema (design) of *in silico* trial repository in order for other CHIC components to be able to store the values of miscellaneous parameters of a particular experiment. The user interface and the backend of *in silico* trial repository have been changed accordingly. The new schema of *in silico* trial repository is included in Deliverable "D8.3 Implementation of the interfaces of the CHIC repositories"

The *in silico* trial repository has been moved to another virtual machine in the CHIC private cloud and it has been totally split from the model and tool repository. This migration resulted in the development of new software modules for the *in silico* trial repository, which aim to facilitate the retrieval of resources from the model repository through web services.

Based on the new requirements from the partners, new web services have been developed for the *in silico* trial repository. More specifically, the "getUserExperiments" web service which returns to the client metadata of all the experiments that have been conducted by the given user, and the 'getUserPendingExperiments" web service which returns to the client metadata of all the pending experiments are some of the newly created web services.

The *in silico* trial repository has been updated so as to automatically create a universally unique identifier for a newly created experiment. This identifier can be exposed to the CHIC clients through the corresponding web services.

A dedicated web page has been developed that allows the user to easily download the input or the output data of an experiment. The user is able through this new page to simultaneously browse the trials, pick an experiment, and download input or output data of the aforementioned experiment.

FORTH:

The new CRAF architectural component for the execution of hypermodels in the clinical setting introduced some requirements for the in silico trial repository. Partners ICCS and FORTH discussed these new requirements and proper changes in the programming interface of the aforementioned repository were made.

Task 8.2 Infrastructure for Semantic Metadata Management (*Subtasks 8.2a, 8.2b, 8.2c, 8.2d*)**UCL:**

UCL has developed the infrastructure, in co-ordination with stakeholders in the consortium, to:

- Refine the hypo/hypermodel metadata schema
- Create applications that leverage this schema
- Provide annotation (RDF) store and ontology DB (Knowledge Base) through RICORDO
- Link RICORDO metadata management web services with the hypermodelling editor
- Bridge radiological data with semantic metadata in models, starting with imaging relevant to the glioblastoma scenario

The interface specification for the relevant repository components was reported in Deliverable 8.3, which was submitted on schedule.

Additional scenario requirements gathered from CRAF (Clinical Research Application Framework)

ICCS:

ICCS has provided feedback to partner UCL in order to develop some template-based SPARQL endpoints. These endpoints will be used by the model and tool repository for storing metadata through high level web services.

FORTH:

The hypermodelling editor is the “consumer” of the semantic metadata annotations for the models managed in CHIC. Additionally, it is the “producer” of corresponding semantic annotations for the hypermodels designed and visualized in it. Therefore, FORTH presented the details and the management of these semantic annotations from the editor’s point of view and contributed to the relevant discussions.

UBERN:

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

A dynamic search query has also been developed. This dynamic search query enables to conduct sophisticated search queries requested by ICCS such as “find all patients for whom we have imaging, clinical and miRNA nephroblastoma data”. The feedback received from an initial version which has been circulated, has been exploited. The developed interface should be suitable to support semantically driven search queries, which will be translated to SPARQL, instead of SQL, and executed by RICORDO in the future.

USAAR:

'HOT Maps' of tumour-specific hallmark knowledge were further discussed led by UCL. USAAR evaluated, structured and optimized the data corpus for nephroblastoma and lung cancer data. This included a digitalization of patient's image data and restructuring the image corpus and the management of miRNA data.

PHILIPS:

Partner PHILIPS worked further on the ontology annotation tool, implementing the normalization algorithms for SNOMED-CT for the long normal form, for both focus concepts and attributes (including representation of groups of attributes).

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

The model and in silico trial repository web services make use of CHIC brokered authentication mechanism. This is essential in order to ensure that only authorized clients have access to model/tool and in silico trial repository web services.

The model/tool and the in silico trial repositories have been integrated into the CHIC security framework and the single sign on mechanism has been implemented for both of them.

Partners ICCS and CUSTODIX have exchanged information related to the SAML metadata, and the PySAML2 library has been configured and integrated into the model and in silico trial projects.

The model and in silico trial repositories have been set up to run behind a CHIC proxy, so that only secure connections (SSL) are being used by the clients.

UBERN, CUSTODIX:

The clinical data repository has been further integrated with the CHIC data protection framework.

USAAR:

USAAR prepared data to conduct manual ground truth annotations and anonymization of nephroblastoma and lung cancer data.

Summary of significant results

ICCS has developed the prototype and the web services for the model/tool and in silico trial repositories. Taking into account feedback from partners, ICCS has slightly updated the schema and the web services of the aforementioned repositories, improved the user interface, fixed some bugs and enriched the repositories with more functionalities. Furthermore, the in silico trial repository has been moved to another virtual machine in the CHIC private cloud and it has been totally split from model and tool repository. Regarding the clinical data repository, it now supports genetic/molecular and histopathology datasets, the REST services have been extended with more functionality, and the repository migrated from database first to code first development approach. Furthermore, the clinical data repository has also received clinical feedback from partner USAAR regarding its structure and the uploading of clinical data and it has been evaluated in an iterative process with external clinicians and researchers. Partner UCL has developed the semantics infrastructure, in co-ordination with stakeholders in the consortium so as to refine the hypo/hypermodel metadata schema, to create applications that leverage the schema, to provide annotation (RDF) store and ontology DB Knowledge Base through RICORDO and to link RICORDO metadata management web services with the hypermodelling editor. Based on this, partners FORTH and ICCS presented the details and the

management of these semantic annotations from the editor's and the model repository's point of view. In parallel, partner UBERN has preliminary integrated the clinical data repository with the RICORDO framework and finalized the dynamic search query builder which enables to conduct sophisticated search queries on the data repository. Partner PHILIPS worked further on the ontology annotation tool, implementing the normalization algorithms for SNOMED-CT for the long normal form, for both focus concepts and attributes (including representation of groups of attributes). On the other hand, partner USAAR continued the iterative process to define 'HOT Maps' of tumour-specific hallmark knowledge and evaluated, structured and optimized the data corpus for nephroblastoma and lung cancer data. Regarding the integration with the security and the legal/ethical framework, partners UBERN and ICCS, in collaboration with partner CUSTODIX, have further integrated the model, the in silico trial and the clinical data repositories with the CHIC data protection framework and partner USAAR has prepared data to conduct manual ground truth annotations and anonymization of nephroblastoma, and lung cancer data. Finally, partners ICCS, UBERN and UCL have documented most of the aforementioned advances in the Deliverables 8.2 and 8.3.

Summary on actions taken to meet the recommendations from the 4th CHIC review

User interfaces have been improved with the ultimate end-user in mind.

New web services have been developed according to the clinicians' requirements in order to enhance the integration of the repositories with the whole platform.

Towards the clinical orientation of the project, the clinical data repository has received clinical feedback from partner USAAR regarding its structure and the uploading of clinical data and it has been evaluated in an iterative process with external clinicians and researchers. Furthermore, in order for the clinical data repository to fulfil the requirements of the clinicians, it now supports additional clinical data formats.

In order to ensure a smooth running of the clinical functionalities provided by the CHIC platform, many bugs in the repositories have been fixed and progress has been made in the infrastructure for semantic metadata management (preliminary integration of the clinical data repository with the RICORDO, refinement of the hypo/hypermodel metadata schema, discussions and agreement between the partners about the management of the semantic annotations, etc.)

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

See above.

Corrective actions

See above.

Statement on the use of the resources

Planned versus actual efforts in WP8			
Partner	Planned PM Total	Planned PM Period 3	Actual PM Period 3
1-ICCS	19.30	4.50	4.50
3-USAAR	3.00	1.00	2.16
7-FORTH	7.00	2.00	3.00
9-UPENN	3.00	1.00	0.00
12-UBERN	15.00	6.00	4.80
13-Custodix	3.00	1.00	1.35
14-Philips	7.00	3.00	8.00*
15-UCL	36.00	12.00	8.99**
Total	93.30	30.50	32.80

*) Work on the sematic representation of models descriptions. A significant part of the work focused on building a tool for the annotation with SNOMED-CT concepts in the context of an HL7-based approach (which is the main standard in the healthcare industry). The tool supports flexible input and implements an algorithm for automatic normalization (conversion to SNOMED normal form).

**) Two developers on CHIC left UCL. There were some delays in recruiting (Dr Helvensteijn started in October, and Dr Kokash started very recently). UCL should be able to re-balance progress within the current project period.

1.9 Work Package 9: Image Processing and Visualization

Main objectives of this WP

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

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

Active tasks in this reporting period:

- T9.2, Visualization techniques for models and data (M3-46)
- T9.3, Statistical data visualization for the simulation outcomes (M9-46)
- T9.4, Visualization of the reporting in data repository (M13-46)
- T9.5, An integrated image processing toolkit for CHIC (M6-46)
- T9.6, Image registration tools (M3-36)
- T9.7, Multimodal and longitudinal brain tumor image analysis (M9-46)
- T9.8, A software platform for the Assessment of Tumor Treatment Response (M8-42)

Summary of progress achieved towards objectives

BED has been working on visualization by developing a software platform called CCGVis. BED has also been developing image segmentation algorithms for nephroblastoma.

FORTH has been working on the development of DoctorEye for the integration of visualization and image processing, as well as the software for tumor response.

USAAR did mainly work on segmentation of Wilms tumors and evaluated the performance of different approaches on imaging data sets. A lot of work was further done on segmentation of Wilms tumors using DoctorEye and developing a (semi-)automatic software for segmentation. A wide range of imaging features with respect to their discriminative potential for nephroblastoma were analysed and a corresponding paper written. It continued to evaluate, structure and optimize the data corpus for nephroblastoma imaging data. They also developed a fast automatic brain tumor segmentation method and the following paper was written and submitted:

“S. Müller, J. Weickert, N. Graf: Automatic brain tumor segmentation with a fast Mumford-Shah algorithm. In M. A. Styner, E. D. Angelini (Eds.): Medical Imaging 2016: Image Processing (San Diego, CA, February 2016), SPIE Vol. 9784, 97842S

A wide range of imaging features with respect to their discriminative potential for nephroblastoma was further analyzed. We also developed a semi-automatic method for the segmentation of nephroblastoma. A corresponding publication is currently under review for GCPR 2016. In addition we contributed to several visualisation techniques for DoctorEye.

ICCS provided partner BED with sample output files of ICCS's lung hypomodel (along with documentation). ICCS provided feedback to partner FORTH with regards to the necessary nephroblastoma imaging data processing steps. ICCS also provided feedback with regards to the nephroblastoma hypermodel output files. ICCS provided feedback to partner FORTH with regard to the presentation template of the pdf reports that the CRAF (Clinical Research Application Framework) produces after the completion of the simulations. Based on the new requirements coming from the CHIC technical architecture, ICCS collaborated with partner FORTH and updated Wilms and lung oncosimulators so as to be able to handle medical images in the form of metaimages (mhd) and write the coordinate offset of the metaimage in the output log file.

UBERN has developed a Dr. Eye plug-in for multimodal brain tumor segmentation which has been integrated and the first tests have been completed. A clinical collaboration to evaluate the developed image registration tool has started (cohort selection, definition of metrics, etc.). An approach to define optimal weights on the CRF model used to regularize segmentation results has been developed and tested. A first clinical evaluation of automatic longitudinal tumor volumetry was performed.

Summary of details for each task

Task 9.2 Visualization techniques for models and data

BED has developed a visualization platform called CCGVis. CCGVis can import, register and visualize medical data, segmentation data and simulations. It can import various formats, singly or as time series, including dicom, mha and CHIC simulations. Visualizations include slice and orthoslice views in 2D and 3D, isosurfaces in 3D, comparisons between real and simulated tumours, and plots of tumour growth.

BED has added rigid registration to the CCGVis platform, in order that medical image sequences and simulations can be visualized and compared in a consistent coordinate system.

FORTH and BED proceeded with the integration of the visualization tool CCGVis and the desktop version of the CRAF application, achieving their seamless integration which in their current version allows the end user to pick the 3D snapshots to be included in the report.

Task 9.3 Statistical data visualization for the simulation outcomes

BED has added statistical visualizations to CCGVis showing plots of tumour growth and image histograms.

FORTH added the necessary functionality in the CRAF applications (web and desktop), for plotting the volume evolution versus time, based on the simulation outcomes. The produced plot is included as a part of the pdf report, produced in CRAF.

Task 9.4: Visualization for the reporting in data repository

BED has added output functionality to CCGVis in the form of images, plots, video and metadata. CCGVis can be configured and launched from the command line, allowing it to integrate with the other components of CHIC.

ICCS provided partner BED with sample output files of ICCS's lung hypomodel (along with documentation) in order for BED to be able to visualize them.

ICCS also provided feedback to partner BED with regards to the nephroblastoma hypermodel output files that need to be visualized.

FORTH has created a report compiling module which is integrated in the CRAF app that dynamically creates reports with all the information needed by the clinicians based on the outcomes of the hypermodels. Based on the guidance of the clinicians, the template of the reports complies with two main requests, to provide a clear answer and include all the necessary information in a minimal, well-structured way.

The reports firstly show the answer to the question which the hypermodel deals with, together with the proper graphical representations and other magnitudes of interest. It also includes all the parameters used by the hypermodel and led it to that outcome.

As the hypermodels produce 3D results, the clinician has the ability to use the CCGVis app from within the CRAF platform, in order to select snapshots of interest from the 3D outcome, as the CCGVis app allows for free three dimensional manipulation of the hypermodel's volume(s). These snapshots can then be included in the report, along with the rest data.

At USAAR, more than 100 segmentations of nephroblastomas were done using DoctorEye.

Task 9.5 An integrated image processing toolkit for CHIC

The Dr. Eye plug-in for multimodal brain tumor segmentation has been integrated and first tests finished by UBERN.

FORTH continues the task to integrate most of the WP9 technologies into a single platform (a DoctorEye based platform) according to the unanimous decision of the consortium. This decision dictates an extension of this task to M48 since it will be an ongoing effort integrating WP9 tools which are constantly updated to match the clinicians' needs (therefore the general image processing development toolkit Task will be prolonged as mentioned). The clinical scenarios are adapting to the real life applications as the clinicians use the relative tools often and during this process they

pinpoint improvements to the developers. All the image processing tools in the platform (DoctorEye, CCViS, Bratumia, etc.) are constantly being updated in order to better adapt and to simplify the work of the clinicians. This WP9 integrator is also an indicator of the clinical relevance of the project since it is being co-developed with the clinical partners of CHIC. A primary version of pre-processing tool has been deployed and is being used in the workflow of CHIC. The pre-processing tool has its own important key role at the CHIC platform, because it is a mediator which converts the input data (medical images and segmentations) into a form exploitable by the hypermodels (e.g. nephroblastoma) and allows their proper initialization.

USAAR: A lot of work was done on segmentation of Wilms tumors using DoctorEye and developing a (semi-)automatic software for segmentation. In order to do so, the performance of different approaches on these data sets was evaluated.

BED has implemented a semi-automatic segmentation method of nephroblastoma in a 3D MRI scans. The segmentation of the tumour is performed by a kernel-based graph cut approach. The results from this study have been submitted to IEEE Transactions on Medical Imaging.

ICCS provided feedback to partner FORTH with regards to the processing steps required to convert the imaging data into a form exploitable by the nephroblastoma hypermodel.

Task 9.6: Image registration tools

A clinical collaboration to evaluate the developed image registration tool has started (cohort selection, definition of metrics, etc.) by UBERN. A clinical collaboration with the department of neurosurgery, Univ. Bern, has started to evaluate clinically the developed image registration technique using point-wise mutual information and landmark-assisted registration

Recent advances on convex relaxation methods allow for a flexible formulation of many interactive multi-label segmentation methods. The building blocks are a likelihood specified for each pixel and each label, and a penalty for the boundary length of each segment. While many sophisticated likelihood estimations based on various statistical measures have been investigated, the boundary length is usually measured in a metric induced by simple image gradients. The work by USAAR shows that complementing these methods with recent advances of edge detectors yields an immense quality improvement.

Task 9.7: Multimodal and longitudinal brain tumor image analysis

An approach to define optimal weights on the CRF model used to regularize segmentation results has been developed and tested. First clinical evaluation of automatic longitudinal tumor volumetry. A first clinically based evaluation of longitudinal tumor segmentation has been performed. A method for finding optimal weights of a CRF model used for regularization has been developed and tested. An approach for defining the uncertainty in the segmentation results has been implemented and tested.

USAAR We proposed a fully automatic method for brain tumor segmentation that does not require any training phase. Our approach is based on a sequence of segmentations using the Mumford-Shah cartoon model with varying parameters. In order to come up with a very fast implementation, we extend the recent primal-dual algorithm of Strekalovskiy et al. (2014) from the 2D to the medically relevant 3D setting. Moreover, we suggest a new confidence refinement and show that it can increase the precision of our segmentations substantially.

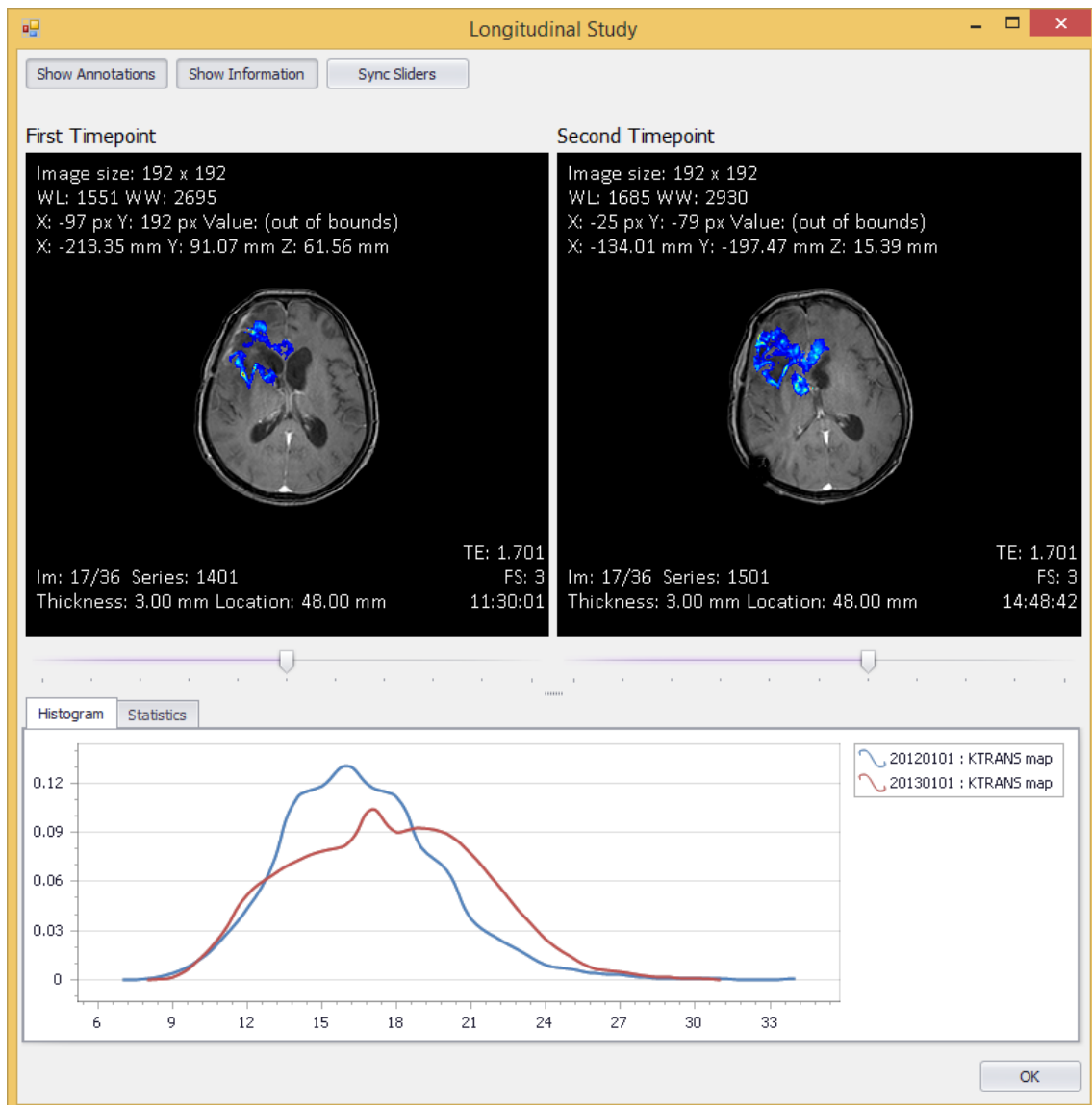
Task 9.8: A software platform for the Assessment of Tumor Treatment Response

The work on the specialized platform of FORTH which is dedicated to comparing regions of interest of the imaging data longitudinally and from different modalities (e.g. ADC maps from DW-MRI in conjunction with anatomical MRIs). This work is designed to help the clinician to understand the actual changes that take place in the treatment process and assess as early as possible if the patient is responding. Our work has been continued by fine tuning and optimizing the code and improving the functionality of the UI of the platform. New statistical measures have been added to the platform, which now can be viewed and compared side by side along with the histogram, thus providing to the clinician a quick overview of all the important information in a single window.

The platform extracts multiple statistical measures for comparing over time and within different modalities/parametric maps that offer temporal and complementary information. During this longitudinal study the clinician has an overview of the volume evolution of the region of interest, and of other available statistical parameters e.g. regarding diffusion or perfusion changes in the ROI. In order to provide a better understanding of the nature of the information, histograms of the selected time points are superimposed on a common axis system providing a quick and exact visual representation of the temporal evolution of the selected ROI.

This software is also being integrated to DoctorEye within the agreed scope of T9.5

A screenshot of the prototype of the platform in its current status is the following.



At USAAR, A wide range of imaging features with respect to their discriminative potential for nephroblastoma was analyzed and a paper written about this: Sabine Müller, Ruslan David , Kostas Marias, Graf N: The standardized histograms of T2 Magnetic Resonance Images (MRI) signal intensities of Nephroblastoma does not predict histopathological diagnostic information. Cancer Informatics Supplement 14(S4):1-5, 2015, doi: 10.4137/CIN.S19340

Summary of significant results

First clinical evaluation (publication submitted) on longitudinal tumor volumetry finished. Results demonstrate the feasibility of automated longitudinal volumetry in the clinics.

USAAR did mainly work on the segmentation of nephroblastoma and evaluated the performance of different approaches on imaging data sets. A wide range of imaging features with respect to their discriminative potential for nephroblastoma response to preoperative chemotherapy was analysed. A semi-automatic method for the segmentation of nephroblastoma is under development and a corresponding paper is written and submitted. Our method is already evaluated on 20 hand-labelled t2 sequences, annotated by 2 human experts. We could show that few user scribbles are sufficient for highly accurate segmentation results.

The fully automatic method for brain tumor segmentation is evaluated on 188 data sets with high-grade gliomas and 25 with low-grade gliomas from the BraTS14 database. Within a computation time of only three minutes, we achieve Dice scores that are comparable to state-of-the-art methods.

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

The CHIC consortium has taken a unanimous decision to integrate most of the WP9 technologies into a single platform (a DoctorEye based platform) and to extend the corresponding Task 9.5 until the end of the project.

This decision dictates an extension of this task to M48 since it will be an ongoing effort integrating WP9 tools which are constantly updated to match the clinicians' needs (therefore the general image processing development toolkit Task will be prolonged as mentioned).

Therefore, FORTH has taken the additional responsibility to extend the DoctorEye platform to be used as a single integrating platform for the WP9 activities.

Due to the Task 9.5 extension, person months and corresponding budget modifications must take place in the Technical Annex in order to reflect the amendments in the additional labor undertaken. An amendment of the project's Technical Annex has been requested to the E.C. in order to reflect the changes in the work planning.

Also, there is a significant change of requirement on visualization which were raised during the discussions in recent meetings. Correspondingly, we have suggested the rename of the visualization tasks to T9.2 the visualization for models and data, T9.3 Statistical data visualization for the simulation outcomes, and T9.4 Visualization for the reporting in data repository.

At UBERN, additional effort was put into Task 9.7 in order to realize a clinically-based evaluation of longitudinal brain tumor segmentation. The findings of this evaluation support the applicability of the developed segmentation algorithm in the clinics and thus also benefit WP11. The results were recently published in Nature Scientific Reports.

An amendment of the project's Technical Annex has been requested to the E.C. in order to reflect the changes in the work 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 WP9			
Partner	Planned PM Total	Planned PM Period 3	Actual PM Period 3
1-ICCS	4.00	1.00	1.00
3-USAAR	15.00	5.00	2.61
5-BED	36.00	10.50	23.00*

7-FORTH	45.29	8.50	8.50
12-UBERN	12.00	3.00	4.10
17-TEI-C	1.00	0.00	0.00
Total	113.29	28.00	39.21

* WP9 is designed to offer services of image processing and visualisation for the rest of the project. At this stage of the project we see a need to increase the resources in WP9, since a substantial amount of changes to the visualisation task have occurred in the project. The visualisation task has been extended to meet the increasing demands of all the clinical scenarios in nephroblastoma, lung cancer, glioblastoma and prostate cancer with new requirements on visualising the input images in various ways, such as 3D slice, isosurface, volume rendering and 2D slice, and presenting different images side-by-side, or possibly as superimposed isosurfaces. Also, there are new requirements to focus on the visualization of heterogeneous and multivariate datasets created by the models and simulations using graphs, parallel coordinates, scatter plots, etc. In addition, integration of the visualization toolkit into the CHIC workflow also requires additional work as added features to DrEye with optional command-line arguments and output as a "screenshot" for reporting purpose. Also, BED has committed a significant amount of resources on medical image processing. Within the reporting period, BED has implemented a semi-automatic segmentation method of nephroblastoma in a 3D MRI scans. The segmentation of the tumour is performed by a kernel-based graph cut approach. The results from this study have been submitted to IEEE Transactions on Medical Imaging.

1.10 Work Package 10: Integrated Platform

Main objectives of this WP

WP10 focuses on the implementation of the CHIC technological architecture as a distributed software platform and the realization of critical components and integration facilities for the realization of the CHIC hypermodels. The specific objectives for this reporting period have been to define the standardized interoperable interfaces for accessing the model repositories, implementation of important components for the data management and computational infrastructure, the design of the CHIC hypermodelling editor, and the implementation of technical components to ensure the clinical relevance of the project's outcomes. According to Annex I the main objectives are:

- To The design of the Portal web interface and the provision of application specific user interface components for it (Task 10.1)
- The definition of the standardized interfaces for accessing the CHIC model repositories (Task 10.2)
- Data Management and Computational infrastructure (Task 10.3)
- Requirement analysis and initial design of the CHIC hypermodelling editor (Task 10.4)
- The design and implementation of the technical components for the connection of the CHIC research domain to the clinical setting in order for the clinicians to take full advantage of the research outcomes for the benefit of their cancer patients (Task 10.5).

Active tasks in this reporting period:

- Task 10.1, Portal (M1-48)
- Task 10.4, Data and hypermodel orchestration (M7-44)
- Task 10.5, The clinical research integrated platform (M32-46)

Summary of progress achieved towards objectives

Task 10.1, Portal

FORTH leads the activities regarding the integration of CHIC tools in the CHIC portal. The integration activities continue taking place and according to the review comments they need to be given more emphasis, thus this task is extended up to the end of the project.

Task 10.3, Data Management and Computational infrastructure

ObTiMA is further extended by USAAR for data storage for the CHIC environment. Data from nephroblastoma are entered in ObTiMA and linked to molecular data and imaging data. Data are uploaded to the CHIC repository. A possible connection between the CHIC clinical data repository and the MyHealthAvatar EU project has been discussed between UBERN, ICCS, Custodix and BEDS. UBERN introduced a new data structure in the Clinical Data Repository (CDR) in order to facilitate the joint testing of MUSCLE coupled models among basic-science modellers. It was implemented on the common CHIC virtual machine and is used for model testing and preparation of CHIC demonstrators.

Task 10.4, Data and hypermodel orchestration

Finalization by CINECA of the first version of the high level hypermodelling language to describe hypermodels with “strongly coupled” hypomodels used by the Hypermodelling editor to submit workflows to the hypermodelling execution framework. ICCS has collaborated with partner FORTH in order to provide documentation regarding the consumption of model/tool repository web services by the hypermodelling editor. FORTH continues the design and implementation of the CHIC Hypermodelling Editor. In this reporting period further interactions with WP6 and WP7 took place in order to integrate the use of the metadata annotations of the models, the definition of the hypermodelling language, and addressing the requirements of the modellers.

Task 10.5, The clinical research integrated platform

FORTH developed a prototype of the CRAF application. ICCS updated the repositories web services after some feedback from FORTH and as a result the communication required between the *in silico* trial repository and the CRAF (clinical research application framework) has been reduced. The aforementioned changes resulted in reduction in the CPU usage of the server that accommodates the *in silico* trial repository.

Summary of details for each task

Task 10.3

Data management for heterogeneous nephroblastoma data is further developed with the usage of ObTiMA. Data are uploaded to the CHIC repository. In order to host data for the upcoming MyHealthAvatar (MHA) review in May 2016 a discussion between UBERN, ICCS, Custodix and BEDS has been initiated to establish a connection with the CHIC clinical data repository. As outcome of this discussion, CHIC will create a user account for each service within MHA that needs to access the CHIC clinical data repository. All data that should be query able by MHA will be accessible by those MHA user accounts (this is the so called synthetic data). UBERN created a common data structure that facilitates coupled execution and testing of CHIC hypo-models.

Task 10.4

CINECA in collaboration with the other representatives of WP7 have analyzed the requirements for supporting “strongly coupled” hypomodels and finalized the first version of the high level hypermodelling language used by the Hypermodelling editor to describe hypermodels with “strongly coupled” hypomodels and to submit them to the hypermodelling execution framework. CINECA also focused on the integration of VPH-HF with all other CHIC components, in particular with the new CRAF application.

ICCS has collaborated with partner FORTH in order to provide documentation regarding the consumption of model/tool repository web services by the hypermodelling editor.

ICCS interacted with the WP10 leader and the rest of WP10 partners in order to ensure that work in WP10 is in line with the updated after the 3rd CHIC review overall priorities of the project.

Task 10.5

Partners started the discussions on the adaptation of the CHIC platform for clinical research and the needed infrastructure to support it. As a main result of this discussion, FORTH undertook the responsibility for the the development of the Clinical Research Application Framework (“CRAF”). This application presents a user friendly graphical interface for the use of the CHIC hypermodels and related infrastructure in the clinical environment. Strong interactions between the WP10 partners and the partners involved in all technical work packages (WPs 5, 6, 7, 8, 9) took place following the use cases and requirements introduced by the clinical partners. The CRAF prototype was successfully demonstrated in the 4th review meeting (January 2016).

Summary of significant results

Documentation regarding the consumption of model/tool repository web services by the hypermodelling editor. The development environment of the CHIC clinical data repository deployed to the CHIC infrastructure will be used to host data for MyHealthAvatar as a temporary solution for the upcoming review in May 2016. The requirements and design for supporting “strongly coupled” hypomodels have been finalized and the first version of the high level hypermodelling language used by the Hypermodelling editor to describe hypermodels with “strongly coupled” hypomodels and to submit them to the hypermodelling execution framework is available. Work on the Data Upload tool and the Hypermodelling Editor continues.

The need for having a “packaged” clinically relevant representation of the CHIC environment led to the introduction of an additional component for the project, the Clinical Research Application Framework (“CRAF”) that is currently under development. This suite of tools and end-user applications will provide a “one-stop” solution for accessing the results of CHIC for clinical research in the clinical domain. The development of this framework is undertaken by FORTH in the context of WP10 with interactions and support from the other technical work packages and especially WP9 which deals with the visualization tools.

Deviations from Annex I and their impact on other tasks as well as on available resources and planning1

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

All critical objectives have been achieved in time.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP10			
Partner	Planned PM Total	Planned PM Period 3	Actual PM Period 3
1-ICCS	7.40	1.90	1.90
3-USAAR	7.00	3.00	3.38
7-FORTH	42.00	7.50	10.50*
12-UBERN	3.00	1.00	1.00
14-Philips	18.00	6.00	15.02**
16-CINECA	8.00	3.50	1.50
17-TEI-C	4.00	1.00	0.00
Total	89.40	23.90	33.30

*) The increased man effort of FORTH in WP10 is due to the following reasons: First of all, there was an immediate need to provide a working demonstrator for the Nephroblastoma hyper model to be shown by Prof. Norbert Graf in the evaluation of the CHIC hyper modeling infrastructure in the 9th International Renal Tumor Biology Conference in Toronto, Canada from the 2nd to the 3rd of April 2016. Because of the requirements of the scenario in terms of the CPU power (especially when multiple users are evaluating it) and the time needed for its completion, it was decided to implement an application level "proxy" for its execution that returns pre-calculated results in a timely manner. Secondly, after initial discussions with the clinical partners, we started the design of a web based version of CRAF in addition to the desktop (java) prototype application that we showed in the previous review.

**) Most of the work was dedicated to the representation of clinical workflows and the integration of models as externalized functionality to be executed in the clinical workflows. Philips has also evaluated workflow frameworks that focus on business process modeling to be applied to modeling and simulation of clinical processes (JBPM and Bonita). Philips has designed, implemented and tested a prototype showing the feasibility of this approach.

1.11 Work Package 11: Clinical Adaptation and Validation

USAAR continued together with all partners of WP11 to consolidate evaluation and validation criteria for enhancing the clinical adaptation of hypermodels. ICCS has 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. Extensive discussions of ICCS with USAAR, KUL and other partners led to the decision to organize CHIC component usability evaluation sessions at different meetings (GPOH Winter School in Söllerbeck, from the 9th to the 13th of January 2016, International Wilms Tumor Biology Meeting in Toronto, from the 2nd to the 3rd of April 2016). All partners of WP11 were involved in these activities.

Main objectives of this WP

According to the different goals and requirements of this project a clinical adaptation and validation process within the project is carried out as a major part of quality control. This guarantees the 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, which will be beyond the timeframe of the CHIC project. Hence, this WP identifies objectives that need to be specifically tested in each case. For that reason proper evaluation criteria are 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. A first evaluation workshop was already reported on (D11.2) now followed by the Report on the second evaluation workshop round (D11.3). 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
- to perform a quantitative validation of the effectiveness of standardized therapies (mainly radiotherapy, chemotherapy and hormonal therapy) versus innovative ones.

Active tasks in this reporting period:

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

Summary of progress achieved towards objectives

- Task 11.3 (Clinical adaptation of the CHIC infrastructures as a whole): Initial discussions were started on the use of the first multi-modeller hypermodel concerning lung cancer for providing the first complete (basic and technology) example for the fine-tuning of the CHIC infrastructure based on the corresponding multiscale clinical data. This discussion was mainly done by ICCS and

USAAR with the participation of modellers and IT-people. Hypomodels describing the interplay between cell populations, which can exhibit mutations and differential response to therapies, are ready for implementation in the lung-cancer hypermodel, provided by UNITO in cooperation with USAAR and other partners. UNITO also finalized the database structure for the validation of the prostate cancer model. In this task UPENN develops 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.

- USAAR intensively enhanced our efforts regarding the clinical relevance of the CHIC project. This was done by a lot of interactions of the whole consortium and resulted in a concrete plan how to achieve this goal in the remaining period of the project. A new document is written that summarizes these efforts for the different diseases (Glioblastoma, neuroblastoma, Non-small cell lung cancer and prostate cancer) enrolled in CHIC. The impact on the CHIC infrastructure is manifold and now clinically oriented.
- USAAR did prepare and successfully run two evaluation workshops with the participation of clinicians and basic researchers outside of the CHIC consortium. The first took place at the GPOH winter school in Söllerbeck, Germany in January 2016 and the second in Toronto, Canada in April 2016. Details are found in D11.3. The deliverable D11.3 was written and submitted.
- The work done for lung cancer was enhanced to neuroblastoma. The neuroblastoma Oncosimulator will be demonstrated at the next review. There will be validations done for each hypomodel as well as for the integrated Oncosimulator.
- Extensive discussions of ICCS with USAAR, KUL and other partners led to the decision to organize CHIC component usability evaluation sessions during the winter CHIC school to take place in Homburg in February/March 2016 followed by the workshop linked to the cancer conference in Toronto taking place in August 2016.
- ICCS worked specifically on the improvement of the clinical usability of CHIC repositories in accordance with the recommendations of the reviewers.
- Extensive discussions of ICCS with USAAR, KUL and other partners led to the decision to organize CHIC component usability evaluation sessions during several other meetings (GPOH Winter School in Söllerbeck, from the 9th to the 13th of January 2016, International Wilms Tumor Biology Meeting in Toronto, from the 2nd to the 3rd of April 2016). ICCS provided a questionnaire for these meetings in order to be used for the evaluation of the clinical data repository and contribution to the preparation of Deliverable 11.3.
- ICCS translated clinical needs and requirements into the definition of particular features of the CHIC infrastructure from both basic science and technology perspectives.
- FORTH introduced the CRAF architectural component that signifies a progress towards utilizing the CHIC platform in the clinical research domain. FORTH also prepared user questionnaires and contributed to D11.3.
- Both the collection of clinical data for model validation and the development of hypo-models in the context of Prostate Cancer have been further continued by UNITO. Available clinical data on prostatectomized (EUREKA1 database) or radically radio-treated (EUREKA2 database) patients are under investigation following two approaches:
 - Statistical analysis (bottom-up) in order to stratify data according to meaningful and clinically significant parameters;
 - Mathematical modelling (up-down) of prostate tumour growth and parameter values validation on the clinical scenarios defined by the above statistical results.

- In addition UNITO is collaborating with CPO-Piemonte Epidemiology Unit to implement EUREKA studies epidemiology evidences and to compare different treatment modalities in homogeneous cohorts. Besides, UNITO is externally validating the two developed models on prostate cancer: a pre-therapy nomogram on RT cases by Gabriele D. et al, and a post-therapy model using PSA follow-up data on surgical patients by Stura I. et al.
- The developed longitudinal segmentation approach has been clinically evaluated by UBERN
- In task 11.4 (Validation of the CHIC infrastructure as a whole) ICCS has been involved in the clinical validation of the whole infrastructure which started on month 36 focusing on the comparison of multiscale clinical data with the simulation outcome of multimodeller hypermodels as this is produced using the whole CHIC infrastructure.
- UPENN reports are found in WP2 and WP3

Summary of details for each task

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 was continued with the nephroblastoma hypermodel.
- USAAR intensively enhanced our efforts regarding the clinical relevance of the CHIC project. This was done by a lot of interactions of the whole consortium and resulted in a concrete plan how to achieve this goal in the remaining period of the project.
- Extensive discussions of ICCS with USAAR, KUL and other partners led to the organization of a CHIC component usability evaluation sessions. Two evaluation workshops took place and are reported in D11.3.
- ICCS using WP3 feedback has been working on the improvement of the usability of CHIC repositories in the clinical environment in accordance with the recommendations of the reviewers.
- In the progress meeting held in Bern, ICCS provided the consortium with a questionnaire in order to be used for the evaluation of the clinical data repository. Consequently, a version of this questionnaire was used for the evaluation of the aforementioned repository in the 9th International Conference on Pediatric Renal Tumor Biology, which took place in Toronto from the 2nd to the 3rd of April 2016.
- ICCS contributed to the preparation of the Deliverable 11.3 “Report on the second evaluation workshops round”.
- Regarding clinical adaptation of the CHIC infrastructure as a whole, ICCS has translated clinical needs and requirements into the definition of particular features of the CHIC infrastructure from both basic science and technology perspectives. On top of this ICCS has extensively worked on the clinical adaptation of multimodeller hypermodels.
- The introduction of “CRAF” (Clinical Research Application Framework) by FORTH after the realization of the importance of the clinical adaptation of the CHIC platform is an important milestone for making the CHIC infrastructure truly clinically relevant. FORTH worked closely with USAAR to design the view and the overall user experience for the clinicians.

- FORTH prepared user questionnaires and contributed to the Deliverable 11.3 (“Report on the second evaluation workshop round”) with respect to the presentation of the evaluation of CRAF in the evaluation workshops.
- UNITO did work on the following topics:
 - Statistical models (Domenico Gabriele): formulation of hypo-models integrating clinical (age, pre-treatment PSA, clinical Staging, bioptic Gleason Score, percentage of positive cores at biopsy), pathologic (pathological Staging, surgical margins) or therapeutic factors (adjuvant radiotherapy, RT dose, adjuvant androgen depriving therapy).
 - Mathematical models (Ilaria Stura): formulation hypo-models describing the interplay between cell populations which can exhibit mutations and differential response to therapies are ready for implementation in the lung cancer and prostate cancer hyper-models (e.g. hormone sensitive versus hormone resistant cells); in addition, the database structure for the validation of prostate cancer model is ready. Several hypo-models finding the correct parameter values during therapies are implemented.
 - The database structure is available and we are ready to share it and to find a common ontology with the other groups. UNITO is also preparing a SW allowing multiple choices by the user and running models with different parameters values (various types of cancer).

1. Collaboration with CPO-Piemonte Epidemiology Unit

UNITO is collaborating with CPO-Piemonte Epidemiology Unit, Director G. Ciccone (local researcher A. Castiglione), with the collaboration of Prof. F. Merletti, to implement EUREKA studies epidemiology evidences:

- a. Calculations of EUREKA-1 data coverage on total Piedmont Region Radical Prostatectomies, comparing our patient numbers with SDO information (Scheda di Dimissione Ospedaliera, hospital dismissal records) concerning RP hospitalizations, subdivided according to treatment hospital and year of surgery;
- b. Compliance to 2009 Piedmont Region Oncology Web guidelines on prostate cancer, with regards to treatment choice according to patient risk-class;
- c. Comparison of surgery and radiation therapy results in homogeneous cohorts (risk-class, year of treatment, geographic area).

2. External validations by UNITO

Up-to-date, we have developed two different models on prostate cancer: a pre-therapy nomogram on RT cases by Gabriele D. et al, and a post-therapy model using PSA follow-up data on surgical patients by Stura I. et al. Of consequence, we are at the extremes of two opposite perspectives.

Firstly, we have to apply our models to the alternative treatments in **external validation** (surgery for RT nomogram and RT for the surgical model).

Secondarily, we have to develop therapeutic models including, for the surgical cohort, pathological features and adjuvant RT, while, for the RT study, RT dose and adjuvant ADT.

Third, we should integrate the single hypo-models (to use conventional terms of the CHIC project) into a complete clinical hyper-model, that would take into consideration different clinical options and variable timing, starting from cancer staging and adding information along with therapeutic performances and follow-up.

- A clinical evaluation of automated longitudinal volumetry has been performed by UBERN. Quantification metrics to compare user delineations and the computer algorithm were designed and used on a chosen cohort of GBM patients. A second clinical study evaluates the use of the proposed segmentation algorithm for quantification of immediate postoperative images of GBM patients as well as its capability to provide bi-dimensional tumor size measures that are widely used in clinics.
- Using the model described in WP3, UPENN has implemented a hypermodel framework to integrate the miRNA data from Wilms tumor patients and predict the response to chemotherapy.
- **In task 11.4** (Validation of the CHIC infrastructure as a whole) ICCS has been involved in the clinical validation of the whole infrastructure which started on month 36 focusing on the comparison of multiscale clinical data with the simulation outcome of multimodeller hypermodels as this is produced using the whole CHIC infrastructure.
- UPENN reports are found in WP2 and WP3 and in WP6.

Summary of significant results

Two successful evaluation workshops were successfully run by USAAR and are reported in D11.3. The CHIC infrastructure is clinically oriented and well recognized by the scientific community also including clinicians.

Introduction of CRAF architectural component constitutes a major progress towards utilizing the CHIC platform in the clinical research domain.

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 is continued with the work on the nephroblastoma hypermodel.

Extensive discussions of ICCS with USAAR, KUL and other partners led to the organization of a CHIC component usability evaluation sessions during the winter CHIC school to take place in Homburg in February/March 2016 followed by the workshop linked to the cancer conference in Toronto taking place in August 2016.

ICCS using WP3 feedback has been working on the improvement of the usability of CHIC repositories in the clinical environment

Clinical adaptation of the CHIC infrastructure for Prostate Cancer is going on by paying attention to the collection of data for model validation and to the formulation of hypo-models to be arranged to produce a clinically oriented hypermodel. The clinical databases EUREKA1 and EUREKA2 are presently on a UNITO server and are potentially available by CHIC partners according to the legal framework. Collaboration with CPO-Piemonte Epidemiology Unit to implement EUREKA studies epidemiology evidences is in progress. Mathematical modeling on prostate cancer has been performed as well using the Universal Phenomenological model and more operative statistical approaches. Models have been provided to CHIC partners involved in lung cancer and nephroblastoma studies. Executable Files are potentially available from CHIC infrastructures.

First clinical evaluation on longitudinal tumor volumetry finished. Results demonstrate the feasibility of automated longitudinal volumetry in the clinics. First results indicate clinical usability for providing bi-dimensional tumor size measurements.

The models of UPENN consist of MAPK, PI3K/Akt, P53, Cell cycle growth and arrest, radiation and chemotherapy induced genotoxic stresses. Based on local, global sensitivity analysis, as well as

network flows, they can project the individual patient characteristics in their model and predict the response to chemotherapy, radiotherapy, and targeted therapy.

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 3	Actual PM Period 3
1-ICCS	7.70	2.20	2.20
3-USAAR	25.00	8.00	6.18
5-BED	8.00	3.00	0.00
7-FORTH	3.07	0.50	0.80
9-UPENN	8.50	1.00	1.00
11-UNITO	20.00	5.00	5.97
12-UBERN	3.00	1.00	1.00
14-PHILIPS	3.00	1.00	1.30
17-TEI-C	1.00	0.00	0.00
Total	79.27	21.70	18.45

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 after the project end;
- to exchange information and establish relationships with current projects and initiatives;
- to coordinate training activities and thereby promote the use of tools and methods created through workshops, conferences and publications.

Active task in this reporting period:

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

Summary of progress achieved towards objectives

In Task 12.1, with regular contributions from EURICE and, whenever needed from other CHIC partners, CINECA took care of the writing and distribution of the electronic bi-monthly newsletters. EURICE was main editor and published the second annual CHIC newsletter, available for download on the CHIC public website (http://chic-vph.eu/fileadmin/chic/downloads/CHIC_Newsletter_2_final.pdf). This second issue contains contribution from ICCS, USAAR, UBERN, CINECA, and BED. EURICE worked actively with the CHIC partners also on the preparation of the third annual newsletter, which has been released immediately after this reporting period. EURICE continuously updated the project website with the latest news from the CHIC partners and other relevant new information from the project; and CINECA kept alive the CHIC social channels with news from the project and from other relevant communities. The dissemination activities actively went on from the previous period both towards clinical, scientific, and general public audience. A detailed reporting of the dissemination events and scientific publications is presented in the respective tables later on in this report.

In Task 12.2, after preparation of D12.3, partners continued with their contributions to exploitation plans and individual exploitation activities. The IPR Memorandum Of Understanding has been completed and signed by all partners. Decisions were taken at consortium level on the exploitation of the CHIC platform as a whole and concrete actions have been defined to achieve the agreement on a complete exploitation plan by the end of the project. The status on the CHIC components exploitation plans together with a first analysis of the CHIC platform, as a whole, exploitation paths have been reported in D12.4.

As part of Task 12.3, contact to clinical partners outside of the CHIC consortium was initiated to collect patients' specific data for testing and evaluating CHIC tools. Partners of CHIC will participate at the International Conference and Exhibition on Pediatric Oncology August 11-13, 2016, in Toronto, Canada (<http://pediatriconcology.conferenceseries.com/#sthash.nV1mWL5w.dpuf>), which will focus

on “Benchmark practices and accelerating computational approaches for Pediatric Oncology”. This three-day conference will cover the latest trends and challenges in Pediatric Oncology and, as it includes computational approaches for Pediatric Oncology, it is an ideal platform for running a workshop at this event. A lot of interaction with the organizers of this Conference took place. CHIC is now a co-organizer of the conference. UBERN co-organised the MICCAI Brain Tumor Segmentation (BRATS) Challenge 2015 and LUH carried out internal teaching of students.

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 partners regarding conferences, publications, workshops, noteworthy achievements, so to feed the CHIC project website and other tools available to the consortium in the dissemination kit. CINECA, in synergy with the website updates, has created and maintains the CHIC social channels (in particular Facebook and Twitter accounts) for the reposting of interesting information to a wider audience. List of activities in this domain are reported in Table 12.1.

Subtask 12.1c: Newsletter

CINECA took care to the main writing, collection of inputs, and distribution of the electronic bi-monthly newsletters with support from EURICE and other partners as needed. Four issues of the electronic newsletter were released in the reporting period. CINECA has also been monitoring the statistics on the newsletter opening and subscriptions, so to take actions if necessary. From the beginning of the project, the number of subscribers increased from 41 to 69 and the “open” statistics are also confirming that the communication from the CHIC project is reaching out to the subscribers.

EURICE is responsible for the regular publication of the annual newsletters, with the goal to provide a more detailed insight into the CHIC project and consortium. The 2nd issue of the annual CHIC newsletter was prepared with contributions collected from the CHIC partners ICCS, USAAR, USFD, UBERN, BED, CINECA as well as from members of the external advisory board. The focus of this second project newsletter was on the technical work accomplished so far. The second newsletter was published in June 19, 2015, and it is available for download from the CHIC website (http://chic-vph.eu/fileadmin/chic/downloads/CHIC_Newsletter_2_final.pdf). A third issue of the annual CHIC newsletter was prepared during this reporting period and published on the 5th of April 2016 (http://chic-vph.eu/fileadmin/chic/downloads/CHIC_3rd_Annual_Newsletter.pdf). This time, the focus lied on the clinical relevance of the CHIC tools and services.

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

Magazine				
Computational Horizons in Cancer	Newspaper/Magazine Article	ICCS	http://viewer.zmags.com/publication/6eced2e8#/6eced2e8/36	2014
Grantee presentation to the Multiscale Modeling Consortium of the Inter Agency Modeling Group	Video	UPENN	https://www.youtube.com/watch?v=ttNG86de3ps	2014
Video introducing Physics Reports article in the author's own words	Video	UPENN	http://audioslides.elsevier.com/getvideo.aspx?doi=10.1016/j.physrep.2014.05.001	2014
CHIC general presentation	Web content	EURICE	http://chic-vph.eu/uploads/media/CHIC_general-presentation.pdf	2013
CHIC Flyer	Flyer	EURICE	http://chic-vph.eu/uploads/media/CHIC-flyer.pdf	2013
CHIC poster		EURICE		
Article about the CHIC Kick-Off Meeting on the Eurice company website	Web content	EURICE	Optimising cancer treatment through in-silico oncology	2013
CHIC website	Web content	EURICE	Hrrp://www.chi-project.eu	
CHIC twitter account	Web content	CINECA	https://twitter.com/CHIC_project	
CHIC Facebook page	Web content	CINECA	https://www.facebook.com/CHIC-project-333884726816111/?ref=hl	
CHIC LinkedIn group	Web content	CINECA	https://www.linkedin.com/groups/8254222	
First annual newsletter	Newsletter	EURICE	http://chic-vph.eu/fileadmin/chic/downloads/CHIC_600841_D12-6_CHIC_1st_Annual_Newsletter_final.pdf	2014
Second annual newsletter	Newsletter	EURICE	http://chic-vph.eu/fileadmin/chic/downloads/CHIC_Newsletter_2_final.pdf	2015
Third annual newsletter	Newsletter	EURICE	http://chic-vph.eu/fileadmin/chic/downloads/CHIC_3rd_Annual_Newsletter.pdf	2016
Bi-monthly electronic newsletters	Newsletter	CINECA	12 issues	2013-2016
Complex Mathematics Against Cancer	Press release	EX	Athens, Greece	10.04.2013
A Novel Cancer (Related) Project	Press release	EX	Athens, Greece	10.04.2013
New Horizons in Cancer Treatment	Press release	EX	Athens, Greece	11.04.2013
Article about "6th Progress Meeting held in Bern" on CHIC project website	Press release	EURICE	http://chic-vph.eu/highlights/details/article/6th-progress-meeting-held-in-bern/	28.03.2016
Article about the " on the CHIC Project website	Press release	EURICE	http://chic-vph.eu/highlights/details/article/international-conference-and-exhibition-on-pediatric-oncology-to-be-organised-by-chic-partners/	09.03.2016
BraTumIA press release - InterPharma	Press release	UBERN	http://newsroom.interpharma.ch/2014-11-21-schnell-im-bild	21.11.2014
BraTumIA press release - Bern Hospital	Press release	UBERN	http://tt.bernerzeitung.ch/region/kanton-bern/Inselspital-entwickelt-HirntumorSoftware/story/15434159	12.11.2014
Swiss Radio -	Press release	UBERN	http://www.srf.ch/news/regional/bern-freiburg-	12.11.2

BraTumIA press release			wallis/berner-software-analysiert-hirntumore-blitzschnell	014
Press Release - BraTumIA - Washington Post	Press release	UBERN	http://www.washingtonpost.com/blogs/innovations/wp/2014/10/01/the-incredible-potential-and-dangers-of-data-mining-health-records/	01.10.2014
BraTumIA NITRC.org website	Press release	UBERN	http://www.nitrc.org/projects/bratumia/	14.05.2014

Table 12.1 - List of dissemination events related to media, press releases and web content

Subtask 12.1d: Dissemination toolkit

EURICE with the contributions from the consortium is keeping up to date the material available in the dissemination kit that each partner can use to carry on its dissemination activities.

For dissemination purposes, ICCS has developed four posters, which briefly outline various aspects of the CHIC project. These posters have been displayed in the 6th progress meeting held in Bern in March 2016. The topics of the aforementioned posters were “An overview of the CHIC project”, “The Overarching Topology and the Basic Science Architecture of the CHIC Multimodeller Hypermodels”, “The ICCS Oncosimulator” and “In Silico Trial and Model Repositories”.

Subtask 12.1e: Conferences, Exhibitions, Workshops

A list of the events and contributions from the different partners for the third year includes (among other things):

- ICCS and USFD participated with CHIC related discussions in the final AVICENNA workshop (Barcelona, 4-5 June 2015).
- Lectures were presented by M. Viceconti and D. Walker (USFD), and K. Duan and D. Tartarini (USFD) presented posters describing CHIC Project with the focus on Hypermodelling Infrastructure at the Insigneo Showcase 2015 on the 08/05/2015. 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 the industry, the health and research sector, and important funding bodies. Additionally, the leaflets describing CHIC were disseminated during this event.
- The CHIC project was presented at the ECCO Congress in Vienna on 29th September 2015, together with p-medicine.
- Contributions were made to the strategic dissemination discussions and explorations by ICCS. One important outcome of these activities is the acceptance of the application to organize a dedicated CHIC workshop within the International Conference and Exhibition on Paediatric Oncology, to take place in Toronto, Canada on August 11-13, 2016. It is noted that the application was accepted in the subsequent reporting period (October 2015).
- UBERN participated at the BRATS Segmentation Challenge (Brain Tumor Segmentation Challenge), obtaining top-level performance in the competition. UBERN co-organized and participated in BRATS segmentation challenge as part of the MICCAI conference 2015 (Münich, Germany). UBERN ranked among the top teams in the competition. The team also participated within the BrainLesion workshop, which took place as part of the same conference.

SubTask 12.1.f: Interfacing with other projects

ICCS has had continuous interaction with the following projects: p-medicine, MyHealthAvatar, DrTherapat, AVICENNA.

The Coordinator (ICCS) participated in the final AVICENNA workshop (Barcelona, 4-5 June 2015) where he outlined the vision, the progress and the achievements of the CHIC project. He also participated in the discussions concerning the roadmap for in silico clinical trials.

Signing of a formal agreement between MyHealthAvatar and CHIC regarding the exploitation of the CHIC data repository by MyHealthAvatar by the coordinator G Stamatakis.

CINECA maintained contact with the project VPH-Share until its end in May 2015.

Task 12.2: Exploitation and IPR issues

After preparation of D12.3 and the successful signature by all partner of the IPR memorandum of understanding, partners continued with their contributions and individual exploitation activities.

ICCS continued the discussions among all CHIC partners, in particular with CINECA, PHILIPS, USAAR, KU Leuven, USFD, regarding the multi-directional exploitation of the expected project outcome. This includes clinical, industrial, research, academic teaching, and legal/legislation exploitation channels. An extensive collaboration with WP4 has ensured the addressing of all major potential issues regarding intellectual rights and other legal and ethical aspects of the joint endeavour.

CINECA, with the contribution of all CHIC partners, drafted a plan for future exploitation activities and concrete actions will follow up in the next months for the definition of the final exploitation plans for the CHIC platform as a whole. More specifically, information related to the technology readiness level (from the beginning till the end of the project), the personnel effort needed for maintenance and support, the software and hardware dependencies, the intellectual property rights, and the exploitation and sustainability plans has been provided for all the CHIC components. This information is included in the deliverable D12.4 "Draft Plan for the Use and Dissemination of Foreground."

A draft and a final version of the Innovation Radar Questionnaire regarding CHIC was submitted to the European Commission in February 2016 and included in D12.4.

A discussion about sustainability and maintenance of the CHIC project via the proposed Study Trial and Research Institute (STaRC) that is part of the maintenance program of p-medicine has continued by USAAR. Further discussions are needed and will be integrated into the final exploitation planning report of CHIC.

Task 12.3: Training activities

USAAR initiated contact to clinical partners outside of the CHIC consortium to recruit patients for testing and evaluating CHIC tools. This was necessary, as the proposed CHIC summer School could not take place as too few participants registered for the event. A new activity started to enhance participation in a new Summer School/Workshop. Contact was established with the International Conference and Exhibition on Pediatric Oncology (August 11-13, 2016 Toronto, Canada), which will focus on "Benchmark practices and accelerating computational approaches for Pediatric Oncology". This three-day conference will cover the latest trends and challenges in Pediatric Oncology and, as it includes computational approaches for Pediatric Oncology, it is an ideal platform for running a workshop at this event.

Web tutorial discussions and a preliminary formulation of the skeleton of the web tutorials have taken place.

FORTH prepared the demonstrators for the presentation and evaluation activities for the 9th International Renal Tumor Biology Conference in Toronto, Canada that took place from the 2nd to the 3rd of April 2016. Training activities have been included in the evaluation session at the same conference.

Summary of significant results

The project website is up to date, regular dissemination of news and highlights via the CHIC newsletters and web channels (web site and socials) is ongoing and effective. The 2nd and 3rd annual newsletters have been released.

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. As a result a relevant number of dissemination items can be reported together with scientific papers publications and participation to conferences:

- 62 publications on peer-reviewed papers or conference proceedings
- 30 activities on other media
- 94 conferences, workshops or other academic events

The discussion about sustainability and maintenance of the CHIC project continued and a plan is in place to reach agreement in the final exploitation paths by the next review.

Contacts to people outside the consortium were initiated. The agreement on a CHIC workshop at the International Conference and Exhibition on Pediatric Oncology is has been reached.

Summary on actions taken to meet the recommendations from the 4th CHIC review

As mentioned in the 3rd CHIC review reviewers' comments, exploitation is becoming one of the central activities for WP12. Exploitation in CHIC is composed of the individual exploitation plans from the project partners and by joint exploitation of foreground. Following WP4 work on IPR and the preliminary plans prepared in the second year, CINECA has prepared a detailed plan with which to build the PUDF update and go towards a concrete exploitation plan for the CHIC project. This plan has and will require inputs and collaboration of all partners in the final part of the project. Preliminary output on the exploitation activities have been presented at the last intermediate review meeting and have been reported in D12.4.

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 WP12			
Partner	Planned PM Total	Planned PM Period 3	Actual PM Period 3
1-ICCS	8.19	2.40	2.78
2-Eurice	12.00	3.00	4.13
3-USAAR	3.00	1.00	0.16
5-BED	6.00	2.00	0.00
6-USFD	7.00	1.89	2.83
7-FORTH	6.00	2.00	0.26
8-LUH	6.00	2.00	0.00*
9-UPENN	6.50	1.50	1.50
10-UOXF	6.00	2.00	0.00
11-UNITO	6.00	2.00	2.04
12-UBERN	5.00	2.00	1.70
13-Custodix	6.00	2.00	1.10
14-Philips	6.00	2.00	0.50
15-UCL	2.00	0.50	0.00
16-CINECA	6.00	1.00	0.97
17-TEI-C	1.00	0.50	0.36
Total	92.69	27.79	18.33

*) LUH dissemination occurred as both RTD (within WP4) and OTH as conferences and lectures and presentations were held for OTH but also for gaining knowledge for our research. The overall WP12 dissemination will be carried out in P4 as results of the ongoing research as well as the law itself (presently undergoing reform) become more concrete and apt for definitive presentation.

1.12.1 Dissemination activities and publications

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

Workshops and conferences

Title	Type	Main leader/ participants	Event	Venue	Date
6th Progress Meeting held in Bern	Press releases	EURICE	Article about "6th Progress Meeting held in Bern" on CHIC project website http://chic-vph.eu/highlights/details/article/6th-progress-meeting-held-in-bern/	Internet	28.03.2016
International Conference and Exhibition on Pediatric Oncology to be organised by CHIC partners	Press releases	EURICE	Article about the "International Conference and Exhibition on Pediatric Oncology" on the CHIC project website http://chic-vph.eu/highlights/details/article/international-conference-and-exhibition-on-pediatric-oncology-to-be-organised-by-chic-partners/	Internet	09.03.2016
Protecting Patient Privacy in Health Informatics	Oral presentation to a wider public	LUH	Lecture (German-Japanese 2016 Law Symposium)	Göttingen, Germany	25.02.2016
CHIC – A Multi-scale Modelling Platform for in-silico Oncology	Oral presentation to a scientific event	UBERN	poster presentation at ICTR-PHE 2016	Geneva, Swiss	19.02.2016
Data Protection and Data Security			Lecture (5th Neuroscience and Ethics Winter School), Humboldt University	Berlin, Germany	18.02.2016

Estimating the tumor growth: a RBF-PSO based method	Oral presentation to a scientific event	UNITO	Miniworkshop Kernel-based methods and function approximation	Turin, Italy	05.02.2016
The CHIC project for cancer clinical research	Oral presentation to a scientific event	USFD	Sheffield Cancer Research Day. Presentation of research activities in the Chic Project	Sheffield, UK	22.01.2016
Let it... Grow? No, Thanks! Math Applied to Tumors	Oral presentation to a wider public	UNITO	PhD days: PhD students talk about their researches to undergraduates	Turin, Italy	12.01.2016
How to predict the timing to relapse with a swarm	Oral presentation to a scientific event	UNITO	PhD Programme: Complex Systems in Life Sciences Students' Reports : Cycle XXIX	Turin, Italy	09.11.2015
Abstract: Clinical Evaluation of a Fully-automatic Segmentation Method for Longitudinal Brain Tumor Volumetry	Posters	UBERN	Poster presentation at the "Tag der klinischen Forschung" of the Medical faculty of the University of Bern.	Bern, Switzerland	04.11.2015
Organization of MICCAI BRATS Challenge 2015, Munich	Organisation of Workshops	UBERN	Organization of Segmentation Challenge for Brain Tumor Segmentation within the framework of the MICCAI 2015 conference.	Munich, Germany	04.10.2015
Meet in Italy for Life Sciences	Oral presentation to a wider public	UNITO	Participation to the Meeting 'Meet in Italy for Life Sciences' – Caterina Guiot	Milano, Italy	30.09.2015
Data Mining in Cancer	Oral presentation to a scientific event	USAAR	ECCO Congress Vienna, Invited keynote lecture about data mining in cancer related to p-medicine and CHIC	Vienna, Austria	29.09.2015
A RBF-based PSO approach for modeling prostate cancer	Oral presentation to a scientific event	UNITO		Rhodes, Greece	28.09.2015
"In silico clinical trials: the future of biomedical product testing	Oral presentation to a wider public	USFD	XXXIV Annual School of the Italian National Bioengineering Group "Approcci ingegneristici per lo sviluppo di metodiche alternative alla sperimentazione in vivo" Bressanone, -ed Magistral Lecture: "In silico	Bressanone, Italy	21.09.2015

			clinical trials: the future of biomedical product testing		
Copyright in Multiscale Cancer Modeling	Oral presentation to a scientific event	LUH	INFOCOMP 2015, 21-26 June, Brussels, http://www.thinkmind.org/index.php?view=article&articleid=info_comp_2015_5_30_60076	Brussels, Belgium	25.06.2015
"Copyright in Hyper-Models"	Oral presentation to a scientific event	LUH		Göttingen, Germany	16.09.2015
D-Day of the Doctoral School	Oral presentation to a wider public	UNITO	Participation to the D-Day of the Doctoral School with a poster on our work about prostate cancer http://dott-scivisa.campusnet.unito.it/do/avvisi.pl/Show?_id=orjh;sort=DEFAULT;search=%20{data}%20ge%20%222015%2F07%2F14%22%20;hits=8 – Domenico Gabriele and Ilaria Stura	Turin, Italy	16.09.2015
Predictive immune modeling in malignant gliomas.	Oral presentation to a scientific event	KU Leuven	Presentation by Dr. Joost Dejaegher at a KU Leuven Research Seminar.	Leuven, Belgium	09.09.2015
UK Royal Academy of Medicine, invited talk: "The Digital Patient"	Oral presentation to a scientific event	USFD	UK Royal Academy of Medicine, invited talk: "The Digital Patient".		09.07.2015
in silico clinical trials: reduce, refine and partially replace human experimentation".	Oral presentation to a wider public	USFD	21st Congress of the European Society of Biomechanics, Prague Invited Perspective talk: "in silico clinical trials: reduce, refine and partially replace human experimentation".	Prague, Czech Republic	05.07.2015
Copyright in Multiscale Cancer Modeling	Oral presentation to a scientific event	LUH	INFOCOMP 2015, 21-26 June, Brussels,	Brussels, Belgium	25.06.2015
Biological Simulation – from simple cells to multiscale frameworks	Oral presentation to a wider public	USFD	Invited seminar: Computational Biology Series, University of Oxford	University of Oxford	09.06.2015

Avicenna research roadmap: the challenges ahead"	Oral presentation to a scientific event	USFD	Avicenna action event 5, Barcelona Closing plenary	Barcelona, Spain	05.06.2015
"Recent developments in in silico Medicine: the impact on the medical device industry"	Oral presentation to a wider public	USFD	Medtronic Corp. Minneapolis,. Invited talk to the technical staff: "Recent developments in in silico Medicine: the impact on the medical device industry".	Minneapolis USA	21.05.2015
'In silico clinical trials: The Avicenna Roadmap".	Oral presentation to a scientific event	USFD	BMES/FDA Frontiers in Medical Devices	USA	18.05.2015
CHIC Computational Horizons in Cancer	Posters	USFD	Insigneo institute 2015 Showcase	Sheffield, UK	07.05.2015
Welcome and closing remarks. Insigneo institute 2015 Show	Exhibition	USFD	Insigneo institute 2015 Showcase	Sheffield, UK	07.05.2015
Big Data in Health	Oral presentation to a scientific event	LUH	Seminar Lecture	Oslo, Norway	05.2015
Brain tumor immunotherapy, what have we learned so far?	Oral presentation to a scientific event	KU Leuven	Presentation by Prof. Van Gool at "24th GPHO Arbeitstagung Experimentelle Neuroonkologie" organised by Prof. Bernhard Erdlenbruch	Minden, Germany	24.04.2015
Copyright in software on the Internet	Oral presentation to a scientific event	LUH	ISLACO 2015	St. Petersburg, Russia	16.04.2015
Immuntherapie	Oral presentation to a scientific event	KU Leuven	Presentation by Prof. Van Gool at the "Trends in der pädiatrischen Onkologie" organised by Prof. Michael Grotzer	Zürich, Switzerland	08.04.2015

Prostate carcinoma: reports from Eureka studies (CHIC project)	Conference	UNITO, CINECA, ICCS, USAAR	Prostate carcinoma: reports from Eureka studies congress. Oral presentations made by Simone Bnà (CINECA), Georgios Stamatakis (ICCS), Norbert Graf (USAAR), Domenico Gabriele , Caterina Guiot and Ilaria Stura (UNITO)	Candiolo, Turin, Italy	28.03.2015
Is there still a role for computed tomography and bone scintigraphy in prostate cancer staging? An analysis from the Eureka-1 database	Conference	UNITO	EAU 2015 International Meeting	Madrid, Spain	20.-24.03.2015
Brain of the Week	Oral presentation to a wider public	UBERN		Bern, Switzerland	20.03.2015
Data Protection and Clinical Data in Pediatric Research and Treatment	Video lecture	LUH	International Childhood Cancer Awareness Day Event in the European Parliament		03.02.2015
Data Protection and Data Security: A Lawyer's View on Personal Clinical Information	Winter School	LUH	Fourth Winter School Ethics and Neuroscience, Bernstein Center for Computational Neuroscience Berlin, Berlin School of Mind and Brain	Berlin	23.02.2015
Threats of Data Protection Regulation	General Assembly	LUH	ENCCA General Assembly	Brussels, Belgium	16.01.2015
Rechtsfragen der personalisierten Medizin	Invited lecture	LUH	Paul Fritzsche Stiftung, Universität des Saarlands	Homburg	29.01.2015
Predicting the Effects of Clinically Observed Kinase Mutations using Molecular Modeling and Machine Learning Algorithms	Meeting	UPENN	ASCB Annual Meeting	Philadelphia PA	2015
Dendritic cell therapy in brain cancer	Conference	KU Leuven	Presentation by Prof. Van Gool at the “VII congresso nacional associacao portuguesa neuro oncologia” organised by Associacao portuguesa neuro oncologia	Lisbon, Portugal	21.11.2014
Providing a Network of Trust in Processing	Conference	CUSTODIX	23rd EICAR ANNUAL CONFERENCE	Frankfurt,	18.11.2014

Health Data for Research			Trust and Transparency in IT Security	Germany	
Providing a Network of Trust in Processing Health Data for Research	Conference	LUH	23 rd EICAR Annual Conference	Frankfurt	17-18.11.2014
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	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
Towards the mathematical principles of the natural philosophy of living matter: In Silico Oncology/ In Silico Medicine	Workshop	ICCS	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
A Modular Semantic Infrastructure Layout for the Management of Hypermodel-Pertinent Metadata in the Context of In Silico Oncology	Workshop	ICCS	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
Modelling Glioblastoma Growth and Inhomogeneous Tumour Invasion with Explicitly Numerically Treated Neumann Boundary Conditions	Workshop	ICCS	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
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	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
In Silico Medicine: The Paradigm of In Silico Oncology	Workshop	ICCS	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
Legal and ethical aspects of in silico based medicine	Workshop	LUH	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
IPR issues in multiscale modelling	Workshop	LUH	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014

A two population Model of Cancer growth with fixed Carrying capacity	Conference	UNITO	6th IARWISOCI –The CHIC Project Workshop	Athens, Greece	3.-4.11.2014
Dendritic Cell Vaccination for Glioblastoma Multiforme	Conference	KU Leuven	Skype-presentation by Prof. Van Gool to the 6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation (IARWISOCI) - The CHIC Project Worskhop	Athens, Greece	04.11.2014
Incorporating Data Protection in In Silico Research: A case of CHIC (publication)	Conference	CUSTODIX	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation	Athens, Greece	03.11.2014
The VPH Hypermodelling Framework for Cancer Multiscale Models in the Clinical Practice	Conference	USFD	Oral Presentations about The CHIC Hypermodelling Framework in Cancer Research	Athens, Greece	02.11.2014
6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation – The CHIC Project Workshop	Workshop	USFD	Daniele Tartarini from USFD team discussed with WP6 partners the adoption of a Hypermodelling language and the technical solutions to decouple tightly coupled models	Athens, Greece	02.11.2014
Keynote lecture on Data Protection Reform	Conference	LUH	Leopoldina Symposium „Keimbahnmutationen bei krebserkrankten Kindern“	Freiburg, Germany	26.09.2014
The Importance of Data Sharing and Data Protection'	Conference	LUH	SIOPE-ENCCA conference 2014	Brussels, Belgium	18.09.2014
Multiscale modelling of cancer (workshop session)	Conference	ICCS	VPH2014	Trondheim, Norway	11.09.2014
In silico Neuro-Oncology: Simulating glioma growth and inhomogeneous invasion under explicitly treated Neumann boundary conditions	Conference	ICCS	VPH2014	Trondheim, Norway	11.09.2014
A Generalized Model of Tumor Growth and Response to Treatment using the PUN	Conference	UNITO	VPH2014	Trondheim, Norway	11.09.2014

approach (poster)					
The VPH Hypermodelling Framework for cancer research	Conference	USFD, CINECA	VPH2014	Trondheim, Norway	11.09.2014
A Two-Clones Model of Tumor Growth and its Response to Treatment	Conference	UNITO	MPDS14 Conference	Turin, Italy	29.08.2014
Nomination to Best Msc thesis work – Automatic Multimodal Brain Tumor Segmentation	Conference	UBERN	SSBE 2014 Annual Meeting	Zurich, Switzerland	27.- 28.08.2014
Cancer cell patterns emerging from agent based movement (poster presentation)	Summer School	FORTH	Spatiotemporal modelling and simulation of biology systems: Biology in Cyber Space	Dresden, Germany	02.- 09.08.2014
Patient-specific Semi-supervised Learning for Postoperative Brain Tumor Segmentation	Summer School	UBERN	Medical Imaging Summer School (MISS) 2014	Favignana, Italy	28.07. – 01.08. 2014
What is the role of in silico modelling and simulation to help translate pre-clinical data into the design of human clinical trials	Invited Lectures	UPENN	Tumor Models Summit, Boston 2014	Boston, MA, USA	22.- 24.07.2014
Invited lecture: What is the role of in silico modelling and simulation to help translate pre-clinical data into the design of human clinical trials	Conference	UPENN	Tumor Models Summit	Boston, MA, USA	21. - 23.07.2014
In Silico Oncology: A generic platform for clinically driven and oriented cancer hypermodeling. The Hypermodel Based Oncosimulator	Conference	ICCS	7th World Congress of Biomechanics	Boston, MA, USA	6.- 11.07.2014
Computational Challenges in Multiscale Modelling	Conference (Podium discussion)	USFD	7th World Congress of Biomechanics	Boston, MA, USA	6.- 11.07.2014
Immunotherapy for relapsed malignant	Conference	KU Leuven	Presentation by Prof. Van Gool at the ISPNO conference at Singapore	Singapor	28.06.2014

glioma in children					
ApiNATOMY: The Generation of Interactive CircuitBoard Views of Complex Physiology Knowledge	Conference	UCL	4th International Conference on Complex Systems and Applications (ICCSA 2014)	Le Havre, France	23.-26.06.2014
Data modeling and simulations. Do they pave the way to personalized medicine?	Workshop	USAAR	SIB/Systems X.ch Summer School	Kandersteg, Switzerland	22.-27.06.2014
Piedmont multicenter retrospective study on operated prostate cancer: first report	Congress/conference	UNITO	24th Annual Meeting of the Italian Society of Uro-Oncology (SIUro)	Bologna, Italy	22.-24.06.2014
Immunotherapy for malignant glioma: preclinical research and clinical experience	Conference	KU Leuven	Presentation by Prof. Van Gool at the "Internal lab meeting seeking for collaboration on oncolytic virus research" organised by Prof. Alan Melcher, Medical Oncology, at Leeds, UK	Leeds, UK	16.06.2014
Data collection for models validation: application to prostate cancer - clinical aspects	Conference	UNITO	IEEE-EMBS International Conferences on Biomedical and Health Informatics (BHI)	Valencia, Spain	1.-4.06.2014
Immunotherapy for malignant glioma: preclinical research and clinical research	Conference	KU Leuven	Presentation by Prof. Van Gool at the 30th National Congress of Neurosurgery, organised by the Portuguese Neurosurgical Society by Dr. Miguel Casimiro, at Lisbon, Portugal	Lisbon, Portugal	30.05.2014
IT Challenges for innovative Clinical Trials	Workshop	USAAR	IT workshop on tools/services for clinical trials	Düsseldorf, Germany	26.-27.05.2014
Participation in Training School	Workshop	UNITO	ESTRO School of Radiotherapy and Oncology: Basic Clinical Radiobiology	Istanbul, Turkey	25.-29.05.2014
Data Protection reform	Invited Lecture	LUH	Datenschutzforum	Berlin, Germany	15.05.2014
Computational medicine: Current and Future prospects	Conference	FORTH	eHealth Forum 2014	Athens, Greece	12.-14.05.2014

Participation in training event	Workshop	CINECA, USFD	VPHHF development training	Bologna, Italy	11.-16.05.2014
Immunotherapy for malignant glioma: preclinical research and clinical research	Conference	KU Leuven	Presentation by Prof. Van Gool at the conference "Oncobiology - genes and tumoral microenvironment" at the Medical Sciences Faculty, Nova University, organised by Prof. José Luis Passos Coelho and Prof. Doutora Ana Felix, at Lisbon, Portugal	Lisbon, Portugal	09.05.2014
Presentation of the CHIC project on a special leaflet	Showcase event	USFD	Insigneo Institute first anniversary showcase event1	Sheffield, UK	08.05.2014
Poster presentation of CHIC	Showcase event	USFD	Insigneo Institute first anniversary showcase event1	Sheffield, UK	08.05.2014
Presentation of the CHIC project	Workshop	USFD	Collaborations Workshop 2014 (CW14) - software in your reproducible research	Oxford, UK	26.04.2014
Immunotherapy for children and adults with malignant glioma: the Leuven experience	Conference	KU Leuven	Presentation by Prof. Van Gool at the Johannes Wesling Klinikum Minden, 23th GPHO Arbeitstagung Experimentelle Neuroonkologie, organised by Prof. Bernhard Erdlenbruch, at Minden, Germany	Minden, Germany	26.04.2014
Data protection issues in ehealth projects	Conference	LUH	EHR4CR First European Hospital Conference	Brussels, Belgium	09.04.2014
Long-term survival data in patients with glioblastoma and relapsed malignant glioma after tumor vaccination: is the paradigm slowly shifting?	Conference	KU Leuven	Presented on 'Annual scientific meeting of the Belgian Society of Neurosurgery' by Dr. Joost Dejaegher.	Brussels, Belgium	29.03.2014
Immuntherapie bei Hirntumoren des Kindes- und Jugendalters	Conference	KU Leuven	Presentation by Prof. Van Gool at "HIT-TAGUNG", organised by Prof. Gudrun Fleisschack, Pediatric oncology, University Essen.	Essen, Germany	28.03.2014
Innovations in Healthcare Industry Open Day	Workshop	USFD	Presentation of the CHIC project at the "Innovations in Healthcare Industry Open Day".	Sheffield, UK	06.03.2014

Immunotherapy for brain tumors: an update	Conference	KU Leuven	Presentation by Prof. Van Gool at "SIOPE-BTG High grade glioma working group meeting", organised by Christof Kramm, Pediatric oncology, University of Göttingen	Göttingen, Germany	27.02.2014
An update of immunotherapy translational research program at KU Leuven	Conference	KU Leuven	Presentation by Prof. Van Gool on the conference "8 Rostock symposium on tumor immunology in pediatrics" organised by Carl-Friedrich Classen, Pediatric oncology, University Rostock.	Rostock, Germany	14.02.2014
n.d.	Invited Lectures	UPENN	Department of Chemical and Biomolecular Engineering, State University of New York Buffalo,	Buffalo NY	2014
11th HGG-IMMUNO-Meeting	Conference	KU Leuven	The HGG-IMMUNO-Meeting is an annual meeting where international research groups and clinicians who perform experimental and clinical research on immunotherapy are invited to share knowledge and experiences.	Leuven, Belgium	21.10.2013
Computational Methods in Cancer Research	Workshop	USFD	Computational Methods in Cancer Research Workshop	Sheffield, UK	10.10.2013
Brain Tumor Segmentation Challenge, MICCAI 2013, Nagoya, Japan	One-day challenge	UBERN	One-day challenge where algorithms for brain tumor segmentation are evaluated and compared. Out of 10 teams, UBERN obtained second place in this competition.	Nagoya, Japan	22.09.2013

Press activities

Title	Type	Main leader	Reference	Date
Facebook and Twitter accounts	Social media	CINECA	facebook.com/CHIC-project-333884726816111	Facebook and Twitter accounts
Homepage Announcement for the 3 rd annual CHIC newsletter: “3 rd annual CHIC newsletter”	Online Article	EURICE	http://chic-vph.eu/highlights/details/article/3rd-annual-chic-newsletter/	05.04.2016
Homepage Announcement 6 th Progress Meeting: “6th Progress Meeting held in Bern”	Online Article	EURICE	http://chic-vph.eu/highlights/details/article/6th-progress-meeting-held-in-bern/	28.03.2016
International Conference and Exhibition on Pediatric Oncology to be organised by CHIC partners	Online Article	EURICE	http://chic-vph.eu/highlights/details/article/international-conference-and-exhibition-on-pediatric-oncology-to-be-organised-by-chic-partners/	09.03.2016
Bi-monthly electronic newsletters	Newsletter	CINECA	12 issues	2013-2016
Third annual newsletter	Newsletter	EURICE	http://chic-vph.eu/fileadmin/chic/downloads/CHIC_3rd_Annual_Newsletter.pdf	2016
Second annual newsletter	Newsletter	EURICE	http://chic-vph.eu/fileadmin/chic/downloads/CHIC_Newsletter_2_final.pdf	2015
BraTumIA press release - InterPharma	Press release	UBERN	http://newsroom.interpharma.ch/2014-11-21-schnell-im-bild	21.11.2014
BraTumla press release - Bern Hospital	Press release	UBERN	http://tt.bernerzeitung.ch/region/kanton-bern/Inselspital-entwickelt-HirntumorSoftware/story/15434159	12.11.2014
Swiss Radio - BraTumIA press release	Press release	UBERN	http://www.srf.ch/news/regional/bern-freiburg-	12.11.2014

			wallis/berner-software-analysiert-hirntumore-blitzschnell	
Press Release - BraTumIA - Washington Post	Press release	UBERN	http://www.washingtonpost.com/blogs/innovations/wp/2014/10/01/the-incredible-potential-and-dangers-of-data-mining-health-records/	01.10.2014
BraTumIA NITRC.org website	Press release	UBERN	http://www.nitrc.org/projects/bratumia/	14.05.2014
CHIC project featured in The Parliament Magazine	Online article	ICCS	Link: http://www.vph-institute.org/news/chic-project-featured-in-the-parliament-magazine.html	05.05.2014
Computational Horizons in Cancer	Newspaper/Magazine Article	ICCS	Link to an online issue of The Parliament Magazine, Issue 389: http://viewer.zmags.com/publication/6eced2e8#/6eced2e8/36	28.04.2014
Grantee presentation to the Multiscale Modeling Consortium of the Inter Agency Modeling Group	Video	UPENN	https://www.youtube.com/watch?v=ttNG86de3ps	2014
Video introducing Physics Reports article in the author's own words	Video	UPENN	http://audioslides.elsevier.com/getvideo.aspx?doi=10.1016/j.physrep.2014.05.001	2014
Article in Physical Review E featured in the journal's kaleidoscope section	Online article	UPENN	http://journals.aps.org/pre/kaleidoscope/pre/90/2/022717	2014
Coverage in Science Daily: Classification of gene mutations in a children's cancer may point to improved treatments	Coverage in Science Daily News	UPENN	link: http://www.sciencedaily.com/releases/2014/11/141110123457.htm	2014
First annual newsletter	Newsletter	EURICE	http://chic-vph.eu/fileadmin/chic/downloads/CHIC_600841_D12-6_CHIC_1st_Annual_Newsletter_final.pdf	2014
Complex Mathematics Against Cancer	Press release	EX	Athens, Greece	10.04.2013
A Novel Cancer (Related) Project	Press release	EX	Athens, Greece	10.04.2013

New Horizons in Cancer Treatment	Press release	EX	Athens, Greece	11.04.2013
CHIC general presentation	Web content	EURICE	http://chic-vph.eu/uploads/media/CHIC_general-presentation.pdf	2013
CHIC Flyer	Flyer	EURICE	http://chic-vph.eu/uploads/media/CHIC-flyer.pdf	2013
Article about the CHIC Kick-Off Meeting on the Eurice company website	Web content	EURICE	Optimising cancer treatment through in-silico oncology	2013
CHIC website	Web content	EURICE	Hrrp://www.chi-project.eu	
CHIC twitter account	Web content	CINECA	https://twitter.com/CHIC_project	
CHIC Facebook page	Web content	CINECA	https://www.facebook.com/CHIC-project-333884726816111/?ref=hl	
CHIC LinkedIn group	Web content	CINECA	https://www.linkedin.com/groups/8254222	

Publications M25-M36

Title of Publication	Contact Person	Involved Institutions	Reference	Category	Publication Date	Co-Authors	Status
A multiscale hypermodel to predict the nephroblastoma response to preoperative chemotherapy	Norbert Graf	ICCS, EURICE, USAAR	9th International Renal Tumor Biology Conference, Toronto, Ontario, Canada	Conference proceedings	02.04.2016	Georgios Stamatakis	Published
Clinical Evaluation of a Fully-automatic Segmentation Method for Longitudinal Brain Tumor Volumetry	Raphael Meier	UBERN	Nature Scientific Reports 6 , DOI: 10.1038/srep23376	Peer-reviewed publication	22.03.2016	Urs peter Knecht, Tina Loosli, Stefan Bauer, Johannes Slotboom, Roland Wiest,	Published

						Mauricio Reyes	
Numerical simulation of vascular tumour growth under antiangiogenic treatment: addressing the paradigm of single-agent bevacizumab therapy with the use of experimental data	Katerina D. Argyri	ICCS	Biol Direct. 2016; 11: 12, DOI: 10.1186/s13062-016-0114-9	Peer-reviewed publication	22.03.2016	Dimitra D. Dionysiou, Fay D. Misichroni, Georgios S. Stamatakis	Published
Automatic brain tumor segmentation with a fast Mumford-Shah algorithm	Sabine Müller	USAAR	Proc. SPIE 9784, Medical Imaging 2016: Image Processing, 97842S (March 21, 2016); doi:10.1117/12.2214552	Conference proceedings	21.03.2016	Joachim Weickert, Norbert Graf	Published
Differentiation resistance through altered retinoblastoma protein function in acute lymphoblastic leukemia: in silico modeling of the deregulations in the G1/S restriction point pathway.	Eleftrios Ouzounoglou	ICCS, EURICE	BMC Systems Biology, 3/2016, 10-23, DOI: 10.1186/s12918-016-0264-5	Peer-reviewed publication	01.03.2016	Dimitra Dionysiou, and Georgios Stamatakis	Published
Beyond D'Amico risk classes for predicting recurrence after external beam radiotherapy for prostate cancer: the Candiolo classifier	Domenico GAbriele	UNITO	Radiat Oncol. 2016, 11: 23, DOI: 10.1186/s13014-016-0599-5	Peer-reviewed publication	24.02.2016	Barbara Jereczek-Fossa, Marco Krengli, Elisabetta Garibaldi, Maria Tessa, Gregorio Moro, Giuseppe Girelli, Pietro Gabriele, and the EUREKA-2 consortium	Published

CHIC – A Multi-scale Modelling Platform for in-silico Oncology	D Abler	UBERN, ICCS	Radiotherapy and Oncology 2016, 118 Supplement 1, S1, DOI: 10.1016/S0167-8140(16)30001-9	Peer-reviewed publication	15.02.2016	Philippe Büchler, Georgios Stamatakos	Published
A brief outline of the CHIC project	Georgios Stamatakos	ICCS	Minerva Urologica e Nefrologica 67 (Suppl. 1 to No 1), 5-6	Conference proceedings	2015		Published
In silico oncology and in silico medicine: from research to clinics and academia	Georgios Stamatakos	ICCS	Minerva Urologica e Nefrologica 67 (Suppl. 1 to No 1), 43-44	Conference proceedings	2015		Published
A RBF-PSO Based Approach for Modeling Prostate Cancer	Emma Perracchione	UNITO	ICNAAM Proceedings, Rhodes, http://arxiv.org/abs/1601.05436	Conference proceedings	01.12.2015	Ilaria Stura	Published
Fully automatic GBM segmentation in the TCGA-GBM dataset: Prognosis and correlation with VASARI features	Emmanuel Rios Velazquez	UBERN	Sci Rep. 2015; 5: 16822. doi: 10.1038/srep16822	Peer-reviewed publication	18.11.2015	Raphael Meier, William D. Dunn Jr, Brian Alexander, Roland Wiest, Stefan Bauer, David A. Gutman, Mauricio Reyes, and Hugo J.W.L. Aerts	Published
A two-clones tumor model: Spontaneous growth and response to treatment.	Ilaria Stura	UNITO	Mathematical Biosciences 271, 19-28 DOI:10.1016/j.mbs.2015.10.014	Peer-reviewed publication	30.10.2015	Ezio Venturino, Caterina Guiot	Published
Parameter Learning for CRF-based Tissue Segmentation of Brain Tumors	Raphael Meier	UBERN	Brainlesion: Glioma, Multiple Sclerosis, Stroke and Traumatic Brain Injuries; series: Lecture Notes in Computer Science, Volume 9556, 156-167, ISBN: 978-3-319-30857-9	Peer reviewed publication	04.10.2015	Venetia Karamitsou, Simon Habegger, Roland Wiest,	published

						Mauricio Reyes	
The multimodal brain tumor image segmentation benchmark	Bjoern H. Menze	UBERN	IEEE Trans Med Imaging, 34, 2015. http://dx.doi.org/10.1109/TMI.2014.2377694	Peer reviewed publication	10/2015	+67 other authors	Published
The Importance of Neighborhood Scheme Selection in Agent-based Tumor Growth Modeling	Georgios Tzedakis	FORTH	Cancer Informatics 2015; 14 (Suppl 4), Libertas Academica, 67-81, DOI: 10.4137/CIN.S19343	Peer reviewed publication	07.09.2015	Eleftheria Tzamali, Kostas Marias, and Vangelis Sakkalis	Published
Assessing Treatment Response Through Generalized Pharmacokinetic Modeling of DCE-MRI Data	Eleftherios Kontopodis	FORTH	Cancer Informatics 2015:Suppl., Libertas Academica, 41-51, DOI: 10.4137/CIN.S19342	Peer reviewed publication	12.08.2015	Georgia Kanli, Georgios C. Manikis, Sofie Van Cauter and Kostas Marias	Published
In Silico Neuro-Oncology: Brownian Motion-Based Mathematical Treatment as a Potential Platform for Modeling the Infiltration of Glioma Cells into Normal Brain Tissue	Markos Antonopoulos	ICCS	Cancer Inform. 2015; 14(Suppl 4): 33–40. DOI: 10.4137/CIN.S19341	Peer reviewed publication	10.08.2015	Georgios Stamatakis	Published
Percentage of positive prostate biopsies independently predicts biochemical outcome following radiation therapy for prostate cancer	Domenico Gabriele	UNITO	Panminerva Medica 2016 June;58(2):109-14	Peer-reviewed publication	24.07.2015	Monica Garibaldi, Giuseppe Girelli, Stefano Taraglio, Eleonora Duregon, Pietro Gabriele, Caterina Guiot, Enrico Bollito,	Published

						The EUREKA-2 Consortium	
Copyright in Multiscale Cancer Modeling	Iryna Lishchuk	LUH	INFOCOMP Proceedings, ISBN: 978-1-61208-416-9, Brussels, Belgium	Peer-reviewed publication	21.06.2015	Marc Stauch	Published
Lymphadenectomy extension for prostate cancer predicts pN+ status	Domenico Gabriele	UNITO	XXV Congress of the SIUrO (Italian Society of Uro-Oncology), Rome, Italy, 21-23 June 2015	Conference Proceedings	21.06.2015	Giovanni Muto, Paolo Gontero, Pietro Gabriele	Published
Perineural and vascular invasion in prostate cancer: a predictive ability evaluation	Domenico Gabriele	UNITO	XXV Congress of the SIUrO (Italian Society of Uro-Oncology), Rome, Italy, 21-23 June 2015	Conference Proceedings	21.06.2015	Enrico Bollito, Francesco Porpiglia, Carlo Terrone, G Arena, Fabio Venzano, S Annoscia, Luca Bellei, M Moroni, Caterina Guiot	Published
Brain tumor immunotherapy: what have we learned so far?	Stefaan Van Gool	KU Leuven	Frontiers in Oncology 2015, 5:98, 1-14, DOI: 10.3389/fonc.2015.00098	Peer-reviewed publication	17.06.2015		Published
A Proposed Paradigm Shift in Initializing Cancer Predictive Models with DCE-MRI Based PK Parameters: A Feasibility Study	Alexandros Roniotis	USAAR, FORTH	Cancer Informatics 2015:Suppl., Libertas Academica, 7-18, DOI: 10.4137/CIN.S19339	Peer-reviewed publication	10.06.2015	Mariam-Eleni Oraiopoulou, Eleftheria Tzamali, Eleftherios Kontopodis, Sofie Van Cauter, Vangelis Sakkalis, and Kostas Marias	Published

A simpler modified Gleason Score performs slightly better than the standard one	Domenico Gabriele	UNITO	,AUA (American Urology Association) Meeting, New Orleans, USA, May 2015. J Urology 2015; 193(4S): e639	Conference Proceedings	15.05.2015	Gabriele, Domenico; Bollito, Enrico; Terrone, Carlo; De Angelis, Paolo; Giacobbe, Alessandro; Bellei, Luca; Graziano, Manuela; Gamba, Patrizia; Gabriele, Pietro	Published
Predictive value of tertiary Gleason Score	Domenico Gabriele	UNITO	AUA (American Urology Association) Meeting, New Orleans, USA, May 2015. J Urology 2015; 193(4S): e637	Conference Proceedings	15.05.2015	Gabriele, Domenico; Bollito, Enrico; Porpiglia, Francesco; Gontero, Paolo; Venzano, Fabio; Genesi, Delia; Manzo, Marco; Giacobbe, Alessandro; Guiot, Caterina	Published
The Standardized Histogram Shift of T2 Magnetic Resonance Image (MRI) Signal Intensities of Nephroblastoma Does Not	Sabine Müller	USAAR, FORTH	Supplementary Issue: Computer Simulation, Visualization, and Image Processing of Cancer Data and Processes; Cancer Informatics 2015; 4(S4) 1–5,	Peer-reviewed publication	12.05.2015	Ruslan David, Kostas Marias, Norbert Graf	Published

Predict Histopathological Diagnostic Information			Libertas Academica, DOI: 10.4137/CIN.S19340				
Personalized Medicine and the way to CHIC. A clinical perspective.	Norbert Graf	USAAR	Minerva Urol Nefrol 2015; 67(Suppl 1): 45	Conference proceedings	28.03.2015		Published
Circulating Serum miRNAs as Potential Biomarkers for Nephroblastoma	Nicole Ludwig	USAAR	Pediatric Blood Cancer 2015;62, Wiley, 1360-1367, DOI: 10.1002/pbc.25481	Peer-reviewed publication	18.03.2015	Nasenien Nourkami-Tutdibi, Christina Backes, Hans-Peter Lenhof, Norbert Graf, Andreas Keller, Eckart Meese	Published
Legal and Ethical Aspects of In Silico Medicine	Iheanyi Nwankwo	LUH	2014 6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation. DOI: 10.1109/IARWISOCI.2014.7034647	Peer-reviewed publication	10.03.2015	Marc Stauch, Alan Dahi, and Nikolaus Forgo	Published
Intellectual Property Rights Issues in Multiscale Cancer Modeling	Iryna Lishchuk	LUH	2014 6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation	Peer-reviewed publication	10.03.2015	Marc Stauch and Nikolaus Forgo	Published
EUREKA-1 database: an epidemiological analysis	Domenico Gabriele	UNITO	Minerva Urol Nefrol 2015; 67 (Suppl. 1 to No. 1): 9-15	Peer-reviewed publication	2015	GABRIELE D, PORPIGLIA F, MUTO G, GONTERO P, TERRONE C, ANNOSCIA S, RANDONE D, BENVENUTI S, ARENA G, STURA I & GUIOT C	Published

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

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

		USAAR, USFD				Neri, A. Bucur, B. de Bono, D. Testi, M. Tsiknakis	
A Model of Tumor Growth Coupling a Cellular Biomodel with Biomechanical Simulations	Farhad Rikhtegar	ICCS- UBERN	In Silico Oncology and Cancer Investigation (IARWISOCI), 2014 6th International Advanced Research Workshop on	Conference proceedings	4.11.2014	Eleni Kolokotroni, Georgios Stamatakis and Philippe Buchler	Published
Dendritic cell vaccination for glioblastoma multiforme: Clinical experience and future directions	Joost Dejaegher	KU LEUVEN	In Silico Oncology and Cancer Investigation (IARWISOCI), 2014 6th International Advanced Research Workshop	Conference proceedings	03.11.2014	Lien Solie, Steven De Vleeschouwer, Stefaan W. Van Gool	Published
The VPH Hypermodelling framework for cancer multiscale models in the clinical practice	Daniele Tartarini	USFD	In Silico Oncology and Cancer Investigation (IARWISOCI), 2014 6th International Advanced Research Workshop, 1-4 DOI: 10.1109/IARWISOCI.2014.7034642	Conference proceedings	03.11.2014	K. Duan ; N. Gruel ; Debora Testi, Dawn Walker ; Marco Viceconti	Published
Incorporating Data Protection in In Silico Research: A case of CHIC	Elias Neri	CUSTODIX	2014 6 th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation, DOI: 10.1109/IARWISOCI.2014.7034643	Peer-reviewed publication	10.03.2015	Wouter Dhaeze	Published
Computational Delineation of Tyrosyl-Substrate Recognition and Catalytic Landscapes by the Epidermal Growth Factor Receptor Tyrosine Kinase Domain	Yingting Liu	UPENN	Molecular Biosystems 10/7, 1890-1904, doi: http://dx.doi.org/10.1039/c3mb70620f	Peer-reviewed publication	26.04.2014	Ravi Radhakrishnan	Published

Mesoscale computational methods for membrane bilayer remodelling by curvature inducing proteins	N. Ramakrishnan	UPENN	Physics Reports 543, DOI: 10.1016/j.physrep.2014.05.001	Peer-reviewed publication	28.04.2014	P. B. Sunil Kumar, Ravi Radhakrishnan	Published
In silico profiling of activating mutations in cancer	Ravi Radhakrishnan	UPENN	Integrative Biology	Peer-reviewed publication	n.d.	Jordan E	Submitted
An Explicit Numerical Treatment of the Three-Dimensional Boundary Conditions Imposed by the Skull on an Inhomogeneous Diffusion-Reaction Tri-scale Model of Glioblastoma Multiforme Tumour Growth and Invasion into the Brain. Clinical Validation Considerations.	Georgios Stamatakis	ICCS	Bulletin of Mathematical Biology	Peer-reviewed publication	n.d.	Giatili S	Submitted
Multiscale Computational Models in Physical Systems Biology of Intracellular Trafficking	Ravi Radhakrishnan	UPENN	IET Syst. Biol. 8 (5), 198-213	Peer-reviewed publication	29.09.2014	Richard Tourdot, Ryan Bradley, Natesan Ramakrishnan	Published
Defining the Free Energy Landscape of Curvature Inducing Proteins on Membrane Bilayers	Ravi Radhakrishnan	UPENN	Phys. Rev. E 90, 022717	Peer-reviewed publication	23.08.2014	Tourdot RW, Ramakrishnan M	Published
High-throughput mutagenesis reveals functional determinants for DNA targeting by Activation-Induced Cytidine	Ravi Radhakrishnan	UPENN	Nucleic Acids Research 42 (15)	Peer-reviewed publication	26.07.2014	Gajula KS, Huwe PJ, Mo CY, Crawford DJ, Stiver JT, Kohli RM	Published (Open Access)
Machine learning predictions of cancer driver mutations	E. Joe Jordan	UPENN	IEEE Proceedings of the 6 th International Advanced Research Workshop on In-Silico Oncology and Cancer investigation, pp1-4.	Conference proceedings	2014	Radhakrishnan R.	In press

			DOI: 10.1109/IARWISOCI.2014.7034632				
Physical chemistry and membrane properties of two phosphatidylinositol bisphosphate isomers	D. R. Slochower	UPENN	Physical Chemistry Chemical Physics (A Royal Society of Chemistry Journal). DOI: 10.1039/c5cp00862j	Peer-reviewed publication	2015	R. Radhakrishnan P. A. Janmey	In press
Exploring the competition between proliferative and invasive cancer phenotypes in a continuous spatial model	Kostas Marias	FORTH	PLoS One 8 (8)	Peer-reviewed publication	08/08/2014	Tzamali E, Grekas G, Sakkalis V	Published (Open Access)
Enabling multiscale modeling in systems medicine	Georgios Stamatakis	ICCS, UOXF	Genome Medicine 6:21	Peer-reviewed publication	2014	Wolkenhauer O, Auffray C, Brass O, Clairambault J, Deutsch A, Drasdo D, Gervasio F, Preziosi L, Byrne H, et al.	Published
The Technologically Integrated Oncosimulator: Combining Multiscale Cancer Modeling with Information Technology in the In Silico Oncology Context	G. Stamatakis	FORTH, ICCS, TEI-C, USAAR	IEEE J. Biomed Health Inform. doi: 10.1109/JBHI.2013.2284276	Peer-reviewed publication	01/05/2014	Dionysiou D, Lunzer A, Belleman R, Kolokotroni E, Georgiadi E, Erdt M, Pukacki J, Rueping S, Giatili S, Donofrio A, Sfakianakis S, Marias K, Desmedt C, Tsiknakis M,	Published

						Graf N.	
Dendritic cell vaccination for glioblastoma multiforme: review with focus on predictive factors for treatment response	Joost Dejaegher	KU LEUVEN	ImmunoTargets & Therapy;2014, Vol. 3, p55, DOI: https://dx.doi.org/10.2147/ITT.S40121	Peer-reviewed publication	22.01.2014	Steven De Vleeschouwer, Stefaan W. Van Gool	Published
Integrative functional assessment of ALK mutations for therapeutic stratification in neuroblastoma	Ravi Radhakrishnan	UPENN	Cancer Cell 26/5, 682-694. DOI: 10.1016/j.ccell.2014.09.019.	Peer-reviewed publication	30.12.2013	Daniel Weiser, Scott Bressler, Peter Huwe, Ravi Radhakrishnan , Mark Lemmon, Yael Mosse	Published
The Virtual Skeleton Database - An open access repository for biomedical research and collaboration	Michael Kistler	UBERN	J Med Internet Res. 2013 Nov; 15(11): e245, doi: 10.2196/jmir.2930	Peer-reviewed publication	15.11.2013	Serena Bonaretti, Marcel Pfahrer, Roman Niklaus, Philippe Büchler	Published
Molecular modeling of ErbB4/HER4 kinase in the context of the HER4 signaling network helps rationalize the effects of clinically identified HER4 somatic mutations on the cell phenotype	Shannon Telesco	UPENN	Biotechnol J. 2013 Dec; 8(12): 1452–1464. doi: 10.1002/biot.201300022.	Peer-reviewed publication	04.11.2013	Rajanikanth Vadigepalli, Ravi Radhakrishnan	Published
Functional tissue units and their primary tissue motifs in multi-	Bernard de Bono	UCL	J Biomed Semantics. 2013 Oct 8;4(1):22. doi: 10.1186/2041-1480-4-22.	Peer-reviewed publication	08.10.2013	Pierre Grenon, Richard Baldock, Peter	Published

scale physiology						Hunter	
In silico oncology: Exploiting clinical studies to clinically adapt and validate multiscale oncosimulators	Georgios Stamatakis	FORTH, ICCS, USAAR	2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), P 5545-5549, DOI: 10.1109/EMBC.2013.6610806	Peer-reviewed publication	03.07.2013	Eleni Kolokotroni, Dimitra Dionysiou, Christian Veith, Yoo-Jin Kim, Astrid Franz, Kostas Marias, Joerg Sabczynski, Rainer Bohle, Norbert Graf	Published
Multiscale Cancer Modeling and In Silico Oncology: Emerging Computational Frontiers in Basic and Translational Cancer Research	Georgios Stamatakis	ICCS, UPENN, USAAR	Journal of Bioengineering & Biomedical Science DOI: 10.4172/2155-9538.1000e114	Peer-reviewed publication	24.05.2013	Norbert Graf, Ravi Radhakrishnan	Published

2. Deliverables and milestones tables

2.1 Deliverables

The deliverables due in this reporting period are highlighted in light blue. The deliverables highlighted in light yellow are subject to change in the 2nd Amendment to the CHIC GA. Further explanation as to the nature of these changes is provided in the comments section of this table. Deliverables of the 1st and 2nd period are highlighted in light grey.

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date	delivery from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
D2.1	State of the art knowledge for building hypermodels	2	7-FORTH	R	PU	30.11.2013		Yes	05.02.2014	
D2.2	Scenario based user needs and requirements	2	3-USAAR	R	PU	30.11.2013		Yes	13.01.2014	
D2.3	Requirements for enhancing hypermodels beyond the domain of cancer	2	14-PHILIPS	R	CO	30.09.2014		Yes	02.12.2014	
D2.4	Acceptance of hypermodels by patients and physicians	2	3-USAAR	R	PU	30.09.2016		No		
D2.5	Clinical relevance of the CHIC project	2	3-USAAR	R	PU	31.12.2015		Yes	31.12.2015	New deliverable, which is formally incorporated in the 2 nd Amendment of the CHIC GA.
D3.1	Report on Scenarios and data from defined patients	3	4-KULEUVEN	R	PU	31.03.2016		Yes	09.05.2016	

Table 1. Deliverables									
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date Annex I	delivery from Delivered Yes/No	Actual / Forecast delivery date	Comments
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	Yes	31.03.2016	
D3.3	Demonstration of the developed Meta- and Hyper-Multiscale Models and Repositories	3	1-ICCS	R	CO	31.03.2017	No	31.03.2017	Nature was changed from "O" to "R", Dissemination level was changed from "PU" to "CO"
D4.1	Initial analysis of the ethical and legal requirements for the sharing of data	4	8-LUH	R	PU	30.09.2013	Yes	30.09.2013	
D4.2	Initial analysis of the copyright-related legal requirements for the sharing of data	4	8-LUH	R	PU	31.12.2013	Yes	06.01.2014	
D4.3.1	Development of the data protection and copyright framework for CHIC first iteration	4	8-LUH	R	PU	31.05.2014	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	4	8-LUH	R	PU	31.03.2016	No	31.03.2016	

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date Annex I	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
	an amended European legal Framework									
D5.1.1	The CHIC technical architecture – initial version	5	7-FORTH	R	PU	31.03.2014		Yes	13.06.2014	
D5.1.2	Deployment models of the CHIC technical architecture and its private cloud	5	7-FORTH	R	PU	31.07.2016		No		D5.1.2 is a new deliverable which is formally incorporated in the 2 nd Amendment to the CHIC GA.
D5.1.3	The final CHIC technical architecture (including the security tools and cloud infrastructure)	5	7-FORTH	P	RE	30.11.2016		No		In the original CHIC DoW, this deliverable was D5.1.2. Due to the addition of another deliverable, renumbering was necessary.
D5.2.1	Security guidelines and initial version of security tools	5	13-CUSTODIX	P	CO	30.09.2014		Yes	01.10.2014 05.05.2015	A first version of D5.1 was submitted in 2014. However, an updated version of D5.2 was produced after a second internal review and sent to the EC in May 2015. The updated version contains the following modifications: Updated security vocabular, updated integration tutorials, added audit Json schema
D5.2.2	Final version of security tools and guidelines	5	13-CUSTODIX	P	CO	30.09.2016		No		D5.2.1 is a new deliverable which is incorporated in the 2 nd Amendment to the CHIC GA.
D5.3	Techniques to build the cloud infrastructure	5	5-BED (7-FORTH)	R	PU	31.03.2015		Yes	31.03.2015	

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date	delivery from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
	available to the community									
D6.1	Cancer hypomodelling and hypermodelling strategies and initial component models	6	1-ICCS	R	CO	30.09.2013		Yes	22.10.2013	
D6.2	CHIC cancer component models: initial tested versions	6	1-ICCS	R	CO	30.11.2014		Yes	05.01.2015	
D6.3	Initial standardized cancer hypermodels	6	1-ICCS	R	CO	31.07.2016		No		Delivery date was postponed from M38 to M40
D6.4	Clinical adaptation and partial validation of hypermodels	6	1-ICCS	R	CO	31.01.2017		No		
D7.1	Hypermodelling Specifications	7	1-ICCS	R	PU	31.03.2014		Yes	02.07.2014	
D7.2	First Release Hypermodelling framework deployed on test nodes	7	16-CINECA	P	RE	31.03.2015		Yes	08.06.2015	
D7.3	Hypermodels annotation services	7	15-UCL	P	RE	31.03.2016		Yes	15.04.2016	
D7.4	Final Hypermodelling framework deployed on test node	7	16-CINECA	O	RE	30.09.2016		No		Delivery date was postponed from M40 to M42
D8.1	Design of the CHIC repositories	8	1-ICCS	R	CO	31.07.2014		Yes	20.11.2014	
D8.2	Prototype implementation of	8	12-UBERN	O	CO	31.03.2015		Yes	04.05.2015	

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date	delivery from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
	the CHIC repositories									
D8.3	Implementation of the interfaces of the CHIC repositories	8	15-UCL	R	PU	30.09.2015		No	28.09.2015	
D8.4	Report on the final system	8	1-ICCS	R	PU	30.09.2016		No		
D9.1	User requirements for the visualization toolkit and image analysis toolkits	9	5-BED	R	PU	30.09.2013		Yes	01.10.2013	
D9.2	A model and data visualization toolkit	9	5-BED	P	RE	31.01.2017		No		
D9.3	A multimodal and longitudinal brain tumour image analysis tool	9	12-UBERN	P	RE	31.01.2017		No		
D9.4	The integrated DrEye platform for image analysis and visualisation	9	7-FORTH	P	RE	31.01.2017		No		The title of the deliverable was modified. The delivery date of this deliverable was postponed from M36 to M46.
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	
D10.3	The CHIC Encryption Services	10	16 - CINECA	O	CO	31.03.2015		Yes	07.04.2015	Lead beneficiary was changed from P13-CUSTODIX to P16-CINECA
D10.4	The CHIC	10	7-FORTH	P	RE	30.11.2016		No		The title of the deliverable was modified.

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date Annex I	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
	Hypermodelling Editor and orchestration environment									The delivery date of this deliverable was postponed from M36 to M44. Nature was changed from “R” to “P”, Dissemination level was changed from “CO” to “RE”
D10.5	The CHIC Clinical Research integrated platform	10	7-FORTH	P	RE	31.01.2017		No		The title was modified to reflect the clinical orientation of the integrated platform. Delivery date was postponed from M44 to M46.
D11.1	Evaluation and validation criteria for clinical adaptation	11	3-USAAR	R	PU	31.03.2014		Yes	02.06.2014	
D11.2	Report on the first evaluation workshops round	11	3-USAAR	R	RE	30.09.2014		Yes	01.12.2014	
D11.3	Report on the second evaluation Workshops round	11	3-USAAR	R	RE	30.04.2016		No	15.04.2016	Delivery date was postponed from M36 to M37.
D11.4	Validation of CHIC infrastructure as a whole	11	1-ICCS	R	RE	31.03.2017		No		
D12.1	Dissemination Plan	12	16-CINECA	R	PU	30.09.2013		Yes	01.10.2013	
D12.2	Dissemination Kit available	12	2-EURICE	O	PU	31.03.2014		Yes	25.03.2014	
D12.3	Preliminary Plan for the Use and Dissemination of Foreground	12	16-CINECA	R	CO	31.03.2015		Yes	30.04.2015	
D12.4	Draft Plan for the Use and Dissemination of	12	16-CINECA	R	CO	31.03.2016		No	31.03.2016	

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
	Foreground									
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 (3rd issue)	05.04.2016	

2.2 Milestones

Milestones of the 3rd period are highlighted in light blue. The deliverables highlighted in light yellow are subject to change in the 2nd Amendment to the CHIC GA. Further explanation as to the nature of these changes is provided in the comments section of this table. Milestones of the 1st and 2nd period are highlighted in light grey.

Table 2. Milestones							
Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I dd/mm/yyyy	Achieved Yes/No	Actual/ Forecast achievement data dd/mm/yyyy	Comments
MS1	Kick-Off Meeting	1	2-Eurice	01.04.2013	Yes	10-12/04/2013	
MS2	Progress meetings	1	2-Eurice	30.09.2013	Yes	17-18/10/2013 20-21/02/2014 15-17/10/2014 26-27/03/2015 21-23/05/2015	

Table 2. Milestones							
Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I dd/mm/yyyy	Achieved Yes/No	Actual/ Forecast achievement data dd/mm/yyyy	Comments
						21-23/03/2016	
MS3	User needs and Requirements are defined	2	3-USAAR	30.11.2013	Yes	13/01/2014	
MS4	Hypermodels are accepted by users	2	3-USAAR	30.09.2016	No		D2.4
MS5	Scenarios and data from nephroblastoma, GBM and NSCLC are available	3	4-KULEUVEN	31.03.2015	Yes	31/03/2015	
MS6	Exploitation of the CHIC infrastructure by prostate cancer	3	4-KULEUVEN	31.03.2016	No		D3.2 Title of the Milestone was changed
MS7	Meta- and Hyper-Multiscale Models can be Demonstrated	3	4-KULEUVEN	31.03.2017	No		D3.3
MS8	The CHIC Data protection and intellectual property framework	4	8-LUH	31.05.2014	Yes	31/05/2014	
MS9	Initial CHIC Architecture and security guidelines	5	7-FORTH	30.09.2014	Yes	01/10/2014	D5.1.1, D5.2.1
MS10	Final version of the CHIC Architecture	5	7-FORTH	30.11.2016	No		D5.1.2, D5.2.2, D5.1.3, D5.3 Delivery date was postponed from M42 to M44
MS11	Initial component models available for all cancer modelling branches	6	1-ICCS	30.09.2013	Yes	22/10/2013	
MS12	Rational, numerical and clinical experience based check of the component models complete	6	1-ICCS	30.11.2014	Yes	05/01/2015	
MS13	Availability of hypermodels for all clinical scenarios compliant w. the guidelines to be prov. by	6	1-ICCS	31.07.2016	No		D6.3, D7.4

Table 2. Milestones							
Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I dd/mm/yyyy	Achieved Yes/No	Actual/ Forecast achievement data dd/mm/yyyy	Comments
	WP7						
MS14	All hypermodels have been quantitatively clinically adapted	6	1-ICCS	31.01.2017	No		D6.4
MS15	First hypermodel infrastructure deployed	7	7-FORTH	31.03.2014	Yes	02/07/2014	
MS16	Folksonomy and Ontology annotation and search services deployed	7	5-BED	31.03.2015	Yes	08/06/2015	
MS17	Hypermodel editor, development and execution application ready	7	7-FORTH	31.03.2016	Yes		D7.3
MS18	Metahypermodels annotation completed	7	6-USFD	31.03.2017	No		Description in 4th annual report
MS19	Design of the CHIC repositories completed	8	1-ICCS	31.07.2014	Yes	21/11/2014	
MS20	Deployment of the CHIC repositories	8	15-UCL	31.07.2015	Yes		D8.2
MS21	Integration with security and ethical framework	8	1-ICCS	30.09.2016	No		D8.3, D4.3.2, D5.2, D10.3
MS22	Scalable & uncertainty visualization techniques	9	5-BED	31.03.2015	Yes	31.03.2015	
MS23	Image segmentation & registration techniques	9	12-UBERN	30.09.2014	Yes	30.09.2014	
MS24	Initial version of the tumor response quantitative platform	9	7-FORTH	31.03.2015	Yes	31.03.2015	
MS25	The CHIC Orchestration Platform and Encrypted Data Services	10	7-FORTH	31.03.2015	Yes	31.03.2015	
M26	The CHIC integrated platform and its adaptation in the clinical	10	7 FORTH	31.01.2017	No		D10.4, D10.5 Title of the Milestone was changed.

Table 2. Milestones							
Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I dd/mm/yyyy	Achieved Yes/No	Actual/ Forecast achievement data dd/mm/yyyy	Comments
	environment						Delivery date was postponed from M36 to M46
MS27	Evaluation and validation criteria for clinical adaptation are ready	11	3-USAAR	31.03.2014	Yes	02.06.2013	
MS28	First evaluation Workshop	11	3-USAAR	30.09.2014	Yes	17.-18.10.2014	
MS29	Second evaluation Workshop	11	3-USAAR	31.03.2016	Yes	02.-03.04.2016	9th International Renal Tumor Biology Conference in Toronto, Canada (2.-03.04.2016) / Participant lists, evaluation reports from participants
MS30	Internal collaborative area and external website	12	2-EURICE	30.06.2013	Yes	28.06.2013	
MS31	CHIC Workshop	12	1-ICCS	30.09.2014	Yes	09.-13.01.2016	Workshop within the framework of the German School of Pediatric Oncology and Hematology that took place in Haus Schönblick am Söllereck (Oberallgäu) on January 9-13, 2016
MS32	First CHIC Winter School	12	3-USAAR	30.09.2015	Yes	3.-4.11.2014	6th IARWISOCI Workshop – The CHIC Workshop took place in Athens, Greece.
MS33	Second CHIC Workshop	12	3-USAAR	30.09.2016	No		A dedicated CHIC workshop will take place at the International Conference and Exhibition on Pediatric Oncology in Toronto, August 11-13, 2016

3. Project management

Consortium management tasks and achievements

The consortium management is covered by WP1 and includes

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

The following achievements were made during M25-M36:

The **3rd CHIC review** (after M24) took place on July 8, 2015. 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 the work done in year 2 of the project following a number of largely technical demonstrators. The overall assessment of the project as communicated in the review report was a positive one. However, the reviewers strongly advise the project consortium to focus its endeavours for the remaining 2 years of CHIC with the goal of ensuring immediate clinical relevance of the project output. Following these key recommendations from the CHIC reviewers, the partners have been involved in intense discussions concerning the way forward. As stated in the WP2 report, a comprehensive 'roadmap' describing the CHIC strategy for the remainder of the project was submitted in the form of a new deliverable, D2.5, "Clinical relevance of the CHIC project – Describing the integrated workflows of the scenarios from a clinical perspective". With regard to the reviewers' recommendations, management partner Eurice specifically asked the consortium members to include a summary of actions taken and to be taken to follow these recommendations in each WP report.

A **5th Progress Meeting (MS2)** was held on 21-23 October 2015 at CINECA in Bologna, Italy. The entire meeting was planned around the recommendations from the 3rd CHIC review, with special focus on the clinical relevance of the project and how to streamline efforts in all WPs to ensure successful, sustainable and high-impact project outcomes. Prof. Metin Akay, member of the CHIC External Advisory Board, attended the meeting, providing valuable input to the CHIC partners. In a dedicated **technical meeting**, which was held on the third day of the meeting, FORTH, in their role of technical integrator, took charge of collecting input from the technical partners as well as from the modelling partners and clinicians in order to develop a comprehensive action plan a) until the subsequent CHIC review, and b) until the end of the CHIC project in general.

The **4th CHIC review** took place on January 29, 2016. One day before, a core group of the CHIC partners met in Brussels to prepare for the review meeting by putting together the respective presentations and demonstrators.

The interim review had been organized to assess whether the refocusing on clinical orientation previously required by the reviewers had been implemented successfully. It was shown that a clinical coordinator had been appointed and a new deliverable D2.5 had been issued with the purpose to provide the usability viewpoint of clinicians when using the system.

During the review meeting detailed descriptions of scenarios and demonstrators illustrating the interactions of the clinician using the hypermodels for clinical decision support were presented. A

dedicated framework (CRAF) featuring the clinician's working environment had been designed and presented by the clinical coordinator, Prof. Norbert Graf from USAAR.

The demonstration was considered effective by the reviewers and the review report states that the clinical dimension was well addressed.

The **6th Progress Meeting (MS2)** of CHIC was held on 21-23 March 2016 at the University of Bern, Switzerland. The main focus of the meeting was the actual status of the project activities, the current developments of various CHIC tools and services as well as discussions about the recommendations that the CHIC consortium received from the reviewers during the 4th review meeting at the European Commission. Prof. David Ingram (University College London) and Prof. Piotr Czauderna (University of Gdansk), both members of the CHIC External Advisory Board, attended the meeting with guest lectures and offered valuable advice to the consortium. In a dedicated **technical meeting**, input from the technical partners as well as from the modelling partners were collected in order to develop a comprehensive action plan until the next CHIC review, which will be held on June 1st, 2016.

Three larger **telephone conferences** were scheduled in order to discuss and strategically plan the next steps in the project. The first of these phone conferences took place on July 17, 2015. Most of the CHIC partners were represented by at least one person. During this meeting, a detailed assessment of the 3rd CHIC review was performed which also included a discussion about the actions to be taken to meet the reviewers' suggestions and demands as effectively and quickly as possible. Detailed minutes of this meeting are available on the CHIC intranet. The second strategic telephone conference involving the management level of CHIC (the Project Management Team and the WP leaders) was held on September 18, 2015. In this telephone conference, a status update about the work performed since the first conference call was given by the work package leaders and the agenda for the 5th progress meeting of CHIC was discussed. The third telephone conference was held of February 25, 2016 to discuss the next steps in the CHIC project (i.e. the upcoming review meeting, the agenda for the Progress Meeting in Bern as well as the periodic newsletter).

The **2nd Progress Report** was successfully finalized and submitted on time. The financial as well as the scientific report were evaluated positively and all deliverables for the period were accepted. After the requests for further information about several partners' cost claims, the EC transferred the 2nd periodic payment to ICCS on October 19, 2015. The funds were distributed in a timely manner among the consortium members according to their requested funding for the period and according to additional calculations made in the context of Eurice's continuous financial monitoring. All in all, the financial assessment of the 2nd project period was that, money wise, the project is well on track. Some partners are currently underspent, but as they will have the bulk of their task in the second half of the project, this underspending is expected to be balanced by the end of the third year of the project.

Within the usual regular and close collaboration between ICCS and Eurice, **scientific and contractual management** of CHIC was implemented effectively and according to plan. ICCS has been in regular contact with the project officer regarding several administrative issues such as the agreement on the review meeting dates, and the organization of a CHIC workshop in the context of the International Conference and Exhibition on Paediatric Oncology, to take place in Toronto, Canada on August 11-13, 2016. Moreover, ICCS has been scientifically coordinating the entire project through a series of communication procedures such as emailing, regular teleconferencing and Skype-conferencing. Decisions at the consortium level have been reached through electronic voting or preference stating platforms such as doodle.

Following the latest reviewers' report, several changes were made with regard to project roles and advisory boards:

In the telephone conference on July 17, 2015 (see above), Prof. Norbert Graf (USAAR) was elected **assistant clinical coordinator of CHIC**. Prof. Graf is supported by a newly created **clinical advisory board** from within the consortium. This clinical board is composed of Prof. Stefaan Van Gool (KULeuven) and Prof. Rainer Bohle (USAAR).

- The **CHIC External Advisory Board** gained two new members. One of Prof. Roger Dale (Imperial College, London), professor for cancer radiobiology, the other of Prof. Piotr Czauderna (Medical University of Gdansk), Head of Surgery and Urology for Children and Adolescents. Both new EAB members have concluded confidentiality agreements with the CHIC consortium. Prof. Dale had planned to attend the 5th progress meeting, but had to cancel his attendance at the very last minute due to personal circumstances.
- FORTH have confirmed their role as the **technical integrator** within CHIC.

The CHIC consortium has prepared an amended version of Annex 1 to the CHIC Grant Agreement. This **amendment** contains the additional project roles as specified above. Moreover, the DoW was edited in order to reflect the changes which occurred during the first two years of CHIC (extension of several tasks, change of PM efforts, etc.) and as a result of the 3rd review (removal of all cancer types apart from nephroblastoma, glioblastoma, lung and prostate cancer and the deletion of corresponding tasks, removal of now redundant deliverables and milestones, addition of new deliverables to monitor the project work more effectively, etc.). Because of the addition or prolongation of several tasks, some of the CHIC partners have changes in their original budgets. They are aware that the overall funding for the project must not be increased, so Eurice, in collaboration with the respective partners, has been investigating all options resulting in the least amount of budget that was shifted with the amendment. Eurice was coordinating the amendment process. A complete amended draft version of Annex I has already been prepared end of December 2015. The official amendment procedure was then launched by ICCS at the beginning of 2016.

Summary of actions taken to meet the recommendations from the 3rd and 4th CHIC review

To meet the reviewers' request for an overview of actions taken by the consortium after each project review, each work package report now contains a concise overview of the work done by each work package in order to comply with the recommendations from the review report. The most important changes which occurred in this reporting period are:

- Appointment of assistant clinical coordinator and clinical advisory board.
- Addition of D2.5, Clinical relevance of the CHIC project – Describing the integrated workflows of the scenarios from a clinical perspective, to illustrate the clinical relevance of CHIC and outline the strategy to maintain this clinical relevance.
- The consortium has changed its approach to the development of the CHIC technologies, starting from an end-user narrative of the clinical application, and then working backward to the technical specifications and the implementations.
- Addition of 2 new EAB members.
- A detailed planning of internal milestones is under way.

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

No serious problems have occurred in project management during M25-M36. However, it has to be noted that several modifications were made to the original CHIC DoW, also following the remarks

from the CHIC reviewers in their latest review report. These changes have been implemented in the 2nd amendment to the CHIC Grant Agreement.

Moreover, it was noted during the 3rd CHIC review that most of the CHIC deliverables were submitted with delays. The CHIC partners were informed about this feedback immediately and ICCS and Eurice are intensifying their efforts to ensure punctual delivery of the pending deliverables (by setting stricter deadlines, launching the deliverable writing process earlier than before and by keeping track of the writing process with the respective lead beneficiaries of the deliverables).

Changes in the consortium

The legal representatives of 2 Partners (Custodix and BED) changed. The respective data has been updated in NEF.

List of project meetings, dates and venues during M25-M36

Title	Date	Venue	Local organizer
6 th Progress Meeting	21-23 March 2016	Bern	UBERN
CHIC Telco: Discussion of next steps	25 February 2016	Skype	Eurice
4 th Review Meeting	29 January 2016	Brussels	EC
5 th Progress Meeting	21-23 October 2015	Cineca Supercomputing Centre, Bologna, Italy	CINECA
CHIC Technical Telco	29 October 2015	Skype	ICCS
Conference Call: Preparation of 5 th Progress Meeting	18 September 2015	Skype	Eurice
Semantics (metadata discussion)	16 September 2015	Skype	UCL
CHIC Technical Telco	10 September 2015 and 24 September 2015	Skype	ICCS
Deliverable 8.3	10 September 2015	Skype	UCL
WP6 Telephone Conference	31 August 2015	Skype	ICCS
Problems in ObTiMA	25 August 2015 01 September 2015 10 September 2015	Skype	KULeuven and USAAR
CHIC Technical Telco	05 August 2015 and 27 August 2015	Skype	ICCS
WP6 Telephone Conference	28 July 2015	Skype	ICCS

Conference Call: 3 rd Review Meeting Recommendations	17 July 2015	Skype	Eurice, ICCS
3 rd CHIC Review Meeting, including Review Preparation Meeting	07-08 July 2015	DGCNECT, Brussels, Belgium	EC
CHIC Technical Telco	02 July 2015 and 23 July 2015	Skype	ICCS
CHIC Technical Telco	11 June 2015 and 25 June 2015	Skype	ICCS
Data sharing	01 June 2015	Skype	KULeuven and Custodix
CHIC Technical Telco	13 May 2015 and 28 May 2015	Skype	ICCS
Data for biomechanical validation study	07 May 2015	Skype	KULeuven and UBERN
Study Events in ObTiMA	29 April 2015	Skype	KULeuven and USAAR
Data sharing	21 April 2015	Skype	KULeuven and Custodix
CHIC Technical Telco	09 April 2015 and 23 April 2015	Skype	ICCS

Related documentation is available in the project management tool.

Cooperation with other projects/programmes


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

Planning and status of resources



















Due to the recent changes which had to be implemented in the CHIC Description of Work, several CHIC partners adjusted their PM efforts in order to provide a more realistic budget breakdown. As far as possible, the partners balanced increased effort in one work package with reduced effort in another work package or shifted free resources in other cost categories to balance additional budget needed for increased personnel hours. All details regarding the changes in the person efforts can be found in the amendment documentation which is available in the CHIC Intranet (Documents > Contracts > Amendment Documents). This also includes a detailed justification for the increased Person Months in several deliverables.


CHIC Public Wiki ProjectAngel Helpdesk Sitemap Logout

Administration
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Who is who
Work Plan

 **Contracts**

Amendment Documents

Title	Comments	Last saved on	Last saved by	Files	
Amendment II (Part A and B) including track changes		18.05.2016 11:42:51	Hauptenthal Melanie		 
Amendment II - Annex I: Description of Work (version 12-05-16)		18.05.2016 11:51:45	Hauptenthal Melanie	 	  
Amendment II - Justification of increased PMs		18.05.2016 11:45:13	Hauptenthal Melanie		 
Amendment II - List of changes		18.05.2016 11:45:00	Hauptenthal Melanie		 

 Add

In line with the amended DoW, the PM effort table now reads as follows:

Partner short name	WP1	WP2	WP3	WP4	WP5	WP6	WP7	WP8	WP9	WP10	WP11	WP12	Total partner
ICCS	8,93	3,20	2,60	2,00	3,40	57,01	7,20	19,30	4,00	7,40	7,70	8,19	130,93
EURICE	38,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	12,00	50,00
USAAR	0,00	25,00	49,00	4,00	0,00	0,00	4,00	3,00	15,00	7,00	25,00	3,00	135,00
KU Leuven	0,00	0,00	68,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	68,00
BED	0,00	0,00	0,00	0,00	10,00	0,00	28,00	0,00	36,00	0,00	8,00	6,00	88,00
USFD	7,40	0,00	0,00	0,00	6,00	0,00	134,00	0,00	0,00	0,00	0,00	7,00	154,40
FORTH	2,03	5,00	0,00	0,00	29,00	28,61	10,00	7,00	45,29	42,00	3,07	6,00	178,00
LUH	0,00	0,00	0,00	48,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	6,00	54,00
UPENN	0,00	5,00	3,00	2,50	0,00	69,00	0,00	3,00	0,00	0,00	8,50	6,50	97,50
UOXF	2,00	0,00	0,00	0,00	0,00	46,00	0,00	0,00	0,00	0,00	0,00	6,00	54,00
UNITO	0,00	0,00	14,00	0,00	0,00	14,00	0,00	0,00	0,00	0,00	20,00	6,00	54,00
UBERN	0,00	0,00	0,00	0,00	4,00	20,00	0,00	15,00	12,00	3,00	3,00	5,00	62,00
CUSTODIX	0,00	1,00	0,00	7,00	19,00	0,00	0,00	3,00	0,00	0,00	0,00	6,00	36,00
PHILIPS	0,00	4,00	0,00	0,00	15,00	1,00	0,00	7,00	0,00	18,00	3,00	6,00	54,00
UCL	0,00	0,00	0,00	0,00	0,00	0,00	36,00	36,00	0,00	0,00	0,00	2,00	74,00
CINECA	1,00	0,00	0,00	0,00	6,00	0,00	36,00	0,00	0,00	8,00	0,00	6,00	57,00
TEI-C	0,00	0,00	0,00	0,00	21,00	0,00	0,00	0,00	1,00	4,00	1,00	1,00	28,00
Total WP	59,36	43,20	136,60	63,50	113,40	235,62	255,20	93,30	113,29	89,40	79,27	92,69	1.374,83

Impact of possible deviations from the planned milestones and deliverables

The CHIC reviewers correctly noted in the 3rd CHIC review that most deliverables were submitted with a delay and that, consequently, delays also occurred with regard to the milestones. The CHIC Management Team takes this very seriously and has reminded the consortium several times to keep within the schedule and consider the deliverable deadlines fixed deadlines. Moreover, the partners

were asked to re-evaluate the list of deliverables and milestones for the 2nd Amendment to the CHIC GA and make sure that the schedule of project outputs also accommodates the recent modifications made to the work plan in terms of timing, relevance, etc.

Ongoing development of the Project website

The CHIC website registers a fairly constant 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 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. All newsletters are available via the website as well. As the project continues over the next months, 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.

Statement on the use of the resources

Planned versus actual efforts in WP1			
Partner	Planned PM Total	Planned PM Period 3	Actual PM Period 3
1-ICCS	8.93	2.15	2.02
2-Eurice	38.00	9.50	12.15*
6-USFD	7.40	1.24	1.58
7-FORTH	2.03	0.50	0.45
10-UOXF	2.00	0.30	0.40
16-CINECA	1.00	0.20	0.15
Total	59.36	13.89	16.75

*) Eurice had additional efforts in Project Management due to an additional review meeting as well as the work related to the preparation of the 2nd Project Amendment.

4. Explanation of the use of the resources

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

Cost Budget Follow-up Table								
Contract n°	600841	Project acronym	CHIC					
PARTICIP.	TYPE OF EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)				Percentage spent	Remaining Budget (EUR)
			Period 1	Period 2	Period 3	Total	Total/ Budget	
			M1-M12	M13-M24	M25-M36			
ICCS	Total Person-month	130,93	30,27	37,22	31,49	98,98	76%	31,95
	Personnel	636.000,00	117.446,00	144.082,00	141.248,00	402.776,00	63%	233.224,00
	Other direct costs	199.313,00	22.114,00	27.490,00	32.698,00	82.302,00	41%	117.011,00
	Subcontracting	23.600,00	0,00	2.896,00	3.266,00	6.162,00	26%	17.438,00
	Adjustments	0,00	0,00	0,00	0,00	0,00		0,00
	Indirect costs	501.187,00	83.734,00	102.942,00	104.367,00	291.043,00	58%	210.144,00
	Total Costs	1.360.100,00	223.294,00	277.410,00	281.579,00	782.283,00	58%	577.817,00
Eurice	Total Person-month	50,00	12,88	11,40	16,28	40,56	81%	9,44
	Personnel	324.500,00	65.313,00	58.709,00	95.438,00	219.460,00	68%	105.040,00
	Other direct costs	34.173,00	5.314,00	1.892,00	3.491,00	10.697,00	31%	23.476,00
	Subcontracting	6.000,00	0,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	1.938,00	-4.979,00	-3.041,00		3.041,00
	Indirect costs	275.825,00	39.978,00	37.057,00	38.328,00	115.363,00	42%	160.462,00
	Total Costs	640.498,00	110.605,00	99.596,00	132.278,00	342.479,00	53%	298.019,00
USAAR	Total Person-month	135,00	11,29	44,10	44,28	99,67	74%	35,33
	Personnel	725.498,00	64.750,00	230.749,00	230.038,00	525.537,00	72%	199.961,00
	Other direct costs	318.431,00	18.692,00	57.705,00	65.372,00	141.769,00	45%	176.662,00
	Subcontracting	5.682,00	0,00	0,00	0,00	0,00	0%	5.682,00
	Adjustments	0,00	0,00	0,00	0,00	0,00		0,00
	Indirect costs	626.357,00	50.065,00	173.071,00	177.245,00	400.381,00	64%	225.976,00
	Total Costs	1.675.968,00	133.507,00	461.525,00	472.655,00	1.067.687,00	64%	608.281,00
KULeuven	Total Person-month	68,00	8,50	20,00	22,00	50,50	74%	17,50
	Personnel	340.000,00	41.421,00	98.601,00	108.743,00	248.765,00	73%	91.235,00
	Other direct costs	161.250,00	9.090,00	6.486,00	13.868,00	29.444,00	18%	131.806,00
	Subcontracting	2.000,00	0,00	0,00	0,00	0,00	0%	2.000,00
	Adjustments	0,00	0,00	7.724,00	11.417,00	19.141,00		-19.141,00
	Indirect costs	300.750,00	30.306,00	63.052,00	73.566,00	166.924,00	56%	133.826,00
	Total Costs	804.000,00	80.817,00	175.863,00	207.594,00	464.274,00	58%	339.726,00
BED	Total Person-month	88,00	14,00	34,80	23,27	72,07	82%	15,93
	Personnel	484.000,00	52.323,00	153.075,00	110.738,00	316.136,00	65%	167.864,00
	Other direct costs	49.000,00	6.988,00	11.504,00	6.598,00	25.090,00	51%	23.910,00
	Subcontracting	5.000,00	0,00	0,00	0,00	0,00	0%	5.000,00
	Adjustments	0,00	0,00	0,00	-15.602,00	-15.602,00		15.602,00
	Indirect costs	319.800,00	35.586,00	98.747,00	70.401,00	204.734,00	64%	115.066,00
	Total Costs	857.800,00	94.897,00	263.326,00	172.135,00	530.358,00	62%	327.442,00

Cost Budget Follow-up Table								
Contract n°	600841	Project acronym	CHIC					
PARTICIP.	TYPE OF EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)				Percentage spent	Remaining Budget (EUR)
			Period 1	Period 2	Period 3	Total	Total/ Budget	
			M1-M12	M13-M24	M25-M36			
USFD	Total Person-month	154,40	32,81	38,43	43,87	115,11	46%	39,29
	Personnel	679.296,00	115.475,00	164.575,00	199.449,00	479.499,00	71%	199.797,00
	Other direct costs	78.001,00	12.986,00	4.574,00	10.655,00	28.215,00	36%	49.786,00
	Subcontracting	4.000,00	0,00	0,00	0,00	0,00	0%	4.000,00
	Adjustments	0,00	0,00	0,00	34.801,00	34.801,00		-34.801,00
	Indirect costs	454.378,00	77.076,00	101.488,00	124.616,00	303.180,00	67%	151.198,00
	Total Costs	1.215.675,00	205.537,00	270.637,00	369.521,00	845.695,00	70%	369.980,00
FORTH	Total Person-month	178,00	60,79	47,62	41,62	150,03	84%	27,97
	Personnel	456.660,00	105.586,00	98.907,00	118.253,00	322.746,00	71%	133.914,00
	Other direct costs	116.504,00	17.911,00	30.938,00	37.785,00	86.634,00	74%	29.870,00
	Subcontracting	6.000,00	0,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	-3.787,00	-72,00	-3.859,00		3.859,00
	Indirect costs	397.295,00	87.636,00	76.158,00	91.055,00	254.849,00	64%	142.446,00
	Total Costs	976.459,00	211.133,00	202.216,00	247.021,00	660.370,00	68%	316.089,00
LUH	Total Person-month	54,00	16,07	17,50	16,17	49,74	92%	4,26
	Personnel	350.622,00	72.235,00	82.369,00	80.249,00	234.853,00	67%	115.769,00
	Other direct costs	23.833,00	2.795,00	4.644,00	5.374,00	12.813,00	54%	11.020,00
	Subcontracting	3.000,00	0,00	0,00	0,00	0,00	0%	3.000,00
	Adjustments	0,00	0,00	0,00	0,00	0,00		0,00
	Indirect costs	224.672,00	45.018,00	52.207,00	51.373,00	148.598,00	66%	76.074,00
	Total Costs	602.127,00	120.048,00	139.220,00	136.996,00	396.264,00	66%	205.863,00
UPENN	Total Person-month	97,50	21,00	32,50	0,00	53,50	55%	44,00
	Personnel	391.564,00	72.110,00	149.824,00	0,00	221.934,00	57%	169.630,00
	Other direct costs	63.501,00	24.241,00	11.168,00	0,00	35.409,00	56%	28.092,00
	Subcontracting	5.000,00	0,00	0,00	0,00	0,00	0%	5.000,00
	Adjustments	0,00	0,00	-410,00	0,00	-410,00		410,00
	Indirect costs	282.141,00	59.738,00	99.814,00	0,00	159.552,00	57%	122.589,00
	Total Costs	742.206,00	156.089,00	260.396,00	0,00	416.485,00	56%	325.721,00
UOXF	Total Person-month	54,00	1,47	19,56	23,89	44,92	83%	9,08
	Personnel	289.078,00	6.217,00	75.016,00	98.498,00	179.731,00	62%	109.347,00
	Other direct costs	55.017,00	735,00	3.054,00	8.207,00	11.996,00	22%	43.021,00
	Subcontracting	3.902,00	0,00	0,00	0,00	0,00	0%	3.902,00
	Adjustments	0,00	0,00	2.431,00	0,00	2.431,00		-2.431,00
	Indirect costs	206.456,00	4.171,00	46.841,00	64.023,00	115.035,00	56%	91.421,00
	Total Costs	554.453,00	11.123,00	127.342,00	170.728,00	309.193,00	56%	245.260,00
UNITO	Total Person-month	54,00	9,59	16,00	17,80	43,39	80%	10,61
	Personnel	270.000,00	35.978,00	108.791,00	87.712,00	232.481,00	86%	37.519,00
	Other direct costs	95.833,00	3.227,00	8.233,00	11.825,00	23.285,00	24%	72.548,00
	Subcontracting	5.000,00	0,00	0,00	2.615,00	2.615,00	52%	2.385,00
	Adjustments	0,00	0,00	0,00	-344,00	-344,00		344,00
	Indirect costs	219.499,00	23.522,00	70.214,00	59.722,00	153.458,00	70%	66.041,00
	Total Costs	590.332,00	62.727,00	187.238,00	161.530,00	411.495,00	70%	178.837,00

Cost Budget Follow-up Table								
Contract n°	600841	Project acronym		CHIC				
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)				Percentage spent	Remaining Budget (EUR)
			Period 1	Period 2	Period 3	Total	Total/ Budget	
			M1-M12	M13-M24	M25-M36			
UBERN	Total Person-month	62,00	11,20	18,90	21,20	51,30	83%	10,70
	Personnel	465.000,00	71.512,00	159.327,00	147.096,00	377.935,00	81%	87.065,00
	Other direct costs	55.834,00	10.972,00	14.124,00	15.162,00	40.258,00	72%	15.576,00
	Subcontracting	4.000,00	0,00	0,00	0,00	0,00	0%	4.000,00
	Adjustments	0,00	0,00	0,00	-1.982,00	-1.982,00		1.982,00
	Indirect costs	312.500,00	49.490,00	104.070,00	97.354,00	250.914,00	80%	61.586,00
	Total Costs	837.334,00	131.974,00	277.521,00	257.630,00	667.125,00	80%	170.209,00
CUSTODIX	Total Person-month	36,00	2,37	6,00	17,02	25,39	71%	10,61
	Personnel	180.000,00	12.227,00	29.788,00	97.253,00	139.268,00	77%	40.732,00
	Other direct costs	26.334,00	1.790,00	2.324,00	1.554,00	5.668,00	22%	20.666,00
	Subcontracting	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0,00	0,00		0,00
	Indirect costs	90.000,00	6.777,00	11.143,00	40.118,00	58.038,00	64%	31.962,00
	Total Costs	296.334,00	20.794,00	43.255,00	138.925,00	202.974,00	68%	93.360,00
PHILIPS	Total Person-month	54,00	1,20	6,40	38,82	46,42	86%	7,58
	Personnel	398.466,00	11.276,00	41.340,00	312.106,00	364.722,00	92%	33.744,00
	Other direct costs	25.000,00	0,00	0,00	0,00	0,00	0%	25.000,00
	Subcontracting	3.000,00	0,00	0,00	0,00	0,00	0%	3.000,00
	Adjustments	0,00	0,00	4.014,00	11.106,00	15.120,00		-15.120,00
	Indirect costs	592.650,00	19.418,00	63.528,00	86.251,00	169.197,00	29%	423.453,00
	Total Costs	1.019.116,00	30.694,00	108.882,00	409.463,00	549.039,00	54%	470.077,00
UCL	Total Person-month	74,00	6,65	13,53	15,98	36,16	49%	37,84
	Personnel	497.978,00	39.837,00	61.092,00	96.504,00	197.433,00	40%	300.545,00
	Other direct costs	161.000,00	4.214,00	4.490,00	11.317,00	20.021,00	12%	140.979,00
	Subcontracting	6.000,00	0,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0,00	0,00		0,00
	Indirect costs	395.386,00	26.430,00	39.349,00	64.692,00	130.471,00	33%	264.915,00
	Total Costs	1.060.364,00	70.481,00	104.931,00	172.513,00	347.925,00	33%	712.439,00
CINECA	Total Person-month	57,00	15,95	23,49	12,56	52,00	91%	5,00
	Personnel	228.000,00	56.196,00	67.069,00	30.974,00	154.239,00	68%	73.761,00
	Other direct costs	49.408,00	5.258,00	5.065,00	4.186,00	14.509,00	29%	34.899,00
	Subcontracting	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	-2.058,00	0,00	-2.058,00		2.058,00
	Indirect costs	313.899,00	92.025,00	83.090,00	52.699,00	227.814,00	73%	86.085,00
	Total Costs	591.307,00	153.479,00	153.166,00	87.859,00	394.504,00	67%	196.803,00
TEI-C	Total Person-month	28,00	3,96	3,70	5,39	13,05	47%	14,95
	Personnel	56.000,00	10.527,00	7.482,00	26.890,00	44.899,00	80%	11.101,00
	Other direct costs	15.867,00	4.065,00	5.711,00	3.597,00	13.373,00	84%	2.494,00
	Subcontracting	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0,00	0,00		0,00
	Indirect costs	43.120,00	8.755,00	7.915,00	18.292,00	34.962,00	81%	8.158,00
	Total Costs	114.987,00	23.347,00	21.108,00	48.779,00	93.234,00	81%	21.753,00
Total	Total Person-month	1.374,83	260,00	391,15	391,64	1.042,79	76%	332,04
	Personnel	6.772.662,00	950.429,00	1.730.796,00	1.981.189,00	4.662.414,00	69%	2.110.248,00
	Other direct costs	1.528.299,00	150.392,00	199.402,00	231.689,00	581.483,00	38%	946.816,00
	Subcontracting	82.184,00	0,00	2.896,00	5.881,00	8.777,00	11%	73.407,00
	Adjustments	0,00	0,00	9.852,00	34.345,00	44.197,00		-44.197,00
	Indirect costs	5.555.915,00	739.725,00	1.230.686,00	1.214.102,00	3.184.513,00	57%	2.371.402,00
	Total Costs	13.939.060,00	1.840.546,00	3.173.632,00	3.467.206,00	8.481.384,00	61%	5.457.676,00

4.2 Budget Explanations

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

4.3 Planned versus actual efforts

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