



PROJECT INTERIM REPORT

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Name, title and organisation of the scientific representative of the project's coordinator:
Research Professor Dr Georgios Stamatakis
Institution of Communication and Computer Systems (ICCS)
National Technical University of Athens

Tel: +30 210 772 2287

Fax: +30 210 772 3557

E-mail: gestam@central.ntua.gr

Project website address: www.chic-vph.eu

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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 at *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, use of validated biosimulators for the conduction of *in silico* clinical trials). 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 ("multimodeller hypermodels") 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 7th semester of the project's implementation (1st April 2016 to 30th September 2016) and the main results achieved. Overall progress of the project implementation

The project has fully achieved the targets foreseen for the 7th semester of its implementation with rather minor adjustments. Special emphasis has been put on *the clinical relevance* of the entire endeavour. In parallel important and extensive progress has been made in the basic science and technology domains. In the following subsections indicative progress and result *examples* from all workpackages are provided. A more comprehensive and detailed listing of the achievements is provided in the corresponding project interim report.

Work Package 1 (WP1): Project Management

The 5th CHIC review meeting took place on June 1st, 2016. The CHIC platform, supported hypermodelling demonstrator (through the nephroblastoma paradigm) as well as the lung cancer demonstrator, was presented by the consortium. Horizontal issues like dissemination and exploitation activities as well as Project Management and Future Planning were also presented and discussed. The overall assessment of the review was positive and it was confirmed that the project was in good progress. The 7th Progress Meeting was held on August 31st to September 2nd at the University of Saarland in Saarbrücken, Germany. The CHIC consortium prepared and submitted a Project Amendment of the CHIC Grant Agreement. The amended version of Annex 1 reflects the changes which occurred during the first two years of the CHIC implementation (extension of several tasks, change of PM efforts, etc.) The final amendment was submitted on June 23, 2016. The 3rd Progress Report (covering M25-36) was prepared and submitted. Within the framework of the regular and close collaboration between the Institute of Communication Systems (ICCS) – National Technical University of Athens and Eurice, scientific and contractual management of CHIC was implemented effectively and according to plan. ICCS was in regular contact with the project officer regarding several administrative issues such as the agreement on the review meeting dates, and the organization of the CHIC workshop in the context of the International Conference and Exhibition on Pediatric Oncology that took place in Toronto, Canada on August 11-13, 2016. Moreover, ICCS scientifically coordinated the entire project through a series of communication procedures such as emailing, regular teleconferencing and Skype-conferencing. Decisions at the consortium level were reached through electronic voting or preference stating platforms such as Doodle.

Work Package 2 (WP2): User Needs and Requirements

Collection of clinical, imaging and molecular data continued. The clinical relevance of the project was further elaborated. Significant results on how to ensure acceptance of hypermodels by both physicians and patients are included in deliverable D2.4. Scenarios and use cases were further developed and/or refined by clinical partners and in close interaction with all other partners. They were further dissected into granular modules. Discussions on several key aspects of the CHIC project related to the acceptance of hypermodels took place during the International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics that was held in Toronto on 11-13 August 2016. Interaction between CHIC and the EC funded and completed projects p-medicine and MyHealthAvatar continued.

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

USAAR, KU Leuven and UNITO continued the collection and provision of nephroblastoma, non small cell lung cancer, glioblastoma and prostate cancer data. ICCS provided feedback to the clinical partners regarding the exploitability of provided data or data that could be provided. They also contributed to the discussions and the formulations concerning the four CHIC translational scenarios. The developed hypermodels were evaluated by the clinical partners.

Work Package 4 (WP4): Legal and Ethical Framework

The CHIC first iteration data protection framework was deployed. Various CHIC datasets such as Nephroblastoma data (ODM XML, MIRNA and DICOM) and Glioblastoma data (ODM XML and DICOM) were de-identified, and the validated data were made ready for data sharing. The second iteration data protection and copyright framework was established, providing for ongoing legal and ethical project data use during the model validation and exploitation phase. The Intellectual Property

Rights (IPR) Memorandum was completed and signed to assist regulation of partner foreground exploitation. The research on the whitepaper conducted within the existing European regulatory framework, including analysis of *in silico* research-relevant data protection, medical device, and IPR issues was completed.

Work Package 5 (WP5): IT Architecture

The CHIC private cloud infrastructure was implemented and became fully functional. The uninterrupted provision of the private cloud infrastructure was a significant step. The CHIC security framework became available, deployed and integrated with all of the CHIC repositories, services and tools. In parallel, extension of the CHIC security framework to support SAML delegation tokens was also an important achievement.

Work Package (WP6): Cancer Models and Hypermodel Design

Important achievements regarding improvements, extensions and refinements of all four CHIC hypermodels - both mechanistic and machine learning (hyper-)models that address nephroblastoma, non small cell lung cancer, glioblastoma and prostate cancer - were made by all involved CHIC modelling partners (ICCS, UBERN, UOXF, FORTH, UPENN, UNITO). An example is a testosterone concentration hypomodel that was developed by ICCS in order to be used with the UNITO prostate hypermodel. The hypomodel captures the dynamics of the Luteinizing Hormone Releasing Hormone (LHRH)-Luteinizing Hormone (LH) –Testosterone (TE) axis that simulates the response of testosterone levels to treatment schemes consisting of LHRH agonists. Another example concerns lung cancer. ICCS performed data analysis and pre-processing of available non small cell lung cancer data and developed a preliminary Naive Bayes classifier based on miRNA data. They also developed and successfully tested a standalone application utilizing the above classifier. The clinical adaptation process continued. All four hypermodels are currently entering their final clinical adaptation and partial clinical validation stage. Submitted deliverable D6.3 outlines all major developments in WP6 pertaining to the creation of the standardized versions of hypermodels.

Work Package 7 (WP7): Hypermodelling infrastructure

A concurrent execution of hypermodels within the VPH-HF platform was made possible. A deployment service through registry application programming interface (API) was implemented. All new (hyper-)models developed by WP6 were deployed in the hypermodelling execution environment. The VPH-HF framework was deployed on a production node and was integrated with the CHIC authentication system. The wrappers' generation was automated. An Alpha version of caching, interactive, and surrogate modelling services was produced.

Work Package 8 (WP8): Model and Data Repositories

ICCS developed a wizard for the Model Repository in order for the user to be able to store a new model through a single page and update its user interface so as for the models to be presented in a more elegant way. A new functionality was also provided to the Model Repository, according to which the user is now able to filter the stored models based on the 13 perspectives proposed by ICCS and approved by the CHIC consortium. Regarding the Clinical Data Repository, UBERN extended its REST services with an endpoint in order to support requests initiated by the search query builder. UCL in collaboration with ICCS, FORTH and UBERN further consolidated the schema for annotations, taking into account updated requirements emerging from the Hypermodelling Editor, the Model Repository, the Clinical Data Repository and CRAF. Based on the feedback received from partners

UCL and UBERN, ICCS prepared, edited and finalized the deliverable entitled “D8.4 Report on the final system” which documents the WP8 related achievements.

Work Package 9 (WP9): Image Processing and Visualization

BED further developed the CCGVis platform. CCGVis is now a mature and scalable platform with a wide range of importers, visualizations and statistical plots, as well as a nascent image processing capabilities. USAAR further worked 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 were analysed. UBERN quantified uncertainty in the image segmentation of a machine learning model in use. This can assist clinicians in the interpretation of the longitudinal segmentation results.

Work Package 10 (WP10): Integrated Platform

The CRAF platform was rendered fully integrated with the majority of the CHIC software components that constitute the “backend” services of the CHIC platform. CRAF was demonstrated and evaluated at different conferences during the reporting period. A Web-based version of CRAF was launched. The high level hypermodelling language for describing hypermodels was finalized. Work on the semantic annotation of the models to aid their composition into higher level hypermodels continued. “Freezing” of (hyper-)models was adopted as a versioning approach to guarantee the reproducibility of results and to secure their provenance. The integration of the Model Repository, the Execution Environment, CRAF, and the Hypermodel Editor was enriched by the introduction of message-oriented middleware to increase efficiency and functionality.

Work Package 11 (WP11): Clinical Adaptation and Validation

The CHIC infrastructure was rendered predominantly clinically oriented and was recognized as such by the scientific community including clinicians. Validation and acceptance of hypermodels were addressed intensively during the reporting period. USAAR successfully presented the CHIC platform and hypermodels at two large international clinical congresses for validation and acceptance purposes. A prostate cancer model application (APP) was under development. Significant interest in the APP by patients and clinicians was expressed. Clinical evaluation of a longitudinal automatic brain tumour segmentation approach suggested that the corresponding technology could provide stable volumetric quantification of tumour progression.

Work Package 12 (WP12): Dissemination and Exploitation

Considerable dissemination efforts took place in order to present the most recent developments of the CHIC project. This is confirmed by the high number of dissemination activities including conferences presentations and peer-reviewed papers. A major event was the scientific organization of the workshop entitled: “Computational Horizons in Cancer: An International Symposium on Multiscale Cancer Modeling,” held at the University of Pennsylvania (UPENN), Philadelphia, USA on 14 Aug. 2016. Preparations for the organization of a major dissemination event to take place in March 2017 continued. The discussion about sustainability and maintenance of the CHIC project was intensified.

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 (hypo-)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 (ana-)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 on the level of a clinical trial (*in silico* clinical trials) **3. Industry** (provision of models, hypermodels, technological infrastructure, tools and integrated 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 and *in silico* clinical trials instead of or in conjunction with real ones.). Within the 7th semester 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) as well as via the Consortium itself and Philips (being part of the consortium) took place. Exploitation related activities progressed significantly. Relevant discussions among all partners are ongoing. Training activities, such as the CHIC workshop that was held within the framework of the International Conference on Pediatric Oncology and Clinical Pediatrics (Toronto, Canada, August, 11-13, 2016) have ensured the clinical dissemination and strengthened the clinical impact of the endeavour. (<http://pediatriconcology.conferenceseries.com/organizing-committee.php>)
http://www.conferenceseries.com/Past_Reports/pediatric-oncology-2016-past/)

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 leaded by USAAR. Main work was further done on specifying the clinical relevance of the project. In addition acceptance of hypermodels by different stakeholders was analysed. The subject was intensively discussed in several Skype conferences and at different congresses and meetings (see below).

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

The only relevant task during this reporting period is task 2.4.

USAAR did take part in task 2.4. In this task USAAR continued analysing the requirements for the acceptance of hypermodels. This is done 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. With the developed questionnaire further answers are collected from patients and physicians. Possibilities for education and training in using hypermodels are analysed. In that task two big clinical conferences were attended to demonstrate the CHIC platform and hypermodels and to discuss the acceptance of hypermodels with different stakeholders. These conferences were:

- From August 11th to August 13th 2016 the 'International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics' in Toronto, Canada
- Between October 19th to 22nd 2016 the 48th Congress of the International Society of Paediatric Oncology (SIOP) in Dublin, Ireland

As a result of the conferences and the answers to the developed questionnaire it can be concluded that three important points are mandatory for getting acceptance of hypermodels for both patients and physicians. These are:

- Clinical relevance of hypermodels
- Education and explanation of hypermodels in order for the users to better understand them
- Validation and certification of hypermodels

Details of these results are given in the deliverable D2.4. This deliverable was elaborated during the reporting period and submitted on October 27th, 2016.

ICCS did contribute in discussions and exploration on several key aspects of the CHIC project related to the acceptance of hypermodels by patients and physicians during the International Conference and Exhibition on Paediatric Oncology and Clinical Pediatrics (Toronto, Canada, August 11-13, 2016). Preparation of the nephroblastoma demonstrator was continued by ICCS as well as the preparation of deliverable "D2.4: How to get acceptance of hypermodels by patients and physicians".

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. To get acceptance of the hypermodels by patients and physicians contact to clinical partners outside of the CHIC consortium was initiated to recruit stakeholders for testing and evaluating CHIC hypermodels. Participation in two major clinical congresses of Paediatric Oncology (see above) was used to discuss this topic with participants. At the SIOP congress in Dublin an ePoster about the hypermodel for nephroblastoma was created and

demonstrated. In addition a video was developed explaining the multimodeler hypermodel for nephroblastoma. This video was demonstrated at both conferences to stakeholders and used as an intro for the developed questionnaire. This activity was done together with WP12 and with partner ICCS. A summary of all activities are written in deliverable D2.4 that was submitted at the 27th of October 2016.

During the CHIC workshop, which was organized by ICCS and USAAR within the framework of the International Conference and Exhibition on Paediatric Oncology and Clinical Pediatrics (Toronto, Canada, August 11-13, 2016) the Coordinator contributed to the discussions on several key aspects of the CHIC project related to the acceptance of hypermodels by patients and physicians. ICCS has also contributed to the preparation of the nephroblastoma demonstrator shown by Prof. Graf during the above mentioned conference.

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 are shared to all other partners.

Summary of significant results

- We continued to collect clinical, imaging and molecular data. The clinical relevance was further elaborated. Significant results how to get acceptance of hypermodels by patients and physicians are elaborated and written in D2.4.
- 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.
- Discussions on several key aspects of the CHIC project related to the acceptance of hypermodels by patients and physicians during the International Conference and Exhibition on Paediatric Oncology and Clinical Pediatrics.
- Preparation, Finalization and submission of deliverable “D2.4: How to get acceptance of hypermodels by patients and physicians”.
- Interaction and collaboration continued with p-medicine and MyHealthAvatar.

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

D2.4 was delayed for 4 weeks, due to the participation of the SIOP congress that was held after month 42 of the CHIC project. This was without any impact on other tasks or the project as a whole.

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 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	3.20	0.90	0.45
3-USAAR	25.00	5.00	3.00
7-FORTH	5.00	1.00	1.00
9-UPENN	5.00	1.00	1.14
13-CUSTODIX	1.00	0.25	0.10
14-PHILIPS	4.00	0.00	0.50
Total	43.20	8.15	6.19

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:

Provision of feedback to the clinicians concerning the nephroblastoma data by continuous interactions with USAAR.

Contribution to the discussion and formulations concerning the translational scenarios in the context of the nephroblastoma branch.

USAAR:

Major work was done in creating the data that will be used in the nephroblastoma scenario. ObTiMA is used for data collection and data are shared for usage for the hypermodel.

UNITO:

The re-growth after treatment has been studied in the light of the Phenomenological Universalities approach.

Task 3.2: Glioblastoma multiforme (M1-M48)

ICCS:

Provision of feedback to the clinicians.

Contribution to the discussion and formulations concerning the translational scenarios in the context of the glioblastoma branch.

KU LEUVEN:

The availability of data and images were kept up to date. Data 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 performed to collect additional data.

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

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

ICCS:

Provision of feedback to the clinicians.

Contribution to the discussion and formulations concerning the translational scenarios in the context of the lung cancer branch.

USAAR:

Major work was done in creating the data that will be used in the non-small cell lung cancer scenario. ObTiMA is used for data collection and data are shared for usage for the hypermodel.

UNITO:

A gross Phenomenological model has been provided to predict the shrinkage of the tumor during chemotherapy.

Summary of details for each task

Task 3.1: Wilms tumor

ICCS:

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

Contribution to the discussion and formulations concerning the translational scenarios in the context of the nephroblastoma branch.

USAAR:

Within the SIOP Renal Tumor Study Group, that is chaired by Norbert Graf (Task Leader) a new clinical trial called UMBRELLA is just finalized and sent for ethical approval. This protocol will use ObTiMA as the data management system. Corresponding CRFs were developed during this reporting period.

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 further elaborated building a tool for automatic annotation of Wilms Tumor. This tool is under validation in a feedback loop with the developer.

All data that are collected so far are submitted to the clinical data repository (CDR) as the legal and ethical framework is in place for CHIC and a user interface is built for easy upload of the data.

The two nephroblastoma hypermodels are further discussed and optimized by an iterative process between developers and clinicians.

UNITO:

The West law can be useful to study the strength of the tumor. In fact, the growth coefficient in West law is linked to the metabolic characteristics of the cancer cells. The West law can therefore show the efficacy of the treatment in terms of time delay in the re-growth.

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

Provision of feedback to the clinicians concerning GBM data. Continuous interactions of ICCS with KUL.

Contribution to the discussion and formulations concerning the translational scenarios in the context of the glioblastoma branch.

KU LEUVEN:

The source data and images were updated at UZ Leuven and the corresponding data sets were updated in *ObTiMA*. Specific parameters (e.g. presenting symptoms, blood counts, etc.) were provided again but with more detail, as requested for modelling purposes. Data were always de-identified before upload to the platform.

Also MRI images were de-identified and uploaded to the platform. Interaction with the partners from Custodix and UBERN took place to facilitate the processing and use of the images.

Interaction with other partners took place during the entire period, especially with Custodix for sharing and uploading the data and images and with ICCS for discussing the processing of the data.

New data sets – with parameters specified by the modellers - were provided for the testing phase of the modelling.

In-depth translational research was performed to collect additional data: immune monitoring in serum, analysis of activation/suppression markers in PBMCs and molecular genetics and immunological characterization of the tumor and its environment in paraffin embedded tumor samples.

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

Provision of feedback to the clinicians concerning lung cancer data. Continuous interactions of ICCS with USAAR.

Contribution to the discussion and formulations concerning the translational scenarios in the context of the lung cancer branch.

USAAR:

Together with WP2 data for the Non-small cell lung cancer hypermodel were further elaborated and continuously collected. This includes clinical data, pathology data and molecular data (EGFR, KRAS, BRAF and EML4-ALK). All these data are uploaded to the CDR. The hypermodel was further optimized in an iterative process together with WP2.

UNITO:

The treatment was simulated using the kill rates provided by the literature. Re-growth was modelled by exponential law in accordance with the literature. Many simulations are given for each patient, perturbing with a stochastic noise the parameters, in order to provide a range of possible scenarios. The output of the model is a range of percentage of shrinkage. This prevision could be refined using kill rates provided by the UPENN model.

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 discussion and formulations concerning the three translational scenarios.

USAAR:

All data for usage in the hypermodels of nephroblastoma and Non-small cell lung cancer are defined and collection of data has continued. The developed hypermodels were evaluated by USAAR.

KU LEUVEN:

The source data and MRI images were updated.

For the previously provided data sets particular parameters were provided with more detail for modelling purposes.

De-identified MRI images were uploaded to the CHIC platform.

New data sets were provided for the testing of the models.

Translational research is done to collect data for immune monitoring and in-depth pathological analyses.

UNITO:

The phenomenological model outputs are in accordance with the data provided by the clinical partners.

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.

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 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	2.60	1.00	0.50
3-USAAR	49.00	13.00	10.00
4-KULeuven	68.00	19.50	8.00
9-UPENN	3.00	0.50	1.77
11-UNITO	14.00	2.00	0.99
Total	136.60	36.00	21.26

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, following the completion of the first iteration framework back in M14. With respect to data protection, that first version of the framework (including pseudonymisation & security) was developed by LUH and Custodix, and deployed (both on the development as the production infrastructure). Retrospective data from USAAR and ULEUVEN 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. For the second iteration, legal, organizational and technical measures have been developed to safeguard the medical data used for the project with particular reference to the project validation and exploitation phases. Concrete measures include patient consent, data protection agreements to be concluded between project partners and other validating users, and a dedicated data security framework protecting the data repositories and flows during validation. Also considered is the required certification of in silico models under the medical devices regime.

Regarding copyright issues, further attention has been paid to the facilitation of partner exploitation of project foreground following the formal end of the project. Thus, besides the IPR Memorandum that was previously completed and signed by all partners in response to a request by the reviewers, an analysis has been made of the IP protection potentially available in the project, which takes account of the specific contributions of relevant partners. To further support the developing parties with making their license choices and to mitigate the potential license incompatibility risks, the software components and models in CHIC are analysed on the subject of license incompatibility issues and the results presented in a software licensing report annexed to deliverable D4.3.2.

Summary of details for each task

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

In Task 4.3, which was the only task still active within the period, LUH completed the development of the second iteration data protection and copyright framework: the relevant deliverable, D4.3.2 “Development of the data protection and copyright framework for CHIC second iteration”, was submitted on time at the end of M42, and built on the previous legal/ethical deliverables – D4.1,

D4.2, D4.3.1 and D4.4, in presenting the concrete legal, organizational and technical measures to safeguard the medical data used for the project. In the second iteration of the framework, a particular emphasis was upon the CHIC project validation and exploitation phases; applicable safeguards include patient consent, revised data protection agreements for conclusion project partners and other validating users (annexed to the Deliverable), and a data security framework protecting the data repositories and flows during validation. Also considered was the required certification of in silico models under the medical devices regime prior to uptake as decision support tools in clinical practice.

Regarding copyright issues, an analysis was made of the protection potentially available in the project, which takes account of the specific contributions of relevant parties. Also, to support the developing parties with making their license choices and to mitigate the potential license incompatibility risks, the software components and models in CHIC were analysed on the subject of license incompatibility issues and the results presented in a software licensing report annexed to the Deliverable.

Custodix contributed, within the same task, in concert with LUH, to the secure-de-identification and privacy checking of retrospective clinical data from the clinical partners for use in model development. ICCS provided documentation with respect to software licensing data for all the components and models that ICCS has developed in the context of CHIC. It also contributed in the preparation of the deliverable D4.3.2 and continuously provided feedback to the legal and ethical partners regarding all major aspects of the project which were of increased legal and ethical importance.

Summary of significant results

- The deployment of the CHIC first iteration 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
- Second iteration data protection and copyright framework established, providing for ongoing legal and ethical project data use during model validation and exploitation phase
- IPR Memorandum completed and signed to assist regulation of partner foreground exploitation
- Research on the whitepaper conducted into the existing European regulatory framework, including analysis of in silico research-relevant data protection, medical device, and IPR issues, completed

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 would manage the relevant patient consent and data security requirements.

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

Not applicable

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

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP4			
Partner	Planned PM Total	Planned PM Period 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	2.00	0.20	0.11
3-USAAR	4.00	1.00	1.00
8-LUH	48.00	12.00	6.91
9-UPENN	2.50	0.50	1.77
13-Custodix	7.00	3.00	2.00
Total	63.50	16.70	11.79

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

During the reporting period WP5 has focused, through regular skype meetings and participation into the planned consortia and technical meetings, on refining aspects of the defined CHIC architecture

and on making seamless integration of the many components of the CHIC platform as easy and straightforward as possible.

In parallel the work also focused on a detailed study of various deployment models of the CHIC private cloud, which – together with the exploitation models to be defined, will enable the final appropriate tuning of the platform in accordance to the selected exploitation and use model. Also the VPH-HF software components have been aligned to WP5 updated security service and guidelines, and the auditing system of the CHIC security framework was incorporated into the data repository.

Summary of details for each task

Task 5.1, Reference Architecture

ICCS, FORTH and TEIC worked closely together with regard to the Data Integration Layer. More specifically, ICCS specified several technical characteristics of the Model and the In Silico Trial Repositories (operating system, programming environment, communication technologies or protocols with other CHIC components, technical dependencies and requirements, computational needs, storage needs, etc.) and appropriate specifications were defined that ease their integration into the platform. In addition, effort was devoted to the analysis, design and refinement of several workflows at the architectural level.

Also, the VPH-HF software components have been aligned to WP5 updated security service and guidelines. Regular assessment of all the software services adopted in the hypermodelling framework has been conducted to keep the framework protected from security issues.

Close interactions were established, through the Architectural Board activities, with a range of other WPs that are responsible for the design and implementation of key architectural elements of the infrastructure. The main emphasis of our work has been to achieve appropriate technical and implementation specific solutions that guarantee interoperability of services, through appropriate interface specifications. Examples of such work include the work done with WP8, which is developing the CHIC Repositories (the Clinical Data Repositories, The Model Repository and the Metadata Repository).

Task 5.2, Security tools and services

Collaborative efforts amongst relevant partners have taken place in order to prepare the In Silico Trial Repository for the storage of simulation results originated from not pseudonymized patient data. Therefore, the needed changes in platform components (the In Silico Trial Repository) were identified in view of the different access rules with regard to pseudonymized and not pseudonymized simulation results, and acted upon. Also, integrative work took place in order to implement the SAML-based delegation mechanism for the In Silico Trial Repository based on the CHIC security requirements.

Finally, the data repository has been adapted 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. The implementation in C# of the audit data model has been published as open-source on the GitHub platform under the MIT license (<https://github.com/niklr/XDASv2Net>). A NuGet package to simplify the management of external dependencies within Microsoft Visual Studio IDE has been released as well. (<https://www.nuget.org/packages/XDASv2Net/>)

Task 5.3, Private cloud infrastructure

Task 5.3 of the CHIC project focused, during the reporting period, on the analysis of the state of the art technologies in cloud computing deployment models as well as the continuous support and management of the private cloud infrastructure so that it provides uninterrupted service to the CHIC community.

The deliverable D5.1.2 “Deployment models of the CHIC technical architecture and its private cloud” was compiled and submitted in time. The Deliverable describes the analysis and evaluation we conducted for the selection of a cloud technology platform, with a special focus on the special legal and security requirements of CHIC. We describe and analyse the architecture of the chosen platform (Openstack) and we elaborate on the security architecture and mechanisms of Openstack in order to demonstrate how the platform fulfils the required functionality. Finally, we provide a brief installation guide with all the required techniques and steps to install, configure and maintain such as a large scale infrastructure for productive usage.

Deliverable D5.1.3 “The final CHIC technical architecture (including the security tools and cloud infrastructure)” is also been prepared and is well advanced, through intense collaborative interactions and contributions by all involved partners.

Summary of significant results

The CHIC private cloud infrastructure is implemented and fully functional. The uninterrupted provision of the private cloud infrastructure is seen as a significant result.

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.

Summary on actions taken to meet the recommendations from CHIC review

No specific recommendations regarding WP5 from the last review report. Previous recommendations, from the 3rd CHIC review that relate to WP5, i.e. 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, continue to be the focus of current work in WP5.

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

No deviations.

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 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	3.40	0.90	0.45
5-BED	10.00	0.00	0.00
6-USFD	6.00	0.74	0.81
7-FORTH	29.00	5.00	4.00
12-UBERN	4.00	1.00	2.01
13-Custodix	19.00	6.50	5.15
14-Philips	15.00	1.00	2.30
16-CINECA	6.00	0.00	0.00
17-TEI-C	21.00	7.00	5.42
Total	113.40	22.14	20.14

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)
(Leader: ICCS, Participants: UPENN, UOXF, UNITO, UBERN, FORTH, PHILIPS)
- Task 6.2, Subcellular cancer modeling (M1-39)
(Leader: UPENN, Participants: ICCS, UOXF, UNITO)
- Task 6.4, The clinical modeling paradigms of nephroblastoma, glioblastoma and lung cancer (M6-46)
(Leader: ICCS, Participants: UPENN, UOXF, UNITO, UBERN)
 - 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)
(Leader: UNITO, Participants: ICCS, FORTH, UBERN)

Summary of progress achieved towards objectives

FORTH (Tasks 6.1, 6.2, 6.4) provides the metabolic network hypomodel that utilizes the generic genome-scale human metabolic network reconstructions and describes the metabolic activity of the chemical reactions at flux level using the Flux Balance Analysis constrained-based method. Adaptations of this hypomodel have been delivered for the various cancer types and the different hypermodels. Modifications in the implementations are needed in order to comply with the requirements of the execution framework, while the different cancer-specific incarnations of the hypomodel are registered in the model repository with the proper annotations.

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.

Task 6.1: Cancer hypomodelling and hypermodelling strategies and elementary models

Refinements regarding the exploitation of multiscale data and especially miRNA data have been suggested by **ICCS** and adopted for nephroblastoma hypermodelling.

Two different approaches regarding non small cell lung cancer hypermodelling have been proposed by **ICCS**: one mechanistic (refined during the period under consideration) and another one based on machine learning approaches.

ICCS has finalized the machine learning approach applied to the glioblastoma hypermodel.

ICCS has proposed the formulation of a multimodeller hypermodel based on UNITO's hypermodel of prostate cancer (and treatment response).

Task 6.2: Subcellular cancer modeling

The molecular data provided within the reported period were utilized by **ICCS** in order to further refine 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 6.4: The clinical modelling paradigms of nephroblastoma, glioblastoma and lung cancer

UBERN: efforts were focused on testing and improving the interaction between BMS and OS hypomodels for the nephroblastoma and lung cancer scenario, as well as the integration of BMS into the CHIC hypermodeling framework.

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 lung tumor and the nephroblastoma are investigated by macroscopic models based on the Universal Phenomenologies in order to investigate the effects of combined chemotherapies on cancer growth.

UOXF (Tasks 6.4.a, 6.4.c): The **UOXF** hypomodel for nutrient (glucose) delivery and vessel growth has been uploaded to the model repository. It is being used with both Nephroblastoma and Lung Cancer demonstrator hypermodels, including direct interaction with **ICCS** and **FORTH** hypomodels.

Both versions of the model are performing as expected in tests on the common virtual machine (CVM). Software maintenance and testing are on going, with details given below.

Full model parameterization requires some fitting to clinical data and full hypermodel execution: this is the subject of on-going work.

Additionally:

UOXF have had discussions with USHFLD regarding the provision of simple hypomodels for the development and testing of surrogate models and caching functionality in WP7. The development of these hypomodels and associated software has started.

UOXF has continued work on the development and parameterization of more fundamental, agent-based models of vascular tumour growth. These fundamental models will prove useful in the parameterization of the continuum, clinical **UOXF** hypomodel, with the aim of reducing the dependence on fitting to clinical data. A library of multi-scale vascular tumour growth and treatment models (Microvessel Chaste) has been developed and is being prepared for public release (www.jmsgrogan.github.io/MicrovesselChaste).

SubTask 6.4.a: The nephroblastoma paradigm

ICCS's Wilms mechanistic hypomodel

ICCS has coordinated and extensively contributed to the preparation of the deliverable D6.3 "Initial standardized cancer Hypermodels".

An additional checking focusing hypermodel scenario of Oncosimulator-Biomechanics model has been implemented in cooperation with partner UBERN.

All necessary technological issues have been dealt with in collaboration with the involved partners.

SubTask 6.4.b: The glioblastoma paradigm

ICCS preprocessed the 82-patient data set provided by KUL and evaluated the performance of a variety of tools (rule-based classification, decision trees, random forests, frequent pattern –based etc.). In cross-validation schemes, all of the classifier structures were outperformed by the naive Bayes classifier. In fact, naïve Bayes was the only classifier structure that provided acceptable results.

An additional independent set of 52 patients was used for testing. None of the 15 classifiers had good performance and the issue is under investigation. New data on immune monitoring are currently being compiled and part of them has been already received.

SubTask 6.4.c: The lung cancer paradigm

A. Lung Oncosimulator

ICCS studied the available lung cancer data in order to identify exploitable cases. All necessary technological issues have been dealt with in collaboration with the involved partners. Refinement of several basic science aspects (data flow between Oncosimulator and the other models, fine tuning of the models etc.).

A separate muscle-enabled hypermodel scenario of Oncosimulator-Biomechanics model has been implemented.

B. Lung Statistical model

ICCS performed data analysis and preprocessing, and developed a preliminary Naive Bayes classifier based on miRNA data only. **ICCS** also developed and successfully tested a standalone application utilizing the above classifier.

Task 6.5: The prostate cancer modelling paradigm

UNITO: clinical validation of the models is given, using EUREKA1 data collection. A nomogram based on our cohort is therefore in progress.

ICCS: A testosterone concentration hypomodel to be used with the **UNITO** prostate hypermodel was initiated by **ICCS** and considerably progressed in the period under consideration. The hypomodel captures the dynamics of the Luteinizing Hormone Releasing Hormone (LHRH)-Luteinizing Hormone (LH) –Testosterone (TE) axis that simulates the response of testosterone levels to treatment schemes consisting of LHRH agonists.

Summary of details for each task

FORTH (Tasks 6.1, 6.2, 6.4) provides the metabolic network hypomodel that utilizes the generic genome-scale human metabolic network reconstructions and describes the metabolic activity of the chemical reactions at flux level using the Flux Balance Analysis constrained-based method. In the reporting period adaptations of this hypomodel have been delivered for the various cancer types and the different hypermodels. Furthermore, modifications in the implementations are needed in order to comply with the requirements of the execution framework, while the different cancer-specific incarnations of the hypomodel are registered in the model repository with the proper annotations.

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.

(For details see Deliverable D6.3).

- **Task 6.1**

Refinements regarding the exploitation of multiscale data and especially miRNA data have been suggested by **ICCS** and adopted for nephroblastoma hypermodelling following pertinent discussions by the involved partners including clinicians.

Two different approaches regarding non small cell lung cancer hypermodelling have been proposed by **ICCS**: one mechanistic (refined during the M37-M42 period) and another one based on machine learning approaches. The proposals have been adopted following pertinent discussions by the involved partners including clinicians.

ICCS has finalized the machine learning approach applied to the glioblastoma hypermodel.

ICCS has proposed the formulation of a multimodeller hypermodel based on **UNITO's** hypermodel of prostate cancer (and treatment response). The proposal has been accepted by the involved partners following pertinent discussions.

In more detail, **ICCS** has refined 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 has been developed.

- **Task 6.2**

The molecular data provided within the reported period were utilized by **ICCS** in order to further refine 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 6.4**

UBERN: BMS was modified to support logging and concurrent model execution within CHIC hypermodeling framework.

Having achieved technical integration of BMS into CHIC hypermodeling framework, this work period focused on evaluating the impact of BMS on overall performance of CHIC-hypermodel. To this end, the parameter exchange between OS and BMS has been verified, and the effect of 'direction-of-least-pressure' information on tumour shape and position evolution has been studied in Nephroblastoma.

Strategies for reducing observed spatial discrepancy between simulated and actual tumour evolution were devised with OS model developers at **ICCS**; their implementation and testing is being finalised.

UNITO: Lung cancer response to gemcitabine and cisplatin has been modelled by the two-population model developed in Task 6.2. Nephroblastoma grows very fast, so a single population model could be the best approximation in this case. West growth law can be used in order to link the physical properties of the tumor cells to their behavior.

UPENN: The nephroblastoma and lung cancer molecular model is composed of two main signaling modules – ErbB receptor mediated Ras-MAPK and PI3K/AKT signaling module and TP53 mediated DNA damage response module.

UOXF: The UOXF_Vasculature_Nephroblastoma and UOXF_Vasculature_LungCancer models have been successfully executed with all necessary partner models as part of the respective clinical demonstrators. A limitation has been identified in that simulation results are no longer realistic if the tumour grows to the extents of the original simulation domain. The problem also affects several partner hypomodels and has been discussed at regular Skype meetings. Otherwise the models are performing as expected.

The software for the models is currently being updated due to changes in the build system of a major dependency, Chaste (www.chaste.cs.ox.ac.uk) [the SCons build system has been replaced with CMake]. This update will help 'future-proof' the UOXF hypomodels.

Additionally:

A software library for multi-scale modelling of vascular tumours has been developed for use with Chaste. The 'Microvessel Chaste' library includes agent-based models of cells and vessels, nutrient, growth-factor and drug transport models (based on reaction-diffusion PDEs), blood flow and structural adaptation and sprouting angiogenesis using on- and off-lattice approaches. The library is

available for use by CHIC partners, currently by request. It will prove useful in rapid hypomodel composition and in better parameterizing the continuum, clinical UOXF hypomodel.

The Microvessel Chaste library has been used to study the radiotherapy response of tissues with mouse tumour vessel network data from 3-D multiphoton images, in collaboration with Professor Ruth Muschel's lab, in Radiation Oncology, Oxford. This on-going collaboration continues to provide a rich-data set of high-resolution 3D tumour geometries for different treatment conditions, which will be valuable for model parameterization.

Analysis of experimental blood flow measurements in micro-fluidics systems is on going, in collaboration with the Alarcon lab, Centre De Recerca Matematica, Barcelona and Miguel Bernabeu, University of Edinburgh. This data will be valuable for validating and parameterizing the flow sub-models used in the multi-scale tumour growth models.

Initial models for use in the testing of surrogate modelling tools with USHFLD are under development.

The Microvessel Chaste library is being used to study whether predictions of simplified models of vascular tumour growth and nutrient and growth factor transport agree with more detailed multi-scale models by means of a detailed model comparison.

SubTask 6.4.a, The nephroblastoma paradigm

ICCS's Wilms mechanistic hypomodel

ICCS has coordinated and extensively contributed to the preparation of the deliverable D6.3 "Initial standardized cancer Hypermodels":

- Model algorithmic description of the Wilms mechanistic hypomodel has been provided.
- The input-output parameters of the model have been analytically described.
- The hypermodel integration-communication scheme of Wilms mechanistic hypomodel with five other hypomodels (image pre-processing tool; molecular component model; vasculature component; metabolic network hypomodel; biomechanics component) has been defined and described for each connection.

An additional checking focusing hypermodel scenario of Oncosimulator-Biomechanics model has been implemented in cooperation with partner UBERN in order to study thoroughly the communication and interaction of the two models separately:

- The OS-Biomechanic scenario has been adapted to muscle environment.
- Several tests have been performed (eg constant direction of least pressure map, inward and outward direction of least pressure map) on one patient in order to check the communication of the two hypomodels as well as the effect on the final simulated tumor shape.

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

Minor deviations between reality and virtuality have been resolved.

Alternative algorithms of Wilms hypomodel on tumor volume reconstruction have been discussed in terms of basic science. Their effect on the interaction of Wilms hypomodel with the biomechanic model have been studied.

Technological issues:

ICCS has provided feedback to partner **BED** in order to form a useful visualization of the hypermodel results. Furthermore, **ICCS** has cooperated with partner **BED** so as to fix minor deviations between reality and virtuality.

ICCS has cooperated with **FORTH** and **CINECA** to clarify issues on definition of muscle environment parameters

ICCS is working on the production of a more detailed logging of Wilms hypomodel.

SubTask 6.4.b, The glioblastoma paradigm

ICCS's GBM statistical model:

- A data set consisting of 82 patients was provided by KUL. The basic clinical questions posed concerned predicting the overall survival (OS) of a patient in terms of two classes : long term survivors (OS>24 months) and short term survivors (OS<24 months). An additional question concerned deciding the optimal vaccination schedule (early/late) according to specific patient characteristics.
- The data were preprocessed. Where possible, missing values were filled with data having a clear medical sense. Patients with missing values that could not be filled in a medically sensible way were disregarded. Following clinicians' advice, additional features with probable relevance were introduced, based on the existing ones.
- Since the vast majority of available data had categorical values, to answer these questions we evaluated the performance of a variety of tools, able to handle categorical data. These included
 1. rule-based based classification methods
 2. decision trees
 3. random forests
 4. frequent pattern based classification methods
 5. TAN, K2, Hill Climbing, Genetic Search and Simulated annealing derived topologies of probabilistic graphical networks [43, 44, 45]
 6. ensemble classification methodologies.
- Feature selection included various heuristic selection methods, including forward/backward elimination and was further optimized by use of genetic algorithms and particle swarm attribute weighting.
- In cross-validation schemes, all of the preceding classifier structures were outperformed by the naive Bayes classifier. In fact, naïve Bayes was the only classifier structure that provided acceptable results. In all cases, ensemble classification methods like AdaBoost did not improve performance.
- A total of 15 classifiers performing robustly good in cross-validation schemes with varying number of folds were created.
- An additional independent set of 52 patients was provided by KU Leuven for testing. None of the 15 classifiers performed good, with statistical robustness being their main issue. Even when some classifiers performed better than others in the test set, when their structures were trained by a different set of patients their performance on the

remaining patients was unstable, and depended greatly on which patients had fallen on the train set and which on the test set.

- The complete data set of 134 patients was redistributed into training and test sets. New classifiers were built, whose performance however, showed statistical instability. Again, results depended on the initial split of the data on training and test sets, and even some fairly good performances were shown to be circumstantial, rather than reflecting some stable pattern in the data.
- New data on immune monitoring are currently being compiled and part of them is already provided by KU Leuven.

SubTask 6.4.c, The lung cancer paradigm

A. ICCS's Lung Oncosimulator:

LUNG Data issues:

- Analysis of the available lung cancer data, in order to clarify which cases are exploitable by the lung cancer mechanistic hypermodel. Four case scenarios are considered a. progression prior to surgery, b. the time to recurrence (either local or distant), c. the progression of recurrent tumor (either local or distant) and d. the response to chemo or radio treatment of recurrent tumors.
- Interaction with FORTH for the segmentation of the DICOM images. Definition of segmentation requirements.

Technological issues:

- Update of the clinical model repository and the common virtual machine with the latest version of Lung Oncosimulator (executable, description of inputs/outputs, muscle configuration files, model description/perspectives, etc).
- Close interaction with **CINECA** to resolve muscle and integration issues
- Successful Integration with CRAF and CHIC hypermodel infrastructure
- Close interaction with **FORTH** for the definition of the required elements to be included in the user graphical interface
- Close interaction with **FORTH** and **BED** for the definition of the outcome report and the visualization of simulation results

Basis Science issues:

- Finalization of the required data flow (variables, format) between Oncosimulator and the Molecular, Biomechanics, Vasculature and Metabolic models and the preprocessing tools.
- Resolve incompatibility issues between models' input/output in terms of parameters' meaning
- Update of the Oncosimulator.
- Fine tuning of the models so as to get biological relevant and tumour specific simulation results after the hypermodel execution.

Close Interaction with UBERN to resolve emerged basic science issues:

A separate muscle-enabled hypermodel scenario of Oncosimulator-Biomechanics model has been implemented:

- The aim is to investigate whether the direction of tumor expansion and shrinkage is compliant to the overall pressure field of the surrounding tissues.
- The coupling of Lung Oncosimulator – Biomechanics simulator has been tested with a nephroblastoma case. No new issues have been revealed regarding the coupling of Lung Oncosimulator –Biomechanics compared to Wilms Oncosimulator – Biomechanics one.
- Redesign and update of volume reconstruction algorithms to ensure a. expansion and shrinkage is performed in the desired direction, b. the internal pressure field of the tumor is properly taken into consideration, c. geometrical cells with artificially low number of biological cells are not created within the tumor c. allow the whole boundary of the tumor to evolve in a more realistic way during shrinkage.

B. ICCS's Lung Statistical model

- Analysis of Lung data
- Interaction with clinicians to clarify the data
- Data processing in order to take a form suitable for further elaboration
- Development of a preliminary Naive Bayes classifier based on miRNA data only
- Development and successful testing of a standalone application utilizing the above classifier, compliant to the CHIC specifications in respect to model deployment and packaging.
- Update of the clinical model repository and the common virtual machine with the developed standalone application (executable, description of inputs/outputs, model description/perspectives, etc)

• Task 6.5

The following hypotheses constitute the base of the **UNITO** models:

- After surgery, tumor regrowth follows a gompertzian or a West law
- The parameters values of the gompertzian function strictly depend on the age of the tumor
- 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

The 'age' of the tumor can be inferred by the Gleason Score and stage (pT) and by other available clinical information.

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 second 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.

Since the West parameters have a biological meaning, considering only one population we can estimate the parameter values in each patient and forecast the behavior of the tumor (relapse, time

to relapse, severity...). We found, in fact, a strict correlation between the West growth rate and the timing to relapse.

Genetic analysis takes an important role in the choose of the best secondary therapy. In fact, RNA analysis can show a preponderance of AD or AI cells in the tumor mass. A collaboration with UPENN partners is started in order to deepen this scenario. Moreover, we want to create a 'repository' of the major used hormone therapies in collaboration with ICCS, in order to link the best therapy with the genetic profile.

ICCS: A testosterone concentration hypomodel to be used with the **UNITO** prostate hypermodel was initiated by **ICCS** and considerably progressed in the period under consideration. The hypomodel captures the dynamics of the Luteinizing Hormone Releasing Hormone (LHRH)-Luteinizing Hormone (LH) –Testosterone (TE) axis that simulates the response of testosterone levels to treatment schemes consisting of LHRH agonists.

4. Summary of significant results

Important achievements regarding improvements, extensions and refinements of all four CHIC hypermodels - both mechanistic and machine learning (hyper-)models that address nephroblastoma, non small cell lung cancer, glioblastoma and prostate cancer - were made by all involved CHIC modelling partners (ICCS, UBERN, UOXF, FORTH, UPENN, UNITO).

The clinical adaptation process continued. All four hypermodels are currently entering their final clinical adaptation and partial clinical validation stage. Submitted deliverable D6.3 outlines all major developments in WP6 pertaining to the creation of the standardized versions of hypermodels

Evaluation of the BMS hypomodel in hypermodel predictions.

An efficient technique to assess the period of possible relapse after prostatectomy has been found and published (see WP12 report).

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 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	57.01	19.01	9.68
7-FORTH	28.61	7.00	4.00
9-UPENN	69.00	19.00	1.77
10-UOXF	46.00	15.27	6.25
11-UNITO	14.00	5.00	1.98
12-UBERN	20.00	3.50	2.16
14-Philips	1.00	0.00	0.00
Total	235.62	68.78	25.84

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

Summary of progress achieved towards objectives

WP7 continue to develop as planned. Tasks 7.1 and 7.2 are now completed.

In Task 7.3 partner CINECA, in collaboration with partner ICCS produced a revision of the data flow inside the hypermodelling framework and support to WP6 modellers in running concurrent execution of hypermodels. Partner USFD completed an alpha version of the caching mechanism and defined the architectural design of the surrogate modelling component. Partners ICCS, USFD and CINECA collaborated to revise the Wilms Tumour and the Lung Cancer oncosimulators to produce outputs using the easylogging++ library. This task is now completed, with the production of deliverable D7.4, the final hypermodelling framework deployed on test node.

In Task 7.4 partner UCL, in collaboration with partner ICCS, has refined and extended the knowledge and metadata services in support for the nephroblastoma models, in particular with respect to the hypo- and hyper-model annotation requirements for the clinical scenario. The metadata schema for models was refined and used in implemented semantic services, with initial prototype work on model parameters. Work on this task will continue until the end of the project.

In Task 7.5 partners CINECA, ICCS, and USFD developed the automatization of the deployment of a model inside the hypermodelling framework. ICCS has also implemented a "freezing" mechanism to avoid the accidental modification of models after their validation is completed. Partner USFD completed an alpha version of an extension to Taverna, called *Interactive Services*, which allow to embed in a Taverna workflow an operation that require human intervention. Partner ICCS update the Model/Tool and In Silico Trial repositories, to comply with the extensions introduced to the hypermodelling infrastructure. While the main objectives of the work package are achieved, it will be necessary to extend the activity of this work package, in order to complete the integration and testing of some of the more advanced features.

Summary of details for each task

Task 7.3 Hypermodels execution

- CINECA worked with WP6 modellers in order to run concurrent executions of the same hypermodel or different hypermodels in the hypermodelling infrastructure. The goal has been achieved thanks to the integration of VPH-HF with the Clinical Data Repository and a revision of the data flow inside the hypermodelling infrastructure (See D7.4). CINECA gave support to WP6 modellers to improve the logging and the error handling.

- USFD, in collaboration with WP6, integrated additional models in the execution environment: a nephroblastoma hypermodel and an equivalent phenomenological model, consisting of three and two hypomodels respectively connected using a DAG topology.
- All partners updated a set of guidelines to organise the model metadata, files and input data in the Model Repository. These new rules have been considered in the Model Repository refactoring carried out by WP8.
- USFD and CINECA developed a Workflow-Wrapper-Compiler (WWC), to simplify and make the process of integration of hypo/hypermodels into the VPH-HF reproducible. This creates the workflow execution file required to run the model using information provided in the Model Repository.
- CINECA, USFD, FORTH, and ICCS have partially developed the automated deployment of hypo/hypermodels from the Model Repository, to the VPH-HF 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.
- ICCS in collaboration with USFD and CINECA is currently updating the Wilms Tumour and the Lung Cancer oncosimulators to produce outputs using the easylogging++ library.
- All WP7 partners contributed to the deliverable "D7.4: Final hypermodelling framework deployed on test nodes".

Task 7.4 Metahypermodels annotation

- UCL, FORTH, and USFD participated in the discussion lead by CINECA relating to the choice of a high level metamodelling language that can best be adopted, or further developed, in order to meet the needs of the CHIC project.
- ICCS, CINECA, FORTH, and USFD refined various web services to support the semantics-based hypomodel integration in the hypermodelling editor.
- Partners ICCS, FORTH and UCL discussed and designed the support for the semantic annotation of model parameters.

Task 7.5 Hypermodelling Infrastructure

- CINECA worked on a deploy service included in the new release of the VPH-HF which deploy binaries and dependencies in the computational infrastructure and generates automatically the model wrapper and the MUSCLE configuration file from the information stored in the Model Repository and the xMML description of the model.
- USFD contributed to the configuration, testing and maintenance of the VPH-HF on both development and production nodes, as well as the documentation of the refactored framework.
- CINECA and USFD aligned VPH-HF software components to WP5 updated security service and guidelines. Regular assessment of all the software services adopted in the hypermodelling framework has been conducted to keep the framework safe from security issues (interface with WP5).
- USFD developed and tested a first version of the cache component. The current cache is integrated into the automatically generated model wrapper and stores all the input/output couples for each model's execution. Installation of this component in the hypermodelling framework in the FORTH cloud is in progress.

- USFD developed a first version of the surrogate model component that provides two functionalities: training of new surrogate models, and store/retrieve finalised surrogate models. In collaboration with WP6 partners, data to train a surrogate model for the basic hypomodels will be generated. A set of suitable surrogate modelling methodologies has been identified to best approximate the WP6 hypomodels. Development of these components is still in progress.
- USFD developed an Interactive service to provide an interface for human users to intervene in the execution process of model workflow. This allows certain steps in workflow to be operated by human users rather than an end-to-end automatic process. This could be useful for steps that cannot be fully automated such as inspection activities. This is designed as a standalone service (to maximise customisation), invoked directly within the Taverna workflow. The technology is currently being integrated with the rest of VPH-HF.
- The Model/Tool and the In Silico Trial Repository web services have been updated based on the new requirements derived from the evolution of the hypermodelling infrastructure. Partners FORTH, USFD and CINECA can have online access to the documentation of the aforementioned updated web services through the CHIC wiki.
- ICCS has collaborated with partners USFD, FORTH and CINECA and agreed on the need for deploying the binaries of the models into the hypermodelling infrastructure in order for them to be tested by the hypermodelling framework. Thereafter, based on the feedback from partner CINECA, ICCS has made the needed changes in the user interface and the business logic of the Model Repository and initiated the implementation of the models deployment mechanism which involves further integration between the Model Repository and the hypermodelling framework.
- The consistency and the immutability of the successfully deployed models is of great importance for the hypermodelling framework. Thereafter, based on the feedback received from partners CINECA and FORTH, ICCS implemented the “freezing” mechanism in the Model Repository. According to the aforementioned mechanism, all the models that have been successfully deployed into the hypermodelling framework are automatically “frozen” and cannot be changed or updated any more by their owners. “frozen” models are considered to be valid models from the perspective of the CHIC technological system and therefore, they can be accessed by the other CHIC components through the Model Repository’s web services.

Summary of significant results

- Concurrent execution of hypermodels within VPH-HF;
- Implementation of the Deployment Service through registry API;
- Writing and submission on time of Deliverable 7.4;
- All new models developed by WP6 were deployed in the hypermodelling execution environment;
- VPH-HF deployed on production node and integrated with CHIC authentication system;
- Automation of wrappers’ generation and deployment & testing of new models;
- Alpha version of caching, interactive, and surrogate modelling services.

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

Originally, WP7 was planned to finish at M42, except for the metahypermodels annotation task, that was expected to continue until the end of the project.

While most of the original objectives have been achieved by now, during the project the need for more advanced features emerged, such as the support for workflows not represented in a DAG topology, and the subsequent integration of MUSCLE into the VPH-HF. As a result, today the hypermodelling framework is a much more complex technology than originally planned, and the integration of planned functions like the Surrogate Modelling support is also significantly more complex.

Also, because of the complexity of the hypermodelling architecture, and of the hypermodels to be executed in it, it became clear that the various repositories require some additional services to ensure the compliance and integrity of the models being deployed.

While all these additional functionalities are now available at least in an alpha version, it is necessary to extend task 7.5 until the end of the project, to ensure that all these new functions are fully tested, properly integrated, and fully deployed on the production nodes.

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

This deviation is simply the reflection of all the technical decisions that were taken during the project in deviation of the DoW, also to follow the recommendations of the reviewers. This extension of task 7.5 will have no negative impact on any other activity, on the achievement of the final objectives, or on the distribution of resources, except for a shift of some effort by partner USFD from this semester to the last.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP7			
Partner	Planned PM Total	Planned PM Period 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	7.20	1.70	1.30
3-USAAR	4.00	2.00	1.00
5-BED	28.00	0.00	0.00
6-USFD	134.00	30.54	26.27
7-FORTH	10.00	4.00	2.50
15-UCL	36.00	12.00	7.82
16-CINECA	36.00	4.00	4.96
Total	255.20	54.24	43.85

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 developed a wizard for the Model Repository in order for the user to be able to store a new model through a single page. Moreover, the user interface of the Model Repository has been further updated and the user is now able to view the content of the Repository in a more elegant way. The main page has been improved, tables and panels have been incorporated in order to lay out the information of the Repository and pagination is being used. Furthermore, ICCS developed a new functionality for the Model Repository, according to which the user is able to filter the stored models based on the 13 perspectives that have been defined within the CHIC project. All the aforementioned implementations have been documented in the deliverable "D8.4 Report on the final system". Additionally, the models provided by FORTH (Nephroblastoma metabolic model, Lung cancer metabolic model) and ICCS (Lung oncosimulator, Wilms oncosimulator, Lung statistical model) have been registered with the CHIC Model Repository according to the guidelines provided by partner ICCS. Finally, partners ICCS and FORTH collaborated for the design of the Model Repository with

respect to the model versioning support in order to provide guarantees about the reproducibility of the execution results.

SubTask 8.1.b, Development of the data repository

UBERN has extended the REST service of the Clinical Data Repository with more functionality. More specifically, an endpoint to support requests initiated by the search query builder has been added and the Open Data Protocol (OData) implementation has been extended in order to be able to filter datasets based on the unique patient identifier/pseudonym. Furthermore, UBERN simplified the publishing procedure of the Clinical Data Repository by making use of the 'Web Deploy' tool, offered by Microsoft. Consequently, both deployed systems (development and production) of the Clinical Data Repository can now be updated with much less effort than it was the case before. Partner ICCS has provided UBERN with additional basic science related needs and requirements, in particular related to the glioblastoma and prostate branches of the project, and partner USAAR has provided clinical feedback regarding the structure of the Clinical Data Repository and the uploading of the data. Finally, the Clinical Data Repository has been 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

Partner ICCS developed a wizard for the *In Silico* Trial Repository in order for the user to be able to store a new experiment through a single page. The user is now able through the aforementioned wizard to store in one page all the related information of the new *in silico* experiment and to dynamically store a variable number of input and output files without changing pages. Moreover, the user interface of the *In Silico* Trial Repository has been updated and the user is now able to view the content of the Repository in a more elegant way. All the *in silico* experiments are grouped by trials, the main page has been improved, tables and panels have been incorporated in order to lay out the information of the *in silico* experiments and the mechanism of pagination has been implemented. ICCS also developed a new functionality for the *In Silico* Trial Repository according to which the *in silico* experiments can be filtered based on the patient pseudonymized identification. Finally, all the aforementioned implementations have been included in the deliverable "D8.4 Report on the final system".

Task 8.2, Infrastructure for Semantic Metadata Management

Partner UCL continued the development and deployment of the CHIC semantics infrastructure in coordination with stakeholders in the consortium, in order to refine the hypo/hypermodel metadata schema, to support the use of schema and data access through the GUI and to maintain and update the annotation (RDF) Triplestore and ontology Knowledge Base through RICORDO. Moreover, partners UCL, ICCS and FORTH, participated in the discussions and the various interactions regarding the semantic annotation of the models, the design of the semantic services and the semantic integration of the Hypermodelling Editor and the Model Repository. The schema used for the annotations has been consolidated taking into account the updated requirements emerging from the Hypermodelling Editor, the Model Repository, the Clinical Data Repository and the CRAF. Based on the feedback received from partner UCL, partner ICCS has made use of the web services of the CHIC RDF storage solution so as to store information related to the categorization of the models through the Model Repository. Through discussions during the Saarbruecken plenary meeting, partner ICCS also contributed to the design of a core knowledge base, to the implementation of resource annotations and to the design of the global metadata search engine. Moreover, partner UBERN continued with the integration of the RICORDO framework within the Clinical Data Repository in

order to simplify the annotation process of the data providers. Finally, partner USAAR continued the work related to the semantic interoperability, and more specifically, the definition of 'HOT Maps' of tumour-specific hallmark knowledge.

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

Based on the feedback received from partner CUSTODIX, ICCS implemented the SAML-based delegation mechanism for the *In Silico* Trial Repository. Moreover, ICCS updated the Model and the *In Silico* Trial Repository web services in order for them to check the AudienceRestriction XML element of the SAML token. Partners UBERN and CUSTODIX collaborated in order to further integrate the Clinical Data Repository with the CHIC data protection framework. Finally, partner USAAR 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:

A wizard has been created for the Model and Tool Repository in order for the user to be able to store a new model through a single page. The user is now able through the aforementioned wizard to store in one page all the related information of a new model (basic information, related files, parameters, references, etc.).

The new implemented wizard aims at facilitating the storage of a new model, since it allows the user to dynamically store a variable number of parameters and files without changing web pages. It also informs the user (modeller, researcher) about the invalidity of the data when submitting the form.

The user interface of the Model Repository has been further updated and the user is now able to view the content of the Repository in a more elegant way. Tables and panels have been incorporated in order to lay out the information of the Model Repository. Moreover, the mechanism of pagination has been implemented in order to provide users with additional navigation options for browsing. Consequently, parts of the Model Repository content are now referred by numbers (of pages).

The main page of the Model Repository has been updated.

A new functionality has been implemented for the Model Repository according to which the user can filter the stored models based on the 13 perspectives that have been defined within the CHIC project.

ICCS has contributed in the preparation of the deliverable "D8.4 Report on the final system" by providing sections related to the Model and Tool Repository. Furthermore, based on the feedback received from partners UCL and UBERN, ICCS prepared and finalized the aforementioned deliverable.

ICCS has updated the model repository with the latest version of lung and Wilms oncosimulators (executable, description of inputs/outputs, muscle configuration files, model description/perspectives, etc).

ICCS has updated the model repository with the latest version of the lung statistical model (executable, description of inputs/outputs, model description/perspectives, etc).

FORTH:

The models provided by the FORTH team have been registered with the CHIC Model Repository according to the guidelines provided by ICCS.

FORTH contributed to the design of the Model Repository regarding the model versioning support in order to provide guarantees about the reproducibility of the execution results.

SubTask 8.1.b, Development of the data repository

UBERN:

The REST service of the Clinical Data Repository has been extended with more functionality. An endpoint to support requests initiated by the search query builder 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 publishing procedure of the Clinical Data Repository has been simplified. For this purpose the mechanism called Web Deploy offered by the Microsoft Visual Studio IDE is used. Both deployed systems (development and production) of the Clinical Data Repository can now be updated with much less effort than it was the case before.

ICCS:

ICCS has provided UBERN with additional basic science related needs and requirements in particular related to the glioblastoma and prostate branches of the project.

USAAR:

USAAR has provided clinical feedback regarding the structure of the Clinical Data Repository and the uploading of the clinical data.

Moreover, 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:

A wizard has been created for the *In Silico* Trial Repository in order for the user to be able to store a new experiment through a single page. The user is now able through the aforementioned wizard to store in one page all the related information of the new *in silico* experiment (description of the *in silico* trial, input and output files of the new *in silico* experiment, description of the experiment, description related to the initial and the final simulated state of the patient, etc.). Based on the aforementioned functionality, the user is allowed to dynamically store a variable number of input and output files without changing pages. The user is also informed whenever invalid data are submitted.

The user interface of the *In Silico* Trial Repository has been updated and the user is now able to view the content of the Repository in a more elegant way. Tables and panels have been incorporated in order to lay out the information of the *In Silico* Trial Repository, the mechanism of pagination has been implemented and parts of the *In Silico* Trial Repository content are now referred by numbers (of pages).

Consequently, all the *in silico* experiments are grouped by trials, and therefore, after the selection of the desired trial, the user can then easily download the input and output files of the simulations,

view the references related to trials or experiments or even view information related to the simulated patient.

The main page of the *In Silico* Trial Repository has been updated.

A new functionality has been implemented for the *In Silico* Trial Repository according to which the user can filter the stored *in silico* experiments based on the patient pseudonymized identification.

ICCS has contributed in the preparation of the deliverable “D8.4 Report on the final system” by providing sections related to the *In Silico* Trial Repository. Furthermore, based on the feedback received from partners UCL and UBERN, ICCS prepared and finalized the aforementioned deliverable.

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

UCL:

UCL continued the development and deployment of the CHIC semantics infrastructure in coordination with stakeholders in the consortium in order to:

- Refine the hypo/hypermodel metadata schema
- Support the use of schema and data access through the GUI (especially through the Model Repository)
- Maintain and update the annotation (RDF) Triplestore and ontology DB (Knowledge Base) through RICORDO
- Link RICORDO metadata management web services with the Model Repository and prepare the integration with the Hypermodelling Editor.

ICCS:

Based on the feedback received from partner UCL, ICCS has made use of the CHIC RDF storage solution for storing information related to the categorization of the models. More specifically, since mathematical and computational cancer models can be categorized depending on the perspective from which they are viewed in the basic science context, the Model/Tool and the CHIC RDF storage solution make use of a common RDF mapping configuration file so as to produce a model (a set of RDF triples) based on the already locally stored relational data. The aforementioned configuration file maps some of the Model Repository's database tables and columns to CHIC RDF vocabularies and OWL ontologies. With this kind of integration between the Model Repository and the CHIC triplestore, the user is able to categorize their model by visiting only one CHIC component, namely the Model Repository.

ICCS has contributed to the design of a core knowledge base to support semantic query of metadata through discussions during the Saarbruecken plenary meeting.

ICCS has been involved to the implementation of resource annotations to support semantic query of metadata through discussions during the Saarbruecken plenary meeting.

ICCS has contributed to the design of global metadata search engine through discussions during the Saarbruecken plenary meeting.

FORTH:

FORTH participated in the discussions and the various interactions among the technical partners for the semantic annotation of the models.

FORTH also contributed to the design of the semantic services infrastructure and its integration with the Hypermodelling Editor.

UBERN:

In order to integrate the RICORDO framework within the Clinical 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 (RICORDO Rdfstore). For this purpose, two libraries have been developed and published as open-source on the GitHub platform under the MIT license. RdfMapperNet is a .NET library to map classes to RDF triples and RdfstoreNet is a .NET library to interact with the RICORDO Rdfstore API. Both libraries are used by the Clinical Data Repository.

- RdfMapperNet
 - GitHub: <https://github.com/niklr/RdfMapperNet>
 - NuGet package: <https://www.nuget.org/packages/RdfMapperNet/>
- RdfstoreNet
 - GitHub: <https://github.com/niklr/RdfstoreNet>
 - NuGet package: <https://www.nuget.org/packages/RdfstoreNet/>

USAAR:

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

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

ICCS:

Based on the feedback received from partner CUSTODIX, ICCS implemented the SAML-based delegation mechanism for the *In Silico* Trial Repository. More specifically, assertions issued for single sign-on can now be sent back to the Identity Provider (after some transformation) in order to retrieve the new delegation SAML tokens. The aforementioned delegation tokens can now be sent to the Model Repository when asking for its web services.

The Model and the *In Silico* Trial Repository web services now check the AudienceRestriction XML element of the SAML token. The AudienceRestriction is a validity condition for the SAML token and it declares that the assertion's semantics are only valid for the relying party named by the URI of that element.

CUSTODIX, UBERN:

Partners CUSTODIX and UBERN collaborated in order to further integrate the Clinical Data Repository 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 developed a wizard for the Model Repository in order for the user to be able to store a new model through a single page and updated its user interface so as for the models to be presented in a more elegant way. A new functionality has also been provided to the Model Repository, according to which the user is now able to filter the stored models based on the 13 perspectives that have been defined within the CHIC project. Additionally, all the models that have been provided from the partners, have been registered within the Model Repository according to the guidelines provided by partner ICCS. Regarding the Clinical Data Repository, partner UBERN extended its REST services with an endpoint in order to support requests initiated by the search query builder. Partner UBERN also simplified the publishing procedure of the Clinical Data Repository by exploiting a mechanism offered by the integrated development environment. With respect to the *In Silico* Trial Repository, a wizard has been implemented which facilitates the storage of all the related information of the new *in silico* experiment through a single page. Furthermore, the user interface of the *In Silico* Trial Repository has been improved and the user is now able to view the content of the Repository in a more elegant way. The aforementioned Repository also provides the service through which the stored experiments can be filtered based on the patient pseudonymized identification. Regarding the infrastructure for semantic metadata management, the focus of this period was to provide the knowledge and metadata services in support for the hypermodelling effort, particularly using the nephroblastoma scenario. More specifically, partner UCL in collaboration with partners ICCS, FORTH and UBERN, further consolidated the schema for annotations, taking into account updated requirements emerging from the Hypermodelling Editor, the Model Repository, the Clinical Data Repository and the CRAF. Moreover, partners UCL, ICCS and FORTH, participated in the discussions and the various interactions regarding the semantic annotation of the models, the design of the semantic services and the semantic integration of the Hypermodelling Editor and the Model Repository. Additionally, partners ICCS and UBERN continued with the integration of the Clinical Data and Model Repositories within the RICORDO framework, and partner USAAR continued the work related to the semantic interoperability and the definition of 'HOT Maps' of tumour-specific hallmark knowledge. Regarding the integration with the security and legal/ethical framework, partners ICCS, UBERN and CUSTODIX collaborated in order to further integrate the Model, the Clinical Data and the *In Silico* Trial Repositories with the CHIC data protection framework. Partner USAAR has also prepared data to conduct manual ground truth annotations and anonymization of nephroblastoma and lung cancer data. Finally, based on the feedback received from partners UCL and UBERN, ICCS prepared, edited and finalized the deliverable "D8.4 Report on the final system" which documents all the progress that has been made so far with respect to WP8.

4.2 Summary on actions taken to meet the recommendations from the 5th CHIC review

In the absence of any deliverables and specific demonstrations, a significant amount of activities has been reported upon in the previous progress report. Thereafter, according to the recommendations from the 5th CHIC review, a great amount of effort has been put in by partners ICCS, UBERN and UCL in order to document in the last WP8 deliverable "D8.4 Report on the final system" the outcome of all the aforementioned activities in a comprehensive manner.

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 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	19.30	6.30	3.30
3-USAAR	3.00	1.00	0.50
7-FORTH	7.00	1.50	1.00
9-UPENN	3.00	1.00	1.77
12-UBERN	15.00	0.00	1.00
13-Custodix	3.00	0.50	0.75
14-Philips	7.00	1.00	0.00
15-UCL	36.00	12.00	7.85
Total	93.30	23.30	16.17

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 continued to optimise features of DoctorEye and the preprocessing tool, and has completed the tumour response software.

ICCS has continued to work with the other partners to refine the requirements of the project components.

USAAR has continued to work on the image segmentation for nephroblastoma and brain tumours.

UBERN: An approach to quantify segmentation uncertainty in multimodal and longitudinal brain tumour image analysis has been developed. Evaluation of longitudinal brain tumour segmentation pipeline on an independent data set (MICCAI BRATS 2016) suggested state-of-the-art performance.

Overall the work has been moving smoothly towards the objectives without significant deviations.

Summary of details for each task

Task 9.2 Visualization techniques for models and data

BED has continued development of the CCGVis visualization platform. 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, nifti 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. In this reporting period, the following features have been added to CCGVis:

- A new comparison view showing real and simulated tumours as superimposed isosurfaces.
- Importers for Nifti images.
- The isosurface views can now visualize multiple tumour components in different colours.
- A Json reader for metadata (eg segmentation labels, timestamps and image projections)
- Better transparency using depth peeling and surface dithering.
- Improved registration across time series data.
- Robust searching for input data in file system.
- Improved layout with better use of space on small screens.
- Architectural changes to allow CCGVis to create and store internally-created images.
- Architectural changes to separate the visualization tasks from the data importing. Tasks are now independent of the input format, allowing better scaling of the software.
- An example image processing task (image threshold)

ICCS has provided feedback to partner BED in order to form a useful visualization of the hypermodel results.

ICCS has cooperated with partner BED so as to fix minor deviations between reality and simulation.

Task 9.3 Statistical data visualization for the simulation outcomes

BED has further developed the statistical visualizations in CCGVis. All visualization tasks now show the image histogram of the clinical tumour, the tumour growth plot and an information panel showing the tumour volume (real and simulated). The plots of simulated tumour growth now include actual data points from the clinical images.

Task 9.4: Visualization for the reporting in data repository

BED has continued to develop the output functionality of 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. CCGVis can now output the 3D visualizations in video format.

ICCS has tightly interacted with partners FORTH and BED for the definition of the outcome report and the visualization of simulation results.

USAAR: A lot of work has continued on the segmentation of Wilms tumours using DoctorEye, and developing a semi-automatic algorithm for segmentation. Images from nephroblastoma patients were manually segmented and compared with the semi-automatic tool. A corresponding paper will soon be submitted.

USAAR: Further manual segmentations of nephroblastomas were done using DrEye.

Task 9.5 An integrated image processing toolkit for CHIC

BED has submitted an image processing paper:

Kaba, D.; McFarlane, N.J.B.; Dong, F.; Müller, S.; Graf, N.; Ye, X. (2016)

Segmentation of Nephroblastoma using Graph Algorithm

(submitted to IEEE Journal of Biomedical and Health Informatics, Nov 2016)

Dissemination: BED gave a presentation about the CHIC project and the nephroblastoma segmentation at a meeting of the EC CARRE project in Alexandroupoli, Greece, on 1.11.16.

FORTH: In the DoctorEye several minor optimizations have been made in order to assist the experts to segment the clinical images faster. The pre-processing tool has been updated (in order to optimize its functionality in the complete integrated platform of CHIC) and is being actively used. 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 and allows their proper initialization.

ICCS has cooperated with partner FORTH for the preprocessing and the tumour segmentation of lung cancer data. More specifically, ICCS has defined the segmentation requirements and indicated the patients that have imaging data, and thus can be exploited by the Lung Hypermodel.

Task 9.6: Image registration tools

USAAR: The work during the last reporting period was continued and advances on convex relaxation methods further elaborated. 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. We show 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

USAAR: We further discussed and propose a fully automatic method for brain tumour 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.

USAAR optimized the developed fast automatic brain tumour segmentation method and evaluated it.

UBERN: The methodology for defining uncertainty in the longitudinal segmentation results has been refined and evaluated on a larger patient cohort. A clinical study investigating the influence of different training set compositions on the segmentation performance in postoperative images has been conducted. The study confirmed preliminary findings that training on both pre- and postoperative imaging data improves overall segmentation performance.

UBERN: Participation in the MICCAI BRATS Challenge 2016, where our methodology yielded the second best performance for longitudinal brain tumour segmentation among 19 competitors.

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

FORTH: 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, has been continued by fine tuning and optimizing the code and improving the visualization of the information provided by the platform. This software is completed and it is fully integrated to DoctorEye within the agreed scope of task 9.5. This task will be reported in detail within Deliverable 9.4 which is due on M46.

USAAR: A wide range of imaging features with respect to their discriminative potential for nephroblastoma was further analyzed to help classify the response to pre-operative chemotherapy. We also developed a semi-automatic method for the segmentation of nephroblastoma. In addition we contributed to several visualization techniques for DrEye.

Summary of significant results

BED has been further developing CCGVis. CCGVis is now a mature and scalable platform with a wide range of importers, visualizations and statistical plots, as well as a nascent image processing capability.

USAAR did further 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 were analysed. A semi-automatic method for the segmentation of nephroblastoma is under further development and a corresponding paper is written and submitted. Our method is evaluated on now more than 20 hand-labelled t2 sequences, annotated by 2 human experts. We could show that few user scribbles are sufficient for highly accurate segmentation results.

USAAR: The fully automatic method for brain tumour segmentation is evaluated on further 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.

UBERN: Uncertainty in the image segmentation of the used machine learning model can be quantified. This will assist clinicians in the interpretation of the longitudinal segmentation results.

UBERN: Second best longitudinal brain tumour segmentation performance at the MICCAI BRATS Challenge 2016.

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

Not applicable.

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

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP9			
Partner	Planned PM Total	Planned PM Period 4 (M37-M48)	Actual PM Period 3 (M37-M42)
1-ICCS	4.00	1.40	0.70
3-USAAR	15.00	5.00	3.00
5-BED	36.00	10.00	11.00
7-FORTH	45.29	8.50	5.00
12-UBERN	12.00	3.00	1.50
17-TEI-C	1.00	0.00	0.00
Total	113.29	27.90	21.20

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

FORTH with contributions from TEI-C continued the development of the Clinical Research Application Framework (CRAF). CRAF is now fully integrated with the majority of the CHIC software components that constitute the “backend” services of the CHIC platform, while a new web-based version was prototyped. CRAF was further tested by USAAR in an iterative way and feedback was given to the developers at FORTH. This also allowed USAAR to demonstrate the CHIC platform and the CRAF in various conferences during the reporting period.

The Hypermodelling Editor is updated to consolidate features, such as the semantic validation of connections, that were requested by the experts in the recent review meeting. The CHIC Hypermodelling Language proposed by CINECA has been adopted and development is in progress for its use as the hypermodel serialization format and the agreed communication specification between the Editor and the VPH-HF execution framework. CINECA kept on the interaction with WP6 and WP7 partners in order to integrate the hypermodelling language into the hypermodelling infrastructure. FORTH, CINECA, and ICCS collaborated in the versioning of model definitions in order to support data and model provenance and the reproducibility of the experiments. A simple approach based on the “freezing” of the models was selected.

ICCS has provided extensive feedback to partner FORTH, regarding changes and updates related to the web services of the Model/Tool and the InSilico Trial Repositories and has successfully integrated Lung and Wilms oncosimulators with CRA. Since the Model Repository is the creator of the semantic annotation of the information related to the categorization of the models, and the Hypermodelling Editor is the consumer of this information, ICCS has cooperated with partners FORTH and UCL in order to define the needed types and predicates for describing all the information related to the categorization of the models based on the 13 perspectives. FORTH continued the work on the utilization of these semantic descriptions in the Hypermodelling Editor and provided feedback on these developments.

An event based communication infrastructure was established between the model repositories, the execution framework, the editor, and the CRAF. This communication is based on the AMQP

(Advanced Message Queuing Protocol) which provides a platform-agnostic method for ensuring information is safely transported between applications and across the Cloud. ICCS has cooperated with partner FORTH in order for the Model Repository to publish events to the hypermodelling editor and the CRAF. Since the modification of the Model Repository database may have a huge impact on the workflows and the processes of the hypermodelling editor and the CRAF, it has been decided to always publish events to the aforementioned CHIC components whenever the Model Repository database changes. The event-based communication is supplementary to the existing request-response interaction implemented through HTTP REST-based mechanisms and improves the performance, efficiency, and scalability of the platform.

Task 10.1: Portal

- FORTH continues to support and maintain the CHIC Portal

Task 10.4: Data and hypermodel orchestration

- FORTH continued the work on the Hypermodelling Editor with emphasis on the use of semantic annotations of the models and the design of the interactions with the VPH-HF execution infrastructure. On the latter point, the use of the CHIC Hypermodelling Language has been agreed as the common representation of the hypermodels both for the design at the Editor's side and the execution at the execution framework. A refactoring of the code is started in order to address some of the issues raised by the reviewers in the 5th review meeting. ICCS has intensively interacted with FORTH for the definition of the required elements to be included in the graphical user interface.
- CINECA finalized 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.
- 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 has kept on the interaction with WP7 and WP6 partners in order to integrate the hypermodelling language into the hypermodelling infrastructure. CINECA developed a tool to translate the hypermodelling language into the format required by the workflow management service (Taverna).
- ICCS has cooperated with partner FORTH and UCL in order to define the needed types and predicates for describing all the information related to the semantic annotation of the categorization of the models based on the 13 perspectives.
- ICCS has cooperated with partner FORTH in order for the Model Repository to publish events to the hypermodelling editor and the CRAF and has provided extensive documentation regarding changes and updates related to the web services of the Model/Tool and the In Silico Trial Repositories.
- The versioning of the models is necessary in order to achieve the reproducibility of past experiments and ensure the stability of the constructed hypermodels. FORTH proposed either the use of the "semantic versioning"^[1] or the "freezing" of models in order to cope with these

¹ <http://semver.org/>

requirements. The “freezing” of the models that have been successfully deployed into the CHIC hypermodelling framework was subsequently agreed between partners ICCS, FORTH, and CINECA as a simpler approach. According to the “freezing” mechanism, all “frozen” models are immutable and cannot be updated anymore by their owners. Thereafter, these models are considered to be valid models from the perspective of the CHIC technological system and can be safely accessed by the hypermodelling editor as building blocks for hypermodels and the CRAF as stable models to be used in the clinical setting.

Task 10.5: The clinical research integrated platform

- FORTH with contributions from TEI-C develops the Clinical Research Application Framework (CRAF) as the suite of tools and applications for the use of the CHIC scientific outcomes (especially the hypermodels) in the daily clinical practice in a clinical domain. In this reporting period, CRAF was ported to a full web-based setting that allows ubiquitous access from a range of consumer devices, operating systems, and personal computers. TEI-C was specifically involved with the integration activities necessary, so that CRAF is fully integrated with the majority of the CHIC software components that constitute the “backend” services of the CHIC platform: the Model Repository, the inSilico Trial Repository, the VPH-HF execution framework, the Clinical Data Repository, the security services (Identity Provider, Secure Token Service), etc. A beta version of CRAF has been successfully demonstrated in the 5th review of the project.
- CINECA continued the integration of the VPH-HF with all the other CHIC components, in particular with the CRAF application.
- ICCS had the supervision for the successful integration of the Lung and Wilms oncosimulators with the CRAF infrastructure, based on the WP10 requirements.
- Data management for heterogeneous nephroblastoma and lung cancer data was further developed by USAAR with the usage of ObTiMA. Data have been uploaded to the CHIC data repository.
- The specialized clinical workflow environment (CRAF) was further tested by USAAR and feedback was provided, in an iterative way, to the developers at FORTH. USAAR also demonstrated CRAF at different clinical conferences, including:
 - 9th International Renal Tumor Biology Conference in Toronto, Canada from the 2nd to the 3rd of April 2016
 - “International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics” in Toronto, Canada from August 11th to August 13th 2016
 - 48th Congress of the International Society of Paediatric Oncology (SIOP) in Dublin, Ireland between October 19th to 22nd 2016

Summary of significant results

- CRAF is now fully integrated with the majority of the CHIC software components that constitute the “backend” services of the CHIC platform
- CRAF was demonstrated and evaluated at different conferences during the reporting period
- Web-based version of CRAF launched

- Finalization of the high level hypermodelling language to describe hypermodels
- Work on the semantic annotation of the models to aid their composition into higher level hypermodels continues
- “Freezing” of models adopted as a versioning approach to guarantee the reproducibility of results and to secure their provenance
- Integration of Model Repository, Execution environment, CRAF, and the Hypermodel Editor enriched by the introduction of message-oriented middleware to increase efficiency and functionality.

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 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	7.40	1.80	0.90
3-USAAR	7.00	2.00	1.00
7-FORTH	42.00	9.21	6.36
12-UBERN	3.00	1.00	0.00
14-Philips	18.00	9.50	4.00
16-CINECA	8.00	0.00	2.00
17-TEI-C	4.00	3.00	1.93
Total	89.40	26.51	16.19

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 Söllereck, 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 continued 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.
- **USAAR** intensively continued and enhanced their 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. The impact on the CHIC infrastructure is manifold and increased clinical orientation is given.
- The work done for lung cancer was further enhanced to neuroblastoma.
- **ICCS:** Contribution in the preparation of the Deliverable 11.3 “Report on the second evaluation workshops round”, by providing extensive description for the Neuroblastoma multimodeller hypermodel and the Wilms oncosimulator. Furthermore, ICCS contributed in the preparation of the questionnaire used for the evaluation of the clinical data repository.
- **FORTH** continued the work on CRAF that signifies a progress towards utilizing the CHIC platform in the clinical research domain. FORTH also contributed to D11.3.
- **UNITO:** A user-friendly mobile phone APP is under construction in collaboration with BED. This APP will be a support for urologists and their patients. A validation of the models is in progress.
- **UBERN:** The developed longitudinal segmentation methodology has further been clinically evaluated, resulting in a scientific publication. Meier et al. “Clinical Evaluation of a Fully automatic Segmentation Method for Longitudinal Brain Tumor Volumetry” Nature Scientific Reports 2016
- **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.
- USAAR did successfully presented the CHIC platform and hypermodels at two big clinical congresses with the participation of clinicians and basic researchers outside of the CHIC consortium. These conferences were:
 - ‘International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics’ in Toronto, Canada from August 11th to August 13th 2016
 - 48th Congress of the International Society of Paediatric Oncology (SIOP) in Dublin, Ireland between October 19th to 22nd 2016

At these congresses validation and acceptance issues related to hypermodels were discussed. This work was done together with WP2. Results are reported in D2.4.

- **ICCS** in collaborated with the clinical partners and the technology developers for the validation of CHIC infrastructure as a whole.

Summary of details for each task

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

- **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** did successfully intensively enhance their 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.
- **ICCS** has contributed in the preparation of the Deliverable 11.3 “Report on the second evaluation workshops round”, by providing extensive description for the Nephroblastoma multimodeller hypermodel and the Wilms oncosimulator.
- Furthermore, **ICCS** contributed in the preparation of the questionnaire used for the evaluation of the clinical data repository. The aforementioned evaluation was conducted in the 9th International Renal Tumour Biology Conference which was held in Toronto, Canada from the 2nd to the 3rd of April 2016.
- **ICCS** has extensively worked on the clinical adaptation of the developed hypermodels in close collaboration with the clinical partners who have provided multiscale data. Several mathematical, statistical and computational methods including machine learning techniques have been recruited in order to optimize and facilitate the demanding clinical adaptation endeavor.
- The further development of “CRAF” (Clinical Research Application Framework) by **FORTH** continued. **FORTH** worked closely with USAAR to optimize the view and the overall user experience for the clinicians.
- **FORTH** evaluated the results of the 9th International Renal Tumor Biology Conference in Toronto, Canada from the 2nd to the 3rd of April 2016, and contributed to Deliverable 11.3 (“Report on the second evaluation workshop round”).
- **UNITO**: In collaboration with BED, a APP for mobile phone is in progress in order to provide to both clinicians and patients a user-friendly data and models storage. In particular, a module of MyHealth Avatar is under construction. This APP will be downloadable on the mobile phone of the patients and the clinicians. The patient will insert his data about prostatectomy and follow-up; the clinician will be able to see in real time the data inserted by the patient and run the models about the probability and the timing of the relapse. Moreover, the APP will provide some rehabilitation exercises for prostatectomized patients in order to improve their pelvic floor. Both the collection of clinical data for model validation and the development of hypo-models in the contest of Prostate Cancer have been further continued.
- **UBERN**: A clinical study has been finished that evaluated the use of the segmentation methodology for estimation of the extent of resection and residual tumor volume in immediate postoperative images of GBM patients, resulting in a recent publication Meier et al. Journal of Neurosurgery 2016.
- **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.
- **USAAR** did successfully presented the CHIC platform and hypermodels at two big international clinical congresses for validation and acceptance purposes.

- **ICCS** has undertaken a major role in the process of validating the CHIC infrastructure as a whole. This has been done in close collaboration with the clinical partners who have provided multiscale data and the involved technology developers. Several mathematical, statistical and computational methods including machine learning techniques have been recruited in order to optimize and facilitate the validation of the CHIC infrastructure in particular from the basic science perspective.
- **UNITO**: In collaboration with **ICCS** and UPENN, a double cross-validation is in progress. In fact, **UPENN** will provide information about the cell kill rate of hormone therapy using genetic data of some prostatectomized patients, while **ICCS** will provide pharmaco-kinetic models, in order to support and validate our treatment hypo-model. Moreover, the Phenomenological Universalities approach is applied on lung cancer and nephroblastoma in order to support and validate the first 'pillar' or 'hyper model' provided by the other partners.

Summary of significant results

- The CHIC infrastructure is clinically oriented and well recognized by the scientific community also including clinicians. Validation and acceptance of hypermodels are addressed intensively during the reporting period.
- **USAAR** successfully presented the CHIC platform and hypermodels at two big international clinical congresses for validation and acceptance purposes.
- **UNITO**: The APP is under construction, but a large consensus and interest has been noted by both patients and clinicians. In fact, we presented a Beta-version during the VPH conference (26th September 2016) and the Researcher's Night (30th September 2016). Some clinicians already asked to test the application. Moreover, we planned to present the first complete and working version during the Urologists Conference in Turin the next February.
- **UBERN**: Clinical evaluation of segmentation methodology suggests that estimates of extent of resection and residual tumor volume are comparable to estimates of human expert raters can be obtained. Clinical evaluation of a longitudinal automatic brain tumor segmentation approach suggests that the technology provides stable volumetric quantification of tumor progression.

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

High-performance compute cluster was utilized for the molecular profiling of mutations and for multiscale modelling of the signalling network.

Planned versus actual efforts in WP11			
Partner	Planned PM Total	Planned PM Period 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	7.70	3.00	1.50
3-USAAR	25.00	8.00	6.00
5-BED	8.00	3.00	0.00
7-FORTH	3.07	1.00	1.00
9-UPENN	8.50	3.50	1.77
11-UNITO	20.00	6.00	2.93
12-UBERN	3.00	1.00	1.00
14-PHILIPS	3.00	2.00	0.00
17-TEI-C	1.00	1.00	0.00
Total	79.27	28.50	14.20

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 third annual CHIC newsletter, available for download on the CHIC public website. This third issue contains contributions from partners ICCS and BED, as well as from a representative of the external advisory board. EURICE continuously updated the project website with the latest news from the CHIC partners and other relevant new information from the consortium; and CINECA kept alive the CHIC social channels with news from the project and from other relevant communities. A number of dissemination channels including peer-reviewed publications, media and alternative media publications, and presentations have been completed. A detailed reporting of the dissemination events and scientific publications taking place in the period is presented 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. 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. Moreover, collaboration was taking place for the deliverable D4.3.2: Development of the data protection and copyright framework for CHIC second iteration".

As part of Task 12.3, contact to clinical partners outside of the CHIC consortium was initiated to recruit patients for testing and evaluating CHIC tools. Scientific co-organisation of the International Conference and Exhibition on Pediatric Oncology August 11-13, 2016 Toronto, Canada (<http://pediatriconcology.conferenceseries.com/#sthash.nV1mWL5w.dpuf>) and in particular the co-charing of the workshop which focused on "Computational Horizons in Cancer: An International Symposium on Multiscale Cancer Modeling".

Summary of details for each task

Task 12.1: Dissemination activities

Subtask 12.1a: Strategic Dissemination Planning

CINECA continuously kept 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.

ICCS, as CHIC co-ordinator with EURICE support, started the organization of a major dissemination event in the European Parliament to take place in March 2017 following the suggestion made by the reviewers during the 5th project review in June 2016.

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.

Specific presence on the web site of the aforementioned Toronto conference and the embedded CHIC workshop was also created.



Fig 1: Website announcing the CHIC workshop of the conference
(<http://pediatriconcology.conferenceseries.com/2016>)

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. CINECA has also been monitoring the statistics on the newsletter reading and subscriptions, so to take actions if necessary. From the beginning of the project, the number of subscribers increased from 41 to 68 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 3rd issue of the annual CHIC

newsletter was prepared with contributions collected from the CHIC partners ICCS and BED, as well as from a member of the external advisory board. The focus of this third project newsletter was on the clinical relevance of the CHIC tools and services with specific description of some of the CHIC components. The third newsletter was published in April 5, 2016, and it is available for download from the CHIC website (http://chic-vph.eu/fileadmin/chic/downloads/CHIC_3rd_Annual_Newsletter.pdf).

Title	Type	Main leader	Reference	Date
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
Article on CHIC Online Survey on hypermodels	Web Content	EURICE	http://chic-vph.eu/highlights/details/article/chic-online-survey-on-hypermodels/	21.09.2016
Article about the last progress meeting	Web Content	EURICE	http://chic-vph.eu/highlights/details/article/chic-meets-up-for-final-spurt/	15.07.2016
6th Progress Meeting held in Bern	Web Content	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/	28.03.2016
International Conference and Exhibition on Pediatric Oncology to be organised by CHIC partners	Web Content	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/	09.03.2016

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 displayed four posters in the 7th progress meeting held in Saarbrücken, Germany. 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

Follows below a list of presentation at conferences or events occurring in the 6 months under reporting:

- Coordination and participation of ICCS and USAAR in the international conference on Pediatric Oncology and Clinical Pediatrics as well as the special CHIC workshop that took place in Toronto, Canada on 11 – 13 August 2016.
- Organization and participation of ICCS and USAAR in the workshop entitled: “Computational Horizons in Cancer: An International Symposium on Multiscale Cancer Modeling,” held at the University of Pennsylvania, Philadelphia, USA, 14 Aug. 2016.

- Participation of ICCS at the VPH (Virtual Physiological Human) 2016 conference, which took place in Amsterdam, the Netherlands on 26-28 September 2016. In the same conference the project co-ordinator presented the CHIC project as well as two other papers related to CHIC.
- UCL presented at the VPH2016 including renal physiology and pathophysiology modeling and knowledge representation in the CHIC and VPH.
- Participation with poster presentation in the Precision Medicine in Radiation Oncology: Personalizing Radiation Treatment, June 16-17, 2016, Bethesda, Maryland.
- Oral presentation to a scientific event by Daniele Tartarini (USFD): "The CHIC project for cancer clinical research"; 21.01.2016 Sheffield Scientific community (higher education; research) Sheffield Cancer Research Day. Presentation of research activities in the Chic Project.
- Prof. Tsiknakis was invited to present the CHIC project and its technical architecture at the National Conference eHealth 2016 in Athens.
- Prof. Tsiknakis has delivered an invited speech at the 1st PanHellenic Conference on Active and Healthy Aging, in which CHIC was disseminated.
- UBERN presented bio-mechanical Brain Tumour Modeling at:
 - 22nd Congress of European Society of Biomechanics (ESB), Lyon.
 - 14th International Symposium Computer Methods in Biomechanics and Biomedical Engineering (CMBBE), Tel Aviv.
 - Virtual Physiological Human Conference VPH 2016, Amsterdam.
- UBERN presented CHIC-CDR at
 - CHIC workshop at 1st International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics, Toronto.
 - CHIC-UPENN meeting at University of Pennsylvania.
- A workshop paper on the impact of dense spatial regularization for Brain Tumor Segmentation was published at the MICCAI 2016 conference. A clinical evaluation study on the estimation of extent of resection and residual tumor volume was accepted for publication in the Journal of Neurosurgery.
- Poster presentation about joint work UNITO-BED in the CHIC project during the 'D-Day 2016' in Turin – 15 September 2016, by Ilaria Stura, <http://dott-scivisa.campusnet.unito.it/avvisi/att/ctq3.allegato.pdf>.
- Interview of Ilaria Stura (UNITO) published online about the results explained in a paper on Cancer Research: <http://medicalresearch.com/author-interviews/math-algorithm-helps-predict-recurrence-of-prostate-cancer/27524/#more-27524>.
- UNITO Participation to the European Researchers' Night 2016 in Turin.
- Interview of Ilaria Stura (UNITO) about CHIC published online: http://www.unitonews.it/index.php/en/news_detail/i-progetti-di-ricerca-europei-di-unito-da-alice-rap-myhealthavatar.
- Participation to Virtual Physiological Human (VPH) conference in Amsterdam by UNITO (Caterina Guiot and Ilaria Stura).

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- Poster presentation about joint work UNITO-BED in the CHIC project during the VPH 2016 conference by Ilaria Stura.
 - UOXF, Oral presentation to a scientific event, Modelling micro-vascular transport in tumours using intra-vital imaging data, 11.07.2016, Nottingham, United Kingdom.
 - UOXF, Oral presentation to a scientific event, A computational framework for multi-scale vascular tumour growth models, 13.06.2016, Computational Life Sciences Workshop, RWTH Aachen, Germany.
 - UOXF, Oral presentation to a scientific event, Integrating multiphoton imaging, microfluidics channels and mathematical modelling to study vascular networks in tumours, 06.06.2016, Cancer Research UK (CRUK) Oxford Annual Symposium, Oxford, United Kingdom.
 - UOXF, Oral presentation to a scientific event, Integrated intravital imaging and mathematical modelling of vascular networks in tumours, 16.05.2016, Quantitative Biology in Oxford (QBIOX) Springboard Meeting, Oxford, United Kingdom.
 - UOXF, Oral presentation to a scientific event, James Grogan, Modelling blood flow and solute transport in solid tumors, Virtual Physiological Human Conference, Amsterdam, September 26-28 2016.
 - UOXF, Oral presentation to a scientific event, Helen Byrne, Modeling Cells and remodeling biological tissues, 01.08.2016, Adelaide, Australia, Invited seminar at the School of Mathematical Sciences.
 - UOXF, Oral presentation to a scientific event, Helen Byrne, The sub cellular and cellular consequences of WNT signaling in the intestinal crypt, 11.07.2016, Nottingham, United Kingdom.
 - USAAR, Oral presentation to a scientific event, Norbert Graf, Data Mining in Cancer, 29.09.2015, ECCO Congress, Vienna.
 - UPENN, Organizing Roles in Scientific Review Panels, Meetings, and Workshops
 - Member of Organizing Committee: Emerging Paradigms in Scientific Computing, Penn Institute of Computational Sciences, Philadelphia PA, 2016.
 - Member of Organizing Committee: Transatlantic Meeting in Computational Horizons in Cancer, Philadelphia PA, 2016.
 - Member of Advisory Committee, The Eighth International Conference on Bioinformatics, Biocomputational Systems and Biotechnology, BIOTECHNO 2016, 2016, Lisbon, Portugal.
 - UPENN, Invited Seminars/Lectures/Presentations
 - Princeton University, Bioengineering, 2016.
 - Department of Pharmacology, Yale University, 2016.
 - Pediatric Oncology Meeting, Toronto Canada, 2016.
 - Systems Biology Meeting, Philadelphia PA, 2016.
 - UPENN, Conference Presentations
 - Wu, W. Guo, A. Kyatyn, M. A. Lemmon, A. Ghosh, R. Radhakrishnan, Can soft signals be oncogenic, PSON (Physical Sciences in Oncology Network) Symposium, Rockville MD, 2016.

- Rammohan, M. McKenzie, N. Ramakrishnan, and R. Radhakrishnan, Cellular adhesion: evaluating the effect of receptor-ligand chemistries, distribution of receptors, and spread versus spherical geometry, Biophysical Society Meeting, Los Angeles CA, 2016.
- Stamatakis et al., Computational Horizons In Cancer (CHIC): Developing meta- and hyper-multiscale models and repositories for in silico oncology – strategies, systems and results, Pediatric conference in oncology, Toronto, Canada.
- N. Ramakrishnan, D. M. Eckmann, P. S. Ayyaswamy, V. Muzykantov, R. Radhakrishnan, Biophysically inspired model for functionalized nanocarrier targeting to live cells, ACS Fall Meeting, Philadelphia PA, 2016.
- J. Jordan, R. Radhakrishnan, In silico profiling of activating mutations in cancer, ACS Fall Meeting, Philadelphia PA, 2016.
- R. P. Bradley, N. Ramakrishnan, R. Radhakrishnan, Curvature-undulation coupling as a basis for curvature sensing and generation in bilayer membranes at molecular and colloidal scales, ACS Fall Meeting, Philadelphia PA, 2016.
- R. Radhakrishnan, H.-Y. Yu, D. M. Eckmann, P. S. Ayyaswamy, Computational models for nanoscale biofluid dynamics and colloid transport inspired by non-equilibrium thermodynamics, ACS Fall Meeting, Philadelphia PA, 2016.
- Lishchuk, Patentability Aspects of Computational Cancer Models, ICNAAM 2016, the sixth symposium on advanced computation and information in natural and applied sciences, 19-25 September 2016, Rhodes, Greece.
- Lishchuk, Cancer Models as medical support tools, 17. Herbstakademie 2016 Smart World - Smart Law? Weltweite Netze mit regionaler Regulierung 14. - 17. September 2016, Hamburg.
- Lishchuk, „Gene Patents: From personal rights to Intellectual Property Rights“, Tagung Junge Wissenschaft –Kolloquium zum Gewerblichen Rechtsschutz, Urheber- und Medienrecht“, 17-18 Juni, 2016, Köln, Germany.
- Iryna Lishchuk, Licensing Implications of the Use of Open Source Software in Research Projects. panelist: Panel on INFOCOMP / MODOPT / SPWID, Topic: Practical Experiences and Best Practice in Scientific and High-end Computing; Is the Future Data-centric and Computing-centric?, session chair: INFOCOMP I, Advanced Applications I, The Sixth International Conference on Advanced Communications and Computation, INFOCOMP 2016, May 22 - 26, 2016, Valencia, Spain: <http://www.iaria.org/conferences2016/ProgramINFOCOMP16.html>
- Lishchuk, Patient Role in Mobile Adaptable Healthcare: Awareness and Accessibility, Privacy Aspects, Panel eTELEMED/DIGITAL HEALTHY LIVING/ MATH, The Eighth International Conference on eHealth, Telemedicine, and Social Medicine eTELEMED 2016, April 24 - 28, 2016 - Venice, Italy, Archived in the free access ThinkMindTM Digital Library: <http://www.thinkmind.org/>.

SubTask 12.1.f: Scientific & Technical Papers Publications

The following journal articles have been published (or have been submitted/accepted for publication) in the reporting period:

- Eleni Kolokotroni, Dimitra Dionysiou, Christian Veith, Yoo-Jin Kim, Jörg Sabczynski, Astrid Franz, Aleksandar Grgic, Jan Palm, Rainer M. Bohle, Georgios Stamatakis, (2016) In Silico Oncology:

Quantification of the In Vivo Antitumor Efficacy of Cisplatin-Based Doublet Therapy in Non-Small Cell Lung Cancer (NSCLC) through a Multiscale Mechanistic Model. *PLoS Comput Biol* 12(9): e1005093. doi: 10.1371/journal.pcbi.1005093.

- Anca Bucur, Jasper van Leeuwen, Nikolaos Christodoulou, Kamana Sigdel, Katerina Argyri, Lefteris Koumakis, Norbert Graf and Georgios Stamatakos. Workflow-driven clinical decision support for personalized oncology. *BMC Medical Informatics and Decision Making* 2016, 16 (Suppl 2):87, doi: 10.1186/s12911-016-0314-3.
- Nikolaos A. Christodoulou, Nikolaos E. Touser, Eleni Ch. Georgiadi, Katerina D. Argyri, Fay D. Misichroni and Georgios S. Stamatakos. A Modular Repository-based Infrastructure for Simulation Model Storage and Execution Support in the Context of In Silico Oncology and In Silico Medicine. *Cancer Informatics* 2016:15 219–235 doi: 10.4137/CIn.s40189.
- S. Giatili and G. Stamatakos, “In Silico Simulation of Glioblastoma Growth and Invasion into the Human Brain Including an Explicit Modelling of the Adiabatic Boundary Condition Imposed by the Skull” accepted to be published in the *Journal of Applied Electromagnetism*, 2016.
- D. M. Freed, J. H. Park, R. Radhakrishnan, M. A. Lemmon, “Deletion mutations keep kinase inhibitors in the loop”, *Cancer Cell*, 2016, 29(4):423-425. DOI: 10.1016/j.ccell.2016.03.017.
- Stura I, Gabriele D, Guiot C, A Simple PSA-Based Computational Approach Predicts the Timing of Cancer Relapse in Prostatectomized Patients, *Cancer Res.* 2016, Sep 1;76(17):4941-7. doi: 10.1158/0008-5472.CAN-16-0460.
- Perracchione E, Stura I, RBF kernel method and its applications to clinical data, *Dolomites Research Notes on Approximation*, Sep. 2016; 9: 13-18. doi: 10.14658/pupj-drna-2016-Special_Issue-3.
- B Markelc, AJ Connor, RJ Muschel, JM Pitt-Franices, PK Maini, HM Byrne, “Predicting the influence of microvascular structure on tumour response to radiotherapy”, *IEEE Trans Biomed Eng*, Submitted, 2016.
- N. Ramakrishnan, R. W. Tourdot, D.M. Eckmann, P.S.Ayyaswamy, V.M.Muzykantov, R. Radhakrishnan, “Biophysically inspired model for nanocarrier adhesion to live cells: roles of mechanical factors and protein expression”, *Royal Society Open Science*, 3, 160260, 2016; doi: <http://dx.doi.org/10.1098/rsos.160260>.
- I. Lishchuk, M. Stauch, *Cancer Models as medical support tools*, *Tagungsband Herbstakademie* 2016, *Smart World - Smart Law? Weltweite Netze mit regionaler Regulierung*, 14. - 17. September 2016, Hamburg, OIWR, pp.885-900.
- I. Lishchuk, M. Stauch, *Multiscale Cancer Modelling in Terms of Copyright*, *International Journal On Advances in Life Sciences*, volume 8, numbers 1 and 2, 2016 // View article [lifsci_v8_n12_2016_6](http://www.thinkmind.org/index.php?view=article&articleid=lifsci_v8_n12_2016_6), Pages: 65 to 75, June 30, 2016, ISSN: 1942-2660, open access: http://www.thinkmind.org/index.php?view=article&articleid=lifsci_v8_n12_2016_6.
- Iryna Lishchuk, *Licensing Implications of the Use of Open Source Software in Research Projects*, conference proceedings: *The Sixth International Conference on Advanced Communications and Computation*, INFOCOMP 2016, May 22 - 26, 2016, Valencia, Spain, open access: ThinkMind Digital Library, ISSN: 2308-3484, ISBN: 978-1-61208-478-7, Location: Valencia, Spain, Dates: from May 22, 2016 to May 26, 2016, <http://www.thinkmind.org/index.php?view=instance&instance=INFOCOMP+2016>.

The following conference articles have been published:

- Eleni Ch. Georgiadi, Nikolaos A. Christodoulou, Christos Kyrourdis, Feng Dong, Norbert Graf, and Georgios S. Stamatakos, “Oncosimulator Models as Components of a Personal Health Record Platform can Enable and Enhance the Provision of Personalized Medical Treatment”, Virtual Physiological Human (VPH) 2016 Conference, Amsterdam, the Netherlands, 26-28 Sept. , Book of Abstracts pp. 297-300.
- Eleftherios Ouzounoglou, Eleni Kolokotroni, Martin Stanulla, and Georgios S. Stamatakos, “In Silico Oncology: Evaluating the Predictability of Acute Lymphoblastic Leukemia Patients’ Response to Treatment Utilizing a Multiscale Oncosimulator Model in Conjunction with Machine Learning Methods”, Virtual Physiological Human (VPH) 2016 Conference, Amsterdam, the Netherlands, 26-28 September 2016, Book of Abstracts pp. 166-169.
- G. Stamatakos, E. Kolokotroni, D. Abler, E. Georgiadi, D. Dionysiou, P. Buechler, M. Antonopoulos, L. Solie, N. Tousert, S. Bna, D. Testi, S. Gool, Rainer Bohle and N.Graf on behalf of the CHIC consortium, “Important Aspects of the Large Scale Integrating EU-US Project CHIC on Advancing In Silico Oncology”, Virtual Physiological Human (VPH) 2016 Conference, Amsterdam, the Netherlands, 26-28 Sept. 2016, Book of Abstracts pp. 319-322.
- G. Stamatakos, “The Oncosimulator - Combining Clinically Driven and Clinically Oriented Multiscale Cancer Modelling with Information Technology in the In Silico Oncology Context,” Invited and accepted to be presented in the International Conference and Exhibition on Pediatric Oncology, August 11-13, 2016 Toronto, Ontario, Canada, <http://pediatriconcology.conferenceseries.com/>.
- G. Stamatakos, D. Dionysiou, R. Bohle, S. Gool, L. Solie, F. Dong, N. McFarlane, M. Viceconti, D. Tartarini, K. Marias, V. Sakkalis, N. Forgo, I. Lishchuk, R. Radhakrishnan, A. Ghosh, H. Byrne, J. Grogan, C. Guiot, I. Stura, P. Buechler, M. Reyes, E. Neri, A. Bucur, B. de Bono, S. Alexander, G. Erbacci, D. Testi, M. Tsiknakis, E. Kolokotroni, E. Georgiadi, N. Tousert, S. De Vleeshouwer, D. Walker, S. Sfakianakis, I. Karatzanis, S. Bnà and N. Graf on behalf of the CHIC consortium, “Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology – Strategies, Systems and Results,” Invited and accepted to be presented in the Inter-national Conference and Exhibition on Pediatric Oncology, August 11-13, 2016 Toronto, Ontario, Canada <http://pediatriconcology.conferenceseries.com/>.
- N. Graf and G. Stamatakos for the CHIC consortium, “A multiscale hypermodel to predict the nephroblastoma response to preoperative chemo-therapy,” accepted to be presented in the 9th International Renal Tumour Biology Conference, Toronto, Ontario, Canada April 2-3, 2016. <http://www.cvent.com/events/9th-international-conference-on-pediatric-renal-tumour-biology/event-summary-448a7f212a9a44488984d5239667e75a.aspx>.
- Molecular and subcellular models in insilico oncology- computational horizons in cancer systems biology and multiscale cancer modelling, A. Ghosh, R. Radhakrishnan, Proceedings of the International Workshop on Pediatric Oncology, Toronto, Canada, 2016.
- Computational horizons in cancer (CHIC): developing meta- and hyper-multiscale models and repositories for in silico oncology – strategies, systems and results, G. Stamatakos, D. Dionysiou, R. Bohle, S. Gool, L. Solie, F. Dong, N. McFarlane, M. Viceconti, D. Tartarini, K. Marias, V. Sakkalis, N. Forgo, I. Lishchuk, R. Radhakrishnan, A. Ghosh, H. Byrne, J. Grogan, C. Guiot, I. Stura, P. Buechler, M. Reyes, E. Neri, A. Bucur, B. de Bono, S. Alexander, G. Erbacci, D. Testi, M. Tsiknakis, E. Kolokotroni, E. Georgiadi, N. Tousert, Joost Dejaegher, S. De Vleeschouwer, D. Walker, S. Sfakianakis, I. Karatzanis, S. Bnà and N. Graf , Proceedings of the International Workshop on Pediatric Oncology, Toronto, Canada, 2016, accepted.

- Abler Daniel, "Evaluation of a mechanically-coupled reaction-diffusion model for macroscopic brain tumour growth", Paper in Proceedings of a Conference/Workshop, CMBBE 2016, 20.09.2016.
- D. Abler, P. Büchler, "Mechanically coupled Reaction-Diffusion Model of Macroscopic Brain Tumour Growth", Paper in Proceedings of a Conference/Workshop, ESB 2016, 10-13 July 2016.

SubTask 12.1.g: Interfacing with other projects

Extensive interactions with the MyHealthAvatar and the Avicenna projects continued till their final reviews and beyond.

Task 12.2: Exploitation and IPR issues

ICCS continued the discussions among all CHIC partners, regarding the multi-directional exploitation and sustainability of the expected project outcomes. These include 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.

ICCS has contributed in the preparation of the deliverable "D4.3.2: Development of the data protection and copyright framework for CHIC second iteration".

Discussion with STaRC continued about sustainability issues.

Further internal discussions on possible exploitation paths have been discussed at the general meeting held in Saarbrücken in September 2016 and actions will follow up in the last six months of the project.

Task 12.3: Training activities

Scientific co-organization of the entire international conference on Pediatric Oncology and Clinical Pediatrics as well as the special CHIC workshop that took place in Toronto, Canada on 11 – 13 August 2016. An official report of the Toronto events is available at: http://www.conferenceseries.com/Past_Reports/pediatric-oncology-2016-past.

Scientific co-organization and co-chairing of the workshop entitled: "Computational Horizons in Cancer: An International Symposium on Multiscale Cancer Modeling," held at the University of Pennsylvania, Philadelphia, USA, 14 Aug. 2016.

Contribution of ICCS to the development of the questionnaires used for the training of clinicians in clinical conferences where the CHIC project was presented.

ICCS has made a presentation for the CHIC project and in particular the work done in WP8 at the 15th International Summer School on Biocomplexity, Biodesign and Bioinnova: from Gene to System, which was held from June 24 - June 30, 2016 in Seferihisar - Izmir, Turkey (<http://2016.biocomplexitysummerschool.org/>).

Contact to clinical partners outside of the CHIC consortium continued to recruit patients for testing and evaluating CHIC tools. Partners of CHIC did participate at the International Conference and Exhibition on Pediatric Oncology August 11-13, 2016 Toronto, Canada. More can be found at: <http://pediatriconcology.conferenceseries.com/#sthash.nV1mWL5w.dpuf>. Pediatric Oncology-2016 did focus on "Benchmark practices and accelerating computational approaches for Pediatric Oncology". This three days conference did cover the latest trends and challenges in Pediatric

Oncology and as it included computational approaches for Pediatric Oncology it was an ideal platform for running a workshop at this event. A lot of interaction with the organizers of this Conference took place. CHIC was a co-organizer of the conference and further promoted. At the SIOP congress in Dublin acceptance of hypermodels were intensively discussed. Results of both conferences are presented in D2.4.

TEI-C has prepared a presentation and demonstrator at the BIG DATA conference organised by the alumni of the University of Crete in September 2016 with presentation and evaluation of CRAF and the relevant infrastructure.

UBERN: Co-organization of the MICCAI BRATS Challenge 2016. The challenge was part of the BrainLes (Brain Lesion) workshop, which was organized for the second time. It realized a comparative evaluation of recently proposed methods for brain tumor segmentation developed by different teams from academia as well as industry.

Summary of significant results

Considerable effort in dissemination has taken place to present the most recent developments of the CHIC project, which is confirmed by the high number of dissemination activities including conferences presentations and peer-reviewed papers.

Main event was the scientific co-organization and co-chairing of the workshop entitled: "Computational Horizons in Cancer: An International Symposium on Multiscale Cancer Modeling," held at the University of Pennsylvania, Philadelphia, USA, 14 Aug. 2016.

Decision and preparations for the organization of a major dissemination event in the European Parliament to take place in March 2017 is ongoing.

The discussion about sustainability and maintenance of the CHIC project continued. Contacts to people outside the consortium continued.

Summary on actions taken to meet the recommendations from the 5th CHIC review

The reviewers have recommended to the consortium to consider the organisation of a larger dissemination event in order to spread the project results to a broader audience of stakeholders in order to insure higher visibility and guarantee sustainability of those results after the end of the project. The coordinator together with EURICE is currently taking care of the organization of such an event.

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 4 (M37-M48)	Actual PM Period 4 (M37-M42)
1-ICCS	8.19	1.39	1.46
2-Eurice	12.00	2.00	0.60
3-USAAR	3.00	1.00	0.50
5-BED	6.00	2.00	0.00
6-USFD	7.00	2.51	1.98
7-FORTH	6.00	2.00	2.69
8-LUH	6.00	2.50	3.65
9-UPENN	6.50	1.50	0.53
10-UOXF	6.00	2.00	0.00
11-UNITO	6.00	2.00	0.52
12-UBERN	5.00	2.00	1.15
13-Custodix	6.00	2.00	1.00
14-Philips	6.00	3.00	4.60
15-UCL	2.00	0.50	0.00
16-CINECA	6.00	2.00	1.57
17-TEI-C	1.00	0.50	0.25
Total	92.69	28.90	20.50

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. New activities are highlighted in light blue.

Workshops and conferences

Title	Type	Main leader/ participants	Event	Venue	Date
In silico profiling of activating mutations in cancer	Oral presentation to a scientific event	UPENN	American Chemical Society	Philadelphia, USA	22.08.2016
CHIC-CDR -- a repository for managing multi-modality clinical data and its application to in-silico oncology	Oral presentation to a scientific event	UBERN	International Conference and Exhibition on Paediatric Oncology	Toronto, Canada	11.08.2016
Mechanically Coupled Reaction-Diffusion Model of Macroscopic Brain Tumor Growth	Oral presentation to a scientific event	UBERN	submitted to ESB 2016 conference	Lyon, France	10.07.2016
Predictive Multiscale Models in Oncology	Oral presentation to a scientific event	UPENN	Yale University, Cancer Biology Institute, Pharmacology	Conneticut, USA	02.06.2016
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,	18.02.2016

				Germany	
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 Stamatakos (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 Fritsche 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 Health Data for Research	Conference	CUSTODIX	23rd EICAR ANNUAL CONFERENCE Trust and Transparency in IT Security	Frankfurt, Germany	18.11.2014

Providing a Network of Trust in Processing Health Data for Research	Conference	LUH	23 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 krebskranken Kindern“	Freiburg, Germany	26.09.2014
The Importance of Data Sharing and Data Protection'	Conference	LUH	SIOPE-ENCCA conference 2014	Brussels, Belgium	18.09.2014
Multiscale modelling of cancer (workshop session)	Conference	ICCS	VPH2014	Trondheim, Norway	11.09.2014
In silico Neuro-Oncology: Simulating glioma growth and inhomogeneous invasion under explicitly treated Neumann boundary conditions	Conference	ICCS	VPH2014	Trondheim, Norway	11.09.2014
A Generalized Model of Tumor Growth and Response to Treatment using the PUN approach (poster)	Conference	UNITO	VPH2014	Trondheim, Norway	11.09.2014
The VPH Hypermodelling Framework for cancer research	Conference	USFD, CINECA	VPH2014	Trondheim, Norway	11.09.2014

A Two-Clones Model of Tumor Growth and its Response to Treatment	Conference	UNITO	MPDS14 Conference	Turin, Italy	29.08.2014
Nomination to Best Msc thesis work – Automatic Multimodal Brain Tumor Segmentation	Conference	UBERN	SSBE 2014 Annual Meeting	Zurich, Switzerland	27.- 28.08.2014
Cancer cell patterns emerging from agent based movement (poster presentation)	Summer School	FORTH	Spatiotemporal modelling and simulation of biology systems: Biology in Cyber Space	Dresden, Germany	02.- 09.08.2014
Patient-specific Semi-supervised Learning for Postoperative Brain Tumor Segmentation	Summer School	UBERN	Medical Imaging Summer School (MISS) 2014	Favignana, Italy	28.07. – 01.08. 2014
What is the role of in silico modelling and simulation to help translate pre-clinical data into the design of human clinical trials	Invited Lectures	UPENN	Tumor Models Summit, Boston 2014	Boston, MA, USA	22.- 24.07.2014
Invited lecture: What is the role of in silico modelling and simulation to help translate pre-clinical data into the design of human clinical trials	Conference	UPENN	Tumor Models Summit	Boston, MA, USA	21. - 23.07.2014
In Silico Oncology: A generic platform for clinically driven and oriented cancer hypermodeling. The Hypermodel Based Oncosimulator	Conference	ICCS	7th World Congress of Biomechanics	Boston, MA, USA	6.- 11.07.2014
Computational Challenges in Multiscale Modelling	Conference (Podium discussion)	USFD	7th World Congress of Biomechanics	Boston, MA, USA	6.- 11.07.2014
Immunotherapy for relapsed malignant glioma in children	Conference	KU Leuven	Presentation by Prof. Van Gool at the ISPNO conference at Singapore	Singapor	28.06.2014
ApiNATOMY: The Generation of Interactive CircuitBoard Views of Complex Physiology Knowledge	Conference	UCL	4th International Conference on Complex Systems and Applications (ICCSA 2014)	Le Havre, France	23.- 26.06.2014

Data modeling and simulations. Do they pave the way to personalized medicine?	Workshop	USAAR	SIB/Systems X.ch Summer School	Kandersteg, Switzerland	22.- 27.06.2014
Piedmont multicenter retrospective study on operated prostate cancer: first report	Congress/conference	UNITO	24th Annual Meeting of the Italian Society of Uro-Oncology (SIUro)	Bologna, Italy	22.- 24.06.2014
Immunotherapy for malignant glioma: preclinical research and clinical experience	Conference	KU Leuven	Presentation by Prof. Van Gool at the "Internal lab meeting seeking for collaboration on oncolytic virus research" organised by Prof. Alan Melcher, Medical Oncology, at Leeds, UK	Leeds, UK	16.06.2014
Data collection for models validation: application to prostate cancer - clinical aspects	Conference	UNITO	IEEE-EMBS International Conferences on Biomedical and Health Informatics (BHI)	Valencia, Spain	1.- 4.06.2014
Immunotherapy for malignant glioma: preclinical research and clinical research	Conference	KU Leuven	Presentation by Prof. Van Gool at the 30th National Congress of Neurosurgery, organised by the Portuguese Neurosurgical Society by Dr. Miguel Casimiro, at Lisbon, Portugal	Lisbon, Portugal	30.05.2014
IT Challenges for innovative Clinical Trials	Workshop	USAAR	IT workshop on tools/services for clinical trials	Düsseldorf, Germany	26.- 27.05.2014
Participation in Training School	Workshop	UNITO	ESTRO School of Radiotherapy and Oncology: Basic Clinical Radiobiology	Istanbul, Turkey	25.- 29.05.2014
Data Protection reform	Invited Lecture	LUH	Datenschutzforum	Berlin, Germany	15.05.2014
Computational medicine: Current and Future prospects	Conference	FORTH	eHealth Forum 2014	Athens, Greece	12.- 14.05.2014
Participation in training event	Workshop	CINECA, USFD	VPHF development training	Bologna, Italy	11.- 16.05.2014
Immunotherapy for malignant glioma:	Conference	KU Leuven	Presentation by Prof. Van Gool at the conference "Oncobiology - genes and	Lisbon,	09.05.2014

preclinical research and clinical research			tumoral microenvironment" at the Medical Sciences Faculty, Nova University, organised by Prof. José Luis Passos Coelho and Prof. Doutora Ana Felix, at Lisbon, Portugal	Portugal	
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
Immunotherapie 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
Homepage Announcement for the CHIC Online Survey	Online Article	EURICE	http://chic-vph.eu/highlights/details/article/chic-online-survey-on-hypermodels/	21.09.2016
Homepage Article for the 7 th Progress Meeting	Online Article	EURICE	http://chic-vph.eu/highlights/details/article/chic-meets-up-for-final-spurt/	15.07.2016
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 - BraTumla press release	Press release	UBERN	http://www.srf.ch/news/regional/bern-freiburg-wallis/berner-software-analysiert-hirntumore-blitzschnell	12.11.2014
Press Release - BraTumla - 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
BraTumla 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	2014

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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
Subcellular membrane mechanotyping using local estimates of cell membrane excess area	N. Ramakrishnan		Biophysical Journal	Peer-reviewed publication	12.10.2016	David Eckmann, Pirtново Ayyaswamy, Valerie Weaver and	Under review

						Ravi Radhakrishnan	
Lipid membrane shape evolution and the actin cytoskeleton	D. R. Slochower	UPENN	Handbook of lipid membranes, molecular and materials aspects	Peer-reviewed publication	01.10.2016	Y.-H. Wang, R. Radhakrishnan, P. A. Janmey	Under review
Evaluation of a mechanically-coupled reaction-diffusion model for macroscopic brain tumour growth	Daniel Abler	UBERN	CMBBE 2016	Paper in Proceedings of a Conference/Workshop	20.09.2016	Philippe Büchler	
The Oncosimulator - Combining Clinically Driven and Clinically Oriented Multiscale Cancer Modeling with Information Technology in the In Silico Oncology Context	Georgios Stamatakis	ICCS	International Conference and Exhibition on Pediatric Oncology, Toronto, Ontario, Canada.	Paper in Proceedings of a Conference/Workshop	11.08.2016		Published
Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology – Strategies, Systems and Results	Georgios Stamatakis	ICCS, USAAR, KU Leuven, BED, USFD, FORTH, LUH, UPENN, UOXF, UNITO, UBERN, CUSTODIX, PHILIPS, UCL, CINECA, TEI-C	International Conference and Exhibition on Pediatric Oncology, Toronto, Ontario, Canada.	Paper in Proceedings of a Conference/Workshop	11.08.2016	Dimitra Dionysiou, Rainer Bohle, Stefaan van Gool, Lien Solie, Feng Dong, Nigel Mcfarlane, Marco Viceconti, Daniele Tartarini, Kostas Marias, Vangelis Sakkalis, Nikolaus	Published

						Forgo, Iryna Lishchuk, Ravi Radhakrishnan , Alok Ghosh, Helen Byrne, James Grogan, Cat	
CHIC-CDR -- a repository for managing multi-modality clinical data and its application to in- silico oncology	Daniel Abler	UBERN	International Conference and Exhibition on Pediatric Oncology, Toronto, Ontario, Canada.	Paper in Proceedings of a Conference/W orkshop	11.08.2016	M. Kistler, R. Niklaus, P. Büchler	Published
Mechanically coupled Reaction- Diffusion Model of Macroscopic Brain Tumour Growth	Daniel Abler	UBERN	ESB 2016 Conference	Paper in Proceedings of a Conference/W orkshop	13.07.2016	Philippe Büchler	Published
Biophysically inspired model for nanocarrier adhesion to live cells: roles of mechanical factors and protein expression	N. Ramakrishnan	UPENN	Royal Society Open Science 29; 3 (6), 2016 doi: 10.1098/rsos.160260	Peer-reviewed publication	09.06.2016	R. W. Tourdot, D.M. Eckmann, P.S.Ayyaswam y, V.M.Muzykant ov,R. Radhakrishnan	Published
Deletion mutations keep kinase inhibitors in the loop	Dan Freed	UPENN	Cancer Cell 11; 29 (4), 2016, 423-425, Cell Press. doi: 10.1016/j.ccell.2016.03.017	Peer-reviewed publication	30.05.2016	J. H. Park, R. Radhakrishnan , M. A. Lemmon	Published
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	Urspeter Knecht, Tina Loosli, Stefan Bauer, Johannes Slotboom, Roland Wiest, Mauricio Reyes	Published
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,	Published

						Gregorio Moro, Giuseppe Girelli, Pietro Gabriele, and the EUREKA-2 consortium	
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:	Ilaria Stura	UNITO	Mathematical Biosciences 271, 19-28	Peer-reviewed	30.10.2015	Ezio Venturino,	Published

Spontaneous growth and response to treatment.			DOI:10.1016/j.mbs.2015.10.014	publication		Caterina Guiot	
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, Mauricio Reyes	published
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	Domenico Gabriele	UNITO	Panminerva Medica 2016 June;58(2):109-14	Peer-reviewed publication	24.07.2015	Monica Garibaldi, Giuseppe	Published

radiation therapy for prostate cancer						Girelli, Stefano Taraglio, Eleonora Duregon, Pietro Gabriele, Caterina Guiot, Enrico Bollito, 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,	Published

						Eleftherios Kontopodis, Sofie Van Cauter, Vangelis Sakkalis, and Kostas Marias	
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;	Published

						Giacobbe, Alessandro; Guiot, Caterina	
The Standardized Histogram Shift of T2 Magnetic Resonance Image (MRI) Signal Intensities of Nephroblastoma Does Not Predict Histopathological Diagnostic Information	Sabine Müller	USAAR, FORTH	Supplementary Issue: Computer Simulation, Visualization, and Image Processing of Cancer Data and Processes; Cancer Informatics 2015; 4(S4) 1–5, Libertas Academica, DOI: 10.4137/CIN.S19340	Peer-reviewed publication	12.05.2015	Ruslan David, Kostas Marias, Norbert Graf	Published
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,	Published

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

						FOSSA B, KRENGLI M, TESSA M, BONA C, FERRAZZA P, BALCET V, RUO REDDA MG, MORO G & GABRIELE P	
Do radiotherapy techniques impact the outcome?	E. Garibaldi	UNITO	Minerva Urol Nefrol 2015; 67 (Suppl. 1 to No. 1): 63-75	Peer-reviewed publication	2015	GARIBALDI E, DELMASTRO E & GABRIELE P	Published
Modeling prostate cancer within CHIC	Ilaria Stura	UNITO	Minerva Urol Nefrol 2015; 67 (Suppl. 1 to No. 1): 97-98	Peer-reviewed publication	2015	STURA I, GABRIELE D & GUIOT C	Published
A multicenter retrospective study on irradiated prostate cancer: preliminary report	Domenico Gabriele	UNITO	Abstract in Anticancer research 2014 : 34	Peer-reviewed publication	2014	Gabriele P, Ruo Redda MG, Garibaldi M, Cattari G, Garibaldi E, Guiot C	Published
Piedmont multi center retrospective study on operated prostate cancer: first report	Domenico Gabriele	UNITO	Abstract in Anticancer research 2014 : 34	Peer-reviewed publication	2014	Gontero P, Terrone C, Porpoglia F, Muto G, Guiot C	Published
Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology - a Brief Technical Outline of the Project.	G.Stamatakis	BED, CINECA, CUSTODIX, FORTH, ICCS, KU Leuven,	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.	Published

		LUH, PHILIPS, TEI-C, UBERN, UCL, UNITO, UOXF, UPENN, USAAR, USFD				Viceconti, K. Marias, V. Sakkalis, N. Forgo, R. Radhakrishnan , H. Byrne, C. Guiot, P. Buechler, E. Neri, A. Bucur, B. de Bono, D. Testi, M. Tsiknakis	
A Model of Tumor Growth Coupling a Cellular Biomodel with Biomechanical Simulations	Farhad Rikhtegar	ICCS- UBERN	In Silico Oncology and Cancer Investigation (IARWISOCI), 2014 6th International Advanced Research Workshop on	Conference proceedings	04.11.2014	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	Peer-reviewed publication	10.03.2015	Wouter Dhaeze	Published

			Cancer Investigation, DOI: 10.1109/IARWISOCI.2014.7034643				
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	Ravi	UPENN	Nucleic Acids Research 42 (15)	Peer-reviewed	26.07.2014	Gajula KS,	Published

reveals functional determinants for DNA targeting by Activation-Induced Cytidine	Radhakrishnan			publication		Huwe PJ, Mo CY, Crawford DJ, Stiver JT, Kohli RM	(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. DOI: 10.1109/IARWISOCI.2014.7034632	Conference proceedings	2014	Radhakrishnan R.	In press
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,	Published

						Rueping S, Giatili S, Donofrio A, Sfakianakis S, Marias K, Desmedt C, Tsiknakis M, Graf N.	
Dendritic cell vaccination for glioblastoma multiforme: review with focus on predictive factors for treatment response	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	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	Published

helps rationalize the effects of clinically identified HER4 somatic mutations on the cell phenotype						Radhakrishnan	
Functional tissue units and their primary tissue motifs in multi-scale physiology	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 Hunter	Published
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. Deliverables of the 1st -3rd reporting period are highlighted in light grey. Deliverables yet to be submitted are not highlighted.

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
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		Yes	27.10.2016	Delivery date was postponed from M42 to M43
D2.5	Clinical relevance of the CHIC project	2	3-USAAR	R	PU	31.12.2015		Yes	31.12.2015	
D3.1	Report on Scenarios and data from defined patients	3	4-KULEUVEN	R	PU	31.03.2016		Yes	09.05.2016	
D3.2	Report on Scenarios and data from other	3	11-UNITO	R	PU	31.03.2016		Yes	31.03.2016	

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
	cancer types for usage by the CHIC infrastructure									
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	
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		Yes	30.09.2016	
D4.4	Whitepaper Recommendations for an amended European legal	4	8-LUH	R	PU	31.03.2016		Yes	31.03.2016	

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
	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		Yes	04.08.2016	Delivery date was postponed from M38 to M40
D5.1.3	The final CHIC technical architecture (including the security tools and cloud infrastructure)	5	7-FORTH	P	RE	30.11.2016		No		
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	
D5.2.2	Final version of security tools and guidelines	5	13-CUSTODIX	P	CO	30.09.2016		Yes	30.09.2016	
D5.3	Techniques to build the cloud infrastructure available to the community	5	5-BED (7-FORTH)	R	PU	31.03.2015		Yes	31.03.2015	
D6.1	Cancer hypomodelling and hypermodelling strategies and initial component models	6	1-ICCS	R	CO	30.09.2013		Yes	22.10.2013	
D6.2	CHIC cancer	6	1-ICCS	R	CO	30.11.2014		Yes	05.01.2015	

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
	component models: initial tested versions									
D6.3	Initial standardized cancer hypermodels	6	1-ICCS	R	CO	31.07.2016		Yes	31.07.2016	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		Yes	30.09.2016	
D8.1	Design of the CHIC repositories	8	1-ICCS	R	CO	31.07.2014		Yes	20.11.2014	
D8.2	Prototype implementation of the CHIC repositories	8	12-UBERN	O	CO	31.03.2015		Yes	04.05.2015	
D8.3	Implementation of the interfaces of the CHIC repositories	8	15-UCL	R	PU	30.09.2015		Yes	28.09.2015	
D8.4	Report on the final system	8	1-ICCS	R	PU	30.09.2016		Yes	30.09.2016	
D9.1	User requirements for	9	5-BED	R	PU	30.09.2013		Yes	01.10.2013	

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 visualization toolkit and image analysis toolkits									
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		
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	
D10.4	The CHIC Hypermodelling Editor and orchestration environment	10	7-FORTH	P	RE	30.11.2016		No		
D10.5	The CHIC Clinical Research integrated platform	10	7-FORTH	P	RE	31.01.2017		No		

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date	delivery from Annex I	Delivered Yes/No	Actual / Forecast delivery date	Comments
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		Yes	15.04.2016	
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 Foreground	12	16-CINECA	R	CO	31.03.2016		Yes	31.03.2016	
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

The deliverables due in this reporting period are highlighted in light blue. Deliverables of the 1st -3rd reporting period are highlighted in light grey. Deliverables yet to be submitted are not highlighted.

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 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		
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	

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
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		
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 WP7	6	1-ICCS	31.07.2016	No		D6.3, D7.4
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

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
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 environment	10	7 FORTH	31.01.2017	No		
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

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
							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	Yes	11.-13.08.2016	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 M37-M42:

The **5th CHIC review meeting** took place on June 1st, 2016. 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. The interim review had been organized to assess the project's progress and the adherence to suggestions made at previous reviews.

At the review meeting itself, the coordinator, Research Professor Dr. Georgios Stamatakos (ICCS) gave a status update and summary including the actions taken regarding the main issues raised in the previous review. The CHIC platform supported hypermodelling demonstrator (through the nephroblastoma paradigm) as well as the lung cancer demonstrator has been presented by the consortium. Horizontal issues like dissemination and exploitation activities as well as Project Management and Future Planning have been presented and discussed. The overall assessment of the review was positive and it was confirmed that the project is in good progress, has achieved most of its objectives and technical goals for the period with relatively minor deviations. Some recommendations concerning the future work have been given: A final review is recommended to be scheduled over two days, so as to have enough time for all demonstrations and finalizing discussions, to be held at Iraklion, site of the Integration Coordinator (FORTH)). An interim review has been recommended for Nov/Dec 2016 to assess progress of the work by then and to ascertain the successful completion of the different tasks and deliverables. Another recommendation from the reviewers is that the consortium should consider the organisation of a larger dissemination event in order to spread the project results to a broader audience of stakeholders in order to insure higher visibility and guarantee sustainability of those results after the end of the project.

A **7th Progress Meeting** was held on August 31st to September 2nd at USAAR in Saarbrücken, Germany. 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 5th review meeting at the European Commission. A special focus was set on how to streamline efforts in all WPs to ensure successful, sustainable and high-impact project outcomes. Prof. Metin Akay (University of Houston, USA) and Prof. Roger Dale (Imperial College London, UK), both members of the CHIC External Advisory Board, attended the meeting with guest lectures and provided valuable input and advice to the CHIC partners. In a dedicated **technical meeting** on the first day of the progress meeting, input from the technical partners as well as from the modelling partners were collected to prepare an action plan for the remaining work in the project.

The CHIC consortium has prepared and submitted a **Project Amendment** of the CHIC Grant Agreement. This amended version of Annex 1 reflects 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. Because of the addition or prolongation of several tasks, some of the CHIC partners have changes in their original budgets. Eurice was coordinating the amendment process. A complete amended draft version of Annex I has already been prepared end of December 2015 and the official amendment procedure was then launched at the beginning of 2016. Due to several rounds of feedback from the EC and also some technical problems with the NEF system, the final amendment could only be submitted on June 23, 2016.

The **3rd Progress Report** (covering M25-36) was due at Mai 31st, 2016. Due to the fact that the above mentioned Amendment was still under preparation during this time, it was technically not possible to submit the report in the system. Thus, the report has been finalized and submitted with minor delays.

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.

Summary of actions taken to meet the recommendations from the 5th CHIC review

- Planning of an interim review (deliverables based) for November 2016
- Organisation of a major dissemination event towards the end of the project

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

No serious problems have occurred in project management during M37-42.

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 M37-42

Title	Date	Venue	Local organizer
CHIC Technical Telco	29 September 2016	Skype	ICCS
CHIC Clinical, WP6 and Technical Telco	19 September 2016	Skype	ICCS

CHIC Technical Telco	15 September 2016	Skype	ICCS
7 th Progress Meeting	31 August – 2 September 2016	Saarbrücken	USAAR
CHIC Technical Telco	28 August 2016	Skype	ICCS
CHIC Technical Telco	04 August 2016	Skype	ICCS
CHIC Clinical, WP6 and Technical Telco	28 July 2016	Skype	ICCS
CHIC Clinical, WP6 and Technical Telco	15 July 2016	Skype	ICCS
CHIC Technical Telco	14 July 2016	Skype	ICCS
CHIC Technical Telco	30 June 2016	Skype	ICCS
CHIC Clinical, WP6 and Technical Telco	29 June 2016	Skype	ICCS
CHIC Technical Telco	17 June 2016	Skype	ICCS
CHIC Clinical, WP6 and Technical Telco	16 June 2016	Skype	ICCS
5 th Review Meeting	1 June 2016	Brussels	EC
CHIC Clinical, WP6 and Technical Telco	27 May 2016	Skype	ICCS
CHIC Technical Telco	26 May 2016	Skype	ICCS
CHIC Technical Telco	12 May 2016	Skype	ICCS
CHIC Clinical, WP6 and Technical Telco	11 May 2016	Skype	ICCS
CHIC Clinical, WP6 and Technical Telco	22 April 2016	Skype	ICCS
CHIC Technical Telco	21 April 2016	Skype	ICCS
CHIC Clinical, WP6 and Technical Telco	07 April 2016	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 changes which had to be implemented in the CHIC Description of Work, partners also had to adjust their PMs. 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

n/a

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 4 (M37-48)	Actual PM Period 4 (M37-M42)
1-ICCS	8.93	2.78	1.45
2-Eurice	38.00	9.50	9.40

6-USFD	7.40	2.36	0.41
7-FORTH	2.03	0.50	0.21
10-UOXF	2.00	0.50	0.51
16-CINECA	1.00	0.20	0.25
Total	59.36	15.84	12.23

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		ACTUAL COSTS (EUR)				
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)					Percentage spent	Remaining Budget (EUR)
			Period 1	Period 2	Period 3	Period 4	Total		
			M1-M12	M13-M24	M25-M36	M37-M42			
ICCS	Total Person-month	130,93	30,27	37,22	31,49	21,80	120,78	76%	10,15
	Personnel	636.000,00	117.446,00	144.082,00	141.248,00	115.953,27	518.729,27	63%	117.270,73
	Other direct costs	199.313,00	22.114,00	27.490,00	32.698,00	32.428,41	114.730,41	41%	84.582,59
	Subcontracting	23.600,00	0,00	2.896,00	3.266,00	0,00	6.162,00	26%	17.438,00
	Adjustments	0,00	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	89.029,01	380.072,01	58%	121.114,99
	Total Costs	1.360.100,00	223.294,00	277.410,00	281.579,00	237.410,69	1.019.693,69	58%	340.406,31
Eurice	Total Person-month	50,00	12,88	11,40	16,28	10,00	50,56	81%	-0,56
	Personnel	324.500,00	65.313,00	58.709,00	95.438,00	61.000,00	280.460,00	68%	44.040,00
	Other direct costs	34.173,00	5.314,00	1.892,00	3.491,00	1.899,04	12.596,04	31%	21.576,96
	Subcontracting	6.000,00	0,00	0,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	1.938,00	-4.979,00	0,00	-3.041,00		3.041,00
	Indirect costs	275.825,00	39.978,00	37.057,00	38.328,00	16.500,00	131.863,00	42%	143.962,00
	Total Costs	640.498,00	110.605,00	99.596,00	132.278,00	79.399,04	421.878,04	53%	218.619,96
USAAR	Total Person-month	135,00	11,29	44,10	44,28	26,00	125,67	74%	9,33
	Personnel	725.498,00	64.750,00	230.749,00	230.038,00	146.000,00	671.537,00	72%	53.961,00
	Other direct costs	318.431,00	18.692,00	57.705,00	65.372,00	38.800,00	180.569,00	45%	137.862,00
	Subcontracting	5.682,00	0,00	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		0,00
	Indirect costs	626.357,00	50.065,00	173.071,00	177.245,00	110.880,00	511.261,00	64%	115.096,00
	Total Costs	1.675.968,00	133.507,00	461.525,00	472.655,00	295.680,00	1.363.367,00	64%	312.601,00
KULeuven	Total Person-month	68,00	8,50	20,00	22,00	8,00	58,50	74%	9,50
	Personnel	340.000,00	41.421,00	98.601,00	108.743,00	41.750,88	290.515,88	73%	49.484,12
	Other direct costs	161.250,00	9.090,00	6.486,00	13.868,00	21.940,07	51.384,07	18%	109.865,93
	Subcontracting	2.000,00	0,00	0,00	0,00	0,00	0,00	0%	2.000,00
	Adjustments	0,00	0,00	7.724,00	11.417,00	189,68	19.330,68		-19.330,68
	Indirect costs	300.750,00	30.306,00	63.052,00	73.566,00	38.214,57	205.138,57	56%	95.611,43
	Total Costs	804.000,00	80.817,00	175.863,00	207.594,00	102.095,20	566.369,20	58%	237.630,80
BED	Total Person-month	88,00	14,00	34,80	23,27	11,00	83,07	82%	4,93
	Personnel	484.000,00	52.323,00	153.075,00	110.738,00	46.576,00	362.712,00	65%	121.288,00
	Other direct costs	49.000,00	6.988,00	11.504,00	6.598,00	30.585,00	55.675,00	51%	-6.675,00
	Subcontracting	5.000,00	0,00	0,00	0,00	0,00	0,00	0%	5.000,00
	Adjustments	0,00	0,00	0,00	-15.602,00	0,00	-15.602,00		15.602,00
	Indirect costs	319.800,00	35.586,00	98.747,00	70.401,00	81.560,00	286.294,00	64%	33.506,00
	Total Costs	857.800,00	94.897,00	263.326,00	172.135,00	158.721,00	689.079,00	62%	168.721,00

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	Period 4	Total		
			M1-M12	M13-M24	M25-M36	M37-M42	Total	Total/ Budget	
USFD	Total Person-month	154,40	32,81	38,43	43,87	29,47	144,58	46%	9,82
	Personnel	679.296,00	115.475,00	164.575,00	199.449,00	105.218,24	584.717,24	71%	94.578,76
	Other direct costs	78.001,00	12.986,00	4.574,00	10.655,00	5.695,89	33.910,89	36%	44.090,11
	Subcontracting	4.000,00	0,00	0,00	0,00	3.092,15	3.092,15	0%	907,85
	Adjustments	0,00	0,00	0,00	34.801,00	0,00	34.801,00		-34.801,00
	Indirect costs	454.378,00	77.076,00	101.488,00	124.616,00	66.548,48	369.728,48	67%	84.649,52
	Total Costs	1.215.675,00	205.537,00	270.637,00	369.521,00	180.554,76	1.026.249,76	70%	189.425,24
FORTH	Total Person-month	178,00	60,79	47,62	41,62	27,76	177,79	84%	0,21
	Personnel	456.660,00	105.586,00	98.907,00	118.253,00	75.680,00	398.426,00	71%	58.234,00
	Other direct costs	116.504,00	17.911,00	30.938,00	37.785,00	17.819,30	104.453,30	74%	12.050,70
	Subcontracting	6.000,00	0,00	0,00	0,00	3.962,00	3.962,00	0%	2.038,00
	Adjustments	0,00	0,00	-3.787,00	-72,00	0,00	-3.859,00		3.859,00
	Indirect costs	397.295,00	87.636,00	76.158,00	91.055,00	68.254,49	323.103,49	64%	74.191,51
	Total Costs	976.459,00	211.133,00	202.216,00	247.021,00	165.715,79	826.085,79	68%	150.373,21
LUH	Total Person-month	54,00	16,07	17,50	16,17	10,56	60,30	92%	-6,30
	Personnel	350.622,00	72.235,00	82.369,00	80.249,00	46.301,42	281.154,42	67%	69.467,58
	Other direct costs	23.833,00	2.795,00	4.644,00	5.374,00	6.354,79	19.167,79	54%	4.665,21
	Subcontracting	3.000,00	0,00	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		0,00
	Indirect costs	224.672,00	45.018,00	52.207,00	51.373,00	31.593,73	180.191,73	66%	44.480,27
	Total Costs	602.127,00	120.048,00	139.220,00	136.996,00	84.249,94	480.513,94	66%	121.613,06
UPENN	Total Person-month	97,50	21,00	32,50	0,00	10,52	64,02	55%	33,48
	Personnel	391.564,00	72.110,00	149.824,00	0,00	47.485,52	269.419,52	57%	122.144,48
	Other direct costs	63.501,00	24.241,00	11.168,00	0,00	707,75	36.116,75	56%	27.384,25
	Subcontracting	5.000,00	0,00	0,00	0,00	0,00	0,00	0%	5.000,00
	Adjustments	0,00	0,00	-410,00	0,00	0,00	-410,00		410,00
	Indirect costs	282.141,00	59.738,00	99.814,00	0,00	29.879,83	189.431,83	57%	92.709,17
	Total Costs	742.206,00	156.089,00	260.396,00	0,00	78.073,10	494.558,10	56%	247.647,90
UOXF	Total Person-month	54,00	1,47	19,56	23,89	6,76	51,68	83%	2,32
	Personnel	289.078,00	6.217,00	75.016,00	98.498,00	30.704,53	210.435,53	62%	78.642,47
	Other direct costs	55.017,00	735,00	3.054,00	8.207,00	4.044,29	16.040,29	22%	38.976,71
	Subcontracting	3.902,00	0,00	0,00	0,00	0,00	0,00	0%	3.902,00
	Adjustments	0,00	0,00	2.431,00	0,00	0,00	2.431,00		-2.431,00
	Indirect costs	206.456,00	4.171,00	46.841,00	64.023,00	20.849,29	135.884,29	56%	70.571,71
	Total Costs	554.453,00	11.123,00	127.342,00	170.728,00	55.598,11	364.791,11	56%	189.661,89
UNITO	Total Person-month	54,00	9,59	16,00	17,80	6,42	49,81	80%	4,19
	Personnel	270.000,00	35.978,00	108.791,00	87.712,00	35.870,15	268.351,15	86%	1.648,85
	Other direct costs	95.833,00	3.227,00	8.233,00	11.825,00	6.770,72	30.055,72	24%	65.777,28
	Subcontracting	5.000,00	0,00	0,00	2.615,00	0,00	2.615,00	52%	2.385,00
	Adjustments	0,00	0,00	0,00	-344,00	0,00	-344,00		344,00
	Indirect costs	219.499,00	23.522,00	70.214,00	59.722,00	25.584,52	179.042,52	70%	40.456,48
	Total Costs	590.332,00	62.727,00	187.238,00	161.530,00	68.225,39	479.720,39	70%	110.611,61

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	Period 4	Total		
			M1-M12	M13-M24	M25-M36	M37-M42		Total/ Budget	
UBERN	Total Person-month	62,00	11,20	18,90	21,20	8,82	60,12	83%	1,88
	Personnel	465.000,00	71.512,00	159.327,00	147.096,00	76.017,68	453.952,68	81%	11.047,32
	Other direct costs	55.834,00	10.972,00	14.124,00	15.162,00	12.565,13	52.823,13	72%	3.010,87
	Subcontracting	4.000,00	0,00	0,00	0,00	0,00	0,00	0%	4.000,00
	Adjustments	0,00	0,00	0,00	-1.982,00	0,00	-1.982,00		1.982,00
	Indirect costs	312.500,00	49.490,00	104.070,00	97.354,00	53.149,69	304.063,69	80%	8.436,31
	Total Costs	837.334,00	131.974,00	277.521,00	257.630,00	141.732,50	808.857,50	80%	28.476,50
CUSTODIX	Total Person-month	36,00	2,37	6,00	17,02	9,00	34,39	71%	1,61
	Personnel	180.000,00	12.227,00	29.788,00	97.253,00	53.000,00	192.268,00	77%	-12.268,00
	Other direct costs	26.334,00	1.790,00	2.324,00	1.554,00	2.000,00	7.668,00	22%	18.666,00
	Subcontracting	0,00	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		0,00
	Indirect costs	90.000,00	6.777,00	11.143,00	40.118,00	18.000,00	76.038,00	64%	13.962,00
	Total Costs	296.334,00	20.794,00	43.255,00	138.923,00	73.000,00	275.974,00	68%	20.360,00
PHILIPS	Total Person-month	54,00	1,20	6,40	38,82	11,40	57,82	86%	-3,82
	Personnel	398.466,00	11.276,00	41.340,00	312.106,00	141.905,00	506.627,00	92%	-108.161,00
	Other direct costs	25.000,00	0,00	0,00	0,00	0,00	0,00	0%	25.000,00
	Subcontracting	3.000,00	0,00	0,00	0,00	0,00	0,00	0%	3.000,00
	Adjustments	0,00	0,00	4.014,00	11.106,00	0,00	15.120,00		-15.120,00
	Indirect costs	592.650,00	19.418,00	63.528,00	86.251,00	64.160,00	233.357,00	29%	359.293,00
	Total Costs	1.019.116,00	30.694,00	108.882,00	409.463,00	206.065,00	755.104,00	54%	264.012,00
UCL	Total Person-month	74,00	6,65	13,53	15,98	15,67	51,83	49%	22,17
	Personnel	497.978,00	39.837,00	61.092,00	96.504,00	67.591,09	265.024,09	40%	232.953,91
	Other direct costs	161.000,00	4.214,00	4.490,00	11.317,00	5.597,58	25.618,58	12%	135.381,42
	Subcontracting	6.000,00	0,00	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		0,00
	Indirect costs	395.386,00	26.430,00	39.349,00	64.692,00	43.913,20	174.384,20	33%	221.001,80
	Total Costs	1.060.364,00	70.481,00	104.931,00	172.513,00	117.101,87	465.026,87	33%	595.337,13
CINECA	Total Person-month	57,00	15,95	23,49	12,56	8,78	60,78	91%	-3,78
	Personnel	228.000,00	56.196,00	67.069,00	30.974,00	28.761,77	183.000,77	68%	44.999,23
	Other direct costs	49.408,00	5.258,00	5.065,00	4.186,00	570,35	15.079,35	29%	34.328,65
	Subcontracting	0,00	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	-2.058,00	0,00	0,00	-2.058,00		2.058,00
	Indirect costs	313.899,00	92.025,00	83.090,00	52.699,00	36.890,30	264.704,30	73%	49.194,70
	Total Costs	591.307,00	153.479,00	153.166,00	87.859,00	66.222,42	460.726,42	67%	130.580,58
TEI-C	Total Person-month	28,00	3,96	3,70	5,39	7,60	20,65	47%	7,35
	Personnel	56.000,00	10.527,00	7.482,00	26.890,00	20.572,20	65.471,20	80%	-9.471,20
	Other direct costs	15.867,00	4.065,00	5.711,00	3.597,00	986,50	14.359,50	84%	1.507,50
	Subcontracting	0,00	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		0,00
	Indirect costs	43.120,00	8.755,00	7.915,00	18.292,00	12.935,22	47.897,22	81%	-4.777,22
	Total Costs	114.987,00	23.347,00	21.108,00	48.779,00	34.493,92	127.727,92	81%	-12.740,92
Total	Total Person-month	1.374,83	260,00	391,15	391,64	229,56	1.272,35	93%	102,48
	Personnel	6.772.662,00	950.429,00	1.730.796,00	1.981.189,00	1.140.387,75	5.802.801,75	86%	969.860,25
	Other direct costs	1.528.299,00	150.392,00	199.402,00	231.689,00	188.764,82	770.247,82	50%	758.051,18
	Subcontracting	82.184,00	0,00	2.896,00	5.881,00	7.054,15	15.831,15	19%	66.352,85
	Adjustments	0,00	0,00	9.852,00	34.345,00	189,68	44.386,68		-44.386,68
	Indirect costs	5.555.915,00	739.725,00	1.230.686,00	1.214.102,00	807.942,33	3.992.455,33	72%	1.563.459,67
	Total Costs	13.939.060,00	1.840.546,00	3.173.632,00	3.467.206,00	2.144.338,73	10.625.722,73	76%	3.313.337,27

4.2 Budget Explanations

Budget explanations are given in the “Financial reporting tables” that were submitted to Eurice.

4.3 Planned versus actual efforts

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