



PROJECT INTERIM REPORT

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¹ Since an extensive amendment to the CHIC Grant Agreement is currently being prepared by the CHIC consortium, this report makes reference to any planned modifications to the original DoW.

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This report is made against the version of Annex I dated March 27, 2013. Since the CHIC partners are currently modifying Annex I in order to incorporate the changes which were made due to the reviewers' requests, this report also refers to the proposed changes to Annex I which will be requested in a formal amendment request by the CHIC coordinator ICCS. The proposed modifications are always clearly indicated in the text.

1. Work progress and achievements during the period

1.1 Work Package 1: Project Management

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

1.2 Work Package 2: User Needs and Requirements

Main objectives of this WP

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

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

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

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

Active tasks in this reporting period:

- T2.4, 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. In this task USAAR is currently analysing the requirements to achieve acceptance of hypermodels. This is done in close cooperation with all partners, as tools, models and hypermodels will only be used in the clinical setting and beyond the domain of cancer if they are validated. For that reason a questionnaire is being further developed in order to find ways of bringing models and hypermodels into clinical practice. Further important requirements in this task are addressed on the legal side including mainly IP issues of composed hypermodels. In addition, requirements for sustainability and maintenance of hypermodels are being elaborated. All partners of the CHIC consortium are included in this work. Work is done in close collaboration with WP11 and WP12.

UPENN has implemented a machine learning approach for predicting the effect of clinical mutations on oncogene activation of signalling proteins using support vector machine framework, which is a machine learning method. Moreover, UPENN has implemented an area-under-the-curve method for assessing the predictions of our mechanistic molecular models for predicting oncogene activation in kinases. UPENN also devised a double-blind validation protocol for assessing the accuracy of our predictive algorithm by computing ROC (receiver operating characteristic) curve. The prediction of the activation status is based on specific interactions (hydrogen bonds etc.) in the dynamics simulations. The double-blind comparison has been validated against a panel of ALK mutations in neuroblastoma and EGFR and ErbB2 mutations in lung cancer.

Summary of details for each task

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

The requirements for getting acceptance of hypermodels are under further elaboration in an iterative process with all members of the CHIC project. USAAR leads this task. A questionnaire is being further elaborated. ICCS took part in initial discussions on how to gain acceptance of hypermodels. In order to gain acceptance of the hypermodels by patients and physicians, contact to clinical partners outside of the CHIC consortium was initiated with the goal of recruiting patients for testing and evaluating the CHIC tools. Presenting the work performed in CHIC in clinical oriented conferences is further pursued. USAAR and ICCS have begun organizing a CHIC workshop within the framework of the *“International Conference and Exhibition on Pediatric Oncology”* to be held in Toronto, Canada on August 04-06, 2016. The EC Project Officer already approved the workshop. Five participants of CHIC will be demonstrating the work of CHIC at this 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 can be shared with all other partners. This was achieved before the consortium meeting in Bologna in October 2015.

Summary of significant results

- We continued to collect clinical, imaging and molecular data. All partners of CHIC give contributions to the requirements analysis for enhancing hypermodels beyond the domain of cancer.
- Scenarios and use cases are under further development by clinical partners and in close interaction with all other partners. They are further dissected into granular modules.
- Interaction and collaboration continued with p-medicine.
- The clinical relevance of the project is discussed and elaborated by all partners of CHIC in an iterative process. A new deliverable D2.5 will be submitted before the next review describing the subject.
- Decision to organize a CHIC workshop within the International Conference and Exhibition on Paediatric Oncology, to take place in Toronto, Canada on August 4-6, 2016

- Double-blind validation: UPENN's computational predictions matched experimental measures of kinase activity as well as experimental measures of cell transformation with over 85% accuracy in the mutations investigated from 1500 patients, and with a significance (p-value) of 0.07.

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

Use cases and scenarios are further refined for the different cancer domains of the project that is lead by USAAR. Main work was done on specifying the clinical relevance of the project. For that purpose an additional deliverable D2.5, "Clinical relevance of the CHIC project – Describing the integrated workflows of the scenarios from a clinical perspective", will be submitted before the next review. The subject was intensively discussed in several Skype conferences as well as on the 5th Progress Meeting in Bologna from October 21-23, 2015.

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

There will be the addition of a deliverable, D2.5 (see section above) to the CHIC DoW. This change is currently implemented in the 2nd Amendment to the CHIC Grant Agreement.

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

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP2			
Partner	Planned PM Total*	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	3.20	0.70	0.15
3-USAAR	25.00	7.00	n/a
7-FORTH	5.00	1.00	0.50
9-UPENN	5.00	1.50	n/a
13-CUSTODIX	1.00	0.25	0.00
14-PHILIPS	4.00	1.50	0.00
Total	43.20	11.95	0.65

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details about planned PM modifications will be delivered in the management section of this report.

1.3 Work Package 3: Clinical and Translational Science Scenarios

Main objectives of this WP

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

Active tasks in this reporting period:

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

Summary of progress achieved towards objectives

During this period an assessment of the exploitability of the nephroblastoma data provided by USAAR took place by ICCS and pertinent feedback was provided to the clinical providers.

The partners of WP3 contributed to the discussion concerning the project's clinical relevance. Major work was done by USAAR providing the data that will be used in the nephroblastoma and non small cell lung cancer scenario. ObTiMA is used for data collection. Data are anonymized and uploaded to the CHIC repository and can be used by developers of the hypermodel. Together with WP2 the hypermodel for nephroblastoma was further defined. A hybrid network modelling framework was built by UPENN, combining mechanistic deterministic network modelling and Boolean modelling of mitogenic signalling pathways and DNA damage and cell cycle pathways. Regarding glioblastoma and non small cell lung cancer, ICCS provided feedback to the clinicians. The availability of data and images for glioblastoma were kept up to date by KULeuven, ongoing issues in *ObTiMA* were solved and data from *ObTiMA* were transferred to the CDP. Based on insights from the clinical trial which serves as the input for CHIC, further experimental research was prepared. Moreover, the clinical relevance of the CHIC project to the glioblastoma scenario was described in a new deliverable in WP2 (D2.5, see WP2 report above). Together with this, the hypermodel for glioblastoma was further defined.

With regard to the application of the CHIC infrastructure to other cancer types, ICCS is in contact with UNITO in order to adapt various models being developed primarily by UNITO to the CHIC framework. In order to implement larger clinical database and to lengthen their follow up an addition to the previously submitted EUREKA1 and EUREKA2 studies has been requested (and obtained) by the Ethical Committee of FPO-IRCCS Center of Candiolo. The EUREKA-1 database will be extended to provisionally 4000 cases (including new clinical data), the EUREKA-2 database will be extended to 6000 cases (including new centres and new techniques). In September 2015, UNITO started a monocentric DICOM data collection at FPO-IRCCS Cancer Center of Candiolo, collecting multidisciplinary data from the Divisions of Radiation Oncology, Medical Physics, Radiology and Nuclear Medicine. As far as the modelling activity is concerned, the EUREKA-2 based nomogram (Candiolo nomogram) has been completed, and the EUREKA-2's one is in progress. Moreover, the application of the West model to predict the timing of prostate cancer recurrence following radical prostatectomy has been completed, while that referred to radical radiotherapy is in progress. Also the application of the Gompertz model using innovative data treatment techniques is currently under study.

Summary of details for each task

■ **Task 3.1: Wilms tumor (M1-48)**

ICCS provided feedback to the clinicians concerning a special set of micro-RNA data. ICCS also contributed to the discussion concerning the project's clinical relevance and the clinical context adjustment of the basic science and technological components of the project for the nephroblastoma branch.

Within the SIOP Renal Tumor Study Group that is chaired by Norbert Graf (task leader) a new clinical trial is still under development. This trial will use ObTiMA as the data management system. Corresponding CRFs are developed. Imaging data (DICOM) are collected from patients with nephroblastoma at the time of diagnosis and after 4 weeks of preoperative chemotherapy. Part of these DICOM data are post-processed by rendering the tumor using DoctorEye. A doctoral thesis is under way building a tool for automatic annotation of Wilms Tumor. This tool is under validation in a

feedback loop with the developer. All data that are collected so far are locally stored and uploaded to the CHIC repository as well. Ethical approval for the collection of the data for the CHIC project is given by the Ärztekammer des Saarlandes (No.: 104/10, dated: 19th August 2013). Using the hybrid network modelling framework described above, a hypermodel framework has been implemented by UPENN to integrate the miRNA data from Wilms tumor patients and predict the response to chemotherapy.

■ **Task 3.2: Glioblastoma multiforme (M1-48)**

ICCS provided feedback to the clinicians and contributed to the discussion concerning the project's clinical relevance and the clinical context adjustment of the basic science and technological components of the project for the glioblastoma branch.

The HGG-2010 clinical trial will serve as the data source of the glioblastoma data for task 3.2. All material and information of the enrolled patients are stored at UZ Leuven as source documents with a continuous follow-up and an update of the local files every 6 months. Previously, 82 patients' data sets were entered in *ObTiMA* but due to technical issues the export of these data sets failed and therefore they were no longer complete/accurate now. Therefore the UZ Leuven source documents - and subsequently the data sets in *ObTiMA* - were updated and at the same time previously missing data types (especially radiological parameters) were yet provided. Also, if possible, the corresponding images were downloaded from the hospital's PACS system and pseudonymized/anonymized, ready for sharing. At the end of the interim reporting period the exported data were shared with the CDP via a sftp, the images will follow.

Interaction with other partners took place during this entire period, especially with USAAR for discussing the issues in *ObTiMA* and with Custodix, as partner of the CDP, for sharing the data.

Based on preliminary results from the HGG-2010 clinical trial, new research questions arose. A retrospective/secondary-use experimental research protocol was designed, the application was filed and the request was acknowledged by UZ Leuven recently. Now ethical approval for the experimental research is pending. In the meantime, all possible preparations were done.

Moreover, at the end of this interim reporting period, the clinical relevance of the CHIC project to the glioblastoma scenario was described in an additional deliverable (D2.5, "Clinical relevance of the CHIC project – Describing the integrated workflows of the scenarios from a clinical perspective"), which was provided by the assistant (clinical) coordinator. Together with the clinical relevance, the hypermodel for glioblastoma was further defined in this document.

■ **Task 3.3: Non small cell lung cancer (M1-48)**

ICCS had continuous interactions with USAAR concerning the exploitability of the lung cancer data. Moreover, ICCS provided feedback to the clinicians and contributed to the discussion concerning the project's clinical relevance and the clinical context adjustment of the basic science and technological components of the project for the lung cancer branch.

At USAAR, data for the Non-small cell lung cancer hypermodel were defined and collected together with WP2. This includes clinical data, pathology data and molecular data (EGFR, KRAS, BRAF and echinoderm microtubule-associated protein-like 4-ALK (EML4-ALK)). All these data are stored locally and are uploaded to the CHIC repository as well and can be used according to the legal and ethical framework of CHIC. The clinical relevance of the corresponding hypermodel was further elaborated in an iterative process with all partners.

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

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

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

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

Database update

Four centers have sent updates of their data for the EUREKA studies, consisting of follow-up data and seminal vesicles irradiation data. Also new centers have sent additional data from new cases for the EUREKA studies. New centers are joining the studies, which brings the total number of hospitals involved to 20. UNITO's final goal is to enhance their total data collection from the present 7314 patients with a 5-year median follow-up to 9000 patients with a median follow-up of at least 7 years (and to collect additional information, such as seminal vesicles irradiation data, pre-RT PSA lists and longer biochemical follow-up).

DICOM data collection

In September 2015 monocentric collection of DICOM images has begun at FPO-IRCCS Cancer Center of Candiolo (EUREKA-2). UNITO is focusing on 99 patients treated homogeneously at the Radiation Oncology Division with IMRT-IGRT technique. Staging and re-staging data will be available too.

In particular, data collected will include:

- a) Radiation therapy images plus DVH data: CT planning, Contouring data, DVH in graph format (and possibly RT plan, RT dose, DVH in .txt format according to human resources committed to the project), all 99 patients available;
- b) mp-MRI (multi-parametric-MRI) data plus medical reports: T2-weighted morphologic scans, DWI and DCE functional sequences, staging exams (69 available) plus re-staging examinations, if available;
- c) Choline-PET-CT data plus medical reports: [18F]-FluoroCholine-PET plus low-dose CT scans, staging exams (28 available) plus re-staging examinations, if available.

Data will be stored on the central servers at FPO-IRCCS Cancer Center of Candiolo and UNITO. Data will be pseudonymized for research purposes; thereafter, the data will be visualized and analyzed through RADIANT software (for radiologic images) and DICOM-PILER software (for RT treatment plans). Data analyses will include: evaluation of target coverage and its relationship with oncologic outcomes; assessment of organs-at-risk DVHs and correlation with observed acute and late toxicities; evaluation of the value of extensive radiologic staging with mp-MRI and choline-PET-CT and its influence on RT treatment planning and outcomes; longitudinal estimate of the response to treatment comparing pre- and post-RT MRI (e.g. ADC maps) or pre- and post-PET images (e.g. SUVmax).

Data collection is foreseen to end within March 2016 and data analysis within June 2016.

Modeling activity:

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

Association studies on prognostic factors

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

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

Statistical modeling

Three papers were written about statistical modeling applied to prostate cancer. Univariate and multivariate regression statistics (mainly logistic, because our outcomes are usually dichotomous) were applied together with Cox Proportional Hazard regression model for time-dependent variables, and log-rank tests to compare Kaplan-Meier survival curves. One paper highlights the independent prognostic value of the percentage of positive prostate biopsies to predict biochemical outcome

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

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

Mathematical modeling

A paper was written about mathematical modeling applied to prostate cancer. In this paper two main models of cancer growth were applied: Gompertzian model and West model (the latter being a more complex growth model with a stressed sigmoid shape due to time and/or tumor size dependent growth spurts driven by tumor biology, host characteristics and their reciprocal physio-pathologic inter-dependence). This paper shows a prediction mathematical tool based on West tumor growth law for predicting the timing of recurrence after Radical Prostatectomy.

Summary of significant results

ICCS:

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

USAAR:

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

KU LEUVEN:

82 patients’ data sets were updated in ObTiMA, exported and transferred to the CDP. Images are ready for sharing. A subsequently experimental research protocol was acknowledged by UZ Leuven. Ethical approval is pending. The clinical relevance of the CHIC project to the glioblastoma scenario and the GBM hypermodel were further defined in an internal document in WP2. This internal document will deliver input for the new deliverable D2.5, the document outlining the clinical relevance of CHIC (see WP2 report).

UPENN:

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

UNITO:

The first phase of data collection in EUREKA-1 and EUREKA-2 has been completed and an extension has been allowed until March 2017. A provisionally cohort of 9000 patients is foreseen. The local clinical database will be shared with other CHIC members according to the signed agreements. A monocentric collection of DICOM data at FPO-IRCCS Cancer Center of Candiolo, collecting multidisciplinary data from the Divisions of Radiation Oncology, Medical Physics, Radiology and Nuclear Medicine started in September 2015. Mathematical and statistical models are in progress. In particular the algorithm estimating the timing to recurrence based on the West law has been completed and submitted for publication.

In conclusion the past, present and future activity related to the CHIC infrastructure applied to prostate cancer can be sketched in the following picture:

hypomodels	Radical prostatectomized patients	Radiotreated (RT) patients	Patients undergoing adjuvant ADT	Patients undergoing other adjuvant therapies
MOLECULAR LEVEL (circulating bio marker PSA)	X (prediction time of recurrence)		X (prediction time of recurrence)	
CELLULAR LEVEL		X (RT treatment schedules)	X (hormone-resistance induction)	X DC vaccination approach
ORGAN-TISSUE LEVEL		X (‘Candiolo’ nomogram)		
WHOLE BODY LEVEL- PERSONALIZED	X (uro-angel SW) rehabilitation	X (uro-angel SW) rehabilitation		

Green = done

Yellow = work in progress

Red = exploitation

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

All partners from WP3, both clinicians as modellers, contributed to the newly created internal deliverable D2.5, “Clinical relevance of the CHIC project – Describing the integrated workflows of the scenarios from a clinical perspective”, which was initiated by the assistant (clinical) coordinator.

Because of their continuous and valuable contributions to CHIC, partner UNITO will remain in the project. The consortium members are in favour of keeping prostate cancer in the project as additional cancer type. All other cancer types will no longer be investigated. This decision will be implemented in the 2nd Amendment to the CHIC Grant Agreement and the wording of Annex I, Part A and B will be adapted accordingly.

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

All other cancer types besides neuroblastoma, glioblastoma, non small cell lung cancer and prostate cancer will no longer be investigated in CHIC. This decision will be implemented in the 2nd Amendment to the CHIC Grant Agreement and the wording of Annex I, Part A and B will be adapted accordingly. Spare resources resulting from this narrowing down of tasks will be used to balance the need for additional resources in other RTD work packages.

Some experimental work still needs to be done at KULeuven. This results in a delay for the availability of these experimental data, which affects ICCS on a comparatively minimal level. Nevertheless, the 82 data sets of the corresponding patients can already be shared with the consortium.

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

At KULeuven, where some experimental work still has to be done, the ethical approval for the retrospective/secondary-use experimental research is still pending.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP3			
Partner	Planned PM Total*	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	2.60	0.40	0.30
3-USAAR	49.00	14.00	n/a
4-KULeuven	68.00	20.00	12.00
9-UPENN	3.00	0.50	n/a
11-UNITO	14.00	4.00	2.79
Total	136.60	38.90	15.09

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

1.4 Work Package 4: Legal and Ethical Framework

Main objectives of this WP

This work package has five objectives:

- To set up an ethical/legal framework to guarantee compliance with existing rules governing the field of patients' medical data. This framework will help partners to process data on valid legal grounds within the project.
- To clearly define who is entitled to do what with existing models and data sets from inside and outside the consortium. Specific attention will be given to the fact that CHIC involves amalgamation of models which adds additional complexity. A deep analysis will be done about the protectability and the pros and cons of copyright protection in the field. Contracts that can be concluded between project partners as well as with interested third parties on copyright protection of the works developed will be provided.
- To help the project to stay compliant with the relevant legislation and jurisdiction and will therefore act as a permanent legal advisor to the other partners.
- To do legal research on the necessary development of the existing European regulatory framework, in order to foster VPH-research initiatives such as CHIC in the areas of data protection, clinical trials regulation and intellectual property. A whitepaper on these issues for the use of the European Commission and other political stakeholders will be produced. Specific focus will be on the amalgamation of models in the field.
- Being legal advisor for all not yet foreseen legal and ethical questions for all partners for the whole duration of the project.

Active tasks in this reporting period:

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

- Task 4.4, Whitepaper preparation on “Recommendations for an amended European legal framework on patients’ and researchers’ rights and duties in E-health related research” (M14-28)

Summary of progress achieved towards objectives

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

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

Research has been conducted in order to develop a Whitepaper and make recommendations to the European Commission and other stakeholders on ways of improving the European legal framework on patients’ and researchers’ rights and duties in E-health related research.

Summary of details for each task

■ **Task 4.3, Development of a data protection and copyright framework**

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

With respect to the IP aspect, all partners reached a consensus and the Memorandum has been signed.

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

The whitepaper on the European legal framework on patients’ and researchers’ rights and duties in e-health-related research will make recommendations to the European Commission and other political stakeholders on the ongoing reforms in the European legal framework in this area. Particular attention has been paid to the data protection and privacy aspect they relate to patients and researchers, while focusing on the amalgamation of models in the field of computer assisted medical research – in silico medical research. All WP partners have contributed in this discussion and the whitepaper will be due by M36.

Summary of significant results

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

- IPR Memorandum completed and signed.
- Research on the whitepaper conducted and publication underway by M36.

Summary of actions taken to meet the recommendations from the 3rd 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 3 (total)	Actual PM M25-M30
1-ICCS	2.00	0.40	0.20
3-USAAR	4.00	1.50	n/a
8-LUH	48.00	12.00	8.17
9-UPENN	2.50	0.50	n/a
13-Custodix	7.00	0.50	1.18
Total	63.50	14.90	9.55

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

1.5 Work Package 5: IT Architecture

Main objectives of this WP

WP5 will focus on the definition of the architecture for subsequent implementation and integration. The architecture specification will provide the software architecture design patterns to effectively guide and support the construction of a coherent and consistent system. Particular emphasis will be given to the definition of appropriate interfaces among the modules to enable interoperability. This work-package ensures that the legal and ethical restrictions defined on WP4 are met by the system through the definition and implementation of the appropriate policies and security mechanisms. In this work-package also the relevant existing standards with impact on the system will be identified, analyzed and selected. We will also investigate and provide techniques to build a private cloud infrastructure to support data processing by utilizing resources within individual institutions. This can potentially facilitate a lot of legal and ethical issues concerning data privacy in remote computing.

Active tasks in this reporting period:

- Task 5.1, Reference Architecture (M1-42)
- Task 5.2, Security tools and services (M1-28; **proposed amendment: M1-46**)
- Task 5.3, Private cloud infrastructure (M1-27; **proposed amendment: M1-48**)

Summary of progress achieved towards objectives

The Review report of the second annual review of the project identifies that there is good overall progress in the work of WP5. In more detail it states that the CHIC technical architecture has been defined covering functionality, information, deployment and security views. Security guidelines and updates of the initial version of security tools has been produced (D5.2) and techniques to build the cloud infrastructure, available to the community (D5.3) has also been produced. In parallel it stresses as excellent the decision of the project (and WP5) to abandon the plans to convert to a public cloud. Nevertheless, it also states that there are deficiencies relating to the fact that a) the reference architecture has not been documented and b) the interplay between the IT architecture and the clinical models is not yet made explicit. In parallel an overall recommendation relates to the need to achieve better integration of the various platform elements, which – partly – relates to the work in WP5.

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

In task 5.1, all partners are involved in the further refinement of reference architecture of the CHIC infrastructure with regards to the provision of functionality for clinicians to reidentify their patients. All partners are also involved in the production of an updated version of D5.1.1 (The initial CHIC Technical Architecture), in an attempt to respond to the specific review comment, i.e. to better document the CHIC the reference architecture.

In task 5.2, the CHIC security framework has been deployed and integrated with the data upload flow and data repository. The main emphasis of the work during this period has been given to better and seamless integration and the study of issues that may affect final architectural specifications. In specific supporting the integration between the data repository within the CHIC security framework has been extended in terms of authentication and authorization, and the model/tool and in silico trial repositories web services were extended to make use of CHIC brokered authentication mechanism. Equally, refinement of the CHIC reference architecture with regards to the provision of functionality for clinicians to re-identify their patients has been implemented.

In task 5.3, the CHIC private cloud infrastructure has been implemented and is fully functional, in line with the objectives of task 5.1. This task, based on the experience with the prototypes and the feedback from WP10, is responsible for implementing the spiral process of the architectural refinement and improvements. During the reporting period all partners have contributed to the production of deliverable D5.3. In specific Custodix has been involved in providing contributions to the refinement of the CHIC reference architecture with regards to the provision of functionality for clinicians to re-identify their patients.

Philips defined uniform interfaces for linking the various CHIC repositories. Philips also proposed an architecture enabling the integration of models as external services with the jBPM framework.

Summary of details for each task

- **Task 5.1, Reference Architecture Definition**

TEI-C and FORTH participate in all the Architectural Board activities, such as meetings and Skype telcos, gathering feedback in order to update and enhance the initial Reference Architecture definition. Equally TEI-C and FORTH participate in and contribute to all the CHIC activities where

feedback from the Reference Architecture perspective is needed, in order to coordinate the implementation and integration of the architecture.

All partners are involved in the further refinement of reference architecture of the CHIC infrastructure with regards to the provision of functionality for clinicians to reidentify their patients. All partners are also involved in the production of an updated version of D5.1.1 (The initial CHIC Technical Architecture), in an attempt to respond to the specific review comment, i.e. to better document the CHIC the reference architecture. Finally, the further refinement of reference architecture of CHIC with regards to the provision of functionality for clinicians to re-identify their patients has been an issue studied.

In parallel CUSTODIX, in conjunction with WP4, has further developed the data protection (security) framework and coordinated its deployment within the CHIC production environment. This included user management, authentication, authorisation and auditing. Since task T5.2 has been completed, security patches and further integration with components will, from now on, be performed under T5.1 and WP8.

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

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

Partners also interacted regularly in order to resolve the technical challenges for the model/tool and in silico trial repositories web services to make use of CHIC brokered authentication mechanism.

■ **Task 5.3, Private cloud infrastructure**

TEI-C and FORTH continue to support the productive cloud infrastructure, providing resources and technical support to the consortium. In parallel a process for the continuous gathering of feedback and additional requirements from the end users of the cloud infrastructure has been put in place, in order to enhance and upgrade the infrastructure as necessary.

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

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

One problem that WP5 faces is the fact that whilst Task T5.3 is officially ending on M27, the relevant decision not to port the CHIC infrastructure on a public cloud, necessitates that this task needs to continue until the end of the project. This will be implemented in the 2nd Amendment to the CHIC Grant Agreement.

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 of actions taken to meet the recommendations from the 3rd CHIC review

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

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

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

- I. All partners in WP5 are involved in the production of an updated version of D5.1.1 (The initial CHIC Technical Architecture), in an attempt to respond to the specific review comment, i.e. to better document the CHIC the reference architecture (D5.1.2). Finally, efforts have been taken to further refine the reference architecture of the CHIC infrastructure with regards to the provision of functionality for clinicians to reidentify their patients.
- II. The integration of architectural elements, under the coordination of the Integration Manager, is currently taking place with emphasis on providing clinically relevant functionality. In this process the interplay of architectural components and models will become much more apparent.

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

Task 5.3 was scheduled in the Technical Annex to finish on M27 and to be followed by the deployment of the CHIC technical infrastructure to a public cloud. Taking into consideration the reviewer's recommendations as well as the strong indications from the legal and ethical partners that use of a public cloud infrastructure is not advisable, the CHIC consortium has agreed to extend the Task 5.3 until the end of the CHIC project, so that the CHIC private cloud, offered, managed and extended by partner FORTH, will be available to the end of the project.

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

This decision has an impact also in WP10 and milestone MS26. The CHIC Technical Annex had the provision that after the end of task T5.3, WP10 would lead the integration activities to deploy the CHIC platform in a public cloud and would be documented in D10.4 (The PhysiomSpace-enabled storage on public clouds). With the extension of task T5.3, this integration activity by WP10 and the corresponding deliverable is not applicable. There are no major deviations from the planned efforts, apart from the fact that some of the partners, although active and contributing to the work of WP5, are not claiming significant efforts in this reporting period.

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

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP5			
Partner	Planned PM Total*	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	3.40	0.70	0.35
5-BED	10.00	0.00	n/a
6-USFD	6.00	1.00	0.60
7-FORTH	33.00	8.50	4.50
12-UBERN	4.00	1.00	0.50
13-Custodix	19.00	3.50	2.30
14-Philips	15.00	5.00	10.00
16-CINECA	6.00	0.00	0.00
17-TEI-C	21.00	4.00	3.42
Total	117.40	23.70	21.67

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

1.6 Work Package 6: Cancer Models and Hypermodel Design

Main objectives of this WP

Work package 6 aims at achieving the following targets:

- To develop new multiscale models or to extend and/or adapt already existing ones in order to spatiotemporally simulate the specific clinical trials and studies addressed by the CHIC project. To clinically adapt and partly validate them based on the data available by the clinical partners of the project.
- To “break down” already developed tumour models, so that models and computer codes of elementary biological processes (biomechanisms) can be provided to the model repository to be developed. Elementary biological processes may include inter alia cell cycling (including e.g. the duration of the various phases of the cell cycle based on the molecular profile of the tumour and interactions among critical molecular entities), the probability of a tumour cell to undergo apoptosis following a particular treatment, such as the administration of a special chemotherapeutic drug or radiotherapy or a targeted therapy agent based on the molecular profile of the tumour (e.g. through the use of molecular networks), the angiogenesis process (e.g. a basic algorithm for creating new blood vessels from existing ones based on the local concentration of TAF) etc.
- To standardize the inputs, outputs and descriptions of such elementary process modules according to the hypermodelling (or integrated modeling) metalanguage to be developed by workpackage WP7 in collaboration with WP6. The set of parameters that could best describe and make widely usable each one of the elementary process models will have to be identified. In order to end up with a reasonable and hopefully universally acceptable and easily usable description of the basic aspects of all multiscale cancer models (input/output parameters, modelling strategy, mathematical methods used etc.), all cancer modellers participating in the CHIC project will have to make suggestions so that a consensus will be finally reached.
- For selected tumour types to fit together the standardized elementary tumour bioprocess modules that will have been produced during steps b and c, so as to end up with a modular “recreation” of existing models referring to the specific cancer type. The resultant hypermodels will be numerically studied and at least partly experimentally and/or clinically adapted and validated using data available from literature and/or collected by collaborating experimentalists and/or clinicians.

This step will serve as an initial demonstrator of the analysis and experimental and/or clinical adaptation and validation process applied to modular hypermodels.

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

Active tasks in this reporting period:

- Task 6.1, Cancer hypomodelling and hypermodelling strategies and elementary models (M1-36; **proposed amendment: M1-39**)
- Task 6.2, Subcellular cancer modeling (M1-36; **proposed amendment: M1-39**)
- Task 6.3, Biomechanics enhanced tumour modeling (M1-36)
- Task 6.4, The clinical modeling paradigms of nephroblastoma, glioblastoma and lung cancer (M6-46)
- ~~Task 6.5, The colon cancer modeling paradigm (M6-46)~~
- Task 6.6, The prostate cancer modeling paradigm (M6-46)

Summary of progress achieved towards objectives

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

Refinement of the basic strategies for developing cancer hypomodels and hypermodels based on the accumulated experience before that period and the reviewers' recommendations took place.

For each paradigmatic tumour type (nephroblastoma, lung cancer, glioblastoma) a palette of hypermodels is under development. At least one hypermodel for each tumour type is to undertake systematic clinical adaptation and partial clinical validation.

The clinical relevance of the component models and hypermodels is thoroughly discussed throughout their development with the assistant clinical coordinator and the members of the clinical committee.

All partners participated in all the modelling coordination activities and continued the development of their component models and the necessary work for the creation of multi-modeller hypermodels with particular emphasis on nephroblastoma cancer, which is the selected tumour type for the upcoming demonstration.

A multi-modeller nephroblastoma hypermodel has been delineated and is under development.

Summary of details for each task

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

A multi-modeller hypermodel concerning lung cancer and addressing crucial molecular, cellular and supercellular aspects of tumour growth and response to treatment for the paradigm of non-small cell lung cancer was delineated by ICCS and adopted by all WP6 partners. A first version of the hypermodel was presented and demonstrated during the 3rd CHIC review. Refinement of the basic strategies for developing cancer hypomodels and hypermodels based on the accumulated experience before that period and the reviewers' recommendations. For each paradigmatic tumour type a palette of hypermodels is under development depending on the degree of detail that is required for

a particular aspect of the biological phenomenon. At least one hypermodel for each tumour type is to undertake systematic clinical adaptation and partial clinical validation.

The clinical relevance of the hypermodels has been thoroughly discussed throughout their development with the assistant clinical coordinator and the members of the clinical committee.

A multi-modeler nephroblastoma hypermodel has been delineated (including inputs, outputs, basic description) and is under development by all modelling partners.

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

FORTH continues the development of the following hypomodels:

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

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

UBERN has re-engineered the existing biomechanical simulator into a standalone hypomodel (BMS) that aims to allow for easy integration into different scientific scenarios and hyper-model execution frameworks by:

- Flexible configuration options:
 - Modeling parameters consist of patient-specific anatomy and mechanical material properties for given clinical scenario. Path and file settings can be adapted through configuration file.
- Standardized interfaces:
 - Spatial input information (patient-specific anatomy and tumour cell concentration map) and model outputs are exchanged as VTK data structures, other configuration parameters can be specified via an xml configuration file. BSM outputs, such as mechanical deformation, and strain, stress or pressure fields, can be visualized directly in any viewer with vtk support.
- Easily adaptable dynamic coupling mechanism with other models:
 - BSM supports dynamic coupling through a MUSCLE-enabled executable or simply through repeated execution of the standalone-executable with modified configuration settings.
 - BSM core functionalities are provided as library functions that can also be compiled directly into other model executables.

The updated version was provided to WP7 for testing.

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

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

The subcellular component models of UPENN (see task 6.2) will connect with the other components of the multi-modeller models through the determination of how drug concentration and mutational status of the oncogenic protein EGFR impact the cell kill rate. This sub-cellular UPENN component is

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

The source code for the existing ODE model of angiogenesis and PDE model of nutrient transport in vascular tumours was provided to all partners and model uploaded to CHIC hypomodel database. A new hypomodel of vascular growth based on Hahnfeldt model is included – the source code was made available to USFD. UOXF implemented and compared a range of models for simulating the oxygen transport and delivery from networks of discrete blood vessels. All models were added to the CHASTE repository and can be included in CHIC's MUSCLE based hypermodelling execution environment, as needed, using Chaste-MUSCLE link. CHASTE-MUSCLE link demonstrated in source code was provided to all modelling partners and USFD.

Models can now use:

- new finite difference based hybrid (discrete vessel-continuum tissue) solver
- new finite element based hybrid solver
- new Green's function based hybrid solver
- new vessel network analysis tools (density and distance map generation)

A new functionality for modeling angiogenesis and vascular tumour growth (lattice-based and lattice-free) was added to CHASTE. The new functionality will facilitate the development of more complex models of the vasculature and tumour growth for use by the CHIC consortium.

There is on-going collaboration with biologists at the Dept. of Oncology, University of Oxford working towards experimental validation of discrete angiogenesis and perfusion models. Moreover, there is a new collaboration with Prof. Tomas Alarcon at Dept. of Computational and Mathematical Biology, CRM, Barcelona to investigate blood rheology in micro-fluidic chambers. This will inform blood flow sub-models in discrete vasculature models and ultimately inform oxygen delivery models.

LQ-based radiotherapy models were implemented in CHASTE (both non-cell cycle phase dependent and cell-cycle phase dependent).

UOXF investigated the process of verification, validation and uncertainty quantification (VVUQ) for models of tumour growth and therapy within a Bayesian framework.

■ Task 6.2 Subcellular cancer modelling

With the objective of linking the mutational status of oncogenic proteins (such as the epidermal growth factor receptor or EGFR, anaplastic lymphoma kinase or Alk, etc.) to the efficacy of small molecule inhibition of these proteins, a series of subcellular models have been developed at UPENN:

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

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

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

A subcellular model was formulated by UOXF as a system of ordinary differential equations, relating cell cycle phase and intracellular levels of VEGF and p53 within normal and cancer cells (see: Owen et al., 2011) implemented in CHASTE. The model can be coupled with existing models of vascular

tumour growth implemented in CHASTE, and could also be coupled to other hypomodels. It takes as input the local oxygen concentration and, in addition to updating cell cycle phase, it outputs a local source of VEGF which modifies the VEGF distribution in the tissue.

■ **Task 6.3 Biomechanics enhanced tumour modelling**

BMS adaptation was done at UBERN to handle tetrahedral meshes which allow varying mesh granularity in different regions of the simulation domain:

- The biomechanical simulator used to operate exclusively on hexahedral meshes that would correspond to the voxel resolution of the image segmentations from which they had been generated. For large simulation domains, this fixed spatial resolution may result in conflicting requirements for short simulation time (coarse mesh) and high accuracy in some specific regions of interest within the domain (fine mesh). As solution to this problem, BMS has been adapted to handle tetrahedral meshes which allow varying mesh granularity in different regions of the simulation domain.
- A new meshing tool has been developed to create 3D tetrahedral models from image segmentations. The mesh granularity can be chosen individually for each image label (i.e. tissue type or organ).

Remeshing mechanism: With increasing deformation, mesh quality deteriorates and can become a limiting factor for mechanical finite element simulations. We also faced this problem when simulating the biomechanics for large changes in tumour volume. A remeshing mechanism has been implemented with the aim to automatically restore mesh quality when needed. First tests suggest that our approach increases the number of successful simulation steps, however, at this moment, successful termination is not guaranteed. We will continue to work on this crucial component.

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

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

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

As part of the elementary modeling team FORTH closely attends and participates in the proposed clinical scenarios contributing in all three cancer types (will be part of the amendment session).

Dynamic coupling of BMS with OncoSimulator via MUSCLE has been tested by UBERN in the context of the Lung Cancer Hyper-modeling scenario. Patient-specific anatomic information was obtained by segmenting suitable CT images obtained from the CHIC data repository. Unlike other models, BMS requires not only a spatial model of tumour geometry, but also information about the surrounding tissues. Such a detailed segmentation is typically not carried out for clinical practice, but has to be considered a necessary image processing step for biomechanical modeling. Given the lack of automatic tools for full soft tissue segmentation in this body region, this step was performed manually. Representative values from mechanical tissue properties were extracted from literature and assigned to the segmented organs. The choice of boundary conditions is challenging as no clear constraints are imposed by the anatomy. Identification of suitable mechanical tissue properties has been started also for Nephroblastoma and Brain scenarios. As in the Lung case, segmentation of Nephroblastoma, kidney components and surrounding organs is a demanding image processing task - development of an automatic tool such as Bratumia for Brain tissue segmentation would be highly desirable.

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

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

A molecular-scale methodology and protocol for computational profiling of kinase mutations using molecular dynamics simulations was established by UPENN. As part of the task a multiscale method to combine the molecular studies with signalling network studies was developed. A hybrid subcellular model for cell fate was implemented to include the effect of STAT signalling.

SubTask 6.4.a: The nephroblastoma paradigm

A multi-modeler nephroblastoma hypermodel has been delineated and is under development. ICCS did an extensive transformation of a pre-existing ICCS simulation code of nephroblastoma growth and treatment response in order to serve as a trunk hypomodel for the nephroblastoma multi-modeler hypermodel. Clinical adaptation studies were performed using the Oncosimulator's nephroblastoma branch based on those parts of the clinical data that had already been provided. UOXF is currently updating the existing vasculature hypomodel to accept input (cell populations) from the ICCS nephroblastoma hypomodel and to provide input (normalized glucose concentration) to the FORTH metabolic hypomodel. All three hypomodels are components of the nephroblastoma hypermodel.

SubTask 6.4.b: The glioblastoma paradigm

ICCS further refined a mechanistic model of the response of GBM to immunotherapy treatment. Moreover, ICCS had intensive interaction with the involved multidisciplinary clinical team of KU Leuven.

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

SubTask 6.4.c: The lung cancer paradigm

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

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

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

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

- Scenario1: Oncosimulator-Biomechanics models
- Scenario2: Oncosimulator-Biomechanics-Metabolic-Dummy vasculature models

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

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

final result must be evaluated further, and mitigation strategies need to be identified in collaboration between UBERN and ICCS.

■ ~~Task 6.5: The colon cancer modelling paradigm~~

This task will be removed in the 2nd Amendment to the CHIC Grant Agreement. The consortium will focus only on nephroblastoma, glioblastoma, lung cancer and prostate cancer.

■ Task 6.6: The prostate cancer modelling paradigm

The first stage of data collection from the Urological and Radiotherapy departments in Regione Piemonte has been completed and 3538 follow-up pertaining to prostatectomized patients are available for model validation. As far as the radiotherapy cohort is concerned, 3500 complete follow-up are available. Further data collection has been allowed by the FPO-IRCCS of Candiolo until March 2017. A nomogram on the probability of relapse using radiotreated patients (EUREKA2 study) has been completed; the development of a similar nomogram on prostatectomized cohort (EUREKA1 study) is in progress. A correlation between the timing of relapse and the growth parameter (West model) has been successfully shown and validated on EUREKA1 data and the same study on EUREKA2 data is in progress.

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

It should be noted that the UNITO model 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, which is of obvious clinical relevance. Since the West parameters have a biological meaning, considering only one population the UNITO model can estimate the parameter values in each patient and forecast the behavior of the tumor (relapse, time to relapse, severity...). In fact, a strict correlation between the West growth rate and the timing to relapse has been found.

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

Summary of significant results

For each paradigmatic tumour type a palette of hypermodels is under development.

Clinical adaptation studies were performed.

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

The clinical relevance of the hypermodels is thoroughly discussed throughout their development with the assistant clinical coordinator and the members of the clinical committee.

A multi-modeler nephroblastoma hypermodel has been delineated and is under development. Two running MUSCLE-enabled lung hypermodel scenarios have been successfully implemented:

- Scenario1: Oncosimulator-Biomechanics models
- Scenario2: Oncosimulator-Biomechanics-Metabolic-Dummy vasculature models

The standalone Biomechanical Simulator (BMS) is ready for interfacing with other hypo-models in hyper-modeling workflows.

CHASTE-MUSCLE link demonstrated in source code was provided to all modelling partners and USFD. Successful application of UNITO models (tumor growth with and without mutation, with and without treatment) in different contexts: breast cancer *in vitro* and *in vivo* (mice), prostate cancer in human patients, lung cancer in human patients.

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

The consortium is currently refining the basic strategies for developing cancer hypomodels and hypermodels based on the accumulated experience before that period and the reviewers'

recommendations. The clinical relevance of the hypermodels is thoroughly discussed throughout their development with the assistant clinical coordinator and the members of the clinical committee.

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

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

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

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP6			
Partner	Planned PM Total*	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	57.01	13.00	5.68
7-FORTH	28.61	7.50	5.00
9-UPENN	69.00	15.00	n/a
10-UOXF	46.00	15.27	13.77
11-UNITO	14.00	4.00	3.97
12-UBERN	20.00	8.00	4.00
14-Philips	1.00	1.00	0.00
Total	235.62	63.77	32.42

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

1.7 Work Package 7: Hypermodelling infrastructure

Main objectives of this WP

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

Active task in this reporting period:

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

Summary of progress achieved towards objectives

The last reviewers' report did not include any specific recommendation for WP7. Among the general ones, the only relevant to WP7 is recommendation #1: "The key word for the future work should be integration - integration of models, hypermodels, tools and components into a usable, reliable, valid and useful clinical Environment".

During the last six months all partners engaged in WP7 have worked toward a complete integration of the IT infrastructure. The VPH-HF was integrated to all other relevant architectural components, with the exception of the in silico trials repository, which has been completed recently and is now being integrated, and the authentication services, which have been revised to increase their usability; also this integration is now being completed.

The VPH-HF has been deployed onto a production node provided by partner FORTH, and it is now being consolidated, debugged, and documented in its production version, while further developments continue in a separate development version. All work aims to ensure to the modellers, the primary users of the hypermodelling infrastructure a user-friendlier environment.

Summary of details for each task

■ **Task 7.1: Models execution**

CINECA, USFD and FORTH completed the final version of the Component Model Generic Stub. ICCS provided a number of toy hypomodels to USFD along with information about their execution, which USFD wrapped and exposed as components in the refactored version of the VPH-HF.

■ **Task 7.2: Metamodels annotation**

UCL has been developing the underlying multiscale anatomy annotation and topological framework for ApiNATOMY and RICORDO to handle the metadata for tumours in general and the nephroblastoma scenario in particular.

BED has maintained the tagging service has released its initial version but it will need to be integrated with WP8 and WP9.

USFD completed the work initiated in the previous period, led a discussion on the minimum metadata annotation set for resources and captured the agreed set in a JSON document.

■ **Task 7.3: Hypermodels execution**

CINECA delivered, in collaboration with USFD, deployed on FORTH production node a refactored version of the VPH-HF, which handled also strongly coupled models. ICCS, in close collaboration with UBERN provided USFD with 2 strongly coupled hypomodels for testing purposes, which were wrapped and executed.

Using the refactored version of VPH-HF USFD has produced two demonstrations of hypermodelling scenarios supplied by WP6 – one based on a Directed Acyclic graph (DAG) workflow and another more complex example involving iteratively coupled hypomodel execution.

BED maintained a local resource metadata repository, which now will be integrated with the repositories developed in WP8 and WP9.

FORTH, CINECA, and USFD worked on the definition of the CHIC hypermodelling language. A number of process description language were considered and analysed, but in the end it was agreed that the best starting point is the Multiscale Modelling Language (xMML) developed as part of the MUSCLE multiscale models execution environment. An in depth analysis of the current version of xMML highlighted some shortcomings with respect to the needs of the CHIC project, especially in the handling of control structures such as iterations and conditional execution. Workgroup formed by experts of the CHIC consortium and of the original MUSCLE developers at the University of Amsterdam has been established, to formally approve a revised version of the xMML language that address these shortcomings, that represents the first version of the CHIC hypermodelling language.

■ **Task 7.4: Metahypermodels annotation**

All WP7 partners participated in regular teleconferences related to metahypermodels annotation.

UCL worked closely with ICCS to establish the web-service solution to support semantics-based hypomodel integration in the hypermodelling editor, in preparation for the D7.3 report on

Hypermodels annotation services due on M36. The primary demonstration of this work will be in support of the nephroblastoma scenario.

FORTH reflected the work developed here in the necessary support by the hypermodelling editor.

■ **Task 7.5: Hypermodelling infrastructure**

FORTH production node now hosts VPH-HF refactored version, deployed by CINECA and USFD. The new version is capable of executing also strongly coupled hypermodels through the MUSCLE sub-system.

ICCS, CINECA, USFD, FORTH completed deliverable “D7.2 first Release hypermodelling framework deployed on test nodes”.

Summary of significant results

The main objective of WP7 is now achieved. We have in production, hosted by FORTH private cloud, a full version of the CHIC hypermodelling execution environment capable of executing both linear and strongly coupled workflows, thanks to the integration of the Taverna and MUSCLE sub-systems. The VPH-HF is full integrated with the rest of the CHIC IT infrastructure, and our experts are debugging and documenting the whole software stack, revising it toward improved usability as more and more hypomodels are deployed and wrapped, and then first full-scale hypermodels are implemented.

The semantic framework for the core annotation of hypo and hypermodels has been agreed and captured in proper formats; it is now being reflected onto the rest of the infrastructure, and in particular toward the hypermodelling editor, which is expected to operate primarily at the semantic level.

We have now defined a first version of the CHIC hypermodelling language that the hypermodelling editor will use to describe the hypermodels the VPH-HF will have to execute. This XML mark-up language represent an evolution of the XMML language developed by the MUSCLE team, which is not collaborating closely with the CHIC experts, to standardise this new version, which offer some advanced features essential to the description of the CHIC models.

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

- Greater emphasis on the deployment in production, the usability and the stability of the software developed
- Clinically driven further development. Starting from clinical deployment scenarios, partners in WP6 are defining specific hypermodels; from these specifications we will continue the development of VPH-HF, making sure we address with the highest priority the needs that impact the clinical deployment scenarios.

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

Deliverable D7.2 was submitted with a two-month delay, due to the unexpected specification emerged from WP6, which required the integration of the MUSCLE sub-system. This delay has been fully reabsorbed, and has not propagated to other tasks.

Following the recommendations of the reviewers to focus on the clinical deployment, partner USFD will reduce the priority of the exploration planned in T7.4 around the use of the linked data paradigm as an alternative mechanism to define very large distributed hypermodels. This investigation, while theoretically interesting, does not seems to map a specification emerging from the clinical deployment, and thus will be assigned a lower priority.

In relation to the two addition features for VPH-HF WP7 would be expected to investigate in the next period, the ability to cope with the incompleteness of the inputs, and that to cope with strongly coupled models, we plan to address these two additional features by first deploying a simulation cache for each hypomodel, where the input/output pairs are stored, then extend the execution environment to run the same hypermodel with multiple inputs, and last to modify the generic stub to support for incomplete inputs and coupled models.

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

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP7			
Partner	Planned PM Total*	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	7.20	1.70	0.90
3-USAAR	4.00	1.00	n/a
5-BED	28.00	12.00	n/a
6-USFD	134.00	34.00	18.29
7-FORTH	11.50	3.00	1.50
15-UCL	36.00	12.00	3.50
16-CINECA	36.00	12.00	3.03
Total	256.70	75.70	27.22

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

1.8 Work Package 8: Model and Data Repositories

Main objectives of this WP

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

This involves the development of:

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

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

Active tasks in this reporting period:

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

Work started early in the following task:

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

Summary of progress achieved towards objective

The web services for model/tool and in silico trial repositories were developed and the web services for clinical data repository have been extended with more functionality so as for the repositories to be fully integrated with the whole platform. Integration of the repositories with the other CHIC components is considered to be substantial, as it will enhance clinical relevance of CHIC project in a way that a clinician will be able to interact with the repositories through other CHIC components in an automatic way. The design and update of repository web services are driven by clinicians' requirements so as for the repositories to be able to expose meaningful clinical information without the need for clinician's direct interaction. Moreover, taking into account feedback from other packages regarding integration, and in view of some new requirements, model/tool and in silico trial repository schemas have been changed accordingly. New requirements of the clinicians have led to adaptation of clinical data repository so as to be able to store additional data format (medical images, clinical studies, genetic and histopathology datasets) and to provide to clinicians sophisticated search queries.

Philips has worked on a solution for the semantic representation of models descriptions and inputs/outputs. This will continue in the next reporting period.

Finally, the progress made in the definition of the semantic metadata information, the refinement of hypo/hypermodel metadata schema and the linkage of RICORDO metadata management web services with the hypermodelling editor are expected to improve semantic interoperability which will finally lead to a more tight integration within CHIC.

Summary of details for each task

■ Task 8.1, Development of repositories

USAAR gave clinical feedback about the structure of the CHIC repositories and how data can be uploaded. The repositories were evaluated in an iterative process with the developers.

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

ICCS has developed the prototype for model/tool repository (frontend and backend) and model/tool's repository web services. Moreover, ICCS contributed in the preparation of deliverable "D8.2, Prototype implementation of the CHIC repositories", by providing sections related to model/tool repository. ICCS contributed to the preparation of deliverable "D8.3 Implementation of the interfaces of the CHIC repositories", by providing sections related to model/tool repository. Taking into account feedback from partners and in view of some new requirements, model/tool schema has been slightly changed. These changes are included in deliverable "D8.3 Implementation

of the interfaces of the CHIC repositories". All modelling partners (ICCS, UOXF, UBERN, UPENN, UNITO, FORTH) have populated the repository with some of their models.

Subtask 8.1.b: Development of the data repository

The REST service has been extended with more functionality. The technical implementation of the authentication mechanism for the REST service has been extended to support SAML delegation tokens. The chunked upload REST endpoint has been implemented to upload large files in small chunks. All the services and endpoints of the service have been documented in deliverable D8.3 and are available online.

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

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

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

ICCS has developed the prototype for *in silico* trial repository (frontend and backend)

ICCS has developed *in silico* trial's repository web services.

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

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

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

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

SubTask 8.2.a: RDF storage solution for semantic metadata

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

SubTask 8.2.c: Resource annotations

Subtask 8.2.d: Global metadata search engine

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

- refine the hypo/hypermodel metadata schema;
- create applications that leverage this schema;
- make use of a middle-man database of annotations (from the Bedfordshire partner) and use mappings and transformations to ontologies over this database;
- provide annotation (RDF) store and ontology DB (Knowledge base) through RICORDO;
- link RICORDO metadata management web services with the hypermodeling editor.

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

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

In order to integrate the RICORDO framework within the upload workflow a close collaboration between UCL and UBERN has been established. The goal was to streamline the interfaces providing

the functionalities needed to simplify the annotation process performed by the data providers. Those interfaces include the search for available ontologies, ontology terms and ontology predicates. Based on the returned results the semantically correct triples can be built and finally stored in the triple store. In order to update/overwrite existing triples an interface providing this functionality has been requested.

For the task 8.2, a prototype / mockup of a search query builder has been developed. This prototype should enable to conduct sophisticated search queries requested by ICCS such as “find all patients for whom we have imaging, clinical and miRNA nephroblastoma data”. An initial version has been circulated in order to get a first feedback. As an overall goal, the interface should be suitable to support semantically driven search queries, which will be translated to SPARQL instead of SQL and executed by RICORDO.

At USAAR, discussion with p-medicine continued how to collaborate in the area of semantic interoperability. In addition ‘HOT Maps’ of tumour-specific hallmark knowledge were further discussed led by UCL. USAAR evaluated, structured and optimized the data corpus for nephroblastoma data. This included a digitalization of patient’s image data and restructuring the image corpus and the management of miRNA data.

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

Ongoing integration of the CHIC clinical data repository with the CHIC data protection framework was done at Custodix. USAAR prepared data to conduct manual ground truth annotations and a first anonymization of nephroblastoma and lung cancer data. At ICCS, model/tool and *in silico* trial repositories web services make use of CHIC brokered authentication mechanism. This is essential in order to ensure that only authorized clients have access to model/tool and *in silico* trial repository web services.

Summary of significant results

The prototype implementation of the CHIC repositories and the implementation of the interfaces of the CHIC repositories were completed.

Clinical data repository:

- REST services were extended with more functionality in line with the defined milestones
- Support for genetic/molecular and histopathology datasets
- Initial integration with RICORDO framework continued
- Prototype implementation of a search query builder

Data from nephroblastoma and lung cancer were anonymized and uploaded to the CHIC platform.

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

For actions already taken see paragraph 2.

User interfaces will be improved with the ultimate end-user in mind.

New web services will be developed according to the clinicians’ requirements in order to enhance the integration of the repositories with the whole platform.

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

A budget shift at UCL will be necessary. While the current focus is on the nephroblastoma scenario, the effort expended on this work suggests that significantly more effort will be needed in generalizing the infrastructure in support of other scenarios (such as lung and glioblastoma). UCL, therefore will convert its own equipment/consumables budget into staffing budget to ensure a level of person-month resource commensurate with the scope of the work required. This budget shift will not negatively affect UCL or any other partners and work packages. The exclusively internal shift of budget will be implemented in the 2nd Amendment to the CHIC Grant Agreement.

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

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP8			
Partner	Planned PM Total*	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	19.30	4.50	2.00
3-USAAR	3.00	1.00	n/a
7-FORTH	8.50	2.00	1.00
9-UPENN	3.00	1.00	n/a
12-UBERN	15.00	6.00	3.00
13-Custodix	3.00	1.00	0.37
14-Philips	7.00	3.00	9.92
15-UCL	36.00	12.00	4.63
Total	94.80	30.50	20.92

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

1.9 Work Package 9: Image Processing and Visualization

Main objectives of this WP

This work package will concentrate on the visualization and image analysis support to the project.

The objectives are:

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

Active tasks in this reporting period*:

- Task 9.2, Scalable visualization techniques (M3-18)
- Task 9.3, Uncertainty data visualization (M9-24)
- Task 9.4, Visualization toolkit for the model/data repository (M13-46)
- Task 9.5, A general image processing development toolkit (M6-18)
- Task 9.6, Image registration tools (M3-36)
- Task 9.7, Multimodal and longitudinal brain tumor image analysis (M9-46)
- Task 9.8, A software platform for the Assessment of Tumor Treatment Response (M8-42)

*) A detailed revision of task names, task descriptions and task durations was made in preparation for the 2nd Amendment to the CHIC Grant Agreement. Further details are provided in the following WP report.

Summary of progress achieved towards objectives

BED has been working on both visualization (by developing a s/w called CCGVis) as well as image segmentation (Nephroblastoma)

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

USAAR did mainly work on segmentation of Wilms tumors and evaluated the performance of different approaches on imaging data sets. A wide range of imaging features with respect to their discriminative potential for nephroblastoma were analysed and a corresponding paper written.

ICCS provided partner BED with sample output files of ICCS's lung hypomodel (along with documentation). ICCS provided feedback to partner FORTH with regards to the necessary nephroblastoma imaging data processing steps. ICCS also provided feedback with regards to the nephroblastoma hypermodel output files.

Summary of details for each task

■ **Task 9.2, Scalable visualization**

BED has looked into scalable visualization techniques to allow the visualization of clinical data along a scalable timeline. The work is implemented in the 3D visualization software called CCGVis.

■ **Task 9.3, Uncertainty data visualization**

In the CCGVis, we will consider the uncertainty issue when visualizing the data from the onco-simulation.

■ **Task 9.4, Visualization toolkit for the model/data repository]**

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

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

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

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

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

FORTH continues the task to integrate most of the WP9 technologies into a single platform (a DrEye based platform) according to the unanimous decision of the consortium. This decision dictates an extension of this task to M48 since it will be an ongoing effort integrating WP9 tools which are constantly updated to match the clinicians' needs (therefore the general image processing development toolkit Task will be prolonged as mentioned). The clinical scenarios are adapting to the real life applications as the clinicians use the relative tools often and during this process they pinpoint improvements to the developers. All the image processing tools in the platform (DrEye, CCVis, Bratumia, etc) are constantly updated in order to better adapt and to simplify the work of the clinicians. This WP9 integrator will also demonstrate the clinical relevance of the project since it is co-developed with the clinicians of CHIC.

A lot of work was done at USAAR on segmentation of Wilms tumors using DoctorEye and developing a (semi-)automatic software for segmentation. In order to do so, the performance of different approaches on these data sets were evaluated. BED has been working with USAAR for the segmentation and registration of nephroblastoma images.

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

■ **Task 9.6, Image registration tool**

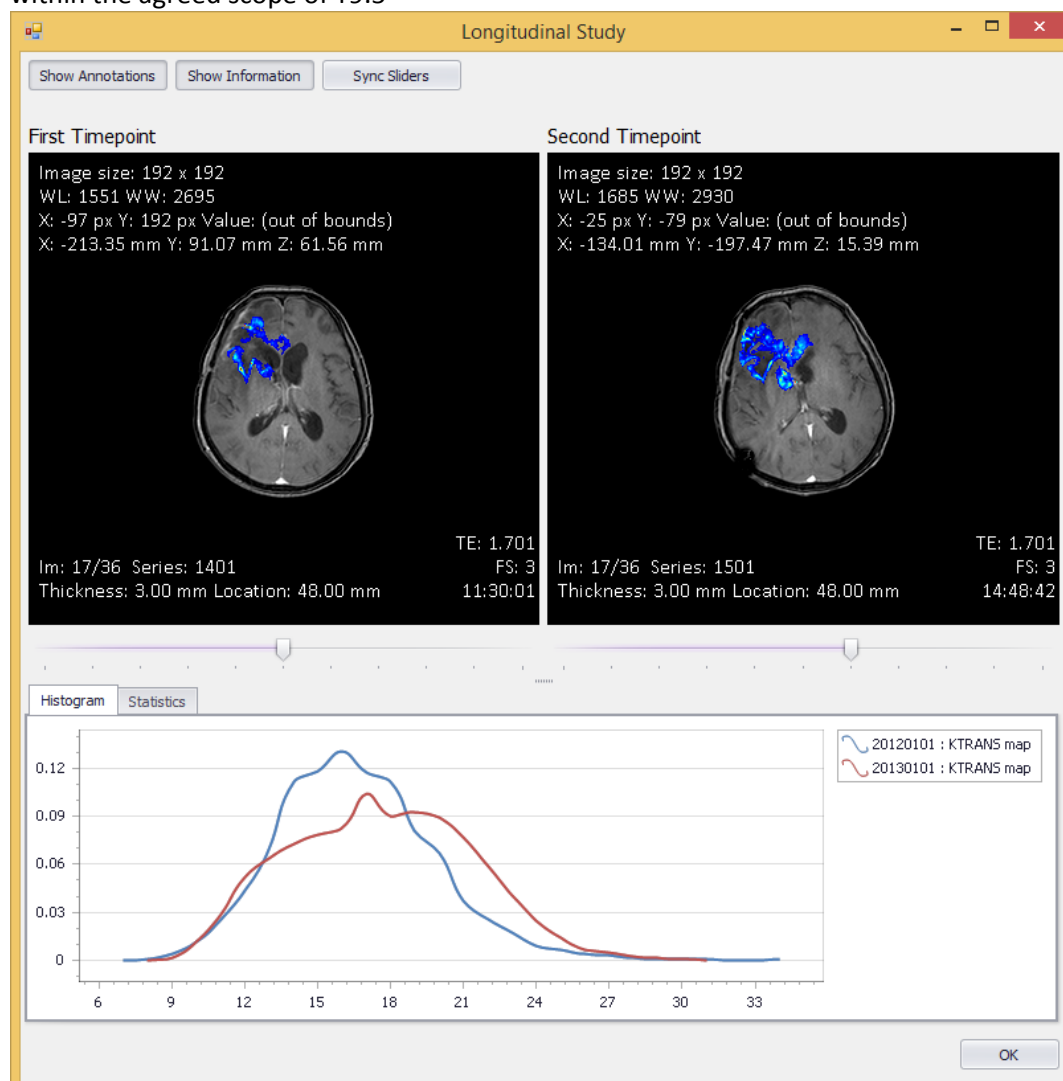
A clinical collaboration to evaluate the developed image registration tool has started (cohort selection, definition of metrics, etc.) by UBERN. USAAR started to evaluate, structure and optimize the data corpus for nephroblastoma imaging data.

■ Task 9.7, Multimodal and longitudinal brain tumor image analysis

An approach to define optimal weights on the CRF model used to regularize segmentation results has been developed and tested. A first clinical evaluation of automatic longitudinal tumor volumetry was carried out.

■ Task 9.8, A software platform for the assessment of tumor treatment response

At FORTH, In order to assist the clinicians in better assessment of the tumor response under treatment, FORTH develops a specialized platform dedicated to comparing regions of interest of the imaging data from different time points and from different modalities (e.g. ADC maps from DW-MRI in conjunction with anatomical MRIs). The platform extracts multiple statistical magnitudes which compares among the selected time points. During this longitudinal study the clinician has an overview of the volume evolution of the region of interest, and of other available statistical parameters. In order to provide a better understanding of the nature of the information, histograms of the selected time points are superimposed on a common axis system providing a quick and exact visual representation of the temporal evolution of the selected ROI. A screenshot of the prototype of the platform in its current status is the following. This software is also being integrated to DrEye within the agreed scope of T9.5



At USAAR, A wide range of imaging features with respect to their discriminative potential for nephroblastoma was analyzed and a paper written about this: Sabine Müller, Ruslan David , Kostas Marias, Graf N: The standardized histograms of T2 Magnetic Resonance Images (MRI) signal

intensities of Nephroblastoma does not predict histopathological diagnostic information. Cancer Informatics Supplement 14(S4):1-5, 2015, doi: 10.4137/CIN.S19340

Summary of significant results

The first clinical evaluation (publication submitted) on longitudinal tumor volumetry was finished. The results demonstrate the feasibility of automated longitudinal volumetry in the clinics.

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

The CHIC consortium has taken a unanimous decision to integrate most of the WP9 technologies into a single platform (a DrEye based platform) and to extend the corresponding Task 9.5 until the end of the project. This decision dictates an extension of this task to M48 since it will be an ongoing effort integrating WP9 tools which are constantly updated to match the clinicians' needs (therefore, the general image processing development toolkit task will be prolonged as mentioned).

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

Due to the extension of Task 9.5, person months and corresponding budget modifications must take place in the Technical Annex (Annex II to the CHIC Grant Agreement) in order to reflect the amendments in the additional labor undertaken. The corresponding 2nd Amendment to the CHIC Grant Agreement is currently being prepared.

Moreover, the partners in WP9 propose a rewritten version of WP9 which reflects more closely the recent developments and discussions and, most importantly, the clinical requirements on visualization, which have emerged especially since the 3rd CHIC Review. In more detail, task titles were modified in several tasks in WP9. The new proposed titles read as follows:

- Task 9.2: Visualization techniques for models and data (due to the extended focus in this task, the partners also propose to extend Task 9.2 to M46)
- Task 9.3: Statistical data visualization for the simulation outcomes (due to the extended focus in this task, the partners also propose to extend Task 9.2 to M46)
- Task 9.4: Visualization for the reporting in data repository
- Task 9.5: An integrated image processing toolkit for CHIC (as mentioned above, this task should be extended to the end of the CHIC project)

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

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP9			
Partner	Planned PM Total*	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	4.00	1.00	0.55
3-USAAR	15.00	5.00	n/a
5-BED	36.00	10.50	n/a
7-FORTH	45.29	9.50	6.50
12-UBERN	12.00	3.00	1.00

17-TEI-C	1.00	0.00	0.00
Total	113.29	29.00	8.05

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

1.10 Work Package 10: Integrated Platform

Main objectives of this WP

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

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

Active tasks in this reporting period:

- Task 10.3, Data Management and Computational infrastructure (M7-36; **proposed amendment: M7-24**)
- Task 10.4, Data and hypermodel orchestration (M7-44)

Other active tasks in this reporting period:

- Task 10.1, Portal (M1-8; **proposed amendment: M1-48**)

Summary of progress achieved towards objectives

The Review report of the second annual review of the project identifies that there is good overall progress in the work of WP10. Deliverables 10.2 ("Design of the orchestration platform, related components and interfaces") and 10.3 ("The CHIC Encryption Services") were approved as being technically sound and clearly documented. At the same time a frequent comment throughout the report is that the consortium should deliver "a clinically relevant, validated and evaluated CHIC environment for clinicians working in the cancer domain". **The experts also pointed out the lack of "a 'packaged' clinically oriented demonstration" and the adaptation of the user interface to be usable by research clinicians.**

WP10 has taken full notice of these remarks and recommendations. In particular, WP10 alongside with WP5 ("Architecture") coordinates the activities (technical meetings, telcos, etc.) for making the work and the outcomes of the CHIC project more "clinically oriented" both at the technical and user access levels. Additionally, WP10 will deliver the necessary infrastructure to extend the CHIC platform in the clinical domain **through the introduction of the Clinical Research Application Framework ("CRAF")** that will support a unified and simple user experience and provide a "CHIC-in-a-box" abstraction for the clinicians to use in clinical research.

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

Task 10.1, in which FORTH leads the integration activities regarding the integration of CHIC tools in the CHIC portal. This task has finished according the current Technical Annex. However, the integration activities continue taking place and according the review comments need to be given more emphasis, thus we need to extend this task up to the end of the project and to allocate adequate resources in order to achieve the goals of this task.

Task 10.3, in which ObTiMA is further extended by USAAR for data storage for the CHIC environment. Data from nephroblastoma are entered in ObTiMA and linked to molecular data and imaging data. Data are uploaded to the CHIC repository. A possible connection between the CHIC clinical data repository and the MyHealthAvatar EU project has been discussed between UBERN, ICCS, Custodix and BEDS. FORTH continues the development of the CHIC Data Upload tool with the incorporation of additional data types, such as the clinical data in CDISC format.

Task 10.4, in which 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. ICCS has collaborated with partner FORTH in order to provide documentation regarding the consumption of model/tool repository web services by the hypermodelling editor. FORTH continues the design and implementation of the CHIC Hypermodelling Editor. In this reporting period further interactions with WP6 and WP7 took place in order to integrate the use of the metadata annotations of the models, the definition of the hypermodelling language, and addressing the requirements of the modellers.

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

Summary of details for each task

■ Task 10.3, Data Management and Computational infrastructure

Data management for heterogeneous nephroblastoma data is further developed with the usage of ObTiMA. Data are uploaded to the CHIC repository. In order to host data for the upcoming MyHealthAvatar (MHA) review in February 2016 a discussion between UBERN, ICCS, Custodix and BEDS has been initiated to establish a connection with the CHIC clinical data repository. As outcome of this discussion, CHIC will create a user account for each service within MHA that needs to access the CHIC clinical data repository. All data that should be query able by MHA will be accessible by those MHA user accounts (this is the so called synthetic data). CHIC users will not have access to this data. MHA users will not have access to any other data. As the CHIC clinical data repository is used as a database there is no further access control within CHIC. End user authentication and authorisation is hence MHA's responsibility. MHA should verify whether the right physician and patient are authenticated for the queried data.

■ Task 10.4, Data and hypermodel orchestration

CINECA, in collaboration with the other representatives of WP7, has 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.

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

ICCS interacted with the WP10 leader and the rest of WP10 partners in order to ensure that work in WP10 is in line with the updated after the 3rd CHIC review overall priorities of the project. We have started the discussions on the adaptation of the CHIC platform for clinical research and the needed infrastructure to support it, as recommended by the reviewers in the 3rd review.

Summary of significant results

Documentation regarding the consumption of model/tool repository web services by the hypermodelling editor. The development environment of the CHIC clinical data repository deployed to the CHIC infrastructure will be used to host data for MyHealthAvatar as a temporary solution for

the upcoming review in February 2016. Work on the Data Upload tool and the Hypermodelling Editor continues.

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

The main recommendations from the 3rd CHIC review that relate to WP10 are:

- “it remains open how the model validity is ensured when allowing editing,”
- “it is difficult to assess the clinical readiness in the absence of a “packaged” clinically oriented demonstration,” and
- “the user interface still remains to be adapted to the CHIC objectives of being usable by (research) clinicians.”

In parallel an overall recommendation relates to the need to achieve better integration of the various platform elements, which also relates to WP10 that is the “integration workpackage”.

In relation to these recommendations WP10 and the Consortium as a whole have taken specific actions which are discussed in the following paragraphs:

- i) Indeed, the validity of a hypermodel at the moment of its construction by a clinician or a computational biologist can not be fully checked. The discussion on the validity of the composition of the models in a hypermodel can touch far-reaching goals, like the “clinical validation” which cannot be currently performed when the hypermodel is built and designed in the Hypermodelling Editor. Nevertheless, FORTH is currently enhancing the hypermodelling editor in order to take advantage of all the available semantics and metadata information that the (hypo)models have been annotated with. It is apparent that the success of this endeavor depends, to a large extent, on the completeness of the model annotations. Therefore, partners participating in WP6, WP7, and WP10 are engaged to bi-weekly teleconferences for dealing with these issues. In addition to that, it should be made clear that the hypermodels which are ready to be used for clinical research are not allowed for further editing, while the platform (Editor, model repositories, and execution framework) are enhanced to keep version information of the deployed hypermodels for provenance and reproducibility.
- ii) **The need for having a “packaged” clinically relevant representation of the CHIC environment led to the introduction of an additional component for the project, the Clinical Research Application Framework (“CRAF”) that is currently under development.** This suite of tools and end-user applications will provide a “one-stop” solution for accessing the results of CHIC for clinical research in the clinical domain. The development of this framework is undertaken by FORTH in the context of WP10 with interactions and support from the other technical work packages and partners and especially WP9 which deals with the visualization tools.
- iii) The user interface of the – under development – CRAF is designed to be simple and smooth by hiding the complexity of the CHIC platform while, at the same time, demonstrating its full potential for clinical research and empowering the clinician to use the underlying technologies for the benefit of the cancer patient.

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

- Although task T10.1 has officially finished according the current Technical Annex Task, the Task 10.1 (The CHIC Portal) continues the integration activities. The CHIC consortium has decided to extend this task until the end of the project and this change will be reflected in the 2nd Amendment to the CHIC Grant Agreement.
- The additional work undertaken by Task T10.1 will be documented in the deliverable D10.5 (The CHIC Integrated platform) that we propose to shift from month M44 to M48 (to be implemented in the 2nd Amendment to the CHIC GA).

- Taking into consideration the reviewer's recommendations as well as the strong indications from the legal and ethical partners that use of a public cloud infrastructure is not advisable, D10.4 ("The PhysiomSpace-enabled storage on public clouds") and the relevant activity are not applicable any more. This deliverable will be removed from the list of deliverables in the 2nd Amendment to the CHIC GA.

Due to the extension of task T10.1 until the end of the project but mainly due to the unforeseen requirement to develop the Clinical Research Application Framework *CRAF* which will demonstrate the clinical relevance of the project, an amendment to the person months and the corresponding budget in Technical Annex is planned. Negotiations for a budget shift within the CHIC consortium are under way.

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

An amendment of the CHIC Grant Agreement is being prepared and has been announced to the EC in order to reflect the changes in the duration and the additionally uptaken labor in task 10.1.

Statement on the use of the resources

Planned versus actual efforts in WP10			
Partner	Planned PM Total*	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	7.40	1.90	0.90
3-USAAR	7.00	3.00	n/a
7-FORTH	48.79	10.00	4.00
12-UBERN	3.00	1.00	0.50
14-Philips	18.00	6.00	10.00
16-CINECA	8.00	3.50	3.03
17-TEI-C	4.00	1.00	0.00
Total	96.19	26.40	18.43

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

1.11 Work Package 11: Clinical Adaptation and Validation

Main objectives of this WP

According to the different goals and requirements of this project specified in detail in the different WPs and tasks, a clinical adaptation and validation process within the project will be carried as a major part of quality control and guarantee for further usage of tools and models, including the Oncosimulator. The spectrum ranges from testing of tools and models up to their usage in clinical trials. Hence, this WP will identify objectives that need to be specifically tested in each case. For that reason proper evaluation criteria will be defined. This WP is crucial in that it will continuously assess the quality of all services and tasks of the CHIC environment and iteratively gives feedback to all responsible persons. In the first 18 months a set of guidelines and check-lists to support evaluators will be created to standardize the clinical adaptation and validation process including standardized reports. Such reports will suggest possible improvements, modifications and other functionalities to the technical WPs in a feedback loop. During that period corresponding checklists from other

projects will be studied and if possible adapted to the specific requirements of CHIC. Furthermore, workshops are to be held to perform dedicated evaluation sessions engaging both users and developers. Besides these task-specific evaluations, another task is to provide combined evaluations covering the whole integrated CHIC environment and their clinical adaptation and validation. In general, this WP will:

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

Specifically this WP will:

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

Active tasks in this reporting period:

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

Summary of progress achieved towards objectives

In task 11.3, initial discussions were started on the use of the first multi-modeller hypermodel concerning lung cancer for providing the first complete (basic and technology) example for the fine-tuning of the CHIC infrastructure based on the corresponding multiscale clinical data. This discussion was mainly done by ICCS and USAAR with the participation of modellers and IT-people. Hypomodels describing the interplay between cell populations, which can exhibit mutations and differential response to therapies, are ready for implementation in the lung-cancer hypermodel, provided by UNITO in cooperation with USAAR and other partners. UNITO also finalized the database structure for the validation of the prostate cancer model. In this task UPENN develops a comprehensive double-blind validation strategy to validate the predictions of molecular models on the activation status of a given clinical mutation in genes relevant to targeted therapy.

USAAR intensively enhanced efforts regarding the clinical relevance of the CHIC project. This was done by a lot of interactions of the whole consortium and resulted in a concrete plan how to achieve this goal in the remaining period of the project. A new document D2.5 is written that summarizes these efforts for the different diseases [Glioblastoma, nephroblastoma, Non-small cell lung cancer and prostate cancer] enrolled in CHIC. The impact on the CHIC infrastructure is now much more clinically oriented (see also WP2 report).

The work done for lung cancer was enhanced by nephroblastoma. The nephroblastoma Oncosimulator will be demonstrated at the next review. There will be validations done for each hypomodel as well as for the integrated Oncosimulator.

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

ICCS worked specifically on the improvement of the clinical usability of CHIC repositories. 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 by UNITO. Available clinical data on prostatectomized (EUREKA1 database) or radically radio-treated (EUREKA2 database) patients are under investigation following two approaches:

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

In addition UNITO is collaborating with CPO-Piemonte Epidemiology Unit to implement EUREKA studies epidemiology evidences and to compare different treatment modalities in homogeneous cohorts. Besides, UNITO is externally validating the two developed models on prostate cancer: a pre-therapy nomogram on RT cases by Gabriele D. et al, and a post-therapy model using PSA follow-up data on surgical patients by Stura I. et al.

The developed longitudinal segmentation approach has been clinically evaluated by UBERN.

Summary of details for each task

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

Initial discussions on the use of the first multi-modeller hypermodel concerning lung cancer for providing the first complete (basic and technology) example for the fine-tuning of the CHIC infrastructure based on the corresponding multiscale clinical data was continued with the nephroblastoma hypermodel.

USAAR intensively enhanced 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.

UNITO can report the following activities and achievements for this reporting period:

- Statistical models (Domenico Gabriele): formulation of hypo-models integrating clinical (age, pre-treatment PSA, clinical Staging, bioptic Gleason Score, percentage of positive cores at biopsy), pathologic (pathologic Staging, surgical margins) or therapeutic factors (adjuvant radiotherapy, RT dose, adjuvant androgen depriving therapy).
- Mathematical models (Ilaria Stura): formulation hypo-models describing the interplay between cell populations which can exhibit mutations and differential response to therapies are ready for implementation in the lung cancer and prostate cancer hyper-models (e.g. hormone sensitive versus hormone resistant cells); in addition, the database structure for the validation of prostate cancer model is ready.
- The database structure is available and we are ready to share it and to find a common ontology with the other groups. UNITO is also preparing a SW allowing multiple choices by the user and running models with different parameters values (various types of cancer).
- UNITO is collaborating with CPO-Piemonte Epidemiology Unit, Director G. Ciccone (local researcher A. Castiglione), with the collaboration of Prof. F. Merletti, to implement EUREKA studies epidemiology evidences:
- Calculations of EUREKA-1 data coverage on total Piedmont Region Radical Prostatectomies, comparing our patient numbers with SDO information (Scheda di Dimissione Ospedaliera,

hospital dismissal records) concerning RP hospitalizations, subdivided according to treatment hospital and year of surgery;

- Update of all the Piedmontese patients (both residing and treated in Piedmont) life/death status (plus cause of death), data available for a total of 5070 patients (2862 surgical cases and 2208 RT cases);
- Compliance to 2009 Piedmont Region Oncology Web guidelines on prostate cancer, with regards to treatment choice according to patient risk-class;
- Comparison of surgery and radiation therapy results in homogeneous cohorts (risk-class, year of treatment, geographic area).

External validations by UNITO:

1. Up-to-date, UNITO has developed two different models on prostate cancer: a pre-therapy nomogram on RT cases by Gabriele D. et al, and a post-therapy model using PSA follow-up data on surgical patients by Stura I. et al. Of consequence, we are at the extremes of two opposite perspectives.
2. Firstly, UNITO has to apply their models to the alternative treatments in external validation (surgery for RT nomogram and RT for the surgical model).
3. Secondly, we have to develop therapeutic models including, for the surgical cohort, pathologic features and adjuvant RT, while, for the RT study, RT dose and adjuvant ADT.
4. Third, we should integrate the single hypo-models (to use conventional terms of the CHIC project) into a complete clinical hyper-model, that would take into consideration different clinical options and variable timing, starting from cancer staging and adding information along with therapeutic performances and follow-up.
5. In addition, UNITO is taking contacts to organize a data collection on prostate cancer patients treated with radical brachytherapy (EUREKA-3 study) at Sassari Hospital, Radiotherapy University Division (Director G. Meloni, Responsible M.F. Dedola, operator A. Carnevale) in partnership with the Urology Division, Alghero Hospital (Director A. Tedde) and the Medical Physics Unit, Sassari Hospital (Director P.G. Marini, operator M. Tamponi).
6. The total number of patients treated with Iodine-125 permanent seeds by 2002 is approximately 200. Besides, in the latter hundred patients (by 2008), the procedure has been technically implemented with the employment of the "Target Scan" device, a 3D stereotactic echography system that improves the precision of image-guided seeds implant.
7. The collection of a brachytherapy cohort may be in particular useful to compare outcomes and collateral effects with EBRT and surgery, and to externally validate RT nomograms in the risk-classes fit for brachytherapy, i.e. low and very-low risk cases.

A clinical evaluation of automated longitudinal volumetry has been performed by UBERN. Quantification metrics to compare user delineations and the computer algorithm were designed and used on a chosen cohort of GBM patients. Using the model described in WP3, UPENN has implemented a hypermodel framework to integrate the miRNA data from Wilms tumor patients and predict the response to chemotherapy.

Summary of significant results

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

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

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

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

First clinical evaluation on longitudinal tumor volumetry is finished. Results demonstrate the feasibility of automated longitudinal volumetry in the clinics by UBERN. Quantification metrics to compare user delineations and the computer algorithm were designed and used on a chosen cohort of GBM patients.

The models of UPENN consist of MAPK, PI3K/Akt, P53, Cell cycle growth and arrest, radiation and chemotherapy induced genotoxic stresses. Based on local, global sensitivity analysis, as well as network flows, they can project the individual patient characteristics in their model and predict the response to chemotherapy, radiotherapy, and targeted therapy.

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

A new document (D2.5) is written that summarizes efforts concerning clinical relevance of the project for the different diseases (Glioblastoma, nephroblastoma, Non-small cell lung cancer and prostate cancer) enrolled in CHIC. The impact on the CHIC infrastructure is manifold and now much more clinically oriented. WP2 and WP11 are working closely together in this issue.

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

Not applicable.

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

Not applicable.

Corrective actions

Not applicable.

Statement on the use of the resources

Planned versus actual efforts in WP11			
Partner	Planned PM Total*)	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	7.70	2.20	0.70
3-USAAR	25.00	8.00	n/a
5-BED	8.00	3.00	n/a
7-FORTH	3.07	0.50	0.77
9-UPENN	8.50	1.00	n/a
11-UNITO	20.00	5.00	3.96
12-UBERN	3.00	1.00	1.00
13-PHILIPS	3.00	1.00	0.00
17-TEI-C	1.00	0.00	0.00

Total	79.27	21.70	6.37
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*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

1.12 Work Package 12: Dissemination and Exploitation

Main objectives of this WP

The objectives of this work package are the following:

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

Active task in this reporting period:

- Task 12.1, Dissemination activities (M1-48)
 - SubTask 12.1.a, Strategic Dissemination Planning
 - SubTask 12.1.b, Web presence
 - SubTask 12.1.c, Newsletter
 - SubTask 12.1.d, Dissemination kit
 - SubTask 12.1.e, Conferences, Exhibitions, Workshops
 - SubTask 12.1.f, Scientific and Technical Papers Publications
 - SubTask 12.1.g, Interfacing with other projects
- Task 12.2, Exploitation and IPR issues (M1-48)
- Task 12.3, Training activities

Summary of progress achieved towards objectives

In Task 12.1, with regular contributions from Eurice and, whenever needed, from other CHIC partners, CINECA took care of the writing and distribution of the electronic bi-monthly newsletters. EURICE was main editor and published the second annual CHIC newsletter, available for download on the CHIC public website². This second issue contains contribution from ICCS, USAAR, UBERN, CINECA, and BED. Immediately after publishing the 2nd newsletter, planning for the 3rd CHIC newsletter began. The partners involved, coordinated by Eurice, will make an effort to publish this issue on time. Moreover, Eurice continuously updated the project website with the latest news from the CHIC partners and other relevant new information from the consortium. The dissemination activities actively went on from the previous period both towards clinical and scientific audience. A detailed reporting of the dissemination events and scientific publications is presented in the respective tables later on in this report.

In Task 12.2, after preparation of D12.3, partners continued with their contributions to exploitation plans and individual exploitation activities. The IPR Memorandum Of Understanding has been completed and signed by all partners. Detailed plans for future exploitation activities have been defined by CINECA and concrete actions will follow up in the next months with contributions from all partners.

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. Contact was established with the International Conference and Exhibition on Pediatric Oncology (August 04-06, 2016 Toronto (Canada)) to run a

² http://chic-vph.eu/fileadmin/chic/downloads/CHIC_Newsletter_2_final.pdf

workshop at that meeting. UBERN co-organised the MICCAI Brain Tumor Segmentation (BRATS) Challenge 2015 and LUH carried out internal teaching of students.

Summary of details for each task

■ **Task 12.1, Dissemination activities**

Subtask 12.1.a, Strategic Dissemination Planning

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

Subtask 12.1.b, 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.

Subtask 12.1.c, Newsletter

CINECA took care of the main share of writing, collection of inputs, and distribution of the electronic bi-monthly/regular newsletters with support from EURICE. Two issues of the electronic newsletter were released in the reporting period. 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 67 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 of providing a more detailed insight into the CHIC project and consortium. The 2nd issue of the annual CHIC newsletter was prepared with contributions collected from the CHIC partners ICCS, USAAR, USFD, UBERN, BED, CINECA as well as from members of the external advisory board. The focus of this second project newsletter was on the technical work accomplished so far. The second newsletter was published in June 19, 2015, and it is available for download from the CHIC website³. A third issue of the annual CHIC newsletter is currently in the making. This time, the focus will lie on the clinical relevance of the CHIC tools and services. The planned publication date is end of March/beginning of April, 2016.

Subtask 12.1.d, Dissemination kit

With the contributions from the consortium, Eurice is keeping up to date the material available in the dissemination kit that each partner can use to carry on its dissemination activities. Depending on the final scope of the Amendment, dissemination materials such as the project flyer and posters might have to be updated.

Subtask 12.1.e, Conferences, Exhibitions, Workshops

A list of the events and contributions from the different partners for M24-30 includes (among other things):

- ICCS and USFD participated with CHIC related discussions in the final AVICENNA workshop (Barcelona, 4-5 June 2015).
- A number of lectures were presented by Marco Viceconti and Dawn Walker from USFD. Kewei Duan and Daniele Tartarini presented posters describing CHIC Project with the focus on Hypermodelling Infrastructure at the Insigneo Showcase 2015 on the 08/05/2015. The focus of the Showcase was on the impact achieved through collaboration with industrial and clinical partners. The event was attended by high profile guests including key representatives

³ http://chic-vph.eu/fileadmin/chic/downloads/CHIC_Newsletter_2_final.pdf

from industry, the health and research sector, and important funding bodies. Additionally, the leaflets describing Project CHIC were disseminated during this event.

- The CHIC project was presented at the ECCO Congress in Vienna on September 29, 2015, together with p-medicine.
- Contributions were made to the strategic dissemination discussions and explorations by ICCS. One important outcome of these activities is the acceptance of the application to organize a dedicated CHIC workshop within the International Conference and Exhibition on Paediatric Oncology, to take place in Toronto, Canada on August 4-6, 2016. It is noted that the application was accepted in the subsequent reporting period (October 2015).

A complete list of the dissemination activities is provided in the table below referring only to the period under reporting. Complete dissemination status and analysis will be provided with the 3rd year progress report.

SubTask 12.1.f, Scientific & Technical Papers Publications

Partners have actively continued submitting and publishing papers on the CHIC results. The table below reports the publications at month 30.

Moreover, the following papers have been submitted and/or are currently under review:

- Eleftherios Ouzounoglou, Dimitra Dionysiou, Georgios S. Stamatakis, "Differentiation resistance through altered retinoblastoma protein function in Acute Lymphoblastic Leukemia: In silico modeling of the deregulations in the G1/S restriction point pathway", BMC Systems Biology, under revision.
- Katerina D Argyri, Dimitra D Dionysiou, Fay D Misichroni and Georgios S Stamatakis, "Numerical simulation of vascular tumour growth under antiangiogenic treatment: addressing the paradigm of single - agent bevacizumab therapy with the use of experimental data", Biology Direct, under revision.
- Beyond D'Amico risk classes for predicting recurrence after external beam radiotherapy for prostate cancer: the Candiolo classifier. Gabriele D, Jercezek-Fossa BA, Krengli M, Garibaldi E, Tessa M, Moro G, Girelli G, EUREKA-2 consortium & Gabriele P. -- Manuscript Draft -- sent to Radiation Oncology, under revision, "Minor Revisions" step.
- Predictability of the timing of recurrence of Prostate Cancer based on the Universal growth Laws. Stura I, Gabriele D & Guiot C. -- Manuscript Draft -- sent to Cancer Research, under revision.
- A Two-Clones Tumor Model: Spontaneous Growth and Response to Treatment (sent to Mathematical Biosciences, under revision).

SubTask 12.1.g, Interfacing with other projects

ICCS has had continuous interaction with the following projects: p-medicine, MyHealthAvatar, DrTherapat, AVICENNA. The Coordinator (ICCS) participated in the final AVICENNA workshop (Barcelona, 4-5 June 2015) where he outlined the vision, the progress and the achievements of the CHIC project. He also participated in the discussions concerning the roadmap for in silico clinical trials. CINECA maintained contact with the project VPH-Share until its end in May 2015.

■ **Task 12.2, Exploitation and IPR issues**

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

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

CINECA drafted a plan for future exploitation activities which is under finalisation with the contribution of Eurice. Concrete actions will follow up in the next months with contributions from all partners. USAAR continued discussions with p-medicine and STaRC about sustainability issues.

■ **Task 12.3, Training activities**

USAAR initiated contact to clinical partners outside of the CHIC consortium to recruit patients for testing and evaluating CHIC tools. This was necessary as the proposed CHIC Summer School could not take place as too few participants registered for the event. A new activity started to enhance participation in a new Workshop. Contact was established with the International Conference and Exhibition on Pediatric Oncology (August 04-06, 2016 in Toronto, Canada). Pediatric Oncology-2016 will focus on "Benchmark practices and accelerating computational approaches for Pediatric Oncology". This three day conference will cover the latest trends and challenges in Pediatric Oncology and as it includes computational approaches for Pediatric Oncology it is an ideal platform for running a workshop at this event.

ICCS will include training activities in the first part of the evaluation sessions of the CHIC winter school to take place in Homburg in February 2016. Web tutorial discussions and a preliminary formulation of the skeleton of the web tutorials have taken place. Eurice supports the local host USAAR in the organisation and dissemination of this event, among other things through an event website, press releases and dissemination via the established CHIC dissemination channels.

Summary of significant results

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

Dissemination of the overall purpose of the CHIC project to audiences comprising academics from several disciplines, as well as clinicians working in the field of oncology and representatives from industry is actively ongoing. As a result a relevant number of dissemination items can be reported together with scientific papers publications and participation to conferences.

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

Contacts to people outside the consortium were initiated. A proposed workshop at the International Conference and Exhibition on Pediatric Oncology is under development.

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

The active dissemination of the clinical relevance of the CHIC project will be one of the focal points in dissemination. The 3rd project newsletter with its clinical emphasis as well as the CHIC workshop at the Pediatric Oncology Conference 2016 are only two examples of such targeted dissemination efforts. As mentioned in the reviewers' comments, exploitation is becoming one of the central activities for WP12. Exploitation in CHIC will be composed of the individual exploitation plans from the project partners and by joint exploitation of foreground. Following WP4 work on IPR and the preliminary plans prepared in the second year, CINECA has prepared a detailed plan with which to build the PUDF update and go towards a concrete exploitation plan for the CHIC project. This plan will require inputs and collaboration of all partners in the next months. Preliminary output on the exploitation activities will be presented at the next intermediate review meeting.

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

The delivery dates of two of the WP12 related milestones have been wrongly inserted in the original DoW. According to the DoW, MS31, the First CHIC summer school, was supposed to be held in M18, whereas the CHIC Workshop (MS32) was supposed to be held in M30. However, the 6th IARWISOCI Workshop (The CHIC Workshop, MS32) already took place as the first in a series of three larger training events (MS31, MS32 and MS33). Therefore, the amended CHIC Description of Work will contain the appropriate delivery dates for MS31 (M30) and MS32 (M18).

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

The First CHIC Summer School (MS31) was planned to be held in September, 2015. However, despite dissemination efforts made by all partners, too few participants signed up for the event. The venue for the First Summer School could be cancelled free of charge. Eurice took down the event website but will reuse it later.

Corrective actions

The organizers decided to postpone and also re-locate the Summer School in order to attract a wider audience. The workshop is planned for late winter/early spring 2016.

Statement on the use of the resources

Planned versus actual efforts in WP12			
Partner	Planned PM Total*)	Planned PM Period 3 (total)	Actual PM M25-M30
1-ICCS	8.19	2.40	1.38
2-Eurice	12.00	3.00	1.88
3-USAAR	3.00	1.00	n/a
5-BED	6.00	3.00	n/a
6-USFD	7.00	2.20	1.01
7-FORTH	6.00	2.00	0.00
8-LUH	6.00	2.00	0.75
9-UPENN	6.50	1.50	n/a
10-UOXF	6.00	2.00	0.00
11-UNITO	6.00	2.00	1.02
12-UBERN	5.00	2.00	1.00
13-Custodix	6.00	2.00	0.06
14-Philips	6.00	2.00	0.28
15-UCL	2.00	0.50	0.00
16-CINECA	6.00	1.00	0.09
17-TEI-C	1.00	0.50	0.00
Total	92.69	29.10	7.47

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

2. Project management

Consortium management tasks and achievements

The consortium management is covered by WP1 and includes

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

The following achievements were made during M25-30:

The **3rd CHIC review** (after M24) took place on July 8, 2015. The day before, the work package leaders and several other CHIC partners met in Brussels to prepare for the review by putting together a common project presentation.

At the review meeting itself, the coordinator, Research Professor Dr. Georgios Stamatakos (ICCS) gave an overview of the progress achieved in the first year of the project, before members of the CHIC consortium presented the work done in year 2 of the project following a number of largely technical demonstrators. The overall assessment of the project as communicated in the review report was a positive one. However, the reviewers strongly advise the project consortium to focus its endeavours for the remaining 2 years of CHIC with the goal of ensuring immediate clinical relevance of the project output. Following these key recommendations from the CHIC reviewers, the partners have been involved in intense discussions concerning the way forward. As stated in the WP2 report, a comprehensive 'roadmap' describing the CHIC strategy for the remainder of the project will be submitted in the form of a new deliverable, D2.5, "Clinical relevance of the CHIC project – Describing the integrated workflows of the scenarios from a clinical perspective". With regard to the reviewers' recommendations, management partner Eurice specifically asked the consortium members to include a summary of actions taken and to be taken to follow these recommendations in each WP report.

A **5th Progress Meeting (MS2)** was held on 21-23 October 2015 at CINECA in Bologna, Italy. The entire meeting was planned around the recommendations from the 3rd CHIC review, with special focus on the clinical relevance of the project and how to streamline efforts in all WPs to ensure successful, sustainable and high-impact project outcomes. Prof. Metin Akay, member of the CHIC External Advisory Board, attended the meeting, providing valuable input to the CHIC partners. In a dedicated **technical meeting**, which was held on the third day of the meeting, FORTH, in their role of technical integrator, took charge of collecting input from the technical partners as well as from the modelling partners and clinicians in order to develop a comprehensive action plan a) until the next CHIC review, which will probably be held early in 2016, and b) until the end of the CHIC project in general.

The **6th progress meeting** of CHIC will be held in Bern in March 2016. The consortium is currently agreeing on a suitable date. Depending on the outcome of the 4th project review, the scope and duration of the meeting will be defined.

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

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

Within the usual regular and close collaboration between ICCS and Eurice, **scientific and contractual management** of CHIC was implemented effectively and according to plan. ICCS has been in regular contact with the project officer regarding several administrative issues such as the agreement on the review meeting dates, and the organization of a CHIC workshop in the context of the International Conference and Exhibition on Paediatric Oncology, to take place in Toronto, Canada on August 4-6, 2016. Moreover, ICCS has been scientifically coordinating the entire project through a series of communication procedures such as emailing, regular teleconferencing and Skype-conferencing. Decisions at the consortium level have been reached through electronic voting or preference stating platforms such as doodle.

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

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

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

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

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

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

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

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

No serious problems have occurred in project management during M25-M30.

However, it has to be noted that several modifications were made to the original CHIC DoW, also following the remarks from the CHIC reviewers in their latest review report. These changes are currently being implemented in the 2nd Amendment to the CHIC Grant Agreement.

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

Changes in the consortium

None.

List of project meetings, dates and venues during M25-M30

Title	Date	Venue	Local organizer
5 th Progress Meeting	21-23 October 2015	Cineca Supercomputing Centre, Bologna, Italy	CINECA
CHIC Technical Telco	29 October 2015	Skype	ICCS
Conference Call: Preparation of 5 th Progress Meeting	18 September 2015	Skype	Eurice
Semantics (metadata discussion)	16 September 2015	Skype	UCL
CHIC Technical Telco	10 September 2015 and 24 September 2015	Skype	ICCS
Deliverable 8.3	10 September 2015	Skype	UCL
WP6 Telephone Conference	31 August 2015	Skype	ICCS
Problems in ObTiMA	25 August 2015 01 September 2015 10 September 2015	Skype	KULeuven and USAAR
CHIC Technical Telco	05 August 2015 and 27 August 2015	Skype	ICCS
WP6 Telephone Conference	28 July 2015	Skype	ICCS
Conference Call: 3 rd Review Meeting Recommendations	17 July 2015	Skype	Eurice, ICCS
3 rd CHIC Review Meeting, including Review Preparation Meeting	07-08 July 2015	DGCNECT, Brussels, Belgium	EC
CHIC Technical Telco	02 July 2015 and 23 July 2015	Skype	ICCS

CHIC Technical Telco	11 June 2015 and 25 June 2015	Skype	ICCS
Data sharing	01 June 2015	Skype	KULeuven and Custodix
CHIC Technical Telco	13 May 2015 and 28 May 2015	Skype	ICCS
Data for biomechanical validation study	07 May 2015	Skype	KULeuven and UBERN
Study Events in ObTiMA	29 April 2015	Skype	KULeuven and USAAR
Data sharing	21 April 2015	Skype	KULeuven and Custodix
CHIC Technical Telco	09 April 2015 and 23 April 2015	Skype	ICCS

*) These meetings took place outside the reporting period.

Related documentation is available in the project management tool.

Cooperation with other projects/programmes

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

Planning and status of resources

Due to the recent changes which had to be implemented in the CHIC Description of Work, several CHIC partners adjusted their PM efforts in order to provide a more realistic budget breakdown. As far as possible, the partners balanced increased effort in one work package with reduced effort in another work package or shifted free resources in other cost categories to balance additional budget needed for increased personnel hours. Some partners indicated that less expensive staff than originally planned was used which freed resources needed for additional efforts in several work packages. The work package reports include the most recent PM figures. Changes to the original CHIC DoW are clearly highlighted. In sum, the following revisions were made:

ICCS:

Partner 1 ICCS	Planned					Revision after year 3				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP1 Project Management	2,00	2,00	2,00	2,00	8,00	2,00	2,00	2,15	2,78	8,93
WP2 User Needs and Requirements	1,00	0,40	0,40	0,20	2,00	1,00	0,60	0,70	0,90	3,20
WP3 Clinical and Fundamental Science Scenarios	0,50	0,50	0,50	0,50	2,00	0,50	0,70	0,40	1,00	2,60
WP4 Legal and Ethical Framework	0,70	0,60	0,50	0,20	2,00	0,70	0,70	0,40	0,20	2,00
WP5 IT Architecture	0,80	0,80	0,80	0,60	3,00	0,80	1,00	0,70	0,90	3,40
WP6 Models and Hypermodel Design	13,00	10,50	10,50	10,00	44,00	13,00	12,00	13,00	19,01	57,01
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	1,50	1,50	1,50	1,50	6,00	1,50	1,60	1,70	2,40	7,20
WP8 Model and Data Repositories	4,00	3,50	3,50	3,00	14,00	4,00	4,50	4,50	6,30	19,30
WP9 Image Processing and Visualization	0,70	0,80	0,80	0,70	3,00	0,70	0,90	1,00	1,40	4,00
WP10 Integrated Platform	1,80	1,80	1,80	1,60	7,00	1,80	1,90	1,90	1,80	7,40
WP11 Clinical Adaption and Validation	1,00	1,50	2,20	2,30	7,00	1,00	1,50	2,20	3,00	7,70
WP12 Dissemination and Exploitation	1,60	2,80	1,80	1,80	8,00	1,60	2,80	2,40	1,39	8,19
Total	28,60	26,70	26,30	24,40	106,00	28,60	30,20	31,05	41,08	130,93

Along with their revised PM effort plan, ICCS provided the following justifications:

-
- **WP1:** Slight increase of person months by shifting part of senior personnel work (related to more trivial management tasks) to an assistant researcher in order to best exploit the potential of each member of the group.
 - **WP2:** Redistribution of effort among ICCS's team members in order to optimally address the issue of the clinical relevance of the project (and contribute to the corresponding additional deliverable), as requested by the reviewers during the last project review.
 - **WP3:** More precise calculation.
 - **WP5:** Increased technical contribution to task 5.2 "Security tools and services": Since CHIC is evolving into a platform to handle personal data, additional security effort will be required for the storage of experiments involving personal data to the in silico trial repository. In addition, the integration of the security framework into the model and in silico trial repositories requires additional effort due to limited support for security standards (such as XML signature, encryption and SAML) in Python.
 - **WP6:** Redistribution of effort among ICCS's members: Effort shifted from senior to more technical personnel (researchers and assistant researchers developing simulation codes) in order to a) respond to the recommendations of the reviewers after the last review of the project, and b) adapt WP6 work to the final technical decisions regarding the CHIC platform.
More specifically:
 - 1) Increased technical effort (simulation code development) due to the introduction of the new metabolic model and its interconnection with the other models
 - 2) Considerably increased technical implementation effort due to the adoption of a multiscale coupling library (MUSCLE) as a dynamic message passing strategy, which results in significant technical adaptations in the model's code.
 - 3) Due to the adoption of additional data analysis and exploitability methods pertaining to the molecular level (e.g. statistical and deterministic miRNA data exploitation techniques) as well as to the rest of the levels, substantially increased technical work is needed for integrating the ICCS hypomodels in the multi-modeler hypermodels.
 - 4) Adaptation of ICCS models' output to the requirement imposed by the need to increase the clinical relevance of the project.
 - **WP7:** Redistribution of effort among ICCS's members in order to respond to the technical needs to:
 - 1) Create the necessary web services needed to expose the contents of the model/tool repository (descriptive information of parameters, models, etc.) to the models annotation ontology component.
 - 2) Interact with WP7 for the integration of several ICCS models into a multiscale coupling library.
 - 3) Work for the annotation of ICCS models
 - **WP8:** Redistribution of effort among ICCS's members: Effort shifted from senior researchers to more technical personnel (assistant researchers involved in code development) in order to respond to the following technical needs which appeared as the project involved:
 - 1) The progress of the CHIC project and the evolution of its individual components, along with the modular approach followed in the development of the repositories, dictate the need for constant revision of the repositories and making all necessary new additions. Features such as semantic annotation of models, development of strongly coupled models, as well as the eventual overall expansion of the CHIC platform, posed new requirements for the creation of supplementary modules/web services that will make the CHIC repositories more comprehensive (Task 8.1.a)
 - 2) Since CHIC is evolving into a platform to handle personal data, additional security effort is required for the storage of experiments derived from non-pseudonymized data.

- 3) It has been decided for the *in silico* trial repository to be used as a validation and training tool for hypermodels. This can be done by comparing predictions based on simulations that are stored in the *in silico* trial repository with the actual quantitative therapy outcome of the patient that is stored in the clinical data repository. Using this comparison for all experiments stored in the *in silico* trial repository will help in the evaluation and adaptation of all hypermodels stored in the model/tool repository (Task 8.1.c)
 - 4) Towards a tight integration with RICORDO VPH infrastructure and semantic interoperability, significant technical effort is required in order for model/tool repository to make use of the software interfaces provided by CHIC semantic infrastructure. The usage of the aforementioned interfaces by model/tool repository is required in order for the user to be able to create RDF annotations for some model characteristics (parameters, perspectives, etc.) through the repository's user interface.
- **WP9:** Redistribution of effort among ICCS's members: Effort shifted from senior researchers to technical personnel (researchers, assistant researchers) in charge of developing simulation codes in order to respond to the following technical needs: Interaction of modelers with WP9 with regards to the development of the new segmentation data processing tool and the visualization of models' output.
 - **WP10, WP11, WP12:** More precise calculation.

USFD, Revision after year 2:

Partner 6 USFD	Planned					Revision after year 2				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP1 Project Management	1,00	1,00	1,00	1,00	4,00	2,00	1,80	1,80	1,80	7,40
WP5 IT Architecture	0,00	6,00	4,00	2,00	12,00	0,00	4,00	1,00	1,00	6,00
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	22,00	22,00	22,00	22,00	88,00	30,00	37,00	34,00	33,00	134,00
WP12 Dissemination and Exploitation	0,60	1,80	1,80	1,80	6,00	0,60	2,00	2,20	2,20	7,00
Total	23,60	30,80	28,80	26,80	110,00	32,60	44,80	39,00	38,00	154,40

According to the CHIC DoW, USFD has 4 PM in WP1. Due to a less senior management staff than originally planned, USFD expect a mildly larger effort (7.4 PM) at a similar cost.

WP7 was expected to start immediately, but delays in the recruitment procedures forced USFD to compensate in the first six months with other staffs, and with the recruitment on the project of a PhD student, who will continue to work in the project. Because of this USFD plan a considerable increase of effort in WP7; however, this will not involve any increase of cost, due to the lower salary scale of the PhD student. Regarding WP12, USFD planned a small increase of PM over the DoW (7 PM instead of 6 PM), in relation to the CHIC dissemination within the Insigneo Showcase, especially in the third and fourth year.

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

BED:

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

Due to the revision of several tasks, partners BED and FORTH needed to revise their person month efforts in various work packages. These revisions do not have any impact on the requested funding. For BED, the total number of PM remains unchanged.

FORTH:

Partner 7 FORTH	Planned					Revised in December 2014				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP1 Project Management	0,50	0,50	0,50	0,50	2,00	0,53	0,50	0,50	0,50	2,03
WP2 User Needs and Requirements	1,00	1,00	1,00	0,00	3,00	2,00	1,00	1,00	1,00	5,00
WP5 IT Architecture	3,00	3,00	3,00	1,00	10,00	9,00	8,50	6,50	4,00	28,00
WP6 Models and Hypermodel Design	2,50	2,50	2,50	1,50	9,00	7,61	7,50	6,50	4,00	25,61
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	1,50	1,50	1,50	1,50	6,00	2,00	2,50	1,50	1,50	7,50
WP8 Model and Data Repositories	1,50	1,50	1,50	1,50	6,00	2,00	1,50	2,00	1,00	6,50
WP9 Image Processing and Visualization	5,00	5,00	5,00	5,00	20,00	19,79	8,50	8,50	6,50	43,29
WP10 Integrated Platform	5,00	6,00	6,00	4,00	21,00	17,29	8,00	7,50	4,00	36,79
WP11 Clinical Adaptation and Validation	0,50	0,50	1,00	1,00	3,00	0,57	1,00	0,50	1,00	3,07
WP12 Dissemination and Exploitation	1,00	1,00	2,00	2,00	6,00		2,00	2,00	2,00	6,00
Total	21,50	22,50	24,00	18,00	86,00	60,79	41,00	36,50	25,50	163,79

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

In connection with the new tasks which had to be created in order to accommodate various review meeting recommendations, FORTH has taken up additional work unforeseen in the original DoW. Apart from several task extensions, especially the Clinical Research Application Framework ("CRAF") that will be developed by FORTH in order to support a unified and simple user experience and provide a "CHIC-in-a-box" abstraction for the clinicians to use in clinical research, will demand additional resources. The CHIC consortium is, therefore, currently negotiating internal budget shifts in order to accommodate these new tasks and responsibility also financially. FORTH provided a new PM effort table which will be one of the subjects of the 2nd Amendment of the CHIC Grant Agreement currently in preparation.

Partner 7 FORTH	Planned original DoW	Revised in December 2014	2nd Amendment
	Total	Total	Total
WP1 Project Management	2,00	2,03	2,03
WP2 User Needs and Requirements	3,00	5,00	5,00
WP5 IT Architecture	10,00	28,00	33,00
WP6 Models and Hypermodel Design	9,00	25,61	28,61
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	6,00	7,50	11,50
WP8 Model and Data Repositories	6,00	6,50	8,50
WP9 Image Processing and Visualization	20,00	43,29	45,29
WP10 Integrated Platform	21,00	36,79	48,79
WP11 Clinical Adaptation and Validation	3,00	3,07	3,07
WP12 Dissemination and Exploitation	6,00	6,00	6,00
Total	86,00	163,79	191,79

UPENN:

Partner 9 UPENN	Planned					Planned				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP2 User Needs and Requirements	1,50	1,00	1,50	1,00	5,00	1,50	1,00	1,50	1,00	5,00
WP3 Clinical and Fundamental Science Scenarios	0,50	0,50	0,50	0,50	2,00	0,50	1,50	0,50	0,50	3,00
WP4 Legal and Ethical Framework	0,50	0,50	0,50	0,50	2,00	0,50	1,00	0,50	0,50	2,50
WP6 Models and Hypermodel Design	15,00	15,00	15,00	16,00	61,00	15,00	20,00	15,00	19,00	69,00
WP8 Model and Data Repositories	1,00	0,00	1,00	1,00	3,00	1,00	0,00	1,00	1,00	3,00
WP11 Clinical Adaptation and Validation	1,00	1,00	1,00	2,00	5,00	1,00	3,00	1,00	3,50	8,50
WP12 Dissemination and Exploitation	1,50	1,50	1,50	1,50	6,00	1,50	2,00	1,50	1,50	6,50
Total	21,00	19,50	21,00	22,50	84,00	21,00	28,50	21,00	27,00	97,50

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

research associate David Slochower for 2.5 PM, which accounts for the added 5.5 PM over 27 PM bringing the total to 32.5 PM.

CUSTODIX:

Partner 13 CUSTODIX	Planned					Revised in year 3				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP2 User Needs and Requirements	0,25	0,25	0,25	0,25	1,00	0,25	0,25	0,25	0,25	1,00
WP4 Legal and Ethical Framework	0,50	0,50	0,50	0,50	2,00	0,50	0,50	3,00	3,00	7,00
WP5 IT Architecture	2,00	3,50	3,50	3,00	12,00	2,00	3,50	7,00	6,50	19,00
WP8 Model and Data Repositories	0,50	1,00	1,00	0,50	3,00	0,50	1,00	1,00	0,50	3,00
WP12 Dissemination and Exploitation	0,50	1,50	2,00	2,00	6,00	0,50	1,50	2,00	2,00	6,00
Total	3,75	6,75	7,25	6,25	24,00	3,75	6,75	13,25	12,25	36,00

Custodix expected CHIC to share data in DICOM and CSV format. As extensive effort was performed in previous projects (such as p-medicine) in getting these data formats de-identified, it was expected that all these datasets could be de-identified and shared with limited effort (no development).

Over the past 2 years though, CHIC has decided to share all clinical data in the ODM XML format. ODM XML has over CSV the big advantage that more metadata information can be exchanged.

The de-identification of ODM XML data though implies that Custodix will have to develop and test new de-identification schemes. In addition to the additional development effort, it is also significantly more complicated to validate whether ODM data files have been sufficiently de-identified and can be shared with the consortium partners.

Due to the above additional development and validation effort required, Custodix expects to spend a total effort of 6PM for Period 3 and 6PM for Period 4 to be able to de-identify all CHIC datasets.

Next to the extension of the CHIC de-identification tools for supporting ODM XML data the additional WP5 effort will also be used to support the recent CHIC evolution into a platform to handle personal data. Although the current platform already implements a lot of security measures, additional security effort will be required for the storage and use of personal data within CHIC. For example move towards patient oriented auditing, centralized authorization, multi factored and strong authentication and the use of a patient identity management system such as PIMS.

UCL:

Partner 15 UCL	Planned					Revision after year 1				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP7 Hypermodelling Infrastructure (Semantic Interoperability)	3,00	7,00	7,00	7,00	24,00	3,00	9,00	12,00	12,00	36,00
WP8 Model and Data Repositories	3,00	15,00	15,00	15,00	48,00	3,00	9,00	12,00	12,00	36,00
WP12 Dissemination and Exploitation	0,50	0,50	0,50	0,50	2,00	0,50	0,50	0,50	0,50	2,00
Total	6,50	22,50	22,50	22,50	74,00	6,50	18,50	24,50	24,50	74,00

Partner UCL also revised their PM planning after the first year of CHIC after recruitment issues were settled, a new Postdoc hired and details about the task ahead had become clearer. The revision of PM planning only contains shifts within and between work packages 7 and 8 but does not affect the overall number of PMs. However, the total number of PM in WPs7 and 8 will change accordingly.

CINECA:

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

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

TEI-C

Similar to FORTH, TEI-C also faces several modifications to the original DoW. These largely include the extension of tasks due to maintenance and further development work until the end of the CHIC project, the addition of relevant deliverables to monitor project work and output and the implementation of CRAF, the Clinically Relevant Application Framework of CHIC that was introduced after the 3rd CHIC review. Consequently, TEI-C is also involved in negotiations with the rest of the consortium to accommodate these changes financially. Some of the additional resources required have already been agreed between TEI-C and some of the partners. In this context, TEI-C provided an updated version of their PM efforts:

Partner 17 TEI-C	Planned					2nd Amendment to the CHIC GA				
	Period 1	Period 2	Period 3	Period 4	Total	Period 1	Period 2	Period 3	Period 4	Total
WP5 IT Architecture	4,00	4,00	4,00	3,00	15,00	4,00	4,00	6,00	7,00	21,00
WP9 Image Processing and Visualization	0,00	1,00	0,00	0,00	1,00	0,00	1,00	0,00	0,00	1,00
WP10 Integrated Platform					0,00			1,00	3,00	4,00
WP11 Clinical Adaptation and Validation					0,00				1,00	1,00
WP12 Dissemination and Exploitation	0,00	0,00	0,50	0,50	1,00	0,00	0,00	0,50	0,50	1,00
Total	4,00	5,00	4,50	3,50	17,00	4,00	5,00	7,50	11,50	28,00

For more detail, reference is made to the reports on the work packages. This deviation does not have any negative impact on other tasks and do not influence the financial resources originally planned.

In sum, the PM effort table now reads as follows:

Partner	WP1	WP2	WP3	WP4	WP5	WP6	WP7	WP8	WP9	WP10	WP11	WP12	Total partner
Short name													
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
KULeuven	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	33,00	28,61	11,50	8,50	45,29	48,79	3,07	6,00	191,79
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	117,40	235,62	256,70	94,80	113,29	96,19	79,27	92,69	1388,62

Impact of possible deviations from the planned milestones and deliverables

The CHIC reviewers correctly noted in the 3rd CHIC review that most deliverables were submitted with a delay and that, consequently, delays also occurred with regard to the milestones. The CHIC Management Team takes this very seriously and has reminded the consortium several times to keep within the schedule and consider the deliverable deadlines fixed deadlines. Moreover, the partners were asked to re-evaluate the list of deliverables and milestones for the 2nd Amendment to the CHIC GA and make sure that the schedule of project outputs also accommodates the recent modifications made to the work plan in terms of timing, relevance, etc.

Any changes to the legal status of any of the beneficiaries

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

Ongoing development of the Project website

The CHIC website registers a 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. The CHIC partners have also decided to enable access to some of the CHIC tools via the website. This way, clinicians can test and familiarize themselves with the CHIC tools and services. Access to the tools will be implemented within the coming weeks. As the project continues over the next 1.5 years, the website will be constantly revised and updated to reflect the project's progress and meet the consortium's requirements. More information about the current status of the project website can be found in the WP12 report above as well as on the CHIC website at www.chic-vph.eu. The features of the website are described in Deliverable D12.1 "Dissemination Plan".

Statement on the use of the resources

Planned versus actual efforts in WP1			
Partner	Planned PM Total*)	Planned PM Period 3 (total)	Actual PM M25-30
1-ICCS	8.93	2.15	1.13
2-Eurice	38.00	9.50	4.25
6-USFD	7.40	1.80	0.62
7-FORTH	2.03	0.50	0.50
10-UOXF	2.00	0.30	0.16
16-CINECA	1.00	0.20	0.15
Total	59.36	14.45	6.81

*) The total planned PM efforts include all PM changes made until the end of the reporting period (30 September 2015). Further details on planned PM modifications will be delivered in the management section of this report.

Dissemination activities and publications

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

Workshops and conferences

Title	Type	Main leader/ Participants	Event	Venue	Date
Oxygen-filled nanocarriers for medical applications	Oral presentation at scientific event	UNITO	Meet in Italy for Life Sciences	Milano, Italy	30 September 2015
Data Mining in Cancer	Oral presentation at scientific event	USAAR	ECCO Congress	Vienna, Austria	29 September 2015
An RBF-PSO Based Approach for Modeling Prostate Cancer	Oral presentation at scientific event	UNITO	13th International Conference of Numerical Analysis and Applied Mathematics	Rhodes, Greece	23-29 September 2015
Predictive models in medicine: from recurrence probability (static) to timing to relapse (dynamic)	Poster presentation	UNITO	D-Day of the Doctoral School in Life and Health Sciences	Turin, Italy	16 September 2015
Copyright in Hyper-Models	Oral presentation at scientific event	LUH	Herbstakademie 2015	Göttingen, Germany	11 September 2015
Predictive immune modeling in malignant gliomas.	Oral presentation at scientific event	KULeuven	KULeuven Research Seminar	KULeuven	09 September 2015
The Digital Patient	Oral presentation at scientific event	USFD	UK Royal Academy of Medicine, invited talk	London, UK	09 July 2015
In silico clinical trials: reduce, refine and partially replace human experimentation	Oral presentation at scientific event	USFD	21st Congress of the European Society of Biomechanics	Prague, Czech Republic	05 July 2015
Copyright in Multiscale Cancer Modeling	Oral presentation at scientific event	LUH	INFOCOMP 2015	Brussels, Belgium	21-26 June 2015
Biological Simulation – from simple cells to multiscale frameworks	Oral presentation at scientific event	USFD	Invited seminar: Computational Biology Series, University of Oxford	Oxford, UK	09 June 2015
Avicenna research roadmap: the challenges ahead	Oral presentation at scientific event	USFD	Avicenna action event 5	Barcelona, Spain	05 June 2015

Title	Type	Main leader/ Participants	Event	Venue	Date
A multiscale model evaluating phenotypes variations in tumors following multiple xeno-transplantation	Oral presentation at scientific event	UNITO	International Conference of Computational Sciences	Reykjavik, Iceland	01-03 June 2015
Recent developments in in silico Medicine: the impact on the medical device industry	Oral presentation at scientific event	USFD	Invited talk: Recent developments in in silico Medicine: the impact on the medical device industry	Minneapolis, USA	21 May 2015
'In silico clinical trials: The Avicenna Roadmap	Oral presentation at scientific event	USFD	BMES/FDA Frontiers in Medical Devices Conference: Innovations in Modeling and Simulation.	Silver Spring (MD), USA	18 May 2015
CHIC - Computational Horizons in Cancer	Poster presentation	USDF	Insigneo Showcase 2015	Sheffield, UK	07 May 2015
Big Data in Health	Oral presentation at scientific event	LUH	Seminar lecture	Oslo, Norway	May 2015
Brain tumor immunotherapy, what have we learned so far?	Oral presentation at scientific event	KULeuven	24th GPHO Arbeitstagung Experimentelle Neuroonkologie	Minden, Germany	24 April 2015
Copyright in software on the Internet	Oral presentation at scientific event	LUH	ISLACO 2015	St. Petersburg, Russia	16 April 2015
Immunotherapie	Oral presentation at scientific event	KULeuven	Lecture: "Trends in der pädiatrischen Onkologie"	Kinderspital Zürich, Switzerland	08 April 2015

Press activities and other media

Title	Type	Main leader	Reference	Date
Facebook and Twitter accounts	Social media	CINECA	facebook.com/CHIC-project-333884726816111	
9 th issue of the CHIC e-mail newsletter	Newsletter	CINECA	Newsletter available at http://us7.campaign-archive1.com/?u=cd11bc7f760317d47eebe00f9&id=276a7631b3	29 June 2015
2 nd issue of the CHIC annual newsletter	Newsletter	Eurice	Newsletter available at http://chic-vph.eu/fileadmin/chic/downloads/CHIC_Newsletter_2_final.pdf	

CHIC website	Website	Eurice	www.chic-vph.eu	Ongoing
CHIC Flyer	Dissemination material	Eurice	Flyer available for download at http://chic-vph.eu/downloads/	

Publications

Title	Main author	Coauthors	Involved institutions	Title of the periodical or the series	Issue Number	Permanent identifiers (if available)	Year	Publication type
Multiscale Cancer Modeling and In Silico Oncology: Emerging Computational Frontiers in Basic and Translational Cancer Research	Stamatakis G	Graf N, Radhakrishnan R	ICCS, USAAR, UPENN	Journal of Bioengineering and Biomedical Sciences	3	10.4172/2155-9538.1000e114	2013	Peer-reviewed publication
A Hybrid Model for Multimodal Brain Tumor Segmentation	Meier R	Bauer S, Slotboom J, Wiest R, Reyes M	UBERN	Miccai 2013 Workshop on Brain Tumor Segmentation	1		2013	Proceedings of a Conference/Workshop
The Virtual Skeleton Database - An open access repository for biomedical research and collaboration	Kistler M	Bonaretti S, Pfahrer M, Niklaus R, Büchler P	UBERN	Journal of Medical Internet Research	15(11)	doi:10.2196/jmir.2930	2013	Peer-reviewed publication
Dendritic cell vaccination for glioblastoma multiforme: review with focus on predictive factors for treatment response	Dejaegher J	Van Gool S, De Vleeschouwer S	KU Leuven	Immuno Targets and Therapy	3	http://dx.doi.org/10.2147/ITT.S40121	2014	Peer-reviewed publication
Computational Delineation of Tyrosyl-Substrate Recognition and Catalytic Landscapes by the Epidermal Growth Factor Receptor Tyrosine Kinase Domain	Liu Y	Radhakrishnan R	UPENN	Molecular Biosystems	10(7)	http://dx.doi.org/10.1039/c3mb70620f	2014	Peer-reviewed publication
Molecular modeling of ErbB4/HER4 kinase in the context of the HER4 signaling network helps rationalize the effects of clinically identified HER4 somatic mutations on the cell phenotype	Telesco SE	Vadigepalli R, Radhakrishnan R	UPENN	Biotechnology Journal	8(12)	10.1002/biot.201300022	2013	Peer-reviewed publication
Mesoscale computational studies of membrane bilayer remodeling by curvature-inducing proteins.	Ramakrishnan N	Sunil Kumar PB, Radhakrishna	UPENN	Physics Reports	543(1)		2014	Peer-reviewed publication

		n R						
Legal and Ethical Aspects of In Silico Medicine	Nwankwo I	Stauch M, Dahi A, Forgo N	LUH	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation		10.1109/IARWISOC I.2014.7034647	2014	Proceedings of a Conference/Workshop
Integrative functional assessment of ALK mutations for therapeutic stratification in neuroblastoma	Radhakrishna n R	Weiser D, Bressler S, Huwe PJ, Radhakrishna n R, Lemmon MA, Mosse Y	UPENN	Cancer Cell	26	10.1016/j.ccell.2014.09.019	2014	Peer-reviewed publication
Multiscale Computational Models in Physical Systems Biology of Intracellular Trafficking	Tourdot RW	Bradley RP, Ramakrishnan N, Ramakrishnan R	UPENN	IET Systems Biology	8(5)	10.1049/iet-syb.2013.0057	2014	Peer-reviewed publication
Defining the Free Energy Landscape of Curvature Inducing Proteins on Membrane Bilayers	Tourdot RW	Ramakrishnan N, Ramakrishnan R	UPENN	Physical Review E	90		2014	Peer-reviewed publication
Computational Methodology for Mechanistic Profiling of Kinase Domain Mutations in Cancers	Huwe PJ	Radhakrishna n R	UPENN	5th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation			2013	Proceedings of a Conference/Workshop
The Technologically Integrated Oncosimulator: combining multiscale cancer modelling with information technology in the in silico oncology context	Stamatakis G	Dionysiou D, Lunzer A, Bellemann R, Kolokotroni E, Georgiadi E, Erdt M, Pukacki J, Rueping S, Giatili S, Donofrio A,	ICCS, USAAR, FORTH, TEI-C	J Biomed Health Inform	18(3)	10.1109/JBHI.2013.2284276	2014	Peer-reviewed publication

		Sfakianakis S, Marias K, Desmedt C, Tsiknakis M, Graf N						
In Silico Oncology: Exploiting Clinical Studies to Clinically Adapt and Validate Multiscale Oncosimulators	Stamatakis G	Dionysiou D, Lunzer A, Bellemann R, Kolokotroni E, Georgiadi E, Erdt M, Pukacki J, Rueping S, Giatili S, d'Onofrio A, Sfakianakis S, Marias K, Desmedt C, Tsiknakis M, Graf N	ICCS, USAAR, FORTH	Conf Proc IEEE Eng Med Biol Soc	2013	10.1109/EMBC.2013.6610806	2013	Proceedings of a Conference/Workshop
Intellectual Property Rights Issues in Multiscale Cancer Modeling	Lishchuk I	Stauch M, Forgo N	LUH	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation		10.1109/IARWISOC I.2014.7034646	2014	Proceedings of a Conference/Workshop
Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology - a Brief Technical Outline of the Project.	Stamatakis	Dionysiou D, Misichroni F, Graf N, van Gool S, Bohle R, Dong F, Viceconti M, Marias K, Sakkalis V, Forgo N, Radhakrishnan R, Byrne H,	ALL	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation		10.1109/IARWISOC I.2014.7034630	2014	Proceedings of a Conference/Workshop

		Guiot C, Buechler P, Neri E, Bucur A, de Bono B, Testi D, Tsiknakis M						
A Model of Tumor Growth Coupling a Cellular Biomodel with Biomechanical Simulations	Rikhtegar F	Kolokotroni E, Stamatakis G, Buchler P	ICCS, UBERN	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation		10.1109/IARWISOC I.2014.7034638	2014	Proceedings of a Conference/Workshop
Incorporating Data Protection in In Silico Research: A case of the CHIC project	Neri E	Dhaeze W	CUSTODIX	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation		10.1109/IARWISOC I.2014.7034643	2014	Proceedings of a Conference/Workshop
EUREKA-1 database: an epidemiological analysis	Gabriele D	Porpiglia F, Muto G, Gontero P, Terrone C, Annoscia S, Randone D, Benventi S, Arena G, Stura I, Guiot C	UNITO	Minerva Urologica and Nefrologica	Suppl. 1 to No. 1		2015	Proceedings of a Conference/Workshop
Gleason Score and other variables	Gabriele D	Oderda M, Gontero P, Muto G, Collura D, Annoscia S, Arena G, Bollito E, Stura I, Guiot C, Gabriele P	UNITO	Minerva Urologica and Nefrologica	Suppl. 1 to No. 1		2015	Proceedings of a Conference/Workshop
The current role of CT and bone scintigraphy in prostate cancer	Oderda M	Gabriele D, Collura D,	UNITO	Minerva Urologica and Nefrologica	Suppl. 1 to No. 1		2015	Proceedings of a Conference/Workshop

staging		Stura I, Fiorito C, Porpiglia F, Terrone C, Zacchero M, Guiot C, Gabriele P						
Report from the study EUREKA-2 on prostate cancer patients treated by radical radiotherapy: first data analysis	Gabriele D	Garibaldi M, Marra AM, Jereczek-Fossa B, Krengli M, Tessa M, Bona C, Ferrazza P, Balcet V, Ruo Redda MG, Moro G, Gabriele P	UNITO	Minerva Urologica and Nefrologica	Suppl. 1 to No. 1		2015	Proceedings of a Conference/Workshop
Do radiotherapy techniques impact the outcome?	Garibaldi E	Delmastro E, Gabriele P	UNITO	Minerva Urologica and Nefrologica	Suppl. 1 to No. 1		2015	Proceedings of a Conference/Workshop
Modeling prostate cancer within CHIC	Stura I	Gabriele D, Guiot C	UNITO	Minerva Urologica and Nefrologica	Suppl. 1 to No. 1		2015	Proceedings of a Conference/Workshop
A two population Model of Cancer growth with fixed Carrying capacity	Stura I	Gabriele D, Guiot C	UNITO	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation			2014	Proceedings of a Conference/Workshop
A multicenter retrospective study on irradiated prostate cancer: preliminary report	Gabriele P	Ruo Redda MG, Garibaldi M, Gabriele D, Cattari G, Garibaldi E, Guiot C	UNITO	Anticancer Research	34		2014	Proceedings of a Conference/Workshop
Piedmont multicenter retrospective study on operated prostate cancer: first report	Gabriele D	Gontero P, Terrone C, Porpiglia F, Muto G, Guiot C	UNITO	Anticancer Research	34		2014	Proceedings of a Conference/Workshop

A Two-Clones Model of Tumor Growth and Its Response to Treatment	Stura I		UNITO	MPDE'14			2014	Proceedings of a Conference/Workshop
A Generalized Model of Tumor Growth and Response to Treatment using the PUN approach	Stura I	Guiot C	UNITO	VPH Conference			2014	Proceedings of a Conference/Workshop
Is there still a role for computed tomography and bone scintigraphy in prostate cancer staging? An analysis from the Eureka-1 database	Gabriele D	Collura D, Oderda M, Fiorito C, Porpiglia F, Terrone C, Zacchero M, Guiot C, Gabriele P	UNITO	EAU 2015 International Meeting			2014	Proceedings of a Conference/Workshop
Patient-Specific Semi-Supervised Learning for Postoperative Brain Tumor Segmentation	Meier R	Bauer S, Slotboom J, Wiest R, Reyes M	UBERN	Med Image Comput Assist Interv	17	http://www.ncbi.nlm.nih.gov/pubmed/25333182	2014	Peer-reviewed publication
The Standardized Histogram Shift of T2 Magnetic Resonance Image (MRI) Signal Intensities of Nephroblastoma Does Not Predict Histopathological Diagnostic Information	Müller S	David R, Marias K, Graf N	USAAR, FORTH	Cancer Informatics	14(S4)	10.4137/CIN.S19340	2015	Peer-reviewed publication
In silico oncology and in silico medicine: from research to clinics and academia.	Stamatakis G		ICCS	Minerva Urologica e Nefrologica	67 (Suppl. 1 to No 1)		2015	Proceedings of a Conference/Workshop
A brief outline of the CHIC project.	Stamatakis G		ICCS	Minerva Urologica e Nefrologica	67 (Suppl. 1 to No 1)		2015	Proceedings of a Conference/Workshop
Copyright in Multiscale Cancer Modeling	Lishchuk I	Stauch M	LUH	INFOCOMP 2015 Proceedings			2015	Proceedings of a Conference/Workshop
Circulating Serum miRNAs as Potential Biomarkers for Nephroblastoma	Ludwig N	Nourkami-Tutdibi N, Backes C, Lenhof HP, Graf N, Keller A, Meese E	USAAR	Pediatric Blood Cancer	62	10.1002/pbc.25481	2015	Peer-reviewed publication

Personalized Medicine and the way to CHIC. A clinical perspective.	Graf N		USAAR	Minerva Urologica and Nefrologica	67 (Suppl. 1 to No 1)		2015	Proceedings of a Conference/Workshop
Brain tumor immunotherapy: what have we learned so far?	Van Gool S		KU Leuven	Frontiers in Oncology	5:98	10.3389/fonc.2015.00098	2015	Peer-reviewed publication
A Brownian motion based mathematical analysis as a potential basis for modeling the extent of infiltration of glioma cells into the surrounding normal brain tissue	Antonopoulos M	Stamatakis G	ICCS	Cancer Informatics	14(S4)	10.4137/CIN.S19341	2015	Peer-reviewed publication
Dendritic cell vaccination for glioblastoma multiforme: clinical experience and future directions	Dejaegher J	Solie L, De Vleeschouwer S, Van Gool S	KU Leuven	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation			2014	Proceedings of a Conference/Workshop
The VPH hypermodelling framework for cancer multiscale models in the clinical practice	Tartarini D	Duan K, Gruel N, Testi D, Walker D, Viceconti M	USFD, CINECA	6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation			2014	Proceedings of a Conference/Workshop
Lymphadenectomy extension for prostate cancer predicts pN+ status.	Gabriele D	Muto G, Gontero P, Randone D, Carchedi MT, Fiorito C, Gillo A, Stura I, Gabriele P	UNITO	XXV Congress of the SIUro (Italian Society of Uro-Oncology)			2015	Proceedings of a Conference/Workshop
Perineural and vascular invasion in prostate cancer: a predictive ability evaluation.	Gabriele D	Bollito E, Porpiglia F, Terrone C, Arena G, Venzano F, Annoscia S, Bellei L, Moroni M, Guiot C	UNITO	XXV Congress of the SIUro (Italian Society of Uro-Oncology)			2015	Proceedings of a Conference/Workshop
Predictive value of tertiary Gleason	Gabriele D	Bollito E,	UNITO	J Urology	193(4S)		2015	Proceedings of a

Score.		Porpiglia F, Gontero P, Venzano F, Genesi D, Manzo M, Giacobbe A, Guiot C						Conference/Workshop
A simpler modified Gleason Score performs slightly better than the standard one.	Gabriele D	Bollito E, Terrone C, De Angelis P, Giacobbe A, Bellei L, Graziano M, Gamba P, Gabriele P	UNITO	J Urology	193(4S)		2015	Proceedings of a Conference/Workshop
Percentage of positive prostate biopsies independently predicts biochemical outcome following radiation therapy for prostate cancer.	Gabriele D	Garibaldi M, Girelli G, Taraglio S, Duregon E, Gabriele P, Guiot C, Bollito E	UNITO	Panminerva Med	n/a		2015	Peer-reviewed publication
Is there still a role for computed tomography and bone scintigraphy in prostate cancer staging? An analysis from the EUREKA-1 database.	Gabriele D	Collura D, Oderda M, Stura I, Fiorito C, Porpiglia F, Terrone C, Zaccherio M, Guiot C, Gabriele P	UNITO	World J Urol	n/a		2015	Peer-reviewed publication

3. Deliverables and milestones tables

3.1 Deliverables

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

Table 1. Deliverables										
No.	Deliverable name	WP no.	Lead participant	Nature	Dissemination level	Due date Annex I	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
D2.1	State of the art knowledge for building hypermodels	2	7-FORTH	R	PU	30.11.2013		Yes	05.02.2014	FORTH, the partner leading this deliverable, informed the coordinator that a one-month extension was necessary, a request to which the coordinator agreed and which was passed on to the EC project officer. The main issue of delay was that although the partners started the discussion on this deliverable at a very early stage there was slow progress especially due to the preparation of the critical 6 month-project review in November. Since this deliverable has a deep impact on the architectural design and most aspects of the project the partners preferred to delay its submission in order to continue the internal discussions and agree on its content.
D2.2	Scenario based user needs and requirements	2	3-USAAR	R	PU	30.11.2013		Yes	13.01.2014	Due to the missing contributions of a crucial partner, the deliverable was delayed.
D2.3	Requirements for enhancing hypermodels beyond the domain of cancer	2	14-PHILIPS	R	CO	30.09.2014		Yes	02.12.2014	An extension of the original deadline (M18) was requested because the partners responsible for the deliverable agreed to go beyond the mentioned atomic/granular models, thereby showing common ways in

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
										reusing models in other domains. Therefore, further information from modelers had to be gathered and incorporated into the deliverable.
D2.4	Acceptance of hypermodels by patients and physicians	2	3-USAAR	R	PU	30.09.2016		No		
D2.5	Clinical relevance of the CHIC project – Describing the integrated workflows of the scenarios from a clinical perspective	2	3-USAAR	R	PU	31.12.2015		No		New deliverable, which is being proposed by the CHIC partners and which will be formally incorporated into the CHIC DoW with the 2 nd Amendment to the CHIC Grant Agreement.
D3.1	Report on Scenarios and data from defined patients	3	4-KULEUVEN	R	PU	31.03. 2016		No		
D3.2	Report on Scenarios and data from other cancer types for usage by the CHIC infrastructure	3	11-UNITO	R	PU	31.03.2016		No		
D3.3	Demonstration of the developed Meta- and Hyper-Multiscale Models and Repositories	3	1-ICCS	O	PU	31.03.2017		No		
D4.1	Initial analysis of the ethical and legal requirements for the	4	8-LUH	R	PU	30.09.2013		Yes	30.09.2013	

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
	sharing of data									
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	May 31 and June 1, 2014, were weekend days, so the deliverable was sent to the EC on Monday, June 2, 2014.
D4.3.2	Development of the data protection and copyright framework for CHIC - second Iteration	4	8-LUH	R	PU	30.09.2016		No		
D4.4	Whitepaper Recommendations for an amended European legal Framework	4	8-LUH	R	PU	31.03.2016		No		
D5.1.1	The CHIC technical architecture – initial version	5	7-FORTH	R	PU	31.03.2014		Yes	13.06.2014	The partners asked for an extension of the deadline of D5.1.1 in order to incorporate adequate amounts of feedback from an end-user perspective as requested in the 6-month review meeting of CHIC. A request for extension was sent to the EC.
D5.1.2	Deployment models of the CHIC technical architecture and its private cloud	5	7-FORTH	R	PU	31.07.2016		No		D5.1.2 is a new deliverable which will be requested in the 2 nd Amendment to the CHIC GA.
D5.1.3	The final CHIC	5	7-FORTH	P	RE	31.12.2016		No		In the original CHIC DoW, this deliverable

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
	technical architecture (including the security tools and cloud infrastructure)									was D5.1.2. Due to the addition of another deliverable, renumbering was necessary. There were no further changes to this deliverable.
D5.2	Security guidelines and initial version of security tools	5	13-CUSTODIX	R	CO	30.09.2014		Yes	01.10.2014 05.05.2015	A first version of D5.1 was submitted in 2014. However, an updated version of D5.2 was produced after a second internal review and sent to the EC in May 2015. The updated version contains the following modifications: Updated security vocabular, updated integration tutorials, added audit Json schema
D5.2.1	Final version of security tools and guidelines	5	13-CUSTODIX	P	CO	30.09.2016		No		D5.2.1 is a new deliverable which will be requested in the 2 nd Amendment to the CHIC GA.
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	The lead of this deliverable is to be changed to FORTH in the 2 nd CHIC amendment.
D6.1	Cancer hypomodelling and hypermodelling strategies and initial component models	6	1-ICCS	R	CO	30.09.2013		Yes	22.10.2013	D6.1 is a very extensive report and is expected to serve as the initial scientific basis for the entire project. The coordinator firmly believes that the quality, the extent and the depth of the document will have an important impact on most of the subsequent CHIC work and deliverables. Therefore, D6.1 should be of the highest quality possible and an extension of the deadline for submission proved to be necessary.

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
D6.2	CHIC cancer component models: initial tested versions	6	1-ICCS	R	CO	30.11.2014		Yes	05.01.2015	This deliverable was postponed by about 3 weeks due to its complex and multidisciplinary nature as well as due to the Christmas break. The EC officer was informed accordingly.
D6.3	Initial standardized cancer hypermodels	6	1-ICCS	R	CO	31.05.2016		No		
D6.4	Clinical adaptation 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	D7.1 could only be submitted after the submission of D5.1.1, "The CHIC technical architecture – initial version," in order to ensure consistency between the CHIC architecture described in D5.1.1 and the components participating in the Hypermodeling infrastructure, which is a subset of the overall architecture.
D7.2	First Release Hypermodelling framework deployed on test nodes	7	16-CINECA	P	RE	31.03.2015		Yes	08.06.2015	The submission of this deliverable was postponed by 2 months and the EC was informed accordingly on 26 March 2015. The reason for this delay was an ongoing consensus process on the architectural design which had to be fully resolved before work on D7.2 could be started.
D7.3	Hypermodels annotation services	7	15-UCL	P	RE	31.03.2016		No		
D7.4	Final Hypermodelling framework deployed on test node	7	16-CINECA	O	RE	31.08.2016		No		

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
D8.1	Design of the CHIC repositories	8	1-ICCS	R	CO	31.07.2014		Yes	20.11.2014	The submission of this deliverable was postponed due to unforeseen workload at the partner in charge. After the CHIC review meeting held on the 3rd of September 2014 and the very valuable comments that we received from the reviewers during the review meeting concerning the data representation (both clinical data and models), the partners decided to wait for the official review report in order to understand more precisely the suggestions of the reviewers. In the meantime a draft version of the deliverable was circulated by email among the involved partners, so the postponement did not cause any delays on the work described in the DoW.
D8.2	Prototype implementation of the CHIC repositories	8	12-UBERN	O	CO	31.03.2015		Yes	04.05.2015	The deliverable was delayed by about 4 weeks. The request for a later submission results from the heavy workload at ICCS, one of the partners strongly involved in the writing of D8.2, that followed a recent change in staff.
D8.3	Implementation of the interfaces of the CHIC repositories	8	15-UCL	R	PU	30.09.2015		Yes	28.09.2015	
D8.4	Report on the final system	8	1-ICCS	R	PU	30.09.2016		No		
D9.1	User requirements for the visualization toolkit and image	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 Annex I	delivery from	Delivered Yes/No	Actual / Forecast delivery date	Comments
	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 tumor response quantitative platform	9	7-FORTH	P	RE	31.01.2017		No		The delivery date of this deliverable was moved from M36 to M46. This is one of the requested modifications in the 2 nd Amendment to the CHIC GA.
D10.1	The CHIC portal	10	7-FORTH	O	RE	30.11.2013		Yes	02.12.2013	
D10.2	Design of the orchestration platform, related components and interfaces	10	14-PHILIPS	O	PU	30.09.2014		Yes	04.12.2014	An extension of the original deadline (M18) was requested because new needs related to the interfaces and the orchestration of the different components were identified during the Technical Meeting in Leuven and it was crucial to incorporate the necessary changes in the deliverable, having in mind the reviewers' recommendation on paying special attention in models and components integration.
D10.3	The CHIC Encryption Services	10	13-CUSTODIX	O	CO	31.03.2015		Yes	07.04.2015	The deliverable was submitted directly after the Easter break.
D10.4	The PhysionSpace enabled storage on public clouds	10	7-FORTH	R	CO	31.03.2016		No		As the option of deploying the CHIC infrastructure on public clouds has been dismissed, D10.4 is not relevant any longer and will be deleted from the list of deliverables in the 2 nd Amendment to the CHIC GA.

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
D10.4	The CHIC Hypermodelling Editor and orchestration environment	10	7-FORTH	R	RE	30.11.2016		No		As public cloud storage has been dismissed, WP10 now features a new deliverable D10.4. This change will be requested for the 2 nd Amendment to the CHIC GA.
D10.5	The CHIC Clinical Research integrated platform	10	7-FORTH	P	RE	31.01.2017		No		The title of D10.5 was slightly modified to reflect the clinical orientation of the integrated platform. Moreover, since a new deliverable D10.4 was introduced, D10.5 was postponed to be delivered at the end of M46 instead of M44. This change will be requested for the 2 nd Amendment to the CHIC GA.
D11.1	Evaluation and validation criteria for clinical adaptation	11	3-USAAR	R	PU	31.03.2014		Yes	02.06.2014	In accordance with the coordinator, D11.1 was postponed by 2 months. The EC was informed accordingly.
D11.2	Report on the first evaluation workshops round	11	3-USAAR	R	RE	30.09.2014		Yes	01.12.2014	The original submission date was 30 September 2014 (M18). However, the deliverable submission was extended by about two months. The reason for the extension of the original deadline was that the CHIC consortium met for a first round of evaluations of the CHIC tools in mid-October, during the CHIC Progress Meeting in Leuven, Belgium. The corresponding report, which is D11.2, was then written after this evaluation workshop.
D11.3	Report on the second evaluation Workshops round	11	3-USAAR	R	RE	31.03.2016		No		

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
D11.4	Validation of CHIC infrastructure as a whole	11	1-ICCS	R	RE	31.03.2017		No		
D12.1	Dissemination Plan	12	16-CINECA	R	PU	30.09.2013		Yes	01.10.2013	
D12.2	Dissemination Kit available	12	2-EURICE	O	PU	31.03.2014		Yes	25.03.2014	
D12.3	Preliminary Plan for the Use and Dissemination of Foreground	12	16-CINECA	R	CO	31.03.2015		Yes	30.04.2015	Due to the slow feedback of some of the CHIC partners, the deliverable was delayed by about 4 weeks. The EC was informed accordingly.
D12.4	Draft Plan for the Use and Dissemination of Foreground	12	16-CINECA	R	CO	31.03.2016		No		
D12.5	Final Plan for the Use and Dissemination of Foreground	12	16-CINECA	R	CO	31.03.2017		No		
D12.6	Periodic Newsletters	12	2-EURICE	R	PU	31.03.2014 31.03.2015 31.03.2016 31.03.2017		Yes (2 nd issue)	16 June 2015	The second issue of the CHIC newsletter is delayed by about 6 weeks, as valuable contributions to its content are missing.

3.2 Milestones

Milestone no.	Milestone name	WP no.	Lead beneficiary	Delivery date from Annex I dd/mm/yyyy	Achieved Yes/No	Actual/ Forecast achievement data dd/mm/yyyy	Comments
MS1	Kick-Off Meeting	1	2-Eurice	01.04.2013	Yes	10-12/04/2013	The Kick-Off Meeting was held at the Royal Olympic Hotel in Athens, Greece from 10-12 April 2013
MS2	Progress meetings	1	2-Eurice	30.09.2013	Yes	17-18/10/2013 20-21/02/2014 15-17/10/2014 26-27/03/2015	The 1 st progress meeting at FORTH, Heraklion, Greece, from 17-18 October 2013 2 nd progress meeting at BED, Luton, UK, from 20-21 February 2014 3 rd progress meeting at KU Leuven, Leuven, Belgium, from 15 to 17 October 2014 4 th progress meeting at UNITO, Turin, Italy, from 26-27 March 2015
MS3	User needs and Requirements are defined	2	3-USAAR	30.11.2013	Yes		
MS4	Hypermodels are accepted by users	2	3-USAAR	30.09.2016	No		
MS5	Scenarios and data from nephroblastoma, GBM and NSCLC are available	3	4-KULEUVEN	31.03.2015	Yes	31/03/2015	
MS6	Exploitation of the CHIC infrastructure	3	4-KULEUVEN	31.03.2016	No		

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
	by further cancer types						
MS7	Meta- and Hyper-Multiscale Models can be Demonstrated	3	4-KULEUVEN	31.03.2017	No		
MS8	The CHIC Data protection and intellectual property framework	4	8-LUH	31.05.2014	Yes	31.05.2014	D4.1, D4.2 and D4.3.1 are available.
MS9	Initial CHIC Architecture and security guidelines	5	7-FORTH	30.09.2014	Yes	01.10.2014	D5.1.1 and D5.2 are available.
MS10	Final version of the CHIC Architecture	5	7-FORTH	30.09.2016	No		
MS11	Initial component models available for all cancer modelling branches	6	1-ICCS	30.09.2013	Yes	22.10.2013	D6.1 is available
MS12	Rational, numerical and clinical experience based check of the component models complete	6	1-ICCS	30.11.2014	Yes	05/01/2015	D6.2 is available
MS13	Availability of hypermodels for all clinic. scenarios compliant w. the guidelines to be prov. by WP7	6	1-ICCS	31.07.2016	No		
MS14	All hypermodels	6	1-ICCS	31.01.2017	No		

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
	have been quantitatively clinically adapted						
MS15	First hypermodel infrastructure deployed	7	7-FORTH	31.03.2014	Yes	02.07.2014	D7.1 is available.
MS16	Folksonomy and Ontology annotation and search services deployed	7	5-BED	31.03.2015	Yes	08/06/2015	D7.2 is available
MS17	Hypermodel editor, development and execution application ready	7	7-FORTH	31.03.2016	No		
MS18	Metahypermodels annotation completed	7	6- USFD	31.03.2017	No		
MS19	Design of the CHIC repositories Completed	8	1-ICCS	31.07.2014	Yes	21.11.2014	D8.1 is available
MS20	Deployment of the CHIC repositories	8	15- UCL	31.07.2015	Yes	31.07.2015	D8.2 is available
MS21	Integration with security and ethical framework	8	1-ICCS	30.09.2016	No		
MS22	Scalable & uncertainty visualization techniques	9	5-BED	31.03.2015	Yes	31.03.2015	Visual analytics techniques were verified by technical experiments on the data used within the project.
MS23	Image segmentation & registration Techniques	9	12- UBERN	30.09.2014	Yes	30.09.2014	Image segmentation and registration techniques were verified by technical

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
							experiments on the data used in the project.
MS24	Initial version of the tumor response quantitative platform	9	7-FORTH	31.03.2015	Yes	31.03.2015	Testing results of the initial version of the platform are available.
MS25	The CHIC Orchestration Platform and Encrypted Data Services	10	7-FORTH	31.03.2015	Yes	31.03.2015	D10.1, D10.2 and D10.3 are available.
MS26	Public cloud Deployment	10	7-FORTH	31.03.2016	No		D10.4 is available.
MS27	Evaluation and validation criteria for clinical adaptation are ready	11	3-USAAR	31.03.2014	Yes	02.06.2014	D11.1 is available.
MS28	First evaluation Workshop	11	3-USAAR	30.09.2014	Yes	01.12.2014	The first evaluation workshop was held during the CHIC progress meeting at KU Leuven.
MS29	Second evaluation Workshop	11	3-USAAR	31.03.2016	No		
MS30	Internal collaborative area and external website	12	2-EURICE	30.06.2013	Yes	28.06.2013	Website is online and operational: www.chic-vph.eu
MS31	First CHIC summer School	12	3-USAAR	30.09.2014 (now 30.09.2015)	No	September 2015	The Project Management Team informed the PO, Mr Jaakko Aarnio, that MS31 and MS32 would have to be turned around. This will also be reflected in the 2 nd Amendment to the CHIC GA. The Summer School

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
							was planned for July, 2015, but had to be postponed due to a lack of participants. The Summer School will now become a winter school and is planned for early 2016.
MS32	CHIC workshop	12	1-ICCS	30.09.2015 (now 30.09.2014)	Yes	3.-4.11.2014	6 th IARWISOCI Workshop – The CHIC Workshop took place in Athens, Greece. The Project Management Team informed the PO, Mr Jaakko Aarnio, that MS31 and MS32 would have to be turned around. This change will be reflected in the 2 nd Amendment to the CHIC GA.
MS33	Second CHIC summer school	12	3-USAAR	30.09.2016	No		

4. Explanation of the use of the resources

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

4.1 Budget Overview

Cost Budget Follow-up Table								
Contract n°	600841	Project acronym	CHIC			CHIC		
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)				Percentage spent	Remaining Budget (EUR)
			Period 1	Period 2	Period 3	Total	Total/ Budget	
			M1-M12	M13-M24	M25-M30			
ICCS	Total Person-month	106,00	30,27	37,22	14,24	81,73	77%	24,27
	Personnel	636.000,00	117.446,00	144.082,00	60.750,55	322.278,55	51%	313.721,45
	Other direct costs	227.000,00	22.114,00	27.490,00	3.959,83	53.563,83	24%	173.436,17
	Subcontracting	6.000,00	0,00	2.896,00	3.200,00	6.096,00	102%	-96,00
	Adjustments	0,00	0,00	0,00		0,00	0%	0,00
	Indirect costs	517.800,00	83.734,00	102.942,00	38.826,23	225.502,23	44%	292.297,77
	Total Costs	1.386.800,00	223.294,00	277.410,00	106.736,61	607.440,61	44%	779.359,39
Eurice	Total Person-month	50,00	12,88	11,40	6,13	30,41	61%	19,59
	Personnel	324.500,00	65.313,00	58.709,00	33.588,75	157.610,75	49%	166.889,25
	Other direct costs	39.173,00	5.314,00	1.892,00	547,90	7.753,90	20%	31.419,10
	Subcontracting	6.000,00	0,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	1.938,00	0,00	1.938,00		-1.938,00
	Indirect costs	275.825,00	39.978,00	37.057,00	13.489,24	90.524,24	33%	185.300,76
	Total Costs	645.498,00	110.605,00	99.596,00	47.625,89	257.826,89	40%	387.671,11
USAAR	Total Person-month	135,00	11,29	44,10		55,39	41%	79,61
	Personnel	725.498,00	64.750,00	230.749,00		295.499,00	41%	429.999,00
	Other direct costs	326.764,00	18.692,00	57.705,00		76.397,00	23%	250.367,00
	Subcontracting	5.682,00	0,00	0,00		0,00	0%	5.682,00
	Adjustments	0,00	0,00	0,00		0,00	0%	0,00
	Indirect costs	631.357,00	50.065,00	173.071,00		223.136,00	35%	408.221,00
	Total Costs	1.689.301,00	133.507,00	461.525,00	0,00	595.032,00	35%	1.094.269,00
KULeuven	Total Person-month	68,00	8,50	20,00		28,50	42%	39,50
	Personnel	340.000,00	41.421,00	98.601,00		140.022,00	41%	199.978,00
	Other direct costs	167.500,00	9.090,00	6.486,00		15.576,00	9%	151.924,00
	Subcontracting	2.000,00	0,00	0,00		0,00	0%	2.000,00
	Adjustments		0,00	7.724,00		7.724,00		-7.724,00
	Indirect costs	304.500,00	30.306,00	63.052,00		93.358,00	31%	211.142,00
	Total Costs	814.000,00	80.817,00	175.863,00		256.680,00	32%	557.320,00
BED	Total Person-month	88,00	14,00	34,80		48,80	55%	39,20
	Personnel	484.000,00	52.323,00	153.075,00		205.398,00	42%	278.602,00
	Other direct costs	49.000,00	6.988,00	11.504,00		18.492,00	38%	30.508,00
	Subcontracting	5.000,00	0,00	0,00		0,00	0%	5.000,00
	Adjustments		0,00	0,00		0,00	0%	0,00
	Indirect costs	319.800,00	35.586,00	98.747,00		134.333,00	42%	185.467,00
	Total Costs	857.800,00	94.897,00	263.326,00	0,00	358.223,00	42%	499.577,00

Cost Budget Follow-up Table								
Contract n°	270089	Project acronym		CHIC				
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)				Percentage spent	Remaining Budget (EUR)
			Period 1	Period 2	Period 3	Total	Total/ Budget	
			M1 -M12	M13-M24	M25-M30			
USFD	Total Person-month	154,40	32,81	38,43	20,52	91,76	46%	62,64
	Personnel	679.296,00	115.475,00	164.575,00	105.930,00	385.980,00	57%	293.316,00
	Other direct costs	78.001,00	12.986,00	4.574,00	27.483,00	45.043,00	58%	32.958,00
	Subcontracting	4.000,00	0,00	0,00	0,00	0,00	0%	4.000,00
	Adjustments	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	454.378,00	77.076,00	101.488,00	80.047,80	258.611,80	57%	195.766,20
	Total Costs	1.215.675,00	205.537,00	270.637,00	213.460,80	689.634,80	57%	526.040,20
FORTH	Total Person-month	163,79	60,79	47,62	24,27	132,68	81%	31,11
	Personnel	412.800,00	105.586,00	98.907,00	71.499,21	275.992,21	67%	136.807,79
	Other direct costs	110.170,00	17.911,00	30.938,00	29.202,07	78.051,07	71%	32.118,93
	Subcontracting	6.000,00	0,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	-3.787,00	0,00	-3.787,00		3.787,00
	Indirect costs	359.136,00	87.636,00	76.158,00	55.054,39	218.848,39	61%	140.287,61
	Total Costs	888.106,00	211.133,00	202.216,00	155.755,67	569.104,67	64%	319.001,33
LUH	Total Person-month	54,00	16,07	17,50	8,17	41,74	77%	12,26
	Personnel	350.622,00	72.235,00	82.369,00	37.561,77	192.165,77	55%	158.456,23
	Other direct costs	28.000,00	2.795,00	4.644,00	2.055,21	9.494,21	34%	18.505,79
	Subcontracting	3.000,00	0,00	0,00	0,00	0,00	0%	3.000,00
	Adjustments	0,00	0,00	0,00	513,64	513,64		-513,64
	Indirect costs	227.173,00	45.018,00	52.207,00	23.770,19	120.995,19	53%	106.177,81
	Total Costs	608.793,00	120.048,00	139.220,00	63.900,81	323.168,81	53%	285.624,19
UPENN	Total Person-month	84,00	21,00	32,50		53,50	64%	30,50
	Personnel	391.564,00	72.110,00	149.824,00		221.934,00	57%	169.630,00
	Other direct costs	63.501,00	24.241,00	11.168,00		35.409,00	56%	28.092,00
	Subcontracting	5.000,00	0,00	0,00		0,00	0%	5.000,00
	Adjustments	0,00	0,00	-410,00		-410,00		410,00
	Indirect costs	282.140,00	59.738,00	99.814,00		159.552,00	57%	122.588,00
	Total Costs	742.204,00	156.089,00	260.396,00	0,00	416.485,00	56%	325.719,00
UOXF	Total Person-month	54,00	1,47	19,56	13,92	34,95	65%	19,05
	Personnel	289.077,00	6.217,00	75.016,00	57.017,60	138.250,60	48%	150.826,40
	Other direct costs	59.184,00	735,00	3.054,00	7.225,63	11.014,63	19%	48.169,37
	Subcontracting	3.902,00	0,00	0,00	0,00	0,00	0%	3.902,00
	Adjustments	0,00	0,00	2.431,00	0,00	2.431,00		-2.431,00
	Indirect costs	208.956,00	4.171,00	46.841,00	38.545,94	89.557,94	43%	119.398,06
	Total Costs	561.119,00	11.123,00	127.342,00	102.789,17	241.254,17	43%	319.864,83
UNITO	Total Person-month	54,00	9,59	16,00	11,74	37,33	69%	16,67
	Personnel	270.000,00	35.978,00	108.791,00	53.957,77	198.726,77	74%	71.273,23
	Other direct costs	100.000,00	3.227,00	8.233,00	6.061,18	17.521,18	18%	82.478,82
	Subcontracting	5.000,00	0,00	0,00	0,00	0,00	0%	5.000,00
	Adjustments		0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	222.000,00	23.522,00	70.214,00	36.011,36	129.747,36	58%	92.252,64
	Total Costs	597.000,00	62.727,00	187.238,00	96.030,31	345.995,31	58%	251.004,69

Cost Budget Follow-up Table								
Contract n°	270089	Project acronym		CHIC				
PARTICIP.	TYPE of EXPENDITURE (as defined by participants)	BUDGET	ACTUAL COSTS (EUR)				Percentage spent	Remaining Budget (EUR)
			Period 1	Period 2	Period 3	Total	Total/ Budget	
			M1-M12	M13-M24	M25-M30			
UBERN	Total Person-month	62,00	11,20	18,90	11,00	41,10	66%	20,90
	Personnel	465.000,00	71.512,00	159.327,00	70.466,00	301.305,00	65%	163.695,00
	Other direct costs	60.000,00	10.972,00	14.124,00	4.790,00	29.886,00	50%	30.114,00
	Subcontracting	4.000,00	0,00	0,00	0,00	0,00	0%	4.000,00
	Adjustments	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	315.000,00	49.490,00	104.070,00	45.153,60	198.713,60	63%	116.286,40
	Total Costs	844.000,00	131.974,00	277.521,00	120.409,60	529.904,60	63%	314.095,40
CUSTODIX	Total Person-month	24,00	2,37	6,00	3,89	12,26	51%	11,74
	Personnel	180.000,00	12.227,00	29.788,00	18.840,00	60.855,00	34%	119.145,00
	Other direct costs	33.000,00	1.790,00	2.324,00	0,00	4.114,00	12%	28.886,00
	Subcontracting	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	90.000,00	6.777,00	11.143,00	7.536,00	25.456,00	28%	64.544,00
	Total Costs	303.000,00	20.794,00	43.255,00	26.376,00	90.425,00	30%	212.575,00
PHILIPS	Total Person-month	54,00	1,20	6,40	30,20	37,80	70%	16,20
	Personnel	398.466,00	11.276,00	41.340,00	190.592,00	243.208,00	61%	155.258,00
	Other direct costs	25.000,00	0,00	0,00	0,00	0,00	0%	25.000,00
	Subcontracting	3.000,00	0,00	0,00	0,00	0,00	0%	3.000,00
	Adjustments	0,00	0,00	4.014,00	0,00	4.014,00		-4.014,00
	Indirect costs	592.650,00	19.418,00	63.528,00	50.331,00	133.277,00	22%	459.373,00
	Total Costs	1.019.116,00	30.694,00	108.882,00	240.923,00	380.499,00	37%	638.617,00
UCL	Total Person-month	74,00	6,65	13,53	8,31	28,49	39%	45,51
	Personnel	627.979,00	39.837,00	61.092,00	51.304,54	152.233,54	24%	475.745,46
	Other direct costs	29.996,00	4.214,00	4.490,00	6.695,42	15.399,42	51%	14.596,58
	Subcontracting	6.000,00	0,00	0,00	0,00	0,00	0%	6.000,00
	Adjustments	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	394.785,00	26.430,00	39.349,00	34.799,98	100.578,98	25%	294.206,02
	Total Costs	1.058.760,00	70.481,00	104.931,00	92.799,94	268.211,94	25%	790.548,06
CINECA	Total Person-month	57,00	15,95	23,49	6,03	45,47	80%	11,53
	Personnel	228.000,00	56.196,00	67.069,00	15.199,34	138.464,34	61%	89.535,66
	Other direct costs	54.408,00	5.258,00	5.065,00	587,16	10.910,16	20%	43.497,84
	Subcontracting	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	-2.058,00	0,00	-2.058,00		2.058,00
	Indirect costs	313.899,00	92.025,00	83.090,00	17.996,61	193.111,61	62%	120.787,39
	Total Costs	596.307,00	153.479,00	153.166,00	33.783,11	340.428,11	57%	255.878,89
TEI-C	Total Person-month	17,00	3,96	3,70	3,42	11,08	65%	5,92
	Personnel	37.400,00	10.527,00	7.482,00	13.419,03	31.428,03	84%	5.971,97
	Other direct costs	11.900,00	4.065,00	5.711,00	2.021,53	11.797,53	99%	102,47
	Subcontracting	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Adjustments	0,00	0,00	0,00	0,00	0,00	0%	0,00
	Indirect costs	29.580,00	8.755,00	7.915,00	9.264,34	25.934,34	88%	3.645,66
	Total Costs	78.880,00	23.347,00	21.108,00	24.704,90	69.159,90	88%	9.720,10
Total	Total Person-month	1.299,19	260,00	391,15	161,84	812,99	63%	486,20
	Personnel	6.840.202,00	950.429,00	1.730.796,00	780.126,56	3.461.351,56	39%	3.378.850,44
	Other direct costs	1.462.597,00	150.392,00	199.402,00	90.628,93	440.422,93	24%	1.022.174,07
	Subcontracting	64.584,00	0,00	2.896,00	3.200,00	6.096,00	4%	58.488,00
	Adjustments	0,00	0,00	9.852,00	513,64	10.365,64		-10.365,64
	Indirect costs	5.538.979,00	739.725,00	1.230.686,00	450.826,68	2.421.237,68	36%	3.117.741,32
	Total Costs	13.906.359,00	1.840.546,00	3.173.632,00	1.325.295,81	6.339.473,81	36%	7.566.885,19

4.2 Budget Explanations

Explanation of the use of resources for				ICCS		
Contract n°	600841	Project acronym	CHIC			
Work Package		Item description	Amount in €		Explanations	
all WPs		Personnel	60.750,55		Salary of senior scientists, PhD students, assistants and junior researchers for a total of 14.24 PM	
WP6, WP8		Travel	2.914,83		3rd Review Meeting, Brussels, 06-09 July 2015	
		Consumables				
		Equipment				
		Subcontracting	3.200,00		Audit	
WP1, WP12		Other	1.045,00		Publication fees and journals' bank fees	
Total Direct Costs			67.910,38			
		INDIRECT COSTS	38.826,23			

Explanation of the use of resources for				EURICE		
Contract n°	600841	Project acronym	CHIC			
Work Package		Item description	Amount in €		Explanations	
WP1, WP12		Personnel	33.588,75		Salaries of project officers, communication officers, project manager, IT support staff for a total of 6.13 PM	
WP1		Travel	533,60		3rd CHIC Review Meeting, Brussels, 06-08 July 2015	
		Consumables				
		Equipment				
		Subcontracting				
WP1, WP12		Other	14,30		Shipping costs	
Total Direct Costs			34.136,65			
		INDIRECT COSTS	13.489,24			

Explanation of the use of resources for			USAAR		
Contract n°	600841	Project acronym	CHIC		
Work Package		Item description	Amount in €		Explanations
		Personnel			
		Due to heavy workload during the preparation period of the 3rd interim report, USAAR wasn't able to provide financial figures for this report.			
	Equipment				
	Subcontracting				
	Other				
Total Direct Costs			0,00		
	INDIRECT COSTS				

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

Explanation of the use of resources for				BED		
Contract n°	600841	Project acronym	CHIC			
Work Package		Item description	Amount in €		Explanations	
		Personnel				
		Due to heavy workload during the preparation period of the 3rd interim report, BED wasn't able to provide financial figures for this report.				
		Consumables				
		Equipment				
		Subcontracting				
		Other				
Total Direct Costs			0,00			
		INDIRECT COSTS				

Explanation of the use of resources for				USFD		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €	Explanations			
WP1, WP5, WP7, WP12	Personnel	105.930,00	Salaries of senior scientists, scientists, PhD student and administrative staff for a total of 20,52 PM			
WP7	Travel	13.837,00	Travel to CHIC review meeting, Brussels, Belgium; 4th Progress Meeting in Turin, VPH 2014 Conference, Trondheim, Norway; MUSCLE Workshop , UK; WP6 Cancer Modellers' Workshop, Amsterdam Netherlands; CHIC bilateral meeting, Bologna, Italy; CHIC meeting, Athens, Greece			
	Consumables	0,00				
WP7	Equipment	13.459,00	Procurement of Dual Xeon Server System (100% allocation to the project)			
	Subcontracting					
WP7	Other					
Total Direct Costs		133.226,00				
INDIRECT COSTS		80.047,80				

Explanation of the use of resources for				FORTH		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €	Explanations			
WP2, WP5, WP6, WP7, WP8, WP9, WP10, WP11	Personnel	71.499,21	Salaries of Senior scientists, scientist, technicians, medical doctor for a total of 24,27 PM			
WP1, WP5, WP6, WP9, WP10, WP12	Travel	11.958,07	4th Progress Meeting, Turin, Italy; 3rd CHIC Review Meeting, Brussels, Belgium; Simcyp Workshop, Cambridge, UK			
	Consumables					
WP6, WP9, WP10	Equipment	15.176,00	Procurement of: Server Dell Poweredge R730; PC DELL Optiplex (6); Monitor DELL 24" (4); Laptop NB DELL LATITUDE E7450 (2); Server Dell Poweredge R720XD (allocation to project: 100%)			
	Subcontracting					
WP6, WP12	Other	2.068,00	Publication fees			
Total Direct Costs		100.701,28				
INDIRECT COSTS		55.054,39				

Explanation of the use of resources for				LUH		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP4	Personnel	37.561,77		Salaries of a professor, a student assistant and research associates for a total of 8.17 PM		
WP4, WP12	Travel	2.055,21		3rd CHIC Review Meeting, Brussels, Belgium; Dissemination: lectures/presentations at Brussels, Belgium, St. Petersburg, Russia, Göttingen, Germany		
	Consumables					
	Equipment					
	Subcontracting					
	Other					
Total Direct Costs		39.616,98				
INDIRECT COSTS		23.770,19				

Explanation of the use of resources for				UPENN		
Contract n°	600841	Project acronym	CHIC			
Work Package		Item description	Amount in €		Explanations	
		Personnel				
		Due to heavy workload during the preparation period of the 3rd interim report, UPENN wasn't able to provide financial figures for this report.				
		Subcontracting				
		Other				
Total Direct Costs			0,00			
		INDIRECT COSTS				

Explanation of the use of resources for				UOXF		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP1, WP6	Personnel	57.017,60		Salaries of senior scientist and junior scientists for a total of 13.92 PM		
WP6	Travel	7.097,15		4th Progress Meeting, Turin, Italy, conferences (IMCS 2015, other conferences) and workshops		
WP6	Consumables	128,48		Hospitality costs, scientific poster		
	Equipment					
	Subcontracting					
	Other					
Total Direct Costs		64.243,23				
INDIRECT COSTS		12.848,65				

Explanation of the use of resources for			UNITO		
Contract n°	600841	Project acronym	CHIC		
Work Package	Item description	Amount in €	Explanations		
WP3, WP6, WP11, WP12	Personnel	53.957,77	Salaries of 8 researchers for a total of 11,75 PM		
WP3	Travel	1.076,06	ICCS Conference, Reykjavik, Iceland, 29 May - 05 June 2015		
WP3	Consumables	2.924,74	Hospitality expenses, printing costs		
	Equipment				
	Subcontracting				
WP3	Other	2.060,38	Hospitality expenses		
Total Direct Costs		60.018,95			
INDIRECT COSTS		36.011,37			

Explanation of the use of resources for			UBERN		
Contract n°	600841	Project acronym	CHIC		
Work Package	Item description	Amount in €	Explanations		
WP5, WP6, WP8, WP9, WP10, WP11, WP12	Personnel	70.466,00	Salaries of senior scientists, administration staff and assistant for a total of 11.02 PM		
WP6, WP8, WP9	Travel	4.790,00	4th Progress Meeting, Turin, Italy; presentation of CHIC technology in the US (Boston, USA, January 2015); 3rd CHIC Review Meeting, Brussels, Belgium		
	Consumables				
	Equipment				
	Subcontracting				
	Other				
Total Direct Costs		75.256,00			
INDIRECT COSTS		45.153,60			

Explanation of the use of resources for				CUSTODIX		
Contract n°	600841	Project acronym	CHIC			
Work Package	XXX	Item description	Amount in €	Explanations		
WP4, WP5, WP8, WP12		Personnel	18.840,00	Salaries of 2 senior scientists for a total of 3.89 PM		
		Travel	0,00			
		Consumables				
		Equipment				
		Subcontracting				
		Other				
Total Direct Costs			18.840,00			
		INDIRECT COSTS	7.536,00			

Explanation of the use of resources for			PHILIPS		
Contract n°	600841	Project acronym	CHIC		
Work Package	Item description	Amount in €	Explanations		
WP5, WP8, WP10	Personnel	187.630,00	Salaries of 7 researchers for 29,92 PM		
WP12	Personnel	2.962,00	salary of 1 researcher for 0.28 PM		
	Travel	0,00			
	Consumables	0,00			
	Equipment	0,00			
	Subcontracting				
	Other				
Total Direct Costs		190.592,00			
		INDIRECT COSTS	50.331,00		

Explanation of the use of resources for			UCL		
Contract n°	600841	Project acronym	CHIC		
Work Package	Item description	Amount in €	Explanations		
WP7, WP8	Personnel	51.304,54	Salaries of 3 senior scientists for a total of 8.13 PM		
WP7, WP12	Travel	6.695,42	4th Progress Meeting, Turin, Italy; 5th Progress Meeting, Bologna, Italy; BioJS Modeling visualisation meeting, Norwich, UK; Pharmaceutical Modelling meeting, Netherlands; Modeling Interoperability Workshop, Auckland; Modeling Visualisation Workshop, Amsterdam, Netherlands; Modeling Visualisation Workshop, London, UK		
	Consumables	0,00			
	Equipment	0,00			
	Subcontracting				
	Other				
Total Direct Costs		57.999,96			
		INDIRECT COSTS	34.799,98		

Explanation of the use of resources for				CINECA		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP1, WP7, WP10, WP12	Personnel	15.199,34		Salaries of 3 employees for a total of 6,30 PM		
WP12	Travel	587,16		Travel to 3rd CHIC review meeting, Brussels, Belgium		
	Consumables	0,00				
	Equipment	0,00				
	Subcontracting					
	Other					
Total Direct Costs		15.786,50				
	INDIRECT COSTS	17.996,61				

Explanation of the use of resources for				TEI-C		
Contract n°	600841	Project acronym	CHIC			
Work Package	Item description	Amount in €		Explanations		
WP5	Personnel	13.419,03		Salaries of 3 scientists for 3.43 PM		
WP5	Travel	2.021,53		3rd Review Meeting, Brussels, Belgium; technical CHIC meeting, Leuven, Belgium		
	Consumables	0,00				
	Equipment					
	Subcontracting					
	Other					
Total Direct Costs		15.440,56				
	INDIRECT COSTS	9.264,34				

4.3 Planned versus actual efforts

A list of planned versus actual efforts is included in each WP description. It has to be noted, however, that the planned efforts are made for the whole period, i.e. M25-M36. Therefore, deviations between planned and actual efforts after until M30 are expected.