THEME [ICT-2011.5.2]
[Virtual Physiological Human]

Grant agreement for: Collaborative project*

Annex I - "Description of Work"

Project acronym: CHIC

Project full title: " Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology "

Grant agreement no: 600841

Version date: 2013-03-27

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Part A

Workplan Tables

A1:
Project summary

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per project

General information			
Project title [3]	Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology		
Starting date [4]	01/04/2013		
Duration in months [5]	48		
Call (part) identifier [6]	FP7-ICT-2011-9		
Activity code(s) most relevant to your topic [7]	ICT-2011.5.2: Virtual Physiological Human		
Free keywords [8]		VPH, multiscale model, repository, metamodel, hypermodel, cancer, in silico oncology, oncosimulator	

Abstract [9]

Developing robust, reproducible, interoperable and collaborative hyper-models of diseases and normal physiology is a sine qua non necessity if rational, coherent and comprehensive exploitation of the invaluable information hidden within human multiscale biological data is envisaged. Responding to this imperative in the context of both the broad Virtual Physiological Human (VPH) initiative and the paradigmatic cancer domain, CHIC proposes the development of a suite of tools, services and secure infrastructure that will support accessibility and reusability of VPH mathematical and computational hypermodels. These will include a hypermodelling infrastructure consisting primarily of a hypermodelling editor and a hypermodelling execution environment, an infrastructure for semantic metadata management, a hypermodel repository, a hypermodel-driven clinical data repository, a distributed metadata repository and an in silico trial repository for the storage of executed simulation scenarios. Multiscale models and data will be semantically annotated using the ontological and annotating tools to be developed. An image processing and visualization toolkit, and cloud and virtualization services will also be developed. The CHIC tools, services, infrastructure and repositories will provide the community with a collaborative interface for exchanging knowledge and sharing work in an effective and standardized way. A number of open source features and tools will enhance usability and accessibility.
In order to ensure clinical relevance and foster clinical acceptance of hypermodelling in the future, the whole endeavour will be driven by the clinical partners of the consortium. Cancer hypermodels to be collaboratively developed by the consortium cancer modellers will provide the framework and the testbed for the development of the CHIC technologies. Clinical adaptation and partial clinical validation of hypermodels and hypermodel oncosimulators will be undertaken.

A2:
List of Beneficiaries

Project Number [1]	600841	Project Acronym [2]	CHIC

List of Beneficiaries

No	Name	Short name	Country	Project entry month[10]	Project exit month
1	INSTITUTE OF COMMUNICATION AND COMPUTER SYSTEMS	ICCS	Greece	1	48
2	EUROPEAN RESEARCH AND PROJECT OFFICE GMBH	EURICE	Germany	1	48
3	UNIVERSITAET DES SAARLANDES	USAAR	Germany	1	48
4	KATHOLIEKE UNIVERSITEIT LEUVEN	KU Leuven	Belgium	1	48
5	UNIVERSITY OF BEDFORDSHIRE	BED	United Kingdom	1	48
6	THE UNIVERSITY OF SHEFFIELD	USFD	United Kingdom	1	48
7	FOUNDATION FOR RESEARCH AND TECHNOLOGY HELLAS	FORTH	Greece	1	48
8	GOTTFRIED WILHELM LEIBNIZ UNIVERSITAET HANNOVER	LUH	Germany	1	48
9	THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA	UPENN	United States	1	48
10	THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD	UOXF	United Kingdom	1	48
11	UNIVERSITA DEGLI STUDI DI TORINO	UNITO	Italy	1	48
12	UNIVERSITAET BERN	UBERN	Switzerland	1	48
13	CUSTODIX NV	CUSTODIX	Belgium	1	48
14	PHILIPS ELECTRONICS NEDERLAND B.V.	PHILIPS	Netherlands	1	48
15	UNIVERSITY COLLEGE LONDON	UCL	United Kingdom	1	48
16	CONSORZIO INTERUNIVERSITARIO CINECA	CINECA	Italy	1	48
17	TECHNOLOGICAL EDUCATIONAL INSTITUTE OF CRETE	TEI-C	Greece	1	48

A3:
Budget Breakdown

Project Number [1]	600841	Project Acronym [2]	CHIC

One Form per Project

Participant number in this project [11]	Participant short name	Fund. % [12]	Ind. costs [13]	Estimated eligible costs (whole duration of the project)					Requested EU contribution
				RTD / Innovation (A)	Demonstration (B)	Management (C)	Other (D)	Total A+B+C+D	
1	ICCS	75.0	T	1,032,000.00	0.00	82,800.00	272,000.00	1,386,800.00	1,128,800.00
2	EURICE	75.0	A	0.00	0.00	471,420.00	174,078.00	645,498.00	645,498.00
3	USAAR	75.0	T	1,625,219.00	0.00	5,682.00	58,400.00	1,689,301.00	1,282,996.00
4	KU Leuven	75.0	T	756,000.00	0.00	2,000.00	56,000.00	814,000.00	625,000.00
5	BED	75.0	T	792,000.00	0.00	5,000.00	60,800.00	857,800.00	659,800.00
6	USFD	75.0	T	1,095,400.00	0.00	41,475.00	78,800.00	1,215,675.00	941,825.00
7	FORTH	75.0	A	800,298.00	0.00	28,952.00	58,856.00	888,106.00	688,031.00
8	LUH	75.0	T	535,462.00	0.00	3,000.00	70,332.00	608,794.00	474,928.00
9	UPENN	75.0	A	675,696.00	0.00	5,000.00	61,510.00	742,206.00	573,282.00
10	UOXF	75.0	T	458,115.00	0.00	23,697.00	79,308.00	561,120.00	446,591.00
11	UNITO	75.0	T	536,000.00	0.00	5,000.00	56,000.00	597,000.00	462,998.00
12	UBERN	75.0	T	772,000.00	0.00	4,000.00	68,000.00	844,000.00	651,000.00
13	CUSTODIX	75.0	A	230,500.00	0.00	0.00	72,500.00	303,000.00	245,375.00
14	PHILIPS	50.0	A	905,992.00	0.00	3,000.00	110,124.00	1,019,116.00	566,120.00
15	UCL	75.0	T	1,024,830.00	0.00	6,000.00	29,534.00	1,060,364.00	804,156.00
16	CINECA	75.0	A	489,750.00	0.00	9,507.00	97,050.00	596,307.00	325,560.00
17	TEI-C	75.0	T	75,360.00	0.00	0.00	3,520.00	78,880.00	60,040.00
Total				11,804,622.00	0.00	696,533.00	1,406,812.00	13,907,967.00	10,582,000.00

Note that the budget mentioned in this table is the total budget requested by the Beneficiary and associated Third Parties.

*** The following funding schemes are distinguished**

Collaborative Project (if a distinction is made in the call please state which type of Collaborative project is referred to: (i) Small of medium-scale focused research project, (ii) Large-scale integrating project, (iii) Project targeted to special groups such as SMEs and other smaller actors), Network of Excellence, Coordination Action, Support Action.

1. Project number

The project number has been assigned by the Commission as the unique identifier for your project, and it cannot be changed. The project number **should appear on each page of the grant agreement preparation documents** to prevent errors during its handling.

2. Project acronym

Use the project acronym as indicated in the submitted proposal. It cannot be changed, unless agreed during the negotiations. The same acronym **should appear on each page of the grant agreement preparation documents** to prevent errors during its handling.

3. Project title

Use the title (preferably no longer than 200 characters) as indicated in the submitted proposal. Minor corrections are possible if agreed during the preparation of the grant agreement.

4. Starting date

Unless a specific (fixed) starting date is duly justified and agreed upon during the preparation of the Grant Agreement, the project will start on the first day of the month following the entry info force of the Grant Agreement (NB : entry into force = signature by the Commission). Please note that if a fixed starting date is used, you will be required to provide a detailed justification on a separate note.

5. Duration

Insert the duration of the project in full months.

6. Call (part) identifier

The Call (part) identifier is the reference number given in the call or part of the call you were addressing, as indicated in the publication of the call in the Official Journal of the European Union. You have to use the identifier given by the Commission in the letter inviting to prepare the grant agreement.

7. Activity code

Select the activity code from the drop-down menu.

8. Free keywords

Use the free keywords from your original proposal; changes and additions are possible.

9. Abstract

10. The month at which the participant joined the consortium, month 1 marking the start date of the project, and all other start dates being relative to this start date.

11. The number allocated by the Consortium to the participant for this project.

12. Include the funding % for RTD/Innovation – either 50% or 75%

13. Indirect cost model

A: Actual Costs
S: Actual Costs Simplified Method
T: Transitional Flat rate
F :Flat Rate

Workplan Tables

Project number

600841

Project title

CHIC—Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology

Call (part) identifier

FP7-ICT-2011-9

Funding scheme

Collaborative project

WT1
List of work packages

Project Number [1]	600841	Project Acronym [2]	CHIC

LIST OF WORK PACKAGES (WP)

WP Number [53]	WP Title	Type of activity [54]	Lead beneficiary number [55]	Person-months [56]	Start month [57]	End month [58]
WP 1	Project Management	MGT	2	55.00	1	48
WP 2	User Needs and Requirements	RTD	3	40.00	1	42
WP 3	Clinical and Translational Science Scenarios	RTD	4	135.00	1	48
WP 4	Legal and Ethical Framework	RTD	8	58.00	1	42
WP 5	IT Architecture	RTD	17	90.00	1	42
WP 6	Cancer Models and Hypermodel Design	RTD	1	195.00	1	46
WP 7	Hypermodelling infrastructure	RTD	6	189.00	1	48
WP 8	Model and Data Repositories	RTD	1	99.00	1	48
WP 9	Image Processing and Visualization	RTD	5	87.00	1	46
WP 10	Integrated Platform	RTD	7	64.00	1	44
WP 11	Clinical Adaptation and Validation	RTD	3	74.00	1	48
WP 12	Dissemination and Exploitation	OTHER	16	91.00	1	48
			Total	1,177.00		

WT2:
List of Deliverables

Project Number [1]	600841	Project Acronym [2]	CHIC

List of Deliverables - to be submitted for review to EC

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D2.1	State of the art knowledge for building hypermodels	2	7	10.00	R	PU	8
D2.2	Scenario based user needs and requirements	2	3	10.00	R	PU	8
D2.3	Requirements for enhancing hypermodels beyond the domain of cancer	2	14	10.00	R	CO	18
D2.4	Acceptance of hypermodels by patients and physicians	2	3	10.00	R	PU	42
D3.1	Report on scenarios and data from defined patients	3	4	45.00	R	PU	36
D3.2	Report on scenarios and data from other cancer types for usage by the CHIC infrastructure	3	11	45.00	R	PU	36
D3.3	Demonstration of the developed Meta- and Hyper-Multiscale Models and Repositories	3	1	45.00	O	PU	48
D4.1	Initial analsis of the ethical and legal requirements for the sharing of data	4	8	13.00	R	PU	6
D4.2	Initial analysis of the copyright-related legal	4	8	13.00	R	PU	9

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
	requirements for the sharing of data						
D4.3.1	Development of the data protection and copyright framework for CHIC first iteration	4	8	7.00	R	PU	14
D4.3.2	Development of the data protection and copyright framework for CHIC - second iteration	4	8	8.00	R	PU	42
D4.4	Whitepaper Recommendations for an amended European legal framework	4	8	17.00	R	PU	36
D5.1.1	The CHIC technical architecture – initial version	5	7	24.00	R	PU	12
D5.1.2	The final CHIC technical architecture (including the security tools and cloud infrastructure)	5	7	24.00	P	RE	42
D5.2	Security guidelines and initial version of security tools	5	13	21.00	P	CO	18
D5.3	Techniques to build the cloud infrastructure available to the community	5	5	21.00	R	PU	24
D6.1	Cancer hypomodelling and hypermodelling strategies and initial component models	6	1	30.00	R	CO	6

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D6.2	CHIC cancer component models: initial tested versions	6	1	50.00	R	CO	20
D6.3	Initial standardized cancer hypermodels	6	1	60.00	R	CO	38
D6.4	Clinical adaptation and partial validation of hypermodels	6	1	55.00	R	CO	46
D7.1	Hypermodelling specifications	7	1	19.00	R	PU	12
D7.2	First Release Hypermodelling framework deployed on test nodes	7	16	54.00	P	RE	24
D7.3	Hypermodels annotation services	7	15	68.00	P	RE	36
D7.4	Final Hypermodelling framework deployed on test node	7	16	48.00	O	RE	40
D8.1	Design of the CHIC repositories	8	1	16.00	R	CO	16
D8.2	Prototype implementation of the CHIC repositories	8	12	31.00	O	CO	24
D8.3	Implementation of the interfaces of the CHIC repositories	8	15	45.00	R	PU	30
D8.4	Report on the final system	8	1	7.00	R	PU	42
D9.1	User requirements for the visualization toolkit and image analysis toolkits	9	5	15.00	R	PU	6

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D9.2	A model and data visualization toolkit	9	5	25.00	P	RE	46
D9.3	A multimodal and longitudinal brain tumour image analysis tool	9	12	22.00	P	RE	46
D9.4	The tumor response quantitative platform	9	7	25.00	P	RE	36
D10.1	The CHIC portal	10	7	6.00	O	RE	8
D10.2	Design of the orchestration platform, related components and interfaces	10	14	16.00	O	PU	18
D10.3	The CHIC Encryption Services	10	13	16.00	O	CO	24
D10.4	The PhysiomSpace-enabled storage on public clouds	10	7	10.00	R	CO	36
D10.5	The CHIC integrated platform	10	7	16.00	P	RE	44
D11.1	Evaluation and validation criteria for clinical adaptation	11	3	18.00	R	PU	12
D11.2	Report on the first evaluation workshops round	11	3	18.00	R	RE	18
D11.3	Report on the second evaluation workshops round	11	3	19.00	R	RE	36
D11.4	Validation of CHIC infrastructure as a whole	11	1	19.00	R	RE	48

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D12.1	Dissemination Plan	12	16	3.00	R	PU	6
D12.2	Dissemination Kit available	12	2	12.00	O	PU	12
D12.3	Preliminary Plan for the Use and Dissemination of Foreground	12	16	12.00	R	CO	24
D12.4	Draft Plan for the Use and Dissemination of Foreground	12	16	12.00	R	CO	36
D12.5	Final Plan for the Use and Dissemination of Foreground	12	16	12.00	R	CO	48
D12.6	Periodic Newsletters	12	2	40.00	R	PU	48
			Total	1,122.00			

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP1	Type of activity [54]	MGT
Work package title	Project Management		
Start month	1		
End month	48		
Lead beneficiary number [55]	2		

Objectives

• to ensure the timely and qualitative achievement of the project results through administrative coordination
• to ensure the quality control of the project results and the risk management of the project as a whole
• to provide the timely and efficient administrative and financial coordination of the project and the compliance with contractual commitments

Description of work and role of partners

Effective management structures, strategies and procedures are of particular importance for a large-scale project like CHIC. Therefore, WP1 will guarantee optimal administrative, financial, contractual as well as scientific consortium management and enable efficient communication between all partners.

In more detail, the aim of this work package is to implement and maintain an efficient management structure in order to
i) coordinate the different project activities between countries and sectors
ii) ensure a smooth workflow to achieve the CHIC objectives
iii) assess the overall progress and the results of each work package
iv) implement quality control mechanisms by defining appropriate project standards.

Task 1.1 Decision making management (M1-48)
(Leader: EURICE, Participant: ICCS)
Periodic project board meetings (WPL meetings, Steering Committee (SC) meetings) will be held for progress review, decision making, risk review and conflict resolution.

Task 1.2 Administrative coordination
(Leader: EURICE, Participant: ICCS)
All administrative tasks will lie in the hands of EURICE. These include the information/advice to partners on administrative, regulative and financial issues, the organization of report distribution and archiving, the creation of a restricted project management area in the internet-based dissemination and communication platform and its implementation in the everyday management workflow.

Task 1.3 Financial management
(Leader: ICCS, Participant: EURICE)
All tasks regarding financial management will lie in the hands of the Coordinator, ICCS. These tasks include the set-up and maintenance of financial records, the coordination and control of annual cost claims and certificates on the financial statements (if needed) submitted by all project partners, follow-up of EC payments, distribution of partners' shares and the monitoring and justification of payments. EURICE will support the Coordinator in these tasks by collecting data and making them available on the web-based management platform (internal part of website).

Task 1.4 Contractual management (M1-48)
(Leader: EURICE, ICCS)

EURICE will be responsible for the preparation, collection and maintenance of the EC Grant Agreement and other contractual documents in close collaboration with ICCS. ICCS will be in charge of monitoring the beneficiaries' compliance with their obligation under the EC Grant Agreement.
The CHIC consortium will conclude a Consortium Agreement, which will include detailed regulations on the consortium's governance structure, responsibilities and duties of the partners, liability towards each other, financial provisions, knowledge management, intellectual property rights, dissemination rules and access rights as well as non-disclosure agreements. Further contracts will be negotiated if necessary.

Task 1.5 Assessment of progress and results (M6-48)
(Leader ICCS, Participants: EURICE, USFD, FORTH, CINECA, UOXF)
ICCS together with the WP leaders and with the support of EURICE will control and monitor work package status measured against deliverables and milestone planning in order to ensure a timely and accurate work plan follow-up, allow for early identification and troubleshooting of possible technical and organisational problems. The assessment of results will be based on workflows and standards to be fixed before the project start. EURICE will administer the reporting procedures, whereas ICCS will review the reports to ensure their quality and verify their consistency with technical and contractual requirements before transmitting them to the Commission. Furthermore the management team will coordinate semi-annual internal progress reports and work plan updates and control deliverable timeliness. If possible, they will arrange for concertation with related national or European projects and initiatives.

Role of participants:

• ICCS as coordinator (CO) will assume the overall responsibility for the project, act as an interface between the consortium and the European Commission, receive the Commission payments, transfer the shares to the individual partners, chair the PCC meetings, ensure the beneficiaries' compliance with the contractual requirements and review the project periodic reports.

• EURICE as the Project Management Office (PMO) will do the day-to-day management together with ICCS, provide the web-based management platform, support the coordinator in all reporting procedures, organise meetings and serve as an information desk concerning all administrative, legal and financial questions.

The role of the CO and PMO is presented in more detail in Chapter 2. Implementation under “management structures”

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	8.00
2	EURICE	38.00
6	USFD	4.00
7	FORTH	2.00
10	UOXF	2.00
16	CINECA	1.00
	Total	55.00

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
		Total	0.00			

WT3:
Work package description

Description of deliverables

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS1	Kick-Off Meeting	2	1	Minutes, presentations and participant list
MS2	Progress meetings	2	6	Project months 12, 18, 24, 30, 36, 42, 48; minutes, presentation and participant list

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP2	Type of activity [54]	RTD
Work package title	User Needs and Requirements		
Start month	1		
End month	42		
Lead beneficiary number [55]	3		

Objectives

WP2 will elaborate 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 Good Clinical Practice (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.

Description of work and role of partners

Task 2.1: State of the Art of Knowledge for building hypermodels (M1-8)
(Leader: FORTH, Participants: PHILIPS, ICCS, UPENN, USAAR)
This task will review current knowledge for building hypermodels. It will analyse systems, tools and software for the seamless integration of clinical care and basic research data including available data warehouses, repositories for tools and models. Special care will be taken in order to ensure that progress and achievements from previous and running EU funded projects will be incorporated if possible. The VPH Toolkit and possible interactions with the p-medicine environment will be addressed in this task (including infrastructures, tools, models, interoperability issues, etc.).

Task 2.2: Scenario based user needs and requirements (M1-8)

(Leader: USAAR, Participants: ALL PARTNERS)
In this task use cases and scenarios will be developed for the different cancer domains of the project. These scenarios and use cases will be clinically driven to guarantee their translation and usage in clinical care. According to results of previous projects they will be categorized according to different levels of usage. The lowest level contains basic scenarios and use cases that can be integrated in different other and more complex scenarios, e.g. roles and rights, pseudonymization, etc. Many of these basic scenarios are already described and corresponding tools are available. Within this task such tools will be collected and analysed for their usability in this project. On the higher levels all scenarios are composed of basic scenarios. This approach is already part of p-medicine and will be adapted to this project. In summary all developed models and tools will be as granular and modular as possible and provide standardized, open interfaces and functionality descriptions (e.g. via something similar to WSDL (Web Services Description Language)), so that a user can easily build new models as a composition of existing granular tools. Such an approach guarantees the re-use of already developed tools and models and avoids rebuilding of tools and models from scratch. This will be cost and time effective.

Task 2.3: Requirements for enhancing hypermodels beyond the domain of cancer (M1-18)
(Leader: PHILIPS, Participants: USAAR, ICCS, UPENN, FORTH)
This task aims to show the benefits of hypermodels in the domain of cancer and beyond. It is of utmost importance to demonstrate that in silico models and hypermodels will be used in clinical settings. This can be shown by developing the so called “in silico trials”.
The idea behind “in silico trials” is that a model is seen as a new drug that needs market approval. To get a drug on the market, preclinical testing and clinical testing within phase I to IV trials are required. In comparison to the situation for drugs, the same needs to be done with in silico models and hypermodels.
The preclinical phase will be done during this project. This preclinical phase needs to show that the tool or model delivers what is supposed to. This means that it gives correct answers without wrong calculations. This kind of validation refers to the correctness of the model from the mathematical viewpoint. After this phase, clinical testing will start with phase I/II trials followed by phase III and phase IV trials. In phase I/II it is important to show that the logistics in running a hypermodel is according to the expectations of the clinicians: that the model can be used in due time, that it will deliver results in a timeframe that will support physicians in decision making, so that the model can be used as a decision supporting service. This is critical, as physicians cannot wait to start treatment in cancer or any other disease. If this problem is solved, a phase III trial can be conducted. Such a trial will be outside the scope of this project, as the time needed to develop, initiate, run and analyse such a trial is much longer than what the timeframe of the project allows. But within CHIC the basis for such trials will be developed. According to phase III trials in drug development, such a trial will be a prospective randomized one, where the standard treatment is randomized against the treatment that is predicted by the model/hypermodel. At the end of the trial both treatment arms can be compared to see if patients treated according to the prediction of the model are doing better than those treated according to the standard conservative approach. In such a situation it is also possible to run the model in the group of patients treated according to the standard treatment. This will help to validate the model as one can see if the model is indicating the right treatment. E.g. A model indicates whether a preoperative chemotherapy scheme is better than primary surgery. One should look on tumour volume reduction predicted by the model. If the model predicts a reduction, chemotherapy is selected; if the model does not predict a reduction, go to primary surgery. In the standard arm all patients will receive preoperative chemotherapy and one could compare the reduction in tumour volume with the predicted reduction by the model as a validation means of the model. Comparing the results between both approaches would reveal whether the model is beneficial for the outcome of a patient.

Task 2.4: How to get acceptance of hypermodels by patients and physicians (M12-42)
(Leader: USAAR, Participants: ICCS, FORTH, CUSTODIX, UPENN, PHILIPS)
This task reviews acceptance issues of hypermodels by different stakeholders, mainly patients and physicians. Primarily a questionnaire will be developed that will ask stakeholders about features that are essential for usage and acceptance of hypermodels. Results of this questionnaire will have a direct impact on the development of hypermodels. Feedback is given to the corresponding work packages and tasks. The validation process and usability issues of developed hypermodels will check if these requirements are considered and models and hypermodels are built accordingly. Possibilities for education and training in using hypermodels will be analysed in this task in close cooperation with WP11 and WP12.

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	2.00
3	USAAR	25.00
7	FORTH	3.00
9	UPENN	5.00
13	CUSTODIX	1.00
14	PHILIPS	4.00
	Total	40.00

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D2.1	State of the art knowledge for building hypermodels	7	10.00	R	PU	8
D2.2	Scenario based user needs and requirements	3	10.00	R	PU	8
D2.3	Requirements for enhancing hypermodels beyond the domain of cancer	14	10.00	R	CO	18
D2.4	Acceptance of hypermodels by patients and physicians	3	10.00	R	PU	42
		Total	40.00			

Description of deliverables

D2.1) State of the art knowledge for building hypermodels: [month 8]

D2.2) Scenario based user needs and requirements: [month 8]

D2.3) Requirements for enhancing hypermodels beyond the domain of cancer: [month 18]

D2.4) Acceptance of hypermodels by patients and physicians: [month 42]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS3	User needs and Requirements are defined	3	8	D2.1, D2.2
MS4	Hypermodels are accepted by users	3	42	D2.4

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP3	Type of activity [54]	RTD
Work package title	Clinical and Translational Science Scenarios		
Start month	1		
End month	48		
Lead beneficiary number [55]	4		

Objectives

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, clinical 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.

Description of work and role of partners

Task 3.1: Wilms tumor (M1-48)
(Leader: USAAR, Participants: ICCS, UNITO, UPENN)
SIOP trials and studies for Wilms tumor are running since the 1970s in Europe. More than 8000 children with Wilms tumor participated in these trials. These trials are always randomized prospective and multicentre trials. Today they are GCP-conform and running in Europe, Brazil and other centres around the world under the umbrella of the International Society of Paediatric Oncology (SIOP). Retrospective data from former trials and prospective data from the current SIOP-2001 trial will be used for evaluation and validation of newly developed and validated models and hypermodels of CHIC.
In up to 100 patients with nephroblastoma, transcriptome analysis of the tumour will be done to get new insights in the biology of nephroblastoma. This data will be used for the development of a system biology model, which will form the basis of the bottom-up approach of the in silico model for nephroblastoma and thus improving the accuracy of the developed in silico Hyper-Multiscale Models.
ObTiMA will be used to serve as a Clinical Data Management System (CDMS) for the SIOP-2001.
Heterogeneous data from ObTiMA, clinical data from syndrome diagnostics, imaging data from MRI, molecular data from serum (autoantibodies, miRNA, proteomics data, whole genome sequencing), as well as data from the planned and realized treatment schedule will be put together for evaluation and validation of the Meta- and Hyper-Multiscale Models and Repositories using existing models from VPH. Data sets will also be used for the integrated Oncosimulator and will be subsequently validated via clinical and oncologic outcome.
The data will provide help to design individualized treatment strategies in future, thereby avoiding unnecessary (long-term) side effects from chemotherapy and radiotherapy.

Task 3.2: Glioblastoma multiforme (M1-48)
(Leader: KU Leuven, Participants: USAAR, ICCS, UPENN)
Patients with malignant glioma have a dismal prognosis despite neurosurgery, radiotherapy and chemotherapy. The median survival after diagnosis is only 15 months. At time of relapse, the median survival is 6 months, and all patients are dead within 18 months. Although the disease belongs to orphan diseases, with an incidence of 3/100000/year, the community burden and the loss of years of life is highest amongst all types of cancers. Immunotherapy is a fast developing fourth treatment modality for patients with malignant glioma. The treatment aims to stimulate the body's own immune defence in order to control the disease. Worldwide, several groups reported interesting clinical data with long-term survivors in small series of patients.

The immunotherapy is based on active specific immunization with the use of dendritic cells (DCs). These cells are the professional antigen-presenting cells in the human body and can be differentiated ex vivo out

of monocytes. DCs can be loaded ex vivo with the proteins derived from the lysate of tumor cells. Finally, DCs are matured with a mixture of pro-inflammatory cytokines IL-1b and TNF-a in combination with the TLR7 ligand imiquimod. Data from in vitro experiments and from the in vivo orthotopic GL261 model demonstrated immunogenicity of these DCm-HGG-L.

In our group, immunotherapy with DCm-HGG-L has been implemented first for patients with relapsed HGG in a cohort comparison trial HGG-IMMUNO-2003. Meanwhile, 179 children and adults with relapsed grade IV glioblastoma multiforme (GBM) have been treated with new surgery to debulk the tumor and obtain tumor material, followed by immunotherapy. Part of the results of these patient group have been published. Overall, current data show median overall survival of more than 10 months in 151 adults with relapsed GBM. For the 25 and 73 patients in cohort C and D, we observe a survival of 20 and 21%, whereas no survivals were observed in historical control series with chemotherapy.

In up to 100 patients with glioblastoma, transcriptome analysis of the tumour will be done to get new insights in the biology of glioblastoma. This data will be used for the development of a system biology model for glioblastoma together with the available immunological data to form the basis of the bottom-up approach of the in silico model for glioblastoma and thus improving the accuracy of the developed in silico Hyper-Multiscale Models.

Based upon our experiences, we integrated immunotherapy within the multimodal primary treatment for adults with reference histology proven GBM. In a group of 77 patients treated, the 6-months PFS was 77%, the median OS was 18 months with a 2-year survival of 39%. Especially patients with RPA class III and IV did better than the published historical control patients treated with Stupp-based regimen.

As a consequence of these data, we designed a prospective double blind placebo controlled randomized clinical trial HGG-2010 with integrated immunotherapy as experimental arm (73 patients) and standard Stupp-based treatment as control arm (73 patients). The hypothesis is an improvement of the 6-month PFS from 57% to 70%. Stratification in the randomization is based on age. The data for this trial are stored in filemaker databases: a database with clinical data and a separate database with all data related to the GMP facility.

Of this patient group in the HGG-2010 trial, we are collecting the clinical risk factors (belonging to the RPA classification of the EORTC), the tissue for molecular and genetic investigations, the radiological findings including perfusion MRI and diffusion MRI at time of diagnosis and eventually at time of immune reactivity, serum and white blood cells at fixed time points during the whole treatment course in both the experimental and the placebo control arm of the trial. Moreover data on the specifications of the DCm-HGG-L (viability, identity, potency, purity, dose) are collected. All these data will be delivered to the CHIC environment.

Immunotherapy obviously induces long-term survival in a subgroup of patients. As this personalized medicine is based on patient-specific advanced therapy medicinal products, of which the production costs are high, it will be of major benefit to have the appropriate models to predict which patient with GBM will benefit from immunotherapy.

Task 3.3: Non small cell lung cancer (M1-48)
(Leader: USAAR, Participants: UNITO, ICCS, UPENN)
Lung cancer is the leading cause of cancer for women and men. Non small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases with the majority of cases detected in advanced stages that do not allow curative surgery. Due to limited success of systemic chemotherapies up to now, the 5-Year Survival Rate amounts to 15%.

New molecular-based “personalized” therapies focus on inhibition of signal transduction pathways i.e. the EGFR pathway, the VEGF pathway, the RAS-, RAF- und EML4 pathway. After selection according to sequencing data or DNA FISH, the first trials could be finished showing the effectiveness of these drugs after molecular tests from tumor tissue after sequential molecular testing for second or third line therapies.

In the near future, it will be necessary to know the tumor-specific pathways very early after tumor diagnosis to choose the most promising therapy as first line therapy, maintenance or adjuvant therapy. For that purpose a system biology model will be developed based on the transcriptome analysis of up to 100 tumour specimen to get new insights in the biology of NSCLC. This data will form the basis for the bottom-up approach of the in silico model for NSCLC and thus improving the accuracy of the developed in silico Hyper-Multiscale Models.

In our group, all relevant clinical data, tumor typing according to the current and new ATS/ERS/IASLC proposals as well as radiological, macroscopic, quantitative microscopic data, proliferation data and angiogenesis data were retrieved or collected prospectively from lung cancer resection specimens of NSCLC. Genetic profiles of the relevant pathways, miRNA data, and deep sequencing data of at least a limited number of well defined NSCLCs, will be added for comprehensive analysis.

For small biopsy specimen of lung cancer, which are often the only tumor tissue available from patients with advanced NSCLC, manual dissection, laser-microdissection, quantitative few cell PCR approaches, DNA sequencing, biochip reverse-phase hybridization, mRNA preamplification and whole genome amplification are available as well as epidemiological and follow-up parameters from the Saarland tumor center and will be integrated into the Meta- and Hypermultiscale Models for In Silico Oncology in order facilitate the therapy-related clinical decisions.

Task 3.4: Applying the CHIC infrastructure to other Cancer types (M12-36)
(Leader: UNITO, Participants: KU Leuven, USAAR, ICCS, UPENN)
Tumors share many common features but also present striking differences, e.g. different cancer staging reflects their different ability to colonize the host and to induce angiogenesis and distant metastasis. These differences also have an impact on their natural history and the different clinical approach by which they are treated.

In this task we will focus primarily on prostate cancer, aiming at:
1. collecting data from patients histories assessing their individual variability and the common features in terms of developmental phases
2. defining a model, based on the general ‘Phenomenological Universalities’, linking an overall growth law with ‘growth spurts’, corresponding to organ invasion, host invasion, near and distant metastasis occurring at proper average±SD times
3. including the specific model in the more general context of multivariate-multiscale models proposed by the CHIC projects

In order to account for a more general applicability of the model to different tumors, in addition to Wilms tumor, glioblastoma multiforme (GBM), non small cell lung cancer (NSCLC), colon cancer and prostate cancer, also breast, head & neck (H&N) and gastro-intestinal (G&I) tumors will be taken into consideration. Data will be collected from the database of the Radiotherapy Units at IRCC and steps 1), 2) and 3) will be similarly performed, in order to define the different developmental phases and their average timing. The assessment of therapies effectiveness and the validation of the model on a large patient sample will be updated to further projects. This is done in collaboration with WP11.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	2.00
3	USAAR	49.00
4	KU Leuven	68.00
9	UPENN	2.00
11	UNITO	14.00
	Total	135.00

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D3.1	Report on scenarios and data from defined patients	4	45.00	R	PU	36
D3.2	Report on scenarios and data from other cancer types for usage by the CHIC infrastructure	11	45.00	R	PU	36
D3.3	Demonstration of the developed Meta- and Hyper-Multiscale Models and Repositories	1	45.00	O	PU	48
		Total	135.00			

Description of deliverables

D3.1) Report on scenarios and data from defined patients: Full title: D3.1 Report on scenarios and data from defined patients (patients from the nephroblastoma SIOP-2001 trial, patients from the HGG-2010 trial, patients with NSCLC) used for building Meta- and Hyper-Multiscale Models and Repositories reused for the integrated Oncosimulator. [month 36]

D3.2) Report on scenarios and data from other cancer types for usage by the CHIC infrastructure: [month 36]

D3.3) Demonstration of the developed Meta- and Hyper-Multiscale Models and Repositories: Full title: D3.3 Demonstration of the developed Meta- and Hyper-Multiscale Models and Repositories for the selected cancer types. [month 48]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS5	Scenarios and data from nephroblastoma, GBM and NSCLC are available	4	24	D3.1
MS6	Exploitation of the CHIC infrastructure by further cancer types	4	36	D3.2
MS7	Meta- and Hyper-Multiscale Models can be demonstrated	4	48	D3.3

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP4	Type of activity [54]	RTD
Work package title	Legal and Ethical Framework		
Start month	1		
End month	42		
Lead beneficiary number [55]	8		

Objectives

This workpackage 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 forseen legal and ethical questions for all partners for the whole durtation of the project

Description of work and role of partners

Task 4.1: Initial analysis of the ethical and legal requirements on the reuse of pseudonymized and anonymized data within CHIC (M1-6)
(Leader: LUH; Participants: ICCS, USAAR, UPENN, CUSTODIX)
The legal and ethical rules governing the processing of patients' medical data for purposes of CHIC will be analyzed.

Task 4.2: Initial analysis of the copyright-related legal requirements for the sharing of data and amalgamation of models within CHIC (M1-9)
(Leader: LUH; Participants: ICCS, USAAR, UPENN, CUSTODIX)
The reuse and/or amalgamation of models and data cause issues of intellectual property which will be studied. Researchers are constantly concerned about the possible loss of economical and scientific interest as a consequence of sharing of models and data. Therefore, this WP will 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. It is unclear whether and to what extent amalgamations of models as such can be protected by intellectual property rights. In many cases they can't be protected by patents as they are either non technical or could be seen as non patentable software "as such" (see art. 52 of the European Patent Convention). They also risk not to be protected by copyright either as they could be regarded as mere (not protected) ideas. It they have to be seen as protected works, it is further doubtful whether such amalgamations can be seen as computer programs and/or databases in the European protective frameset. Therefore, 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.

Task 4.3: Development of a data protection and copyright framework for CHIC (M1-42)
(Leader: LUH; Participants: CUSTODIX, ICCS, USAAR, UPENN)
Legal research will be done 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. This task will be undertaken in two iterations. The first iteration will give guidelines for further development of CHIC in a relatively early stage of the project after month 14. The second iteration will serve as a guideline for the transition of the project into the exploitation phase.

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)
(Leader: LUH; Participants: USAAR, CUSTODIX, ICCS, UPENN)
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.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	2.00
3	USAAR	4.00
8	LUH	48.00
9	UPENN	2.00
13	CUSTODIX	2.00
	Total	58.00

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D4.1	Initial analsis of the ethical and legal requirements for the sharing of data	8	13.00	R	PU	6
D4.2	Initial analysis of the copyright-related legal requirements for the sharing of data	8	13.00	R	PU	9
D4.3.1	Development of the data protection and copyright framework for CHIC first iteration	8	7.00	R	PU	14
D4.3.2	Development of the data protection and copyright framework for CHIC - second iteration	8	8.00	R	PU	42
D4.4	Whitepaper Recommendations for an amended European legal framework	8	17.00	R	PU	36
		Total	58.00			

Description of deliverables

WT3:
Work package description

D4.1) Initial analsis of the ethical and legal requirements for the sharing of data: Full title: D4.1 Initial analysis of the ethical and legal requirements on the reuse of pseudonymized and anonymized data within CHIC. [month 6]

D4.2) Initial analysis of the copyright-related legal requirements for the sharing of data: Full title: D4.2 Initial analysis of the copyright-related legal requirements for the sharing of data and amalgamation of models within CHIC [month 9]

D4.3.1) Development of the data protection and copyright framework for CHIC first iteration: [month 14]

D4.3.2) Development of the data protection and copyright framework for CHIC - second iteration: [month 42]

D4.4) Whitepaper Recommendations for an amended European legal framework: Full title: D4.4 Whitepaper "Recommendations for an amended European legal framework on patients' and researchers' rights and duties in E-health related research" [month 36]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS8	The CHIC Data protection and intellectual property framework	8	14	D4.1, D4.2, D4.3.1

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP5	Type of activity [54]	RTD
Work package title	IT Architecture		
Start month	1		
End month	42		
Lead beneficiary number [55]	17		

Objectives

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.

Description of work and role of partners

Task 5.1: Reference Architecture Definition (M1-42)
(Leader: TEI-C, Participants: FORTH, CUSTODIX, BED, USFD, PHILIPS, ICCS)
This task will consolidate the user requirements defined in WP2, the fundamental science scenarios provided by WP3 and the restrictions put by WP4 in order to extract the requirements relevant for the overall architecture. In particular the CHIC Reference Architecture (RA) Model will describe the essential elements of SOA-based systems, including its actors, information, processes and relationships between these elements. The CHIC-RA Model will be a conceptual model; hence it will be technology neutral and business-scale independent. The governing aspects will be handled through the Architecture Board – a body to be established as early as possible - which is the technical decision making authority of the project and includes architects from the key CHIC technical partners.
This task will produce the first draft reference architecture specification that will provide the basis for software development. Based on the experience with the prototypes, and the feedback from WP10 the architecture will go through cycles of refinement and improvements. It is the responsibility of this task to provide the final, validated, CHIC reference architecture specification.

Task 5.2: Security tools and services (M1-28)
(Leader: CUSTODIX, Participants: FORTH, BED, PHILIPS, USFD)
This task will deal with all the security aspects of CHIC's technological platform, ranging from user authentication, authorization, and auditing, to data integrity and privacy to pseudo anonymization and re identification of patient data.
CHIC will encourage interoperability by building as much as possible upon widely accepted security standards (e.g. SAML, Liberty-Alliance, WS-*, PKIX, XACML, etc). This will facilitate integration with existing systems and will allow the functional interoperability with 3rd party systems. The security tools and policies that will be developed in this task will ensure and enforce the legal and regulatory compliance and will encompass the appropriate auditing mechanisms which are needed by the legislation.

Task 5.3: Private cloud infrastructure (M1-27)
(Leader: BED, Participants: FORTH, PHILIPS, UBERN, ICCS)
In this task, we will analyse the state-of-art technologies in cloud computing and provide a private community cloud by harvesting existing IT facilities. The deployment of this private cloud will mainly use open source

platforms (for example, Eucalyptus for low-level middleware and service management, and Hadoop for distributing computation across all the computing nodes). During deployment and service development, this task will particular focus on distributed processing biomedical data in the cloud. 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 work will also cover licensing and legal issues in such a private cloud computing environment.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	3.00
5	BED	19.00
6	USFD	12.00
7	FORTH	10.00
12	UBERN	4.00
13	CUSTODIX	12.00
14	PHILIPS	15.00
17	TEI-C	15.00
	Total	90.00

List of deliverables

Deliverable Number [61]	Deliverable Title	Lead beneficiary number	Estimated indicative person-months	Nature [62]	Dissemination level [63]	Delivery date [64]
D5.1.1	The CHIC technical architecture – initial version	7	24.00	R	PU	12
D5.1.2	The final CHIC technical architecture (including the security tools and cloud infrastructure)	7	24.00	P	RE	42
D5.2	Security guidelines and initial version of security tools	13	21.00	P	CO	18
D5.3	Techniques to build the cloud infrastructure available to the community	5	21.00	R	PU	24
		Total	90.00			

Description of deliverables

D5.1.1) The CHIC technical architecture – initial version: [month 12]

D5.1.2) The final CHIC technical architecture (including the security tools and cloud infrastructure): [month 42]

D5.2) Security guidelines and initial version of security tools: [month 18]

D5.3) Techniques to build the cloud infrastructure available to the community: [month 24]

WT3:
Work package description

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS9	Initial CHIC Architecture and security guidelines	7	18	D5.1.1, D5.2
MS10	Final version of the CHIC Architecture	7	42	D5.1.2, D5.3

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP6	Type of activity [54]	RTD
Work package title	Cancer Models and Hypermodel Design		
Start month	1		
End month	46		
Lead beneficiary number [55]	1		

Objectives

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

Description of work and role of partners

Workpackage 6 aims at achieving the following targets:
a) 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.
b) 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.
c) 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.
d) 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 “re-creation” of existing models referring to the specific cancer type. The resultant hypermodels will be numerically studied and at least partly experimentally and/or clinically adapted and validated using data available from literature and/or collected by collaborating experimentalists and/or clinicians. This step will serve as an initial demonstrator of the analysis and experimental and/or clinical adaptation and validation process applied to modular hypermodels.
e) To contribute to the creation of multi-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.

f) To make available the standardized models and any data necessary for experimental and/or clinical validation purposes to the wider cancer modelling community after approximately 3 1/2 years from the beginning of the implementation of the (eventual) project.

The previous targets will be achieved through the following tasks:

Task 6.1: Cancer hypomodelling and hypermodelling strategies and elementary models (M1-36)
(Leader: ICCS, Participants: UPENN, UOXF, UNITO, UBERN, FORTH, PHILIPS)
The elementary process models (hypomodels or component models) for cancer will be defined following intensive interactions involving all modellers participating in the CHIC proposal. An initial definition of the component models will subsequently be revised based on the accumulated experience gained from the project's implementation. Hypermodelling specifications for the cancer domain will be developed in a similar way. Both existing and new models developed within the framework of the CHIC project will be decomposed into their elementary component models and re-created according to the guidelines developed by WP7 in collaboration with the present workpackage. Multi-modeller hypermodels will also be created. Hypermodels will be tested for robustness and will be clinically adapted and partly validated. Both standardized hypomodels and hypermodels along with pertinent validation data will populate the model and data repositories being developed.

Task 6.2: Subcellular cancer modelling (M1-36)
(Leader: UPENN, Participants: ICCS, UOXF, UNITO)
In this task a suite of molecular up to cellular models will be developed. They will be mainly utilized for the development of integrated multiscale models (hypermodels) by acting as perturbators of critical cellular and supercellular level parameter values. Such parameters may be the duration of cell cycle, the probability of a cell to undergo apoptosis following the administration of a particular chemotherapeutic treatment etc. A bottom-up modelling approach involving network theories, molecular modelling, and physically–based multiscale modelling will be adopted. The following aspects to be addressed exemplify the approach of the task:
a. Inference of network topologies
b. Inference of genes controlling genome dynamics and protein interaction networks
c. Multiscale modelling of functional interactions in signalling networks through multiscale hybrid physical/systems approaches
d. Altered intracellular trafficking in cancer development – development of minimal models
e. Molecular modelling of oncogenic kinase structures to profile driver versus passenger mutations

Task 6.3: Biomechanics enhanced tumour modelling (M1-36)
(Leader: UBERN, Participants: ICCS, UPENN, FORTH)
Building on previous results this task will advance the state of the art primarily in brain tumour modelling (including glioblastoma modelling) from a macroscopic viewpoint. In order to effectively increase the accuracy and robustness of current solutions proposed for tumour analysis, the entire set of image information available will be used to model the biomechanical behaviour of the tissues, including cell diffusion of tumour cells in the normal tissue neighbourhood. As an example the calculation of pressure gradients will be achieved through a combination of cell proliferation, material properties and boundary conditions via biomechanical analysis (e.g. using finite elements techniques). These continuous/discrete models will provide information on the macroscopic evolution of tumours. The advanced multimodal brain tumour image segmentation to be developed in WP9 will provide spatial and tissue-characterization information to multiscale tumour growth models. By applying the strategies to be developed in collaboration with WP7 both hypomodels and hypermodels of macroscopic aspects of tumour dynamics will be produced.

Task 6.4: The clinical modelling paradigms of nephroblastoma, glioblastoma and lung cancer (M6-46)
(Leader: ICCS, Participants: UPENN, UOXF, UNITO, UBERN)
This task will be driven by the three clinical scenarios and the corresponding clinical trials/studies undertaken by the CHIC clinical partners. It will serve as a demonstrator of the top-down modelling approach. Hypomodelling and hypermodelling startegies will also be applied. The following three subtasks refer to the three distinct tumour types to be considered namely nephroblastoma (Wilm's tumour), glioblastoma and lung cancer.

SubTask 6.4.a: The nephroblastoma paradigm
An already developed four dimensional (4D) model of nephroblastoma response to chemotherapy according to the SIOP 2001/GPOH clinical trial will be extended in order to refine primarily its histological component. The latter has proved to play a crucial role in the treatment response of the tumour. Multiscale data to be provided by USAAR will be used in order to drive, clinically adapt and partly validate the model.

SubTask 6.4.b: The glioblastoma paradigm
A 4D glioblastoma treatment response model will be developed in order to simulate the therapeutic outcome of a combined treatment including chemotherapy, radiation therapy and immunotherapy. The clinical trials HGG-IMMUNO-2003, HGG-2006, HGG2010 will serve as possible data providers.

SubTask 6.4.c: The lung cancer paradigm
A molecularly enhanced 4D multiscale model of non small cell lung cancer (NSCLC) response to chemotherapeutic and/or radiotherapeutic treatment will be developed. Data will be provided by USAAR. Genome sequencing will be provided for a number of cases.

Task 6.5: The colon cancer modelling paradigm (M6-46)
(Leader: UOXF, Participants: ICCS, FORTH)
This task will focus on the paradigm of colon cancer modelling. Several tumour growth processes will be demonstrated in silico through modelling of various stages of colon cancer as well as of related normal tissue dynamics. These will inter alia include:
a) A multiscale model of the colonic crypt
b) A continuum model of the growth of a mutant clone of tumour cells within a crypt
c) A model of the early stages of colorectal cancer
d) A multiscale model of vascular tumour growth
Hypo- and hyper-modelling strategies will be applied. Data from literature as well as from experimental collaborators of UOXF will be utilized in order to validate the models.

Task 6.6: The prostate cancer modelling paradigm (M6-46)
(Leader: UNITO, Participants: ICCS, FORTH, UBERN)
Task T6.6 will focus on the paradigm of prostate cancer. A model describing the natural history and evolution of prostate cancer will be considerably extended and refined. The model will account for crucial biological processes such as the avascular tumour growth phase, the angiogenetic switch, host invasion and near and far metastatic pathways as steps occurring at certain times along with characteristics statistically distributed according to clinical experience. The inputs, outputs and descriptions of this tumour evolution model will be implemented in a modular way in order to facilitate standardization according to the hypermodelling metalanguage to be developed. The predictions of the above model will be compared with clinical data provided by an already available patient database. The latter resides in the Institute for Cancer Research and Treatment (IRCC) in Turin, Italy. The tumour response to standard radio-, chemo-, and hormonotherapies will be modelled on the basis of stand-alone modules simulating their effects as functions of time. Hypo- and hypermodelling will lead to the production of several standardized modelling modules.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	44.00
7	FORTH	9.00
9	UPENN	61.00
10	UOXF	46.00
11	UNITO	14.00
12	UBERN	20.00
14	PHILIPS	1.00
	Total	195.00

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D6.1	Cancer hypomodelling and hypermodelling strategies and initial component models	1	30.00	R	CO	6
D6.2	CHIC cancer component models: initial tested versions	1	50.00	R	CO	20
D6.3	Initial standardized cancer hypermodels	1	60.00	R	CO	38
D6.4	Clinical adaptation and partial validation of hypermodels	1	55.00	R	CO	46
		Total	195.00			

Description of deliverables

D6.1) Cancer hypomodelling and hypermodelling strategies and initial component models: [month 6]

D6.2) CHIC cancer component models: initial tested versions: [month 20]

D6.3) Initial standardized cancer hypermodels: [month 38]

D6.4) Clinical adaptation and partial validation of hypermodels: [month 46]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS11	Initial component models available for all cancer modelling branches	1	6	D6.1
MS12	Rational, numerical and clinical experience based check of the component models complete	1	20	D6.2
MS13	Availability of hypermodels for all clinic. scenarios compliant w. the guidelines to be prov. by WP7	1	40	D6.3, D7.4
MS14	All hypermodels have been quantitatively clinically adapted	1	46	D6.4

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP7	Type of activity [54]	RTD
Work package title	Hypermodelling infrastructure		
Start month	1		
End month	48		
Lead beneficiary number [55]	6		

Objectives

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.

Description of work and role of partners

We define integrative model (or hypermodel) a choreography of component models, each describing a biological process at a characteristic space-time scale, and of relation models, which define the relevant relations across scales. Integrative models can become component models for other integrative models. Other definitions that will be used are:
- Metamodels are semantically defined abstract classes;
- Models are concrete instances of metamodels;
- Metahypermodels are semantically defined, abstract choreographies of metamodels;
- Hypermodels are concrete instances of metahypermodels, i.e. orchestrations of models.

In WP7, we shall use a progressive level of abstractions:
a) Models are exposed as cloud services (Task 7.1) through the hypermodelling infrastructure (Task 7.5);
b) Metamodels are exposed as semantic annotations of cloud services (Task 7.2);
c) Hypermodels are exposed as cloud services orchestrations, written as meta-modelling language descriptions of the control and data flow (Task 7.3);
d) Metahypermodels are exposed as models choreographies, written in purely semantic terms, and independent from the concrete implementation and execution aspects (Task 7.4).

Task 7.1: Models execution (M1 –27)
(Leader: ICCS, Participants: USFD, FORTH, CINECA)
At out set partner ICCS will define a first list of component models (including their specifications for control and data flow) that need to be hosted by the IT infrastructure. In parallel, by M6 partner FORTH will develop in collaboration with partner USFD the Component Model Generic Stub, which will provide an abstraction layer on which all knowledge management and meta-modelling services will anchor. This specification document will be revised and extended every year until a third revision will be considered the final specification for component models (M27).

Task 7.2: Metamodels annotation (M7 –36)
(Leader: BED, Participants: UCL, USFD, ICCS, CINECA)
By M12 partner USFD will provide basic annotation and tags management services, that partner BED will use to develop the folksonomy annotation and search services while partner UCL will consolidate all the free tags used into a first ontology revision including the ontology-base search services (MS16) due by M24, and a second time by M36. As soon as the first release of annotations and search services are available (M24), all CHIC partners will be requested to use these services to annotate the component and relation models that they expose through the end of the task. In the third project year in parallel partner BED will consolidate and deploy the final metamodel annotation services, which will also be ready for M36.

Task 7.3: Hypermodels execution (M7 –42)

(Leader: CINECA, Participants: USFD, ICCS, FORTH)
The execution of the hypermodels will be made possible using a hypermodelling framework developed by partners CINECA and USFD as part of a previous project (VPHOP). This core technology will be in this project revised and generalised to serve also specific modelling needs of the cancer research community. The specific developments of the framework to be done during CHIC will be defined in a specification document written by partner ICCS in collaboration with partner CINECA, to be ready by M12 (D7.1). During the project the hypermodels will execute on two nodes. The first, called test node, will be used primarily for development purposes, and to test distributed executions, and will be installed at partner CINECA (by M9). The second, that will host most of the models executions during the project, will be hosted by partner FORTH and will be deployed by partner CINECA before M24 (D7.2). In the second year partner CINECA will complete the definition of a high-level hypermodelling language (PM30) that every partner will use to develop new simulations, through the Hypermodelling Editor to be developed by partner FORTH by M36; also, partner BED will deploy the relation models required (by M30 as well). In parallel partner USFD will work on two additional modelling services, to cope with the incompleteness of the inputs, and that to cope with strongly coupled models. Both services should be completed by M42, when partner CINECA will make the final deployment of the hypermodelling framework on the main node (D7.4).

Task 7.4: Metahypermodels annotation (M25 – 48)
(Leader: UCL, Participants: BED, USFD, FORTH, CINECA, ICCS)
In M25, when the models annotation ontology is deployed (from Task 7.2/MS16), it is possible to start the development of the hypermodels annotation services. Partner UCL should make available the basic services by M36 (D7.3). After that some advanced research activities will be conducted in very innovative areas. Partner USFD will explore the use of the linked data paradigm as an alternative mechanism to define very large distributed hypermodels; partner UCL instead will explore the use of semantic reasoning to assist modellers in the creation of new metahypermodels. Due to the complexity involved, these research activities will continue until M48 (MS18), when the project ends.

Task 7.5: Hypermodelling infrastructure (M7 – 42)
(Leader: FORTH, Participants: USAAR, CINECA, USFD, ICCS, BED, UCL)
In the first year the core computing cloud should be deployed by partner FORTH (MS15), providing exposure for core component and relation models as standardised RPCs. Meanwhile partner FORTH, in collaboration with partners CINECA and USFD, will continue to develop the hypermodelling infrastructure. By M36 should be available the hypermodel development and execution application with all the features described above (MS17). In M42 with the completion of the distributed logging services by partner CINECA, partner FORTH will be able to deliver the complete hypermodelling infrastructure.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	6.00
3	USAAR	4.00
5	BED	19.00
6	USFD	88.00
7	FORTH	6.00
15	UCL	24.00
16	CINECA	42.00
	Total	189.00

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D7.1	Hypermodelling specifications	1	19.00	R	PU	12
D7.2	First Release Hypermodelling framework deployed on test nodes	16	54.00	P	RE	24
D7.3	Hypermodels annotation services	15	68.00	P	RE	36
D7.4	Final Hypermodelling framework deployed on test node	16	48.00	O	RE	40
		Total	189.00			

Description of deliverables

D7.1) Hypermodelling specifications: [month 12]

D7.2) First Release Hypermodelling framework deployed on test nodes: [month 24]

D7.3) Hypermodels annotation services: [month 36]

D7.4) Final Hypermodelling framework deployed on test node: [month 40]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS15	First hypermodel infrastructure deployed	7	12	D7.1
MS16	Folksonomy and Ontology annotation and search services deployed	5	24	D7.2
MS17	Hypermodel editor, development and execution application ready	7	36	D7.3
MS18	Metahypermodels annotation completed	6	48	Description in 4th annual report

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP8	Type of activity [54]	RTD
Work package title	Model and Data Repositories		
Start month	1		
End month	48		
Lead beneficiary number [55]	1		

Objectives

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 quering
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.

Description of work and role of partners

This work package will follow the guidelines to be produced by other work packages, especially WP2 (User needs and requirements) and WP5 (IT Architecture).
In the implementation of the CHIC repositories open environments and open-source software will be used.

Task 8.1: Development of repositories (M1-M48)
(Leader: ICCS, Participants: FORTH, CUSTODIX, USAAR, PHILIPS, UPENN, UCL, UBERN)

SubTask 8.1.a: Development of the model/tool repository
The CHIC model/tool repository will permanently host the models that will be developed in the context of the CHIC project. It will also host tools such as linkers and data transformation tools necessary for the construction of hyper-models, as described in WP6. Furthermore, the CHIC model/tool repository will be able to host multiscale cancer models/tools developed within the framework of other EC funded research projects, such as ACGT (Advancing Clinicogenomic Trials on Cancer), ContraCancrum (Clinically Oriented Cancer Multilevel Modeling), TUMOR (Transatlantic TUmour MOdel Repositories) and p-Medicine (From data sharing and integration via VPH models to personalized medicine).
The CHIC model/tool repository will be built based on the experience already accumulated during the implementation of the TUMOR project. Close collaboration with WP6 (Cancer Models and Hypermodel Design) will take place.

For each model the CHIC model/tool repository will contain all the related information including:
• descriptive information (abstract and detailed description, references etc.),
• input and output parameters (for proper linking with other models/tools),
• different versions of the source code (using well established version control strategies),
• different versions of binaries (depending on the target computational environment),

Information about model authorship, ownership and access permissions will also be included.

A web-based interface (GUI and services) will be designed and implemented in order to allow users to interact with the model/tool repository. The aforementioned interface will also expose the contents of the model/tool repository to other tools developed in the CHIC project, such as the hypermodelling editor.

SubTask 8.1.b: Development of the data repository
The CHIC data repository will permanently host all the related medical data produced or collected by the project. This data will not come directly from the clinical environment. On the contrary they will pass though de-identification and (pheudo)-anonymization processes, as described in WP4. The CHIC data repository will also have the capability of saving links to data residing in other data repositories developed within the framework of other EC funded research projects, such as ContraCancrum and p-medicine.
Additionally, interfaces that will allow to import and export the contents of the CHIC data repository will be developed. Appropriate services will be implemented in order to import medical data from other data repositories (as the aforementioned ones) into the CHIC data repository. In this way the data can be sustained after the expiration of the project's lifetime and reused and exploited continuously. The export services that will be created will also assist in this direction, as many of the data sets to be gathered by the CHIC project will be easily reusable by future projects (always in compliance with the ethical and legal framework).
The CHIC data repository will contain for each patient all the relevant medical data including clinical data, imaging data, histological data, therapy etc. The data types that will be hosted in the data repository will be imaging data (DICOM etc), descriptive/structural data (age, sex etc), other files (histological reports), links (to other data repositories) etc.
The CHIC data repository will be built based on the experience already accumulated during the implementation of other data repositories, such as the ones developed within the framework of p-Medicine and VSD (Virtual Skeleton Database).

SubTask 8.1.c: Development of the in silico trial repository
Usually biological simulations require many computational resources, especially when the simulations involve multiscale imaging data. This is the main reason why the development of an in silico trial repository is critically important. The in silico trial repository will be used for the persistent storage of the simulation scenarios and the in silico predictions. The input data (the original state of the patient), the simulation scenario (the in silico treatment) and the output data (the state of the patient after in silico treatment) will be stored persistently after the completion of the simulation scenario. The aforementioned data will be readily available for evaluation, comparison and validation without the need for executing the same simulation again.

The CHIC in silico trial repository will contain for each in silico trial all the related information including:
• original input (medical data without any processing),
• model input (processed medical data that can be used as input to the specific model or hypermodel used in the simulation),
• model or hypermodel (not the actual model/hypermodel code used in the simulation, but information about it (version etc))
• model output.

A web-based user interface will be designed and implemented in order to allow users to interact with the in silico trial repository. The user will have the ability to easily store and retrieve all the data concerning a complete in silico trial (i.e. a set of simulation runs) that they or someone else has run.
Moreover, special interfaces will be developed, so that the in silico trial repository will successfully interact with the hypermodelling executional environment, in order to automatically store the outcome of a simulation (and all the related data that constitutes the in-silico-trial).

Task 8.2: Infrastructure for Semantic Metadata Management (M1-M48)
(Leader: UCL, Participants: ICCS, USAAR, FORTH)
This task builds on ongoing efforts in the VPH community to provide a robust infrastructure with which to (i) effect annotation of semantic metadata across the CHIC spectrum of computational models, and then (ii) openly share and reason over this metadata. In particular, this task will work with the efforts in WP7 to effectively interact with metadata for models and data. The activities in this task will test, integrate and extend the RICORDO VPH infrastructure to support semantic interoperability of resources within CHIC community based on the management (storing and inference-based querying) of their ontology-based annotations.

SubTask 8.2.a: RDF storage solution for semantic metadata
This sub-task will develop a distributed RDF repository solution to store metadata from each partner. The key aim is to uncouple RDF based metadata from the data and model resources to ensure that metadata distribution

is not limited by any privacy or security constraints that may be imposed on the resources themselves. Partners will each maintain an RDF store for their meta-data.
This task will also involve developing software interfaces for querying and editing metadata. A specification for template-based SPARQL end point will be developed to support communal access to each RDF repository. Partners will be responsible for maintaining their own SPARQL end points.

SubTask 8.2.b: A core knowledge base to support semantic querying of metadata
This sub-task is concerned with setting up a core knowledgebase using the RICORDO infrastructure that supports real-time reasoning over multiple large ontologies. This knowledge base will support the expression of complex ontology concepts and use these concepts to retrieve relevant resource metadata. It will store all the ontologies that are relevant to the CHIC community.
A requirement analysis for the ontologies will be carried out to find the core set of ontologies that are relevant to the communities. A workflow will be implemented to maintain these ontologies and extending the knowledgebase by constructing complex ontology concepts following the RICORDO composite grammar.
This sub-task will also involve further developing and adapting RICORDO software interfaces for querying and editing the core knowledge base.

SubTask 8.2.c: Resource annotations
This sub-task will create a software package for manipulating resource annotations following the annotation standard specification developed in RICORDO. The package will provide functionality to interact with individual RDF repositories for reading annotations, creating RDF annotations for given resources and writing the annotations back into the RDF repositories.
A simple graphical user interface (GUI) will be developed to interact with the annotations. The GUI will use the interface developed in subtask 8.2.a to interact with the RDF repositories. The GUI will enable identified users to view annotations, create annotations, and save the annotations in relevant RDF repositories for which they have sufficient rights. The GUI will also interact with the RICORDO infrastructure web services to enable users to find relevant ontological concepts with which to annotate. In addition, the GUI will enable users to construct complex concepts to find relevant ontological terms, view parts of ontological trees, add new ontological concepts, and select relevant ontological concepts to annotate.

Subtask 8.2.d: Global metadata search engine
This subtask will deploy a search engine for querying over metadata repositories. This step will integrate the RICORDO infrastructure to find relevant ontological terms with template based SPARQL end point interfaces developed in task 8.2.a to access RDF repositories to retrieve relevant resource metadata. A web-based interface will be developed to search across the different RDF repositories.

Task 8.3: Integration with the security and the legal/ethical framework (M10-M48)
(Leader: ICCS, Participants: CUSTODIX, UCL, FORTH, UBERN)
Both the data and the models stored in the CHIC repository environment must conform to the legal and ethical framework developed in WP4. In addition, appropriate authentication and authorisation mechanisms will be implemented, in order to ensure that only authorized persons have access to the content of the repositories. These mechanisms are required for a) the secure storage of models and data and their associated information into the CHIC repositories and b) the retrieval of this information by the different tools used in CHIC.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	14.00
3	USAAR	3.00
7	FORTH	6.00
9	UPENN	3.00
12	UBERN	15.00
13	CUSTODIX	3.00
14	PHILIPS	7.00

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
15	UCL	48.00
	Total	99.00

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D8.1	Design of the CHIC repositories	1	16.00	R	CO	16
D8.2	Prototype implementation of the CHIC repositories	12	31.00	O	CO	24
D8.3	Implementation of the interfaces of the CHIC repositories	15	45.00	R	PU	30
D8.4	Report on the final system	1	7.00	R	PU	42
		Total	99.00			

Description of deliverables

D8.1) Design of the CHIC repositories: [month 16]

D8.2) Prototype implementation of the CHIC repositories: [month 24]

D8.3) Implementation of the interfaces of the CHIC repositories: [month 30]

D8.4) Report on the final system: [month 42]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS19	Design of the CHIC repositories completed	1	16	D8.1
MS20	Deployment of the CHIC repositories	15	28	D8.2
MS21	Integration with security and ethical framework	1	42	D8.3, D4.3.2, D5.2, D10.3

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP9	Type of activity [54]	RTD
Work package title	Image Processing and Visualization		
Start month	1		
End month	46		
Lead beneficiary number [55]	5		

Objectives

This work pacage will concentrate on the visualization and image analysis support to the project. The objectives are:
1) To provide a set of visualization tools for model and data analysis
2) To provide a set of image analysis tools for image data processing
3) To provide tools for assessing the tumor change from functional tomographic data

Description of work and role of partners

Task 9.1: User requirement analysis (M1- 6)
(Leader: BED, Participants: UBERN, USAAR, FORTH, ICCS)
This task will gather user requirement on the visual analysis suite and image analysis tools. Typical approaches and examples that are expected to get benefit from the use of visualization and image analysis will be identified and analysed. We will look into current problems and needs in the model and data analysis and understand the scales of the model and data repositories. The questionnaire that will be developed will collect information from relevant stakeholders regarding acceptance, user needs and requirements. Documentation of the requirement and analysis will be prepared.

Task 9.2: Scalable visualization techniques (M3–18)
(Leader: BED, Participants: UBERN, USAAR, FORTH, TEI-C)
This task will develop scalable visualization techniques to support the visualization of large scale data. These will include data removal and filtering techniques, which will allow users to focus on their targeted data; aggregation techniques, which will allow users to combine details and create different levels of overviews in hierarchies and will support users to perform “overviews first and details on demand”; dimension reduction techniques (e.g. subspace clustering), which will be able to help identify the meaningful cohort of data in a subset of relevant dimensions.
To allow effective handling of large scale visualization, we will investigate new aggregation techniques based on the traditional approaches, such as binning, abstraction, etc. Hierarchical clustering techniques can be used to create effective aggregation of data at different levels of details. Also, we shall investigate uncertainty-aware aggregation, which creates data aggregation with uncertainty information to enhance user understanding towards the aggregated data.
Subspace clustering will be another key area of interest. Given a dataset with high dimensionality, the number of possible sub feature space is exponentially high. Fully automatic machine learning normally does not do a good job in terms of identifying the clusters. A recent trend is to involve human experts, which couples user interaction with the subspace clustering process.

Task 9.3: Uncertainty data visualization (M9-24)
(Leader: BED, Participants: UBERN, USAAR, FORTH)
This task will focus on the visualization of uncertainty information in abstraction forms to visually present the heterogeneous and multivariate datasets created by the models and simulations using graphs, matrix views, parallel coordinates, scatter plots, etc.
The visual representation will reflect the uncertainty lying within the dataset. This may include, the uncertainty of the parameters used in the simulation, which may be represented in terms of intervals; the connections between

the parameters and the outcomes; the uncertainty of the results, etc. Different visual representations will be experimented for the uncertainty, including the use of geometries, colours, etc.
We will investigate the portrayal of uncertainty information in graphs. For example, how to represent the uncertainty originated from the node filtering or node clustering in a visual form? how to aggregate uncertainty information in the graph? How does the uncertainty affect the analysis of the graph structures (e.g. identifying key nodes, graph path, etc..)
Volume visualization will be used for the representation of 3D and 4D (3D+time) structural and temporal information from the results of tumor modeling and simulation, which involves a high degree of uncertainty. This task will investigate a range of adequate visual techniques for the portrayal of the uncertainty that is inherent in the volumetric structures, including the use of colours, image noise, bump (geometry) noise. One of the focuses will be to investigate how to integrate uncertainty information with the transfer function, which is used to control the visual information in the volume visualization.

Task 9.4: Visualization toolkit for the model/data repository (M13–46)
(Leader: BED, Participants: UBERN, USAAR, FORTH, ICCS)
This task will focus on the work of building visualization toolkit to visualize the models and their associated data within the model repository. More specifically, the toolkit will need to:
1) visualize the structure of the models and data repository to allow an overall picture of the model/data repository.
2) visualize information associated to the models, e.g. parameters. The information can be regarded as a set of multi-dimensional data.
3) visualize the data in the data repository. The data visualization here will cover two individual aspects, namely visualization of the information of the data (which can be viewed as a net of multi-dimensional data in a similar way to the models); and visualization of the data itself.
The visualization toolkit will visualize the set of models/data involved in the repository. The data sets can be either collected clinical data or the results from the simulation. The toolkit will be able to visualize the collection of the models/data as a whole using image icons or thumbnails, etc., supporting interactive user exploration on the repositories. The layout of the models/data will be arranged in multiple ways, including their similarity measure or other properties. Hierarchical views will also be considered.

Task 9.5: A general image processing development toolkit (M6–18)
(Leader: UBERN, Participants: BED, USAAR, FORTH)
This task is to create a general development environment for the image processing and analysis tasks in Task9.6 and 9.7. The purpose is to lay down a foundation to allow for technical development in a consistent style. There are many open sources available nowadays including ITK, OpenCV. The environment should support a range of functionalities, including those for image denoising, filtering and enhancing, edge detection, transformations, bias field correction, image re-sampling, invariant feature extraction, segmentation and registration.
Segmentation is a very important task in this project. A number of segmentation techniques will be made available to support the segmentation tasks in this work, such as watershed segmentation, mean shift segmentation, classification based segmentation, etc.
Our special interest will be on the MRF energy minimization based approach, which achieves quite good results through the incorporation with the traditional segmentation techniques. This approach attempts to perform segmentation based on the search for a global energy minimal point, which attempts to solve the problem at the global scale. Different energy minimization approaches such as graph cut, belief propagation, tree reweighted message passing will be under investigation. Also, we will look into the combination of the different segmentation methods and results in order to achieve the best possible outcomes. Similar ideas have been applied successfully in face detection, where a number of detectors are cascaded to achieve largely enhanced performance.

Task 9.6: Image registration tools (M3–36)
(Leader: UBERN, Participants: BED, USAAR, FORTH)
For rigid registration, tools based on monomodal image intensity based techniques will be integrated, whereas for non-rigid registration fast diffeomorphic demons based registration will be integrated, with a special focus on intra-patient registration for follow-up studies and atlas to patient registration for functional brain mapping. To cope with the presence of varying size tumors in the images (especially for longitudinal studies), landmark-assisted variants of the previous registration algorithms will be also considered.

Task 9.7: Multimodal and longitudinal brain tumor image analysis (M9–46)

(Leader: UBERN, Participants: BED, USAAR, FORTH)
Building on previous results we propose to advance the state of the art in brain tumour modelling and segmentation through a multiscale and multidisciplinary approach that combines brain image analysis and tumor growth modeling techniques. We hypothesize that in order to effectively increase the accuracy and robustness of current solutions proposed for brain tumour analysis, the entire set of image information obtained through the clinical imaging protocol can be used in conjunction with the biomechanical behavior and cellular replication process of brain gliomas (developed as part of T6.3). Furthermore, the characteristics of the clinical imaging protocol have to be appropriately considered in order to develop clinically relevant solutions.

This work package will develop a brain tumor analysis framework that makes use of a brain tissue classification technique developed to work on the highly anisotropic multichannel clinical MRI images, which in turns provides spatial and tissue-characterization information to a multiscale tumour growth model and a finer tissue-aware atlas based brain tissue segmentation technique. With this development it is expected to make important contributions in computer-assisted morphometric analysis of brain tumours, patient follow- up, radiotherapy and surgical planning as well as to pave the way towards the development of effective tools to interpret and utilize the complex set of spatial and temporal information inherent in brain tumor patients.

Longitudinal tumour models for improved analysis of tumour pseudo-progression and pseudo-response has been remarked by the neuro-oncology community, and specifically through the RANO working group strategy (Response Assessment in Neuro Oncology), as crucial step to advance the progress in the assessment of brain tumours by establishing more reliable criteria that can truly reflect the progression of the disease with respect to its response to therapy. The aim in this regard is to develop computational models and means to assist on the efforts being made by the neuro-oncology community. More specifically, it is proposed to investigate, develop and comprehensively evaluate modeling strategies that take into account the updates suggested to the RECIST guidelines (Response Evaluation Criteria in Solid Tumors) and improvements to the Macdonald Criteria, which have become more important in light to the increased incidence of pseudoprogression in patients receiving radiotherapy with temozolomide, and antiangiogenic therapies affecting the permeability of tumour vasculature. It is clear that such progress necessitates a multidisciplinary team featuring expertise at the different spatio-temporal and physiological levels of modeling. We believe that these developments will have a great impact to the improvement of assessing high-grade gliomas.

Task 9.8: A software platform for the Assessment of Tumor Treatment Response (M8–42)
(Leader: FORTH, Participants: UBERN, USAAR, BED)
This task will develop an extensible software platform providing functionalities such as diffusion and perfusion MRI analysis in a single, user friendly environment that allows the clinician to easily and objectively evaluate tumour response to therapy. This tool will be used in order to compare predictions based on simulations to the actual quantitative therapy outcome of the patient. The software platform will be an extension of the DrEye tool developed in the ContraCancrum project and will provide novel analysis methods for ADC pre and post therapy data as well as Angiomap based analysis from temporal CE data. This software will both assist the initialization of the cancer models (imaging biomarkers) and their validation by comparison to the computed measures of tumor changes from tomographic data.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	3.00
3	USAAR	15.00
5	BED	36.00
7	FORTH	20.00
12	UBERN	12.00
17	TEI-C	1.00
	Total	87.00

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D9.1	User requirements for the visualization toolkit and image analysis toolkits	5	15.00	R	PU	6
D9.2	A model and data visualization toolkit	5	25.00	P	RE	46
D9.3	A multimodal and longitudinal brain tumour image analysis tool	12	22.00	P	RE	46
D9.4	The tumor response quantitative platform	7	25.00	P	RE	36
		Total	87.00			

Description of deliverables

D9.1) User requirements for the visualization toolkit and image analysis toolkits: [month 6]

D9.2) A model and data visualization toolkit: [month 46]

D9.3) A multimodal and longitudinal brain tumour image analysis tool: [month 46]

D9.4) The tumor response quantitative platform: [month 36]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS22	Scalable & uncertainty visualization techniques	5	24	Visual analytics techniques verified by technical experiments on the data used within the project.
MS23	Image segmentation & registration techniques	12	18	Image segmentation and registration techniques verified by technical experiments on the data used in the project.
MS24	Initial version of the tumor response quantitative platform	7	24	The testing results of the initial version of the platform.

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP10	Type of activity [54]	RTD
Work package title	Integrated Platform		
Start month	1		
End month	44		
Lead beneficiary number [55]	7		

Objectives

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

Description of work and role of partners

The ambitious objectives of CHIC require the provision of a computational and data management infrastructure to support the building, sharing, integration, execution, and validation of cancer “hypermodels”. This work package contains the following tasks:

Task 10.1: Portal (M1–8)
(Leader: FORTH, Participants: PHILIPS, USAAR, CINECA, ICCS)
A portal will be the main “point of entrance” to the CHIC platform, offering access to the model repositories for publishing and discovery of models and hypermodels, providing links to specific tools (e.g. for anonymization), supporting the upload of new data sets and the management of the existing ones, assisting the creation of new hypermodels by linking existing ones, etc.

Task 10.2: Interoperable interfaces for retrieving model and hypermodel descriptions from the corresponding repositories (M1–18)
(Leader: PHILIPS, Participants: FORTH, USAAR, CINECA, ICCS, UBERN)
WP8 will provide the design and the implementation of these model repositories in close cooperation with WP7 (Semantic based description of the models) and WP6 (hypermodeling design and metalanguage). This task aims to standardize the programmatic interfaces for accessing the repositories so that to strengthen the integration of the CHIC platform and to allow its future extension and outreach with other related research efforts.

Task 10.3: Data Management and Computational infrastructure (M7–36)
(Leader: CINECA, Participants: UBERN, FORTH, PHILIPS, USAAR, ICCS)
The VPH research in CHIC calls for a platform where the data produced or consumed can efficiently and securely stored and maintained. It is also important the provenance of the data is supported to guarantee the validation of the experimental results and the reproducible research in general. State of the art data storage and computational solutions such as the Grid and the Cloud will be considered for the implementation of the platform. Especially cloud virtualization technologies are highly relevant to the computational requirements of CHIC and will be evaluated for addressing these specific needs.
Partner CINECA will deploy, leveraging on its PhysiomeSpace service, some basic storage services for both data and metadata. In year two, partner CINECA will extended the double encryption scheme, already in deployment in PhysiomeSpace, to be more robust and efficient, so that in principle it should make possible

to store safely even confidential data on public storage services such as Amazon S3. These strongly encrypted data services should be ready by M24 (M25), so as to make possible for partner USFD to develop a PhysiomeSpace-compatible storage server, deployable as a virtual machine on the Amazon cloud services, so as to provide considerable scalability also to the storage services.

Task 10.4: Data and hypermodel orchestration (M7–44)
(Leader: FORTH, Participants: USFD, PHILIPS, USAAR, CINECA, ICCS, BED)
A specialized clinical workflow environment will be developed to allow the integration of the CHIC data repository, data processing tools and hypermodels. Such linking can be supported in an effective way by a graphical tool that allows the composition of complex clinical workflows. This task therefore will make extensive use of the repositories' programmatic interfaces defined in Task 10.2 and the other semantic descriptions and schemas proposed in the corresponding work packages.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	7.00
3	USAAR	7.00
7	FORTH	21.00
12	UBERN	3.00
14	PHILIPS	18.00
16	CINECA	8.00
	Total	64.00

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D10.1	The CHIC portal	7	6.00	O	RE	8
D10.2	Design of the orchestration platform, related components and interfaces	14	16.00	O	PU	18
D10.3	The CHIC Encryption Services	13	16.00	O	CO	24
D10.4	The PhysiomSpace-enabled storage on public clouds	7	10.00	R	CO	36
D10.5	The CHIC integrated platform	7	16.00	P	RE	44
		Total	64.00			

Description of deliverables

D10.1) The CHIC portal: [month 8]

D10.2) Design of the orchestration platform, related components and interfaces: [month 18]

D10.3) The CHIC Encryption Services: [month 24]

D10.4) The PhysiomSpace-enabled storage on public clouds: [month 36]

D10.5) The CHIC integrated platform: [month 44]

WT3:
Work package description

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS25	The CHIC Orchestration Platform and Encrypted Data Services	7	24	D10.1, D10.2, D10.3
MS26	Public cloud deployment	7	36	D10.4

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP11	Type of activity [54]	RTD
Work package title	Clinical Adaptation and Validation		
Start month	1		
End month	48		
Lead beneficiary number [55]	3		

Objectives

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

Description of work and role of partners

Task 11.1: Formulate evaluation and validation criteria for enhancing clinical adaptation of hypermodels (M1-12) (Leader: USAAR, Participants: UPENN, ICCS, UNITO, PHILIPS, BED, FORTH, UBERN)
Considering the user needs as described in WP2, the aims for developing hypermodels based on clinical scenarios within an infrastructure compliant with legal and ethical requirements, this task will define evaluation and validation criteria and will identify specific application objectives to be tested during the validation process. Procedures in monitoring the development of hypermodels according to the defined evaluation and validation

criteria will be elaborated and criteria for their execution by specific user groups will be defined. Work from other EU projects will be checked for adaptation.

Task 11.2: Coordinate evaluation activities by partners (M6-18)
(Leader: UNITO, Participants: FORTH, ICCS, BED, PHILIPS)
Feedback reports will provide issue reports and suggest possible improvements, modifications, and additional functionalities for enhancing the clinical adaptation of hypermodels and the CHIC infrastructure. In addition a workshop will be held to bring together the groups implementing tools and models with the testing groups to enhance this process. All participants will be provided with the developed criteria from Task 11.1. WP11 will coordinate this workshop and will report on progresses achieved and remaining problems to be addressed. WP11 will also provide a comprehensive overview of key demonstration results by highlighting the benefits and existing problems of the hypermodels based on the developed validation criteria and on interactions between all stakeholders.

Task 11.3: Clinical adaptation of the CHIC infrastructure as a whole (M12-48)
(Leader: USAAR, Participants: UPENN, UNITO, ICCS, UBERN, FORTH, PHILIPS)
In addition to the validation activities in Task 11.2, this task will carry out centralized clinical adaptations of the whole environment under development. These activities will in particular target novice users from the respective user groups and evaluate the usability of the system in the context of the daily work of the user for enhancing the clinical adaptation of the infrastructure as a whole. Important aspects that will be checked are the consistency and self-descriptiveness of the CHIC infrastructure, its user-orientation, and the interface design and availability of proper documentation and user guidance.
A second evaluation workshop will be carried out together with WP10 that is responsible for the integrated platform. This workshop will focus on the clinical adaptation for further improvements of the integrated environment of CHIC. During this workshop a guided evaluation of the system will be carried out for a representative of each user group. During this procedure the participant will be asked to run selected scenarios within CHIC. All interactions between the user and the system will be recorded. An in-depth analysis of these interactions by a usability engineer will help to identify problems and bottlenecks and to give improvement recommendations.

Task 11.4: Validation of the CHIC infrastructure as a whole (M36-48)
(Leader: ICCS, Participants: USAAR, FORTH, BED, UBERN, UNITO, PHILIPS)
In the last year of the project a validation of the CHIC infrastructure will be done using two approaches. The first approach will be to run the developed hypermodels within the integrated CHIC platform by using prospective data provided by the respective clinical partners. This validation concentrates mainly on the different types of the Oncosimulator. This validation process will start as soon as the clinical adaptation of the platform is finalized to allow the execution of the Oncosimulator within the integrated CHIC environment. The validation process includes
1. assessing the effectiveness of the most popular therapeutic approach
2. finding their optimal timing and dose, and
3. validating the model prediction on a large patient sampling.

The second approach will be a ‘deep log analysis’ of web traffic that is undertaken to get a very deep understanding of what people actually seek in terms of CHIC and how often they access the CHIC platform via the portal. A questionnaire will be automatically presented to every user of the platform to rate the integrated platform according to usability criteria and to ask for comments. These answers will be analysed and used for further adaptation and improvement.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	7.00
3	USAAR	25.00
5	BED	8.00
7	FORTH	3.00

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
9	UPENN	5.00
11	UNITO	20.00
12	UBERN	3.00
14	PHILIPS	3.00
	Total	74.00

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D11.1	Evaluation and validation criteria for clinical adaptation	3	18.00	R	PU	12
D11.2	Report on the first evaluation workshops round	3	18.00	R	RE	18
D11.3	Report on the second evaluation workshops round	3	19.00	R	RE	36
D11.4	Validation of CHIC infrastructure as a whole	1	19.00	R	RE	48
		Total	74.00			

Description of deliverables

D11.1) Evaluation and validation criteria for clinical adaptation: [month 12]

D11.2) Report on the first evaluation workshops round: [month 18]

D11.3) Report on the second evaluation workshops round: [month 36]

D11.4) Validation of CHIC infrastructure as a whole: [month 48]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS27	Evaluation and validation criteria for clinical adaptation are ready	3	12	D11.1
MS28	First evaluation workshop	3	18	Participant lists, evaluation reports from participants
MS29	Second evaluation workshop	3	36	Participant lists, evaluation reports from participants

WT3:
Work package description

Project Number [1]	600841	Project Acronym [2]	CHIC

One form per Work Package

Work package number [53]	WP12	Type of activity [54]	OTHER
Work package title	Dissemination and Exploitation		
Start month	1		
End month	48		
Lead beneficiary number [55]	16		

Objectives

The objectives of this workpackage are the following:
• to coordinate the dissemination of this project's outputs, approaches and results to target groups, new users and communities
• 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

Description of work and role of partners

WP12 consists of the following three main tasks:
- Task 12.1 Dissemination activities
- Task 12.2 Exploitation and IPR issues
- Task 12.3 Training activities

Task 12.1: Dissemination activities (M1-48)
(Leader: EURICE, Participants: ALL PARTNERS)
A successful project is not only associated to the delivery of high quality technical and scientific results but also to make the community aware of the project outputs and to find synergies and collaboration with other similar or interested initiatives. To carry out an efficient and fruitful dissemination a series of activities should be carried out which are mapped into different of sub-tasks with respective activity leaders.

SubTask 12.1.a: Strategic Dissemination Planning, Task Leader: CINECA
Dissemination planning and execution will be closely coordinated by the lead partner (CINECA) with other tasks and WP leaders. At the start of the project, all proper dissemination and community building opportunities will be identified, recorded, structured and planned (D12.1). As part of the annual report, this plan will be updated.

SubTask 12.1.b: Web presence, Task Leader: EURICE
During the first months of the project, a web presence will be established, composed of an internal as well as an external area which will be updated on a regular basis (MS30). While the internal area will serve as a management tool for the preparation of reports and for an efficient communication between the partners, the external area is intended for the purpose of providing information and disseminating news and publications regarding the project to the general public.
The creation to the purpose of a building on Biomed Town (http://www.biomedtown.org) community portal managed by CINECA will be evaluated for both the management of the private area and establishing a dissemination channel within the hosted biomedical community. By interlinking with Biomed Town, its objectives will be to promote not only the project and inform about its activities, but to serve as a medium to create collaborative environments that support researchers and their scientific discourses, and to link to related EU and global activities as early as possible.
From early in the project, the news, announcements and events will be posted related to CHIC on a regular basis on the Biomed Town VPH News RSS feed.
Major scientific milestones will be advertised on specialised mailing lists and forums.

SubTask 12.1.c: Newsletter, Task Leader: EURICE
The aim of this task is to create full size newsletters that will be published once a year (normally these will be ready together with the annual reporting documents so to capitalise on the material produced at the end of the year by each partner, D12.6 a,b,c,d) and to not only give an overview of the project's progress and publications, but also include in-depth articles and more detailed information on various aspects of the project, including pictures, diagrams, partners profiles etc. The contents of the newsletter will be closely coordinated between the partners and they may all contribute to its contents.
These scientific and detailed full size newsletters will be associated to a by-monthly one, to be sent out only by email to the CHIC contacts list. This more frequent communication will provide a summary of news and events related to the project, allowing to follow the project progress and also the project "life".

SubTask 12.1.d: Dissemination Kit, Task Leader: EURICE
The aim of this task is to produce a dissemination kit, which will include tools based on public information for all partners to be used in their dissemination activities (D12.2). Examples of what will be available in the dissemination kit are the logo, public presentations, leaflets and multimedia material, as required, which will be presented and distributed on the occasion of conferences and meetings.

SubTask 12.1.e: Conferences, exhibitions, workshops, Task Leader: BED
This task strives at stimulating the exchange of information with the international scientific community. The partners are encouraged to take part in international scientific discussions and attend conferences, meetings and workshops where the approaches and results of the CHIC project are to be promoted.
Apart from organising own workshops and summer schools as presented in Task 12.3 "Training", the partners will strive to organise common workshops with other relevant projects as mentioned below.

SubTask 12.1.f: Scientific & Technical Papers Publications, Task Leader: ICCS
The aim of this task is to disseminate scientific knowledge to the international community.
The dissemination will be supplemented by publishing the results in specialised journals as described with more details in the dissemination 3.2 section.
Abstracts of the papers will be also reported in the e-newsletter and in other web presence tools. The Leader will take care of the respects of the Project confidentiality and publication rules (reference to EC grant agreement and to the involved partners). The publications will be announced via and archived in the publication feature which will be part of the project website. A synthesis of all abstracts of publications will be available at the end of the project as part of D12.6.

SubTask 12.1.g: Interfacing with other projects; Task Leader: CINECA
This activity aims at enhancing the collaboration with other research activities and initiatives in the fields concerned by making use of existing synergies.
Contacts will be established with relevant EU projects as well as other national and international initiatives in the field. EU projects will include running projects such as p-medicine, VPH-Share, INTEGRATE, EURECA and others. The task is considered essential to increase synergies and seek complementarities in other running initiatives in the VPH community at large; therefore, an extensive overview of related running (EU/Non-EU) projects will be periodically performed and contacts established to them accordingly.

Task 12.2: Exploitation and IPR issues (M1-48)
(Leader: CINECA, Participants: ALL PARTNERS)
The aim of this task is to ensure the exploitation of the project's output. Throughout the project, the partners will continuously contribute to the identification of the project's results that may qualify for IPR protection. This activity includes:
1. Development of the Exploitation Strategy. This activity will focus on the development of globally focused exploitation plans. This involves extrapolating and distilling the synergies that derive from the combined strong exploitation strategies already in place. Exploitation plans include the definition of deployment scenarios (timeline; application areas; options for common policies on licensing, industrialisation and other licensing opportunities; joint actions with industry key players, the clinical research community, and the standardisation community; joint efforts with the VPH-NoE).
2. Exploitation Planning Report. This will focus on the reporting of exploitation activities, progress monitoring of deployment scenarios and time plans, all in close cooperation with all project partners. Exploitation scenarios will be constantly assessed, and strategies will be recommended that will ensure that no barriers are created to the exploitation opportunities. A business plan for exploitation will be available together with dissemination plan every year starting from Mo24 (D12.3, D12.4, D12.5).

Task 12.3: Training activities (M12-48)
(Leader: USAAR, Participants: ALL PARTNERS)

SubTask 12.3.a: Workshops/Summer schools, Task Leader: USAAR
In order to train potential users on the use of the CHIC platform and get feedback from them from early on in the project's lifetime, a series of workshops/summer schools will be organised starting after the end of the first year until the end of the project with a minimum of three events organised (MS31, MS32, MS33).
For these events whenever possible they will be co-organised in association to big events or conferences relevant to the CHIC objectives, i.e. Summer School on Computational Oncology series and the International Advanced Research Workshop on In Silico Oncology and Cancer Investigation (IARWISOCI) workshop series.

The first event has been already identified by the project partners.

CHIC-6th IARWISOCI workshop
During the project's lifetime the 6th IARWISOCI (6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation), organized by ICCS, will take place (in autumn 2014). ICCS will include into the workshop's programme a dedicated section for the dissemination of CHIC-related work achieved by that time and the training of interested researchers. The IARWISOCI workshop series are held every other year. They were initiated by ICCS- in Sparta, Greece in 2004. The second workshop took place in Chania, Crete, Greece in 2006. The 2008 event took place in Istanbul, Turkey, after having become an IEEE (Institute of Electrical and Electronics Engineers) technically co-sponsored event. The 2010 event took place in Athens, and included dedicated sections for the EU-projects ContraCancrum and TUMOR.

SubTask 12.3.b: Web tutorials, Task Leader: CINECA
Training materials will be made available in the form of web tutorials.
Videos and other multimedia material will be produced and shared also with the most accessible web tools like a dedicated YouTube Channel.
Specific Webinars will be organised on specific needs, which allows sharing the presenter's computer screen with a presentation or a running demo, with a remote audience that viewed the presentation on their own computers. The audio can be equally broadcast completely via the computer. This means of communication will allow reducing costs associated to training activities while keeping the number of attendees as high as possible.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	ICCS	8.00
2	EURICE	12.00
3	USAAR	3.00
5	BED	6.00
6	USFD	6.00
7	FORTH	6.00
8	LUH	6.00
9	UPENN	6.00
10	UOXF	6.00
11	UNITO	6.00
12	UBERN	5.00
13	CUSTODIX	6.00
14	PHILIPS	6.00
15	UCL	2.00

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
16	CINECA	6.00
17	TEI-C	1.00
	Total	91.00

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D12.1	Dissemination Plan	16	3.00	R	PU	6
D12.2	Dissemination Kit available	2	12.00	O	PU	12
D12.3	Preliminary Plan for the Use and Dissemination of Foreground	16	12.00	R	CO	24
D12.4	Draft Plan for the Use and Dissemination of Foreground	16	12.00	R	CO	36
D12.5	Final Plan for the Use and Dissemination of Foreground	16	12.00	R	CO	48
D12.6	Periodic Newsletters	2	40.00	R	PU	48
		Total	91.00			

Description of deliverables

D12.1) Dissemination Plan: [month 6]

D12.2) Dissemination Kit available: [month 12]

D12.3) Preliminary Plan for the Use and Dissemination of Foreground: [month 24]

D12.4) Draft Plan for the Use and Dissemination of Foreground: [month 36]

D12.5) Final Plan for the Use and Dissemination of Foreground: [month 48]

D12.6) Periodic Newsletters: [month 48]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS30	Internal collaborative area and external website	2	3	Website is online and operational
MS31	First CHIC summer school	3	18	Participant lists, presentations
MS32	CHIC workshop	1	30	Participant lists, presentations

WT3:
Work package description

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS33	Second CHIC summer school	3	42	Participant lists, presentations

WT4:
List of Milestones

Project Number [1]	600841	Project Acronym [2]	CHIC

List and Schedule of Milestones

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS1	Kick-Off Meeting	WP1	2	1	Minutes, presentations and participant list
MS2	Progress meetings	WP1	2	6	Project months 12, 18, 24, 30, 36, 42, 48; minutes, presentation and participant list
MS3	User needs and Requirements are defined	WP2	3	8	D2.1, D2.2
MS4	Hypermodels are accepted by users	WP2	3	42	D2.4
MS5	Scenarios and data from nephroblastoma, GBM and NSCLC are available	WP3	4	24	D3.1
MS6	Exploitation of the CHIC infrastructure by further cancer types	WP3	4	36	D3.2
MS7	Meta- and Hyper-Multiscale Models can be demonstrated	WP3	4	48	D3.3
MS8	The CHIC Data protection and intellectual property framework	WP4	8	14	D4.1, D4.2, D4.3.1
MS9	Initial CHIC Architecture and security guidelines	WP5	7	18	D5.1.1, D5.2
MS10	Final version of the CHIC Architecture	WP5	7	42	D5.1.2, D5.3
MS11	Initial component models available for all cancer modelling branches	WP6	1	6	D6.1
MS12	Rational, numerical and clinical experience based check of the component models complete	WP6	1	20	D6.2

WT4:
List of Milestones

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS13	Availability of hypermodels for all clinic. scenarios compliant w. the guidelines to be prov. by WP7	WP6	1	40	D6.3, D7.4
MS14	All hypermodels have been quantitatively clinically adapted	WP6	1	46	D6.4
MS15	First hypermodel infrastructure deployed	WP7	7	12	D7.1
MS16	Folksonomy and Ontology annotation and search services deployed	WP7	5	24	D7.2
MS17	Hypermodel editor, development and execution application ready	WP7	7	36	D7.3
MS18	Metahypermodels annotation completed	WP7	6	48	Description in 4th annual report
MS19	Design of the CHIC repositories completed	WP8	1	16	D8.1
MS20	Deployment of the CHIC repositories	WP8	15	28	D8.2
MS21	Integration with security and ethical framework	WP8	1	42	D8.3, D4.3.2, D5.2, D10.3
MS22	Scalable & uncertainty visualization techniques	WP9	5	24	Visual analytics techniques verified by technical experiments on the data used within the project.
MS23	Image segmentation & registration techniques	WP9	12	18	Image segmentation and registration techniques verified by technical experiments on the data used in the project.
MS24	Initial version of the tumor response quantitative platform	WP9	7	24	The testing results of the initial version of the platform.
MS25	The CHIC Orchestration Platform and	WP10	7	24	D10.1, D10.2, D10.3

WT4:
List of Milestones

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
	Encrypted Data Services				
MS26	Public cloud deployment	WP10	7	36	D10.4
MS27	Evaluation and validation criteria for clinical adaptation are ready	WP11	3	12	D11.1
MS28	First evaluation workshop	WP11	3	18	Participant lists, evaluation reports from participants
MS29	Second evaluation workshop	WP11	3	36	Participant lists, evaluation reports from participants
MS30	Internal collaborative area and external website	WP12	2	3	Website is online and operational
MS31	First CHIC summer school	WP12	3	18	Participant lists, presentations
MS32	CHIC workshop	WP12	1	30	Participant lists, presentations
MS33	Second CHIC summer school	WP12	3	42	Participant lists, presentations

WT5:
Tentative schedule of Project Reviews

Project Number [1]	600841	Project Acronym [2]	CHIC

Tentative schedule of Project Reviews

Review number [65]	Tentative timing	Planned venue of review	Comments, if any
RV 1	12	TBD	
RV 2	24	TBD	
RV 3	36	TBD	
RV 4	48	TBD	

WT6:
Project Effort by Beneficiary and Work Package

Project Number [1]	600841	Project Acronym [2]	CHIC

Indicative efforts (man-months) per Beneficiary per Work Package

Beneficiary number and short-name	WP 1	WP 2	WP 3	WP 4	WP 5	WP 6	WP 7	WP 8	WP 9	WP 10	WP 11	WP 12	Total per Beneficiary
1 - ICCS	8.00	2.00	2.00	2.00	3.00	44.00	6.00	14.00	3.00	7.00	7.00	8.00	106.00
2 - 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
3 - 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
4 - KU Leuven	0.00	0.00	68.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	68.00
5 - BED	0.00	0.00	0.00	0.00	19.00	0.00	19.00	0.00	36.00	0.00	8.00	6.00	88.00
6 - USFD	4.00	0.00	0.00	0.00	12.00	0.00	88.00	0.00	0.00	0.00	0.00	6.00	110.00
7 - FORTH	2.00	3.00	0.00	0.00	10.00	9.00	6.00	6.00	20.00	21.00	3.00	6.00	86.00
8 - 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
9 - UPENN	0.00	5.00	2.00	2.00	0.00	61.00	0.00	3.00	0.00	0.00	5.00	6.00	84.00
10 - 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
11 - 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
12 - 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
13 - CUSTODIX	0.00	1.00	0.00	2.00	12.00	0.00	0.00	3.00	0.00	0.00	0.00	6.00	24.00
14 - 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
15 - UCL	0.00	0.00	0.00	0.00	0.00	0.00	24.00	48.00	0.00	0.00	0.00	2.00	74.00
16 - CINECA	1.00	0.00	0.00	0.00	0.00	0.00	42.00	0.00	0.00	8.00	0.00	6.00	57.00
17 - TEI-C	0.00	0.00	0.00	0.00	15.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00	17.00
Total	55.00	40.00	135.00	58.00	90.00	195.00	189.00	99.00	87.00	64.00	74.00	91.00	1,177.00

WT7:
Project Effort by Activity type per Beneficiary

Project Number [1]	600841	Project Acronym [2]	CHIC

Indicative efforts per Activity Type per Beneficiary

Activity type	Part. 1 ICCS	Part. 2 EURICE	Part. 3 USAAR	Part. 4 KU Leuv	Part. 5 BED	Part. 6 USFD	Part. 7 FORTH	Part. 8 LUH	Part. 9 UPENN	Part. 10 UOXF	Part. 11 UNITO	Part. 12 UBERN	Part. 13 CUSTODI	Part. 14 PHILIPS
1. RTD/Innovation activities														
WP 2	2.00	0.00	25.00	0.00	0.00	0.00	3.00	0.00	5.00	0.00	0.00	0.00	1.00	4.00
WP 3	2.00	0.00	49.00	68.00	0.00	0.00	0.00	0.00	2.00	0.00	14.00	0.00	0.00	0.00
WP 4	2.00	0.00	4.00	0.00	0.00	0.00	0.00	48.00	2.00	0.00	0.00	0.00	2.00	0.00
WP 5	3.00	0.00	0.00	0.00	19.00	12.00	10.00	0.00	0.00	0.00	0.00	4.00	12.00	15.00
WP 6	44.00	0.00	0.00	0.00	0.00	0.00	9.00	0.00	61.00	46.00	14.00	20.00	0.00	1.00
WP 7	6.00	0.00	4.00	0.00	19.00	88.00	6.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
WP 8	14.00	0.00	3.00	0.00	0.00	0.00	6.00	0.00	3.00	0.00	0.00	15.00	3.00	7.00
WP 9	3.00	0.00	15.00	0.00	36.00	0.00	20.00	0.00	0.00	0.00	0.00	12.00	0.00	0.00
WP 10	7.00	0.00	7.00	0.00	0.00	0.00	21.00	0.00	0.00	0.00	0.00	3.00	0.00	18.00
WP 11	7.00	0.00	25.00	0.00	8.00	0.00	3.00	0.00	5.00	0.00	20.00	3.00	0.00	3.00
Total Research	90.00	0.00	132.00	68.00	82.00	100.00	78.00	48.00	78.00	46.00	48.00	57.00	18.00	48.00
2. Demonstration activities														
Total Demo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3. Consortium Management activities														
WP 1	8.00	38.00	0.00	0.00	0.00	4.00	2.00	0.00	0.00	2.00	0.00	0.00	0.00	0.00
Total Management	8.00	38.00	0.00	0.00	0.00	4.00	2.00	0.00	0.00	2.00	0.00	0.00	0.00	0.00
4. Other activities														
WP 12	8.00	12.00	3.00	0.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	5.00	6.00	6.00

WT7:
Project Effort by Activity type per Beneficiary

4. Other activities														
Total other	8.00	12.00	3.00	0.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	5.00	6.00	6.00

Total	106.00	50.00	135.00	68.00	88.00	110.00	86.00	54.00	84.00	54.00	54.00	62.00	24.00	54.00

WT7:
Project Effort by Activity type per Beneficiary

Activity type	Part. 15 UCL	Part. 16 CINECA	Part. 17 TEI-C	Total
1. RTD/Innovation activities				
WP 2	0.00	0.00	0.00	40.00
WP 3	0.00	0.00	0.00	135.00
WP 4	0.00	0.00	0.00	58.00
WP 5	0.00	0.00	15.00	90.00
WP 6	0.00	0.00	0.00	195.00
WP 7	24.00	42.00	0.00	189.00
WP 8	48.00	0.00	0.00	99.00
WP 9	0.00	0.00	1.00	87.00
WP 10	0.00	8.00	0.00	64.00
WP 11	0.00	0.00	0.00	74.00
Total Research	72.00	50.00	16.00	1,031.00
2. Demonstration activities				
Total Demo	0.00	0.00	0.00	0.00
3. Consortium Management activities				
WP 1	0.00	1.00	0.00	55.00
Total Management	0.00	1.00	0.00	55.00
4. Other activities				
WP 12	2.00	6.00	1.00	91.00
Total other	2.00	6.00	1.00	91.00
Total	74.00	57.00	17.00	1,177.00

WT8:
Project Effort and costs

Project Number [1]	600841	Project Acronym [2]	CHIC

Project efforts and costs

Beneficiary number	Beneficiary short name	Estimated eligible costs (whole duration of the project)						Requested EU contribution (€)
		Effort (PM)	Personnel costs (€)	Subcontracting (€)	Other Direct costs (€)	Indirect costs OR lump sum, flat-rate or scale-of-unit (€)	Total costs	
1	ICCS	106.00	636,000.00	6,000.00	227,000.00	517,800.00	1,386,800.00	1,128,800.00
2	EURICE	50.00	324,500.00	6,000.00	39,173.00	275,825.00	645,498.00	645,498.00
3	USAAR	135.00	725,498.00	5,682.00	326,764.00	631,357.00	1,689,301.00	1,282,996.00
4	KU Leuven	68.00	340,000.00	2,000.00	167,500.00	304,500.00	814,000.00	625,000.00
5	BED	88.00	484,000.00	5,000.00	49,000.00	319,800.00	857,800.00	659,800.00
6	USFD	110.00	679,296.00	4,000.00	78,001.00	454,378.00	1,215,675.00	941,825.00
7	FORTH	86.00	412,800.00	6,000.00	110,170.00	359,136.00	888,106.00	688,031.00
8	LUH	54.00	350,622.00	3,000.00	28,000.00	227,172.00	608,794.00	474,928.00
9	UPENN	84.00	391,564.00	5,000.00	63,501.00	282,141.00	742,206.00	573,282.00
10	UOXF	54.00	289,078.00	3,902.00	59,184.00	208,956.00	561,120.00	446,591.00
11	UNITO	54.00	270,000.00	5,000.00	100,000.00	222,000.00	597,000.00	462,998.00
12	UBERN	62.00	465,000.00	4,000.00	60,000.00	315,000.00	844,000.00	651,000.00
13	CUSTODIX	24.00	180,000.00	0.00	33,000.00	90,000.00	303,000.00	245,375.00
14	PHILIPS	54.00	398,466.00	3,000.00	25,000.00	592,650.00	1,019,116.00	566,120.00
15	UCL	74.00	497,978.00	6,000.00	161,000.00	395,386.00	1,060,364.00	804,156.00
16	CINECA	57.00	228,000.00	0.00	54,408.00	313,899.00	596,307.00	325,560.00
17	TEI-C	17.00	37,400.00	0.00	11,900.00	29,580.00	78,880.00	60,040.00
Total		1,177.00	6,710,202.00	64,584.00	1,593,601.00	5,539,580.00	13,907,967.00	10,582,000.00

1. Project number

The project number has been assigned by the Commission as the unique identifier for your project. It cannot be changed. The project number **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

2. Project acronym

Use the project acronym as given in the submitted proposal. It cannot be changed unless agreed so during the negotiations. The same acronym **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

53. Work Package number

Work package number: WP1, WP2, WP3, ..., WPn

54. Type of activity

For all FP7 projects each work package must relate to one (and only one) of the following possible types of activity (only if applicable for the chosen funding scheme – must correspond to the GPF Form Ax.v):

• **RTD/INNO =** Research and technological development including scientific coordination - applicable for Collaborative Projects and Networks of Excellence

• **DEM =** Demonstration - applicable for collaborative projects and Research for the Benefit of Specific Groups

• **MGT =** Management of the consortium - applicable for all funding schemes

• **OTHER =** Other specific activities, applicable for all funding schemes

• **COORD =** Coordination activities – applicable only for CAs

• **SUPP =** Support activities – applicable only for SAs

55. Lead beneficiary number

Number of the beneficiary leading the work in this work package.

56. Person-months per work package

The total number of person-months allocated to each work package.

57. Start month

Relative start date for the work in the specific work packages, month 1 marking the start date of the project, and all other start dates being relative to this start date.

58. End month

Relative end date, month 1 marking the start date of the project, and all end dates being relative to this start date.

59. Milestone number

Milestone number:MS1, MS2, …, MSn

60. Delivery date for Milestone

Month in which the milestone will be achieved. Month 1 marking the start date of the project, and all delivery dates being relative to this start date.

61. Deliverable number

Deliverable numbers in order of delivery dates: D1 – Dn

62. Nature

Please indicate the nature of the deliverable using one of the following codes

R = Report, **P** = Prototype, **D** = Demonstrator, **O** = Other

63. Dissemination level

Please indicate the dissemination level using one of the following codes:

• **PU =** Public

• **PP =** Restricted to other programme participants (including the Commission Services)

• **RE =** Restricted to a group specified by the consortium (including the Commission Services)

• **CO =** Confidential, only for members of the consortium (including the Commission Services)

• **Restreint UE =** Classified with the classification level "Restreint UE" according to Commission Decision 2001/844 and amendments

• **Confidentiel UE =** Classified with the mention of the classification level "Confidentiel UE" according to Commission Decision 2001/844 and amendments

• **Secret UE =** Classified with the mention of the classification level "Secret UE" according to Commission Decision 2001/844 and amendments

64. Delivery date for Deliverable

Month in which the deliverables will be available. Month 1 marking the start date of the project, and all delivery dates being relative to this start date

65. Review number

Review number: RV1, RV2, ..., RVn

66. Tentative timing of reviews

Month after which the review will take place. Month 1 marking the start date of the project, and all delivery dates being relative to this start date.

67. Person-months per Deliverable

The total number of person-month allocated to each deliverable.

PART B

COLLABORATIVE PROJECT

Table of Contents

B1 CONCEPT AND OBJECTIVES, PROGRESS BEYOND THE STATE-OF-THE-ART, S/T METHODOLOGY AND WORKPLAN

B.1.1 Concept and project objectives

B1.1.1 S&T Objectives

B1.1.1.1 Rationale of CHIC

The impressive rate of generation of human biological data during the last decades has dictated the development of numerous statistical, computational and mathematical methods, in order to extract, analyze and exploit the hidden wealth of information. Unquestionably systems biology has been established as a key player in this arena. However, despite its maturation over the last decade a number of obstacles render it difficult for systems biology to be directly exploitable by clinical practice.[1] Recognizing that in most medical conditions crucial biological phenomena are manifested at several spatiotemporal scales, including scales lying far above the subcellular level - which is traditionally addressed by systems biology- researchers have proposed a number of ways to integrate super-cellular levels into systems biology approaches. Such initiatives have taken various forms and names such as systems physiology[2], systems medicine, multiscale modeling and Virtual Physiological Human (VPH). Despite the differences in each one's emphasis, they all essentially try to reach and serve the clinic, since the latter appears to be the ultimate goal of the main bulk of biological research. In the specific paradigmal VPH domain of cancer, where the multiscale character of the disease is exceptionally pronounced, there is particularly demanding need for biomodels to address several organizational levels and scales *concurrently*. If one takes into account the additional complexity which is due to the host of involved elementary bioprocesses (biomechanisms) including angiogenesis, the numerous cancer types and subtypes and the clinically available treatments which may be rather complicated (*Figure 1.1.1.1-a*), one can readily realize that the requirements for a cancer model to be comprehensive and versatile so as to potentially be of use to the clinic are tremendous.

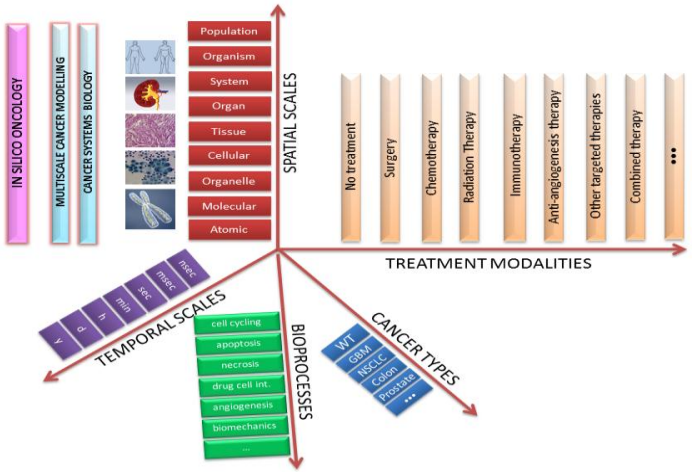

Figure 1.1.1.1-a Dimensions of cancer manifestation and treatment

This remark suggests that cancer in the clinical context dictates the development of integrative hypermodels consisting of simpler and more manageable constituent component models which may already be available. Nevertheless, in order for models generally developed by different modellers or modeling groups to be reusable, there are a number of prerequisites that have to be satisfied. Models should be robust, reproduceable and interoperable. This implies that standardization of model description and operation is a sine qua non necessity if rational, coherent and comprehensive exploitation of the invaluable information hidden within human multiscale biological data is envisaged. Responding to this imperative in the context of both the broad (VPH) initiative and the paradigmal cancer domain, CHIC proposes the development of a suite of tools and services in a secure

[1] G. Clermont et al. "Bridging the gap between systems biology and medicine," Genome Medicine 2009, 1:88 (doi:10.1186/gm88)
[2] H. Kitano, "Grand challenges in systems physiology,"Frontiers in Physiology, 2010, 1:1-3

infrastructure that will support accessibility and reusability of VPH mathematical and computational hypermodels. The proposed objective is primarily centered around the development of a hypermodelling environment which, although will be applicable to the broad VPH space, it will be driven by and originally tested in the cancer domain. In order to ensure clinical relevance and foster clinical acceptance of hypermodelling in the future, the whole endeavour will in practice be driven by the clinical partners of the consortium. Cancer hypermodels to be collaboratively developed by the consortium cancer modellers will provide the framework and the testbed for the development of the CHIC technologies. Clinical adaptation and partial clinical validation of hypermodels and hypermodel oncosimulators will be undertaken. The VPH hypermodelling environment that will be developed in CHIC, starting from an advanced prototype developed in the VPHOP project, will expose by the end of the CHIC project a set of features so advanced and

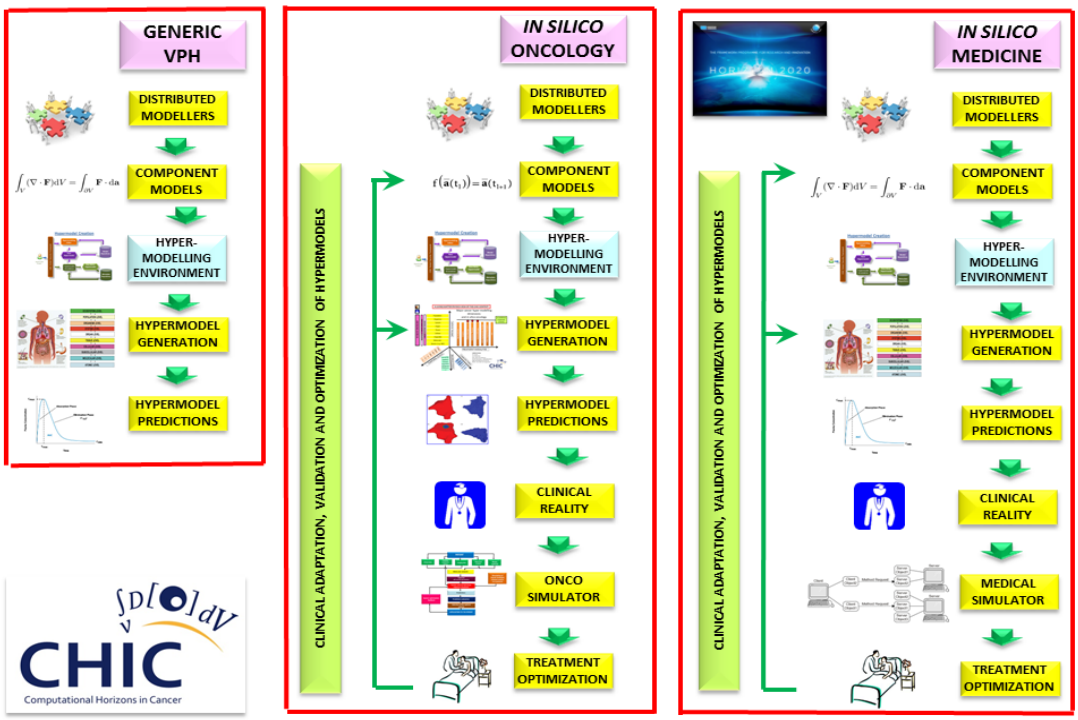

Figure 1.1.1.1-b The niche of the hypermodelling environment to be developed within the framework of VPH, in silico oncology and in silico medicine in general

sophisticated to be easily identified as the leading solution worldwide for this specific problem. CHIC is expected to foster the further development of the VPH initiative, as it transits towards its second stage of maturity, the vision of the so-called *in silico* medicine that will be the primary target of Horizon 2020. CHIC already includes fundamental elements in its design anticipating this vision in particular and will provide a testbed for some of the most challenging concepts. *In silico* oncology addressed by CHIC is to serve as a concrete messenger of this vision. *Figure 1.1.1.1-b* depicts the positioning of the hypermodelling environment to de developed in the current phase of VPH, in the emergent *in silico* oncology context and ultimately in the vision of general *in silico* medicine.

CHIC will actually be deployed on the transatlantic research environment, since one of the key consortium partners is from the US. In this context the concrete outcome of previous joint EU-US initiatives such as the First Transatlantic Workshop on Multiscale Cancer Modelling[3],[4] will be exploited to the full.

[3] ***http://ec.europa.eu/information_society/events/ict_bio/2008/ta-cancer-wkshp/index_en.htm***
[4] ***http://ecancer.org/tv/pubdate/105***

B1.1.1.2 Aim and Objectives of CHIC

a. Aim

The CHIC proposal aims at developing cutting edge ICT **tools**, **services** and **secure infrastructure** to foster the development of elaborate and reusable **integrative models** (hypermodels) and **larger repositories** so as to demonstrate benefits of having both the multiscale data and the correponding models readily available. Although the broader VPH domain is the primary target of the hypermodelling infrastructure to be developed by CHIC, the primary application domain will be cancer and *in silico* oncology.

In the mid and long term CHIC aims to pave the way for reliable *in silico* clinical trials, lying at the heart of the vision of *in silico* medicine, and subsequently for patient individualized treatment optimization based on *in silico* experimentation.

b. Objectives

CHIC proposes the development of clinical trial driven tools, services and secure infrastructure that will support the creation of multiscale cancer hyper-models (integrative models). The latter are defined as **choreographies of component models**, each one describing a biological process at a characteristic spatiotemporal scale, and of relation models/metamodels defining the relations across scales. Integrative models can become component models for other integrative models. The development of a secure **hypermodelling infrastructure** consisting primarily of a *hypermodelling editor* and a *hypermodelling execution environment* is a central generic VPH geared objective of CHIC.

In order to render models developed by different modellers semantically interoperable, an infrastructure for **semantic metadata management** along with **tools and services for ontology-based annotations** will be developed. Existing approaches such as the one developed by the EC funded RICORDO project will be exploited and extended. Facilitated operations will range from automated dataset matching to model merging and managing complex simulation workflows. In this way **standardization** of cancer model and data annotation allowing multiscale hypermodelling will be fostered.

The following entities will also be developed: a **hypermodel repository**, a **hypermodel-driven clinical data repository**, a **distributed metadata repository** and an ***in silico* trial repository** for the storage of executed simulation scenarios, an **image processing toolkit**, a **visualization toolkit** and **cloud and virtualization services**.

In order to ensure that the entire project will be clinically driven and clinically oriented, three concrete **clinical trials/studies** will be adopted and addressed. They concern nephroblastoma treated by combined chemotherapy, glioblastoma treated by immunotherapy in combination with chemotherapy and radiotherapy and non-small cell lung cancer treated by a combination of chemotherapy and radiotherapy.

The multiscale data generated by these trials/studies will be exploited so as to both drive the development of a number of **integrative multiscale cancer models (hypermodels)** and **hypermodel oncosimulators** and clinically adapt and partly validate them.

The whole process will be supported by the technological tools, services and infrastructure to be developed and will serve as a paradigm of applicability and usability of the latter. Additional available multiscale data concerning colon and prostate cancer will be exploited in a similar way. The participation of five prominent multiscale cancer modelling groups from both EU and the US covering all spatiotemporal scales (from the molecular up to the organism and from nsecs up to years) and all the fundamental biological processes of cancer as well as some aspects of the treatment response of normal tissues will ensure a comprehensive coverage of the domain of cancer. The latter refers to both the process of annotating component models and hypermodels as well as pertinent multiscale data and the development of exemplary clinically driven and clinically validatable hypermodels.

This is expected to considerably advance the exploitation of both existing models and models to be developed in the future. **An integrative platform** dictated by the IT architecture of the project will

provide access to all hypermodelling tools and services to be developed. Apart from the tools addressing semantic interoperability, a number of data pre-processing tools, services and resources will be developed and/or made available. These will include inter alia image segmentation, three-dimensional reconstruction, several forms of data and model prediction visualization and cloud computing.

The **legal and ethical aspects** of patients' data handling will be addressed by a workpackage dealing with both the legal and the IT aspects of data anonymization and pseudonymization, patient's consent etc. The same work package will also address the **intellectual rights issues** arising from the amalgamation of component models potentially developed by different modellers in order to construct integrative models.

The dissemination and exploitation of the CHIC proposal will target all stakeholders, namely clinicians, fundamental science researchers, IT specialists and engineers, industry and patients. Similarly, the project is expected to have a significant impact on all the corresponding domains. More precisely, CHIC aspires to make a breakthrough in multiscale cancer modelling through greatly facilitating multi-modeller cancer hypermodelling and its clinical adaptation and validation. Standardization of model description and model "fusion" will be two of the core means to achieve this goal. The creation of such elaborate and refined hypermodels is expected to sharply accelerate the clinical translation of multiscale cancer models and oncosimulators following their prospective clinical validation (*in silico* oncology). Addressing intellectual property issues in a multi modeller setting will foster the community spirit in the VPH domain.

B1.1.1.3 Architecture and main building blocks of CHIC

CHIC will develop a variety of tools and repositories that will assist the researcher in searching and retrieving models and data, composing and saving hypermodels, executing models and hypermodels and last but not least validating the outcome of the simulations *(Figure 1.1.1.3-a)*.

The core reference point for the users will be the CHIC **portal**. All the components of CHIC will reside under the “umbrella” of the **security framework** that will deal with the issues of secure and safe storing, acquisition and sharing of models and data.

Four individual repositories will be implemented in CHIC.

- A **model repository** that will store the multiscale models, the complimentary tools and modules that will be needed in order to construct hypermodels and the hypermodels themselves. In the model repository will also reside the **visualization** and **image processing** tools that will be developed in CHIC.
- A **data repository** that will store the heterogeneous multiscale data coming from clinical environment (clinical trials etc.). Especially for the storage of “sensitive” patient-specific data a special **pseudo-anonymization/anonymization** procedure will be followed in compliance with the **legal and ethical framework.** Due to legal limitations, the CHIC repositories, especially the ones that are dealing with patient data, will be implemented so as to be easily deployable in local or private cloud infrastructures of medical, educational and research institutions.

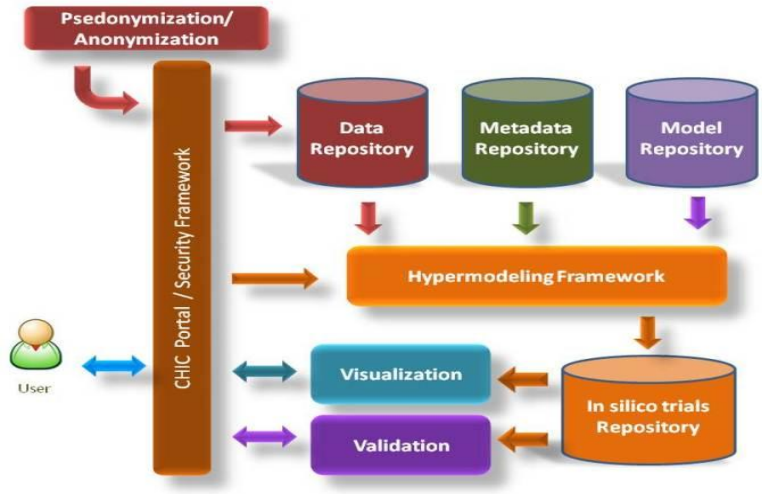

Figure 1.1.1.3-a Main technological components of CHIC directly related to the hypermodelling workflow

- A **metadata repository** that will store the machine-readable documentation material that will semantically represent both models and data.
- An ***in silico*** **trial repository** which will store the input and output of the *in silico* simulations along with the complete profile of each simulation, including the model/hypermodel used in the simulation and its version, the model/hypermodel configuration parameters etc.

The users will upload their models and the complimentary tools in the model repository. In addition the user will use the model annotation framework to add semantic information to his/her models and data. This information will be used later on by the hypermodelling framework in order to construct and execute hypermodels (Figure 1.1.1.3-b).

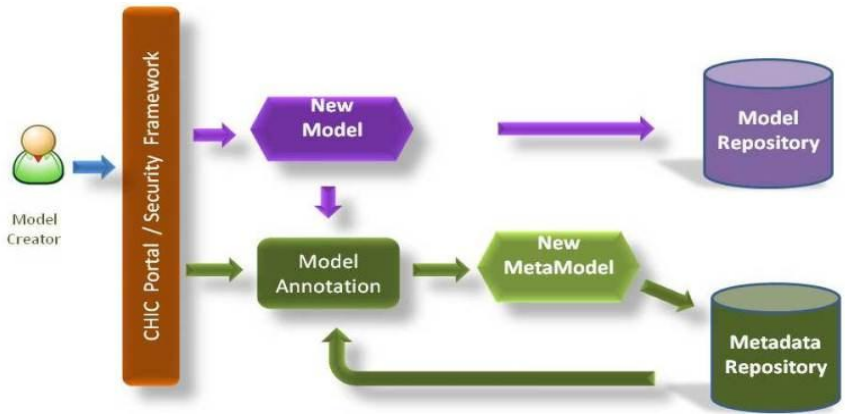

Figure 1.1.1.3-b Model and metamodel creation workflow

The composition and execution of hypermodels will be done by the **Hypermodelling Framework**. This will consist of the Hypermodelling Editor and the Hypermodel Executional Framework. The **Hypermodelling Editor** will communicate with the model and metadata repositories and will guide the user in easily and effectively constructing hypermodels *(Figure 1.1.1.3-c)* by

- exposing information about existence and availability of models,
- presenting interconnection possibilities,
- indicating the model/modules that need to be developed in order to fill in the gaps,
- visually constructing the hypermodels, provided that all needed components are available, either as implemented models/modules or as a " to be implemented" dummy black boxes.

The Hypermodel Executional Framework will communicate with the model, the metadata and the data repository, in order to retrieve the relevant information to be used in the simulation (in silico trial). The outcome of the execution will be send to the in silico trial repository for persistent storage. The user will be able to retrieve the results of a simulation from the in silico trials repository (Figure 1.1.1.3-d).

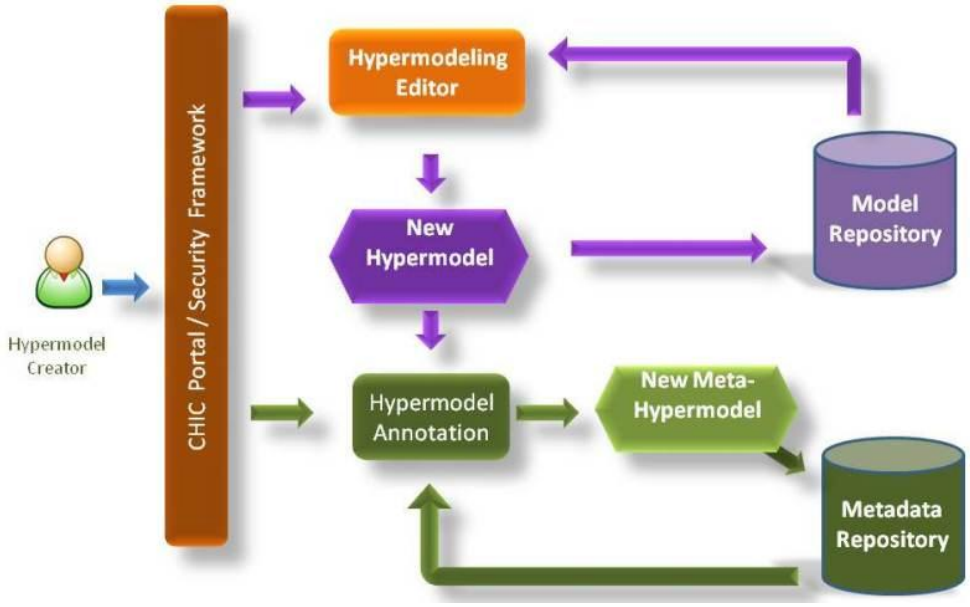

Figure 1.1.1.3-c Hypermodel and meta-hypermodel creation workflow

The CHIC image processing tools will be used in the preprocessing of imaging data in order to be prepared for usage in the simulations. The results of the simulations will use the CHIC visualization tools in order to be presented to the user.

Figure 1.1.1.3-e shows the gross overall CHIC architecture from a clinical study and trial centered perspective.

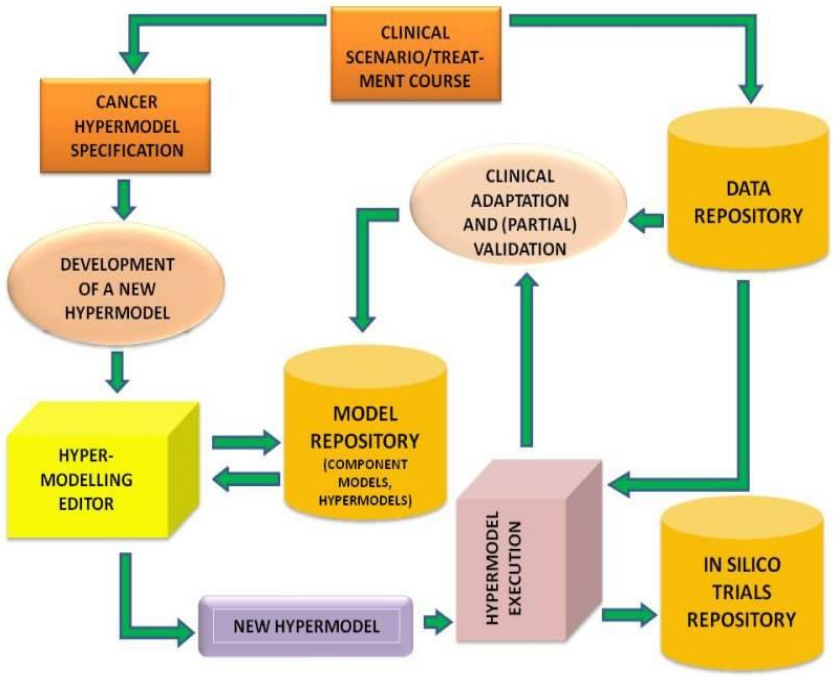

Figure 1.1.1.3-d Clinical scenario driven hyper- model development

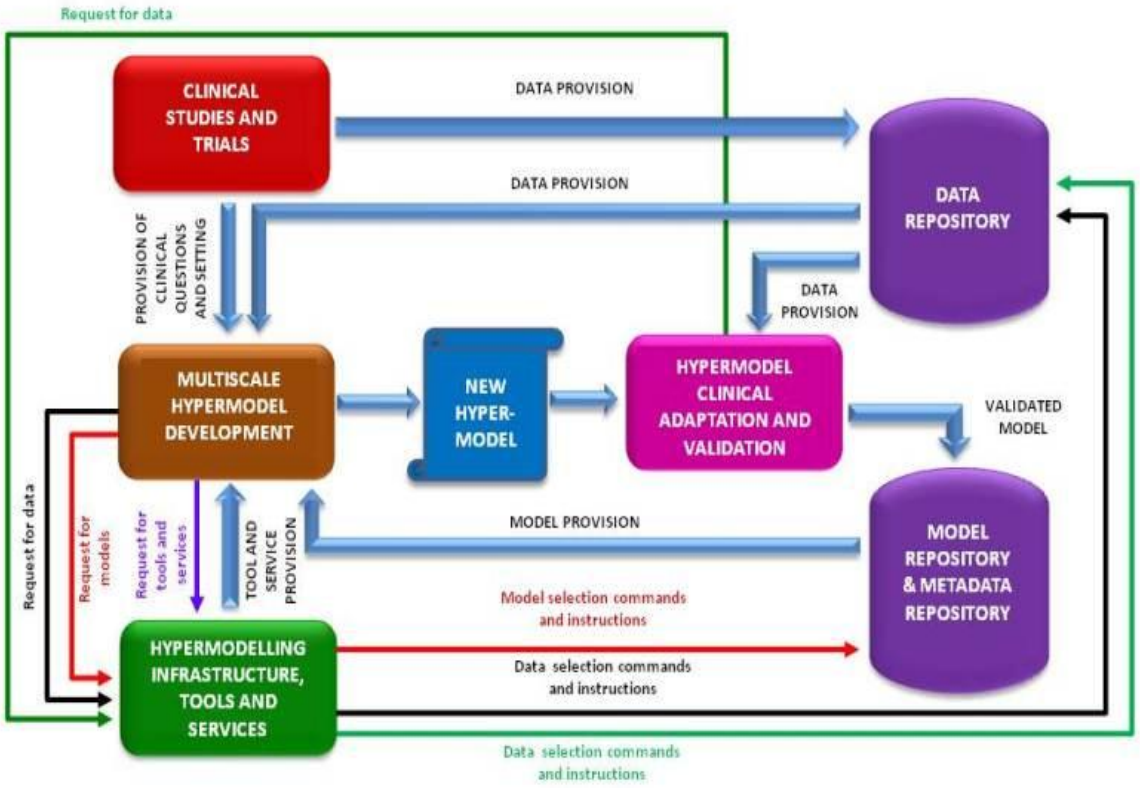

Figure 1.1.1.3-e The overall CHIC architecture from a clinical study and trial centered perspective

The **Hypermodel Oncosimulator** is an extension of the notion and the system of the original Oncosimulator[5] so as to make use of cancer and normal tissue hypermodels. The (hypermodel) Oncosimulator is at the same time a concept of multilevel integrative cancer biology, a complex algorithmic construct, a biomedical engineering system and eventually in the future a clinical tool which primarily aims at supporting the clinician in the process of optimizing cancer treatment in the patient individualized context through conducting experiments *in silico* i.e. on the computer. Additionally it is a platform for simulating, investigating, better understanding and exploring the *natural phenomenon* of cancer, supporting the design and interpretation of clinicogenomic trials and finally training doctors, researchers and interested patients alike[17,18,19]. A synoptic outline of the clinical utilization of a specific version of the *Oncosimulator*, as envisaged to take place following an eventually successful completion of its clinical adaptation, optimization and validation process is provided in the form of steps (*Figure 1.1.1-3-f*).

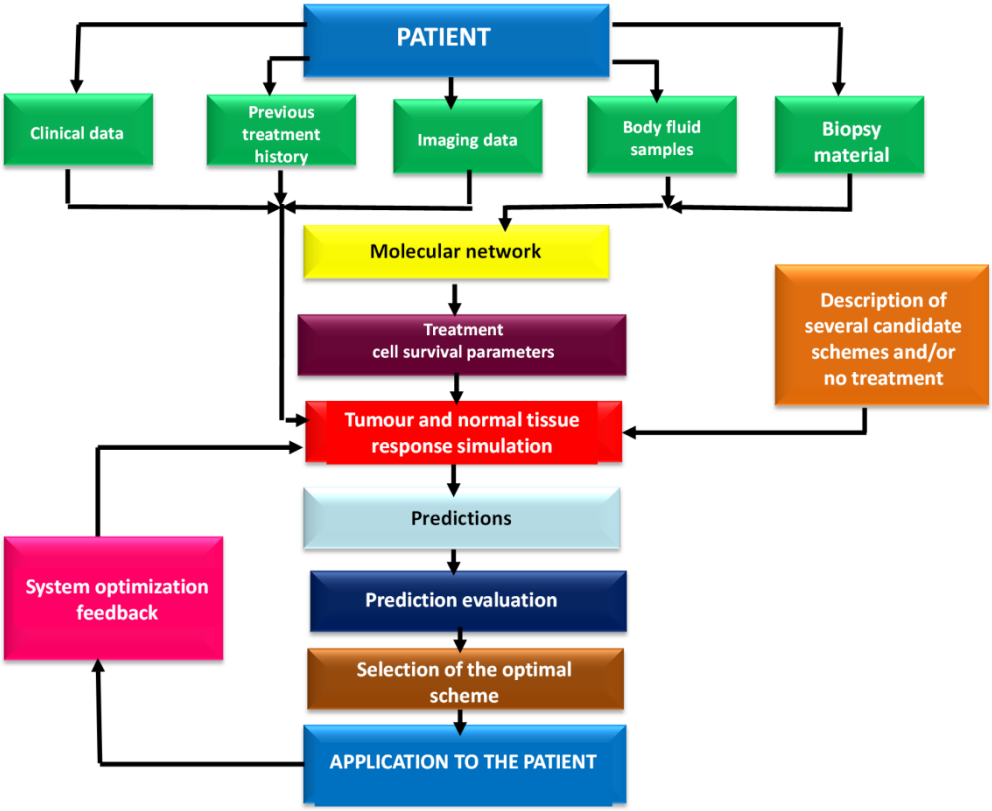

***Figure 1.1.1.3-f* A synoptic diagram of the hypermodel based oncosimulator**

[5] *G.Stamatakos "In Silico Oncology Part I: Clinically Oriented Cancer Multilevel Modeling Based on Discrete Event Simulation" In T.Deisboeck and G. Stamatakos Eds 407-436 2011-01-01 CRC Press, Print ISBN: 978-1-4398-1440-6 eBook ISBN: 978-1-4398-1442-0 DOI: 10.1201/b10407-19 Boca Raton, Florida, USA, 2011*

B1.1.2 Relevance to the ICT call topic

The CHIC proposal focuses on the **Objective ICT-2011.5.2 b) Virtual Physiological Human (VPH)**. The concrete way in which CHIC responds to the specific topics addressed by the call is outlined below and reveals a perfect fit of the proposal:

"ICT tools, services, infrastructure and larger repositories"

CHIC will develop a suite of ***ICT tools, services, secure infrastructure and larger repositories*** usable within both the generic VPH framework and the cancer/*in silico* oncology special domain. These will include:

1. *Repositories* [model repository for storing VPH multi-scale models, data repository for storing heterogeneous data coming from the clinical environment**,** distributed RDF enabled metadata repository*, in silico* trial repository for storing complete simulation scenarios, including information about model and data] **2. *Hypermodelling Infrastructure*** [hypermodelling editor, hypermodelling execution environment] **3**. ***Infrastructure for semantic metadata management*** [core knowledge base to support semantic querying of metadata, metamodelling and metahypermodelling language, metamodel and metahypermodel annotation services, global metadata search engine] **4. *Visualization*** [general development environment for visualization, visual analysis suite for model repositories, visual analysis suite for data repositories]**, 5. *Image Processing*** [brain tumour image analysis framework, general image processing development toolkit, image registration tools, software platform for the assessment of tumour treatment response]**, 6. *Cloud & Virtualization*** [compute cloud services, storage cloud services, virtualized access to high performance computing environment]

"more elaborate and reusable multi-scale models"

The aforementioned CHIC tools, services, infrastructures and repositories will provide the CHIC partners with a collaborative interface for exchanging knowledge and sharing technical work in an effective and standardized way. Researchers involved in developing, enhancing and improving multi-scale models will be equipped with the necessary tools and working environments to retrieve other researchers' models and model-related information, compare models, test them and eventually **reuse** them, either alone or combined with other models. This **collaborative procedure** will ultimately lead, following an extensive population of the model repository, to the desired goal of **more elaborate and reusable multi-scale models**.

"to show benefits of having both the data and models readily available"

CHIC will provide the environment for storing, acquiring and sharing of models and data and will make ***both data and models readily available.*** In that way CHIC will: 1. enable modelers and clinicians to conduct simulations and data analysis, 2. permit the comparison, validation and exploitation of the outcome of the aforementioned simulations, 3. make the procedure of running multiple instances of simulations, for the purpose of an *in silico* trial, as automated as possible, 4. provide a means for testing and validation studies of multi-scale models, which will ***ensure acceptance*** from the scientific community and the industry, 5. advance cancer multiscale modelling through the exchange, interconnection and evolution of the already existing models and those created in the context of CHIC, 6. set up ***standards*** that will make the vision of different models collaborating in action a reality, 7. contribute to patient-specific cancer treatment optimization , 8. shorten the gap between basic research and clinical practice for cancer treatment, 9. enable the transfer of these technologies to the european medical industry.

"robustness and reproducibility essential to allow models to be re-used when a model representing a physiological function is incorporated into a more comprehensive model"

At the technical level the CHIC approach aims to abstract cancer models into ***reusable*** software components that are deployed into the cloud infrastructure. The notion of hypermodels takes advantage of these technical implementations so that the building of more comprehensive, integrative

models becomes possible. The model reuse and integration into higher level modelling entities, crossing biocomplexity and spatiotemporal scale levels, is therefore inherent into the CHIC methodology. The ***robustness*** of the resulting complex models will be supported at the technical level by the architecture and the cloud technology (e.g. by adopting scalable technologies and state-of-the-art engineering best practices) and at the domain-specific level, by testing and validation on multiple different input data sets. The introduction of the semantics-based descriptions and metamodelling languages into this setting will further strengthen the ***reusability and reproducibility*** of the models. Annotation of models and hypermodels with appropriate metadata and use of provenance information, as a byproduct of the models' execution trace, will provide information about the circumstances when the models were run, input data, output data etc. Monitoring of the models' execution and accumulation of this provenance information using well-defined formalisms (e.g. the Open Provenance Model - OPM[1]) will reinforce ***reproducible research.***

"Standards for models and data, tools and repositories to achieve a high level of robustness and reproducibility of models for re-use"

Moreover, ***robustness*** and ***reproducibility*** of models for re-use will be achieved by following or developing ***standards*** for models and data, tools and repositories. More specifically, the present standards will be endorsed, in order to represent in a more comprehensive and complete way models and data, enable maximum exploitation of data and effective re-usage of models. ***Standard format*** will be used for data storage and retrieval. In case that such a standard is yet unavailable, the consortium will discuss the most appropriate storage option and provide ***open-source tools*** for data reading and writing. Multi-scale models and data will be semantically annotated using the ***ontological and annotating tools*** developed in the context of CHIC. These tools will be based on already existing ontologies and mark-up languages, but not limited to them.

"VPH Infostructure including sustainable VPH model and data repositories.

The CHIC workflow execution software environment and the aforementioned repositories, thanks to their generality, will constitute fundamental components of the general VPH infostructure, allowing easy connection of models and data.

"Appropriate tools (e.g. version control, archiving, upgrades…) and attributes such as usability and accessibility should be particularly addressed to ensure VPH community acceptance"

A number of features and tools that will be incorporated into CHIC will enhance, among others, ***usability*** and ***accessibility***, and reinforce ***VPH community acceptance***. More specifically:

1. **A lightweight dynamic security architecture** based on commonly used standards and implementations (e.g. SAML, XACML, etc.) will be adopted, covering the security needs related to large networks exchange of sensitive medical data. 2. **A friendly-user interface** accompanying each repository will give the user administrator or basic access rights 3. **Special web services** will be implemented for each repository, in order for its content to be accessible for manipulation by other components of CHIC or by non-CHIC tools or services. The aforementioned web services will utilize at least one of the **commonly used interoperable methods/standards** like SOA, REST or RPC. 4. The above-mentioned GUI and web services will use, apart from any built-in authentication framework of the repository, at least one **method/protocol for "Single Sign On"**, like OAuth2. 5. **Versioning of the repository implementation**, along with the **versioning of its content**, will be central features of each repository. The model repository will be capable of hosting different versions of models/hypermodels. The data repository will include object versioning mechanisms that will allow users to track the various versions of the stored objects and results. No object will be deleted from the system. The repositories themselves will have a **built-in versioning system**, taking into account that alterations in the repository's source code might prove necessary, in order to fix bugs or add features, either in the scope of CHIC or in the scope of a future project that would re-use the CHIC repository source code. 6. **Special upgrade patches** will be available so that the migration from one version of a repository to another will be made smoothly and without loss of content. 7. Different versions of the repositories implementation and source code will be available as **archives in a publicly accessible file server**, so as to be easily retrievable online. The aforementioned upgrade patches will also be available as archives in the file server.

"The use of open environments and open-source software is expected to improve the accessibly and evolution of the repositories"

In order to improve the accessibility and evolution of the repositories **open environments and open-source software** will be used. The design and implementation will also focus on how to make the toolkit of CHIC **deployable in different locations and infrastructures** with minimum alterations. If such alternations are needed, then the source code will be available in order to make the process quick, easy and cost-free. The CHIC workflow execution software environment will also be developed relying on **state of the art open-source software solutions** and will be released as open-source under a BSD-like license that will favor the accessibility and the adoption by the VPH community at large. The **dynamic nature of the security architecture** (e.g. the loose coupling) will allow it to evolve over time according to newly arising requirements. With this approach, the security architecture will offer service providers a tool to achieve "**compliance by default**". It will reduce the effort needed to reach compliance with governing legislation and thus minimise the well-known "data protection barrier" to data access.

B1.1.3 Expected results of CHIC

CHIC is expected to produce the following major end results

1. Provision of a VPH infrastructure which will support the development of robust, reproducible, interoperable and collaborative hyper-models of diseases and normal physiology. This infrastructure will consist mainly of a hypermodelling editor and a hypermodelling execution environment
2. Provision of a semantic annotation facility using the ontological and annotating tools to be developed
3. Provision of an infrastructure for semantic metadata management
4. Provision of a hypermodel repository, a hypermodel-driven clinical data repository, a distributed metadata repository and an *in silico* trial repository for the storage of executed simulation scenarios
5. Provision of image processing and visualization kits
6. Provision of multiscale data from the clinical trials/studies integrated into CHIC
7. Provision of hypermodels driven by the clinical trial multiscale data
8. Provision of clinically adapted multiscale hypermodels
9. Provision of the overall CHIC architecture and integrated IT platform
10. Provision of open source code regarding several components to be developed

B1.2 Progress beyond the state-of-the-art

CHIC is expected to bring about progress in several domains of the VPH initiative due to its strongly multidisciplinary character. In the following, the state of the art in the major fields in which CHIC is expected to contribute towards advancement is outlined. The anticipated progress beyond the state of the art is also provided. The specific fields have been grouped into four major areas (Information Technologies, Multiscale Cancer Modeling, Clinical Medicine, Law and Ethics).

B1.2.1 INFORMATION TECHNOLOGIES: Computing infrastructures for biomodelling

State-of-the-art

The term *hypermodel* in relation to modelling was first used in a 1992 paper on decision support systems[6]. This paper described also as a theoretical possibility a dynamic distributed system where models could run in a coordinated fashion. The term was re-invented in the context of the Virtual Physiological Human in 2008[7] and again in 2011 in the more general context of computational sciences[8]. A hypermodel is a concrete instance of an integrative model, built as the orchestration of multiple computer models that might run on different computers at different locations, using different simulation software stacks. A first concrete implementation, based on web services was tested on biochemical models[9]. More recently, the VPHOP consortium presented preliminary results based on their hypermodelling technology running on an IBM PLX supercomputer[10]. The VPHOP hypermodelling technology uses an open source distributed bus architecture called MAF3 Bus module, to orchestrate both the control and the data flows among different sub-models developed with different modelling software that are wrapped using the VPHOP hypermodelling templates so as to expose a standardised communication and data management layer. While the VPHOP proved to be effective in many regards, its implementation is only partial as it is missing key functionalities such as distributed authentication, a statistical module, etc. More in general the VPHOP hypermodelling technology totally lacks all the services that would make possible for large and uncoordinated groups of researchers to contribute independently to model repositories where these models can be combined and reused by other researchers.

Contribution of CHIC

CHIC will develop a "Hypermodelling infrastructure". The partners active in the corresponding workpackage will collaborate to the development of the Component Model Generic Stub and will provide basic annotation and tags management services. In addition, they will work on the development of two modelling services, to cope with the incompleteness of the inputs, and to cope with strongly coupled models. The general philosophy can be described as follows:

A requesting service submits an input set and a request for an output set:

- if the input set is complete
    - if the model has already been run with that input set, then the outputs databases return the output to the requester (low latency)

[6] *Balasubramanian, P. Isakowitz, T. ; Johar, H. ; Stohr, E.A. Hyper model management systems. System Sciences 3:462-472 (1992). Proceedings of the Twenty-Fifth Hawaii International Conference on System Sciences*

[7] *Viceconti M. The skeleton of the Virtual Physiological Human. Presented at "The Living Human Project: building the musculoskeletal physiome" mini-symposium, MBEC2008 Antwerp (BE)*

[8] *Fishwick P.A. Hypermodelling: an integrated approach to dynamic system modelling. Journal of Simulation (2012)* ***6,*** *2–8*

[9] *Guha R. Flexible Web Service Infrastructure for the Development and Deployment of Predictive Models J. Chem. Inf. Model. (2008), 48(2):456–464*

[10] *Viceconti M. et al. Image-based, personalised and multiscale modelling to predict the risk of fracture in osteoporotic patients: the VPHOP integrated project. Imagine Scientific Exhibit, European Congress of Radiology (ECR2012), Vienna March 2012*

- if the model has never run with that input set, a cache miss event is raised to the surrogate model. If the surrogate model can estimate the output within tolerance, then the estimated output is returned to the DB and the requester and an offline run of the model is requested for that input set. If the surrogate model cannot estimate within tolerance, then a runtime run of the model is requested.

- if the input set is incomplete, then the partial input set is passed to population inputs DB, a surrogate input is generated and passed to the surrogate model, and then same as above

Last but not least, it will be explored if and how Linked Data can be used in this context.

B1.2.2 INFORMATION TECHNOLOGIES: Standards and methods for the annotation, sharing and reasoning over 'semantic metadata' of data and model resources (DMRs): The RICORDO effort

State-of-the-art

In order to improve the automated integration of VPH data and model resources (DMRs) in terms of biological meaning, the RICORDO[11,12] effort has fostered standards and methods for the annotation, sharing and reasoning over 'semantic metadata' of DMRs. 'Metadata' refers to machine-readable documentation material that is linked to a corresponding DMR element indicating appropriate content interpretation. 'Semantic metadata' ascribes a DMR element with some meaning. The goal of achieving semantic interoperability for a set of DMRs is motivated by the need to automate the coherent interpretation of DMR content over a large number of diverse DMRs. A key result of attaining this goal is the ability to automatically identify DMRs that are related to each other solely on the basis of their metadata documentation. The key to relating diverse VPH DMRs in RICORDO is to make use of a small set of knowledge-rich ontologies in the annotation of resource sematic metadata. Specifically, a small set of ontologies about biology knowledge are applied in the annotation of multiscale biological structure, measurable qualities, as well as associated units of measurement. A second critical step is to apply reasoning tools to infer relations between DMR metadata. Metadata annotation, storage and reasoning tools are part of the RICORDO VPH infrastructure. The RICORDO toolkit is modular and its components can be combined to implement the workflow we envision for annotation of DMRs. The Composite Component enables the creation of composite terms and accesses and modifies the ontologies used by the RICORDO ToolKit. The Annotation Component creates annotations of DMRs and deposits them in the Metadata Store. The Query Component combines reasoning over ontologies and access to the Metadata Store to perform queries over DMRs. Biomedical DMRs are encoded over a wide range of formats and are subject to a variety of constraints on their distribution to the rest of the community. The RICORDO approach ensures the structural integrity and security constraints of such DMRs. The provision of RICORDO metadata catalogues that allow the uncoupling of annotation distribution from that of their corresponding resource (with the additional benefit of protecting DMR integrity) is a strategy that has been successfully adopted by clinical and pharmaceutical communities. In other words, RICORDO annotations would be accessible as a catalogue for querying by third parties, without having to necessarily provide access to the original models or datasets. No significant change to the format of a DMR may be required if related metadata can be stored in a separate file as long as it holds a mapping to the DMR element Uniform Resource Identifiers (URIs). This approach may therefore provide a viable semantic interoperability solution despite the inevitable heterogeneity of resource formats: for instance, tumor models written in different languages may share the same

[11] *Wimalaratne, S.M., Grenon, P., Hoehndorf, R., Gkoutos, G.V., de Bono, B. An Infrastructure for Ontology-Based Information Systems in Biomedicine: RICORDO Case Study. Bioinformatics 1;28(3):448-50 (2011)*

[12] *de Bono, B. et. al. The RICORDO approach to semantic interoperability for biomedical data and models: strategy, standards and solutions. BMC Research Notes 4:313 (2011)*

metadata standard along with datasets of this pathology (which may also be stored over a number of heterogeneous formats).

Contribution of CHIC

CHIC will build on ongoing efforts in the VPH community to provide a robust infrastructure with which to (i) effect annotation of semantic metadata across the CHIC spectrum of computational models, and then (ii) openly share and reason over this metadata. In particular, CHIC will work to effectively interact with metadata for models and data. It will test, integrate and extend the RICORDO VPH infrastructure to support semantic interoperability of resources within the CHIC community based on the management (storing and inference-based querying) of their ontology-based annotations. A core knowledge base using the RICORDO infrastructure that supports real-time reasoning over multiple large ontologies will be set. This knowledge base will support the expression of complex ontology concepts and use these concepts to retrieve relevant resource metadata. It will store all the ontologies that are relevant to the CHIC community.

B1.2.3 INFORMATION TECHNOLOGIES: Model and Data Repositories

State-of-the-art

There are considerable differences in the currently available biomodel repositories, in terms of their scopes and orientations so as to render it imperative to carefully check their real ability and functionalities when considering either using any of them or the development of a new repository. Six indicative model repositories of interest to CHIC are: BioModels Database is a repository of peer-reviewed, published, computational models, involving primarily the field of systems biology. CellML Model Repository is a repository populated with a collection of standardized models that can readily be recombined to model different biological systems using the inherent modularity support of the CellML 1.1 model exchange format. The scope of CellML Model Repository is primarily the cell level. PhysiomeSpace is a digital library service for sharing biomedical data and models. myExperiment is a collaborative environment for safe publication and sharing of workflows and experiment plans. CViT model repository is geared to experimental cancer research. The TUMOR Project Repository, currently under development, will be a European clinically oriented semantic-layered cancer digital model repository interoperable with the US grid enabled semantic-layered digital model repository platform at CViT.org which is NIH/NCI-caGRID compatible. Regarding medical data repositories, their use for research purposes is subject to considerable legal and ethical constraints. Additionally it is not straightforward that existing data repository architectures and content can efficiently respond to the needs of particular clinically-driven and clinically-oriented multiscale VPH /cancer multiscale models.

Contribution of CHIC

In order to meet one of the major goals of the CHIC proposal, i.e. to create a hypermodeling infrastructure and a hypermodelling environment addressing the strongly multiscale *clinically* oriented VPH context in the cancer domain, a clear need to construct a new model repository has been identified. Additionally in order to be able to efficiently address all the legal and ethical constraints related to the efficient exploitation of the medical data to be provided by the CHIC clinical partners for research purposes, a new data repository will also be developed by CHIC. Nevertheless, use of the *PhysiomeSpace* will be made in the beginning of the project in order to meet urgent data storage needs despite Physiome's limited functionality for the needs of the CHIC proposal. Additionally there will be access to repositories developed by previous EC or running funded projects such as ContraCancrum and p-medicine, whose responsible partners participate in CHIC. Thus ensuring easy access to both model and data will allow the CHIC consortium to show the benefits of having both the data and models readily available.

B1.2.4 INFORMATION TECHNOLOGIES: Cloud Computing and Virtualization

State-of-the-art

Cloud technology is particularly attractive due to the sharing of data at low cost capabilities for application domains with high requirements for storage and/or computational resources and/or requiring the aggregation of large amounts of intrinsically distributed heterogeneous data within complex workflows. Pioneered by Amazon's IaaS and EC2[13], Cloud Computing has become attractive for both enterprise and research. Most current available Cloud Computing facilities, particularly commercial public Cloud Computing (e.g. Amazon EC2, S3[14]), are built on dedicated machines within the data centre. These services show the benefits of Cloud Computing in the aspects of elastic, dynamic, unlimited storage and computation capacity.

However, concerns arise when considering employing them into scientific research, including security, ethical and legal issues, regulation and performance. Private (community) clouds become very useful for biomedical scientific research in order to have a full control on data access, reliability and storage management. Rather than making investment on massive dedicated machines, a private cloud provides a greener and more cost-effective solution by using existing heterogeneous computing facilities within an organization. While all these participated hardware facilities are not specifically dedicated to the cloud, they can be added when required at an acceptable resource allocation level. The private cloud will harvest the underused computing resources within the institution, thus save the cost of purchasing new servers and reduce electric energy consumption.

In order to be able to fully realize the potential of clouds, several issues need to be addressed first: 1. Applications and workflows in the medical domain are currently not designed to make use of virtualized cloud resources and to benefit of the high mobility and flexibility offered by clouds. 2. While clouds offer resources at low cost, migrating data and applications from the hospital environment to the clouds is not trivial due to limited bandwidth capabilities of the infrastructures owned by the healthcare organizations, and potentially high latencies.

Contribution of CHIC

Key research challenges in the area of Cloud computing and Virtualization will be addressed by the CHIC project, which will include: a) Proposing a completely new paradigm of application design so that they are suitable for deployment on cloud resources: Scalable, flexible, mobile, composable, highly-distributed, use low bandwidth, deal with high latency, etc., federation of necessary medical data (including meta-data) and knowledge without explicitly exporting it out of one system and importing it to another is challenging; b) Investigating how current cloud capabilities need to be enhanced to be used in the medical domain which has strict requirements for reliability, availability, performance and security; c) Select the most suitable from the variety of cloud offerings that are available in order to be used in the medical domain; d) Investigating how to avoid the lock-in of a single cloud provider; e) Adopting and proposing an approach to the use of cloud that is coherent, coordinated and suit multiple applications; f) Investigating the benefits of using private (community) clouds in the medical domain.

B1.2.5 INFORMATION TECHNOLOGIES: Workflow composition and execution in the CHIC domain

State-of-the-art

The always increasing need for high performance computing facilities and distributed computational resources for simulating large and physically complex systems has recently led to a continuous and significant growth of the role of workflows composition and execution within the scientific community and the VPH community in particular. While a certain level of consensus and standardisation has been recently reached by the business community, the heterogeneous nature of scientific workflows and its

[13] *http://aws.amazon.com/ec2/*
[14] *http://aws.amazon.com/s3/*

data-oriented paradigm has made so far difficult this standardisation effort in the biomedical domain and has facilitated the proliferation of the number of software environment to address this need. Each of the currently available solutions has its own weaknesses and strengths and usually expresses the particular needs of a scientific sub-domain for which it has been developed. This results in the availability of very specialized implementations and composition languages for each scientific sub-domain.

Contribution of CHIC

Most of the proposed solutions are able to handle workflows composed by a number of specific tools and algorithms. However, in many clinical settings, like in CHIC, the multiscale and patient-specific modelling needs a well-designed choreography of component models, each describing a biological process at a characteristic space-time scale, and of relation models, which define the relevant relations across scales. CHIC will provide the metamodelling and metahypermodelling language description that integrated with state of the art workflow execution software framework will completely solve the above issue. In particular, CHIC will create a workflow execution software framework, which can be used in different biomedical applications, by relying on the recent developments in this area achieved within the VPHOP[15]. The VPHOP software solution[16] relies on ad-hoc MAF[17]-based components and the external workflow choreographer (Taverna[18]); this framework even if proved effective in the specific deployment does not have yet the necessary generality to achieve the CHIC objectives. The provided extensions, together with the development of software general components, will provide a state of the art workflow composition and execution software environment for complete multiscale workflows execution, which might be easily adopted by other VPH research projects. The release of this software framework in open-source will facilitate future adoption and acceptance by the VPH community.

B1.2.6 INFORMATION TECHNOLOGIES: Visualization

State-of-the-art

Recently, many application areas are increasingly incorporating methods that demand the analysis and fusion of the unprecedented volumes of data. The trend of rapid data increase brings new challenges associated with a rapid increase of complexity. The new data are often heterogeneous, dynamic and ambiguous and may need to be fused to allow timely retrieval of valuable information. To this end, information visualization has become an important component of Visual Analytics[19]. Through Visual Analytics, information visualization greatly facilitates the retrieval of information by shifting from confirmatory to exploratory data analysis, in which hidden knowledge is uncovered by integrating heterogeneous information with expert knowledge. While significant progresses have been made in visual representation and exportation of large datasets, scalability still remains as a challenging issue. Indeed, large amount of datasets can lead to overplotting, which significantly hampers the capability of human vision in identifying data patterns. While great efforts have been made towards the scalability issue[20], the techniques that deal with large datasets still attract a lot of research attentions. In addition, the prediction of tumour development is clearly an area of high uncertainty, and the development of means by which the uncertainty can be made evident and be taken into account within the clinical process would be very useful. Also, data aggregation involved in

[15] *http://www.vph-op.eu*

[16] *D Testi, D Giunchi, X Zhao, G Clapworthy, "Hypermodelling Technology for Multiscale Simulations", VPH2012, submitted, 2012*

[17] *Multimod Application Framework, MAF, http://www.openmaf.org*

[18] *http://www. Taverna.org*

[19] *Daniel Keim (Scientific Coordinator of VisMaster), Jörn Kohlhammer (Coordinator of VisMaster), Geoffrey Ellis and Florian Mansmann, Mastering the information age: solving problems with Visual Analytics, Eurographics Association, 2010*

[20] *H. Piringer, Large Data Scalability in Visual Analysis, PhD Dissertation, 2011*

large scale visualization produces a considerable amount of uncertainty. Currently, no visualization work has considered uncertainty originated from data aggregation.

Contribution of CHIC

Within the scope of this project, the following issues will be taken to address the scalability issue: a) *Filtering techniques* to allow users to focus on their selected targeted data; b) *Aggregation*[21] to combine details and create different levels of overviews in hierarchies. To allow effective handling of large scale visualization, we will investigate new aggregation techniques based on the traditional approaches, such as binning, abstraction, etc. Hierarchical clustering techniques can be used to create effective aggregation of data at different levels of details. Also, we shall investigate uncertainty-aware aggregation, which creates data aggregation with uncertainty information to enhance user understanding towards the aggregated data; c) *Dimension reduction* is very useful in reducing data volumes. Subspace clustering will be able to help identify the meaningful cohort of data in a subset of relevant dimensions. Given a dataset with high dimensionality, the number of possible sub feature space is exponentially high. Fully automatic machine learning normally does not do a good job in terms of identifying the clusters. A recent trend is to involve human experts[22], which couples user interaction with the subspace clustering process. This project will also deal with the following issues regarding the uncertainty: a) *Visualization of uncertainty related to data aggregation* – the technique will need to visually present the uncertainty within aggregated data. This helps to present a faithful picture of the dataset after the aggregation; b) *Presentation of uncertainty information within a graph.* Typical techniques include node-link, matrix view, etc. Nowadays a typical graph visualization contains multiple types of nodes, which reflects the heterogeneous nature of the data. While various techniques and tools exist for visualizing uncertainty[23], little attention has been paid towards the uncertainty information in graphs. We will investigate how to represent the uncertainty originated from the node filtering or node clustering in a visual form, and how the uncertainty affects the analysis of the graph structures (e.g. identifying key nodes, graph path, etc).

B1.2.7 INFORMATION TECHNOLOGIES: Image processing

State of the art

The existing segmentation methods can be divided into two different categories. In most cases, classification methods with a certain degree of spatial regularization are employed for the segmentation of multimodal datasets[24], while atlas-based segmentation is an established way for segmenting monomodal image[25]. Using atlas-based segmentation on the high-resolution monomodal image is attractive thanks to its robustness and its versatile usability. Most atlas based segmentation methods establish initial correspondence between a healthy atlas and a pathologic patient image by seeding the atlas with a patient-specific tumor prior. The deformation field, which is obtained after non-rigid registration of the modified atlas to the patient can be used for warping the atlas label image,

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[21] *ELMQVIST N., DO T.-N., GOODELL H., HENRY N.,FEKETE J.-D.: Zame: Interactive large-scale graph visualization. In Proceedings of IEEE Pacific Visualization Symposium (2008), pp. 215–222*

[22] *B. J. Ferdosi, et al. Find and visualizing relevant subspaces for clustering high-dimensional astronomical data using connected morphological operators, IEEE Symposium on visual analytics science and technology, 2010, Salt Lake City*

[23] *Potter, K., Kniss, J., Riesenfeld, R., Johnson, C. R. (2010). Visualizing Summary Statistics and Uncertainty. Computer Graphics Forum 29, 3, 823–832*

[24] *] S. Bauer, L. Nolte, M. Reyes: Fully automatic segmentation of brain tumor images using support vector machine classification in combination with hierarchical conditional random field regularization. In: Fichtinger, G., Martel, A., Peters, T. (eds.) MICCAI International Conference on Medical Image Computing and Computer-Assisted Intervention. Lecture Notes in Computer Science, vol. 14, pp. 354-61. Springer Berlin Heidelberg, Toronto, Jan 2011*

[25] *S. Bauer, C. May, D. Dionysiou, G. Stamatakos, P. Buchler, M. Reyes: Multi-Scale Modeling for Image Analysis of Brain Tumor Studies. IEEE Transactions on Biomedical Engineering 59(1), 25-29, 2012*

thus obtaining an implicit segmentation of the patient image. The shortcomings of most current approaches include the need for a manual segmentation of the tumor area as an input for the tumor growth process and no optimal utilization of the segmented healthy tissues during atlas-based segmentation. In addition, in order to bring these emerging technologies into clinical practice it is crucial to design and develop them taking into account current clinical imaging protocols. Also, special attentions have been paid towards a group of global energy minimization based methods that cast the segmentation into an energy minimization problem, which lead to improved results due to the consideration of the segmentation at a global scale. Different energy minimization approaches such as graph cut[26], belief propagation[27], tree reweighted message passing[28] have been investigated.

Contribution of CHIC

The segmentation work within this project will endeavour to combine the strength of the traditional and recent methods. Especially, we will look into the combination of different segmentation methods and their results in order to achieve the best possible outcomes. Similar ideas have been applied successfully in face detection, where a number of detectors are cascaded, leading to a largely enhanced performance.

For the specific case of high grade glioblastomas, this project will deliver a clinically-relevant (i.e. complying with the standard clinical imaging protocols) brain tumor image analysis framework that enables automatic segmentation of high grade glioblastomas brain tumors making use of the entire set of information and the biomechanical tumor growth model that will be developed.

B1.2.8 MULTISCALE CANCER MODELLING: A general overview

State of the art

The extreme complexity of the *natural phenomenon* of cancer in conjunction with the seriousness of the *disease* have dictated the development of highly demanding mathematical and computational cancer models aiming at promoting both biological insight and clinical medicine. In the last decade it became clear that cancer modeling should become explicitly multi-scale, so as to address several levels of biocomplexity concurrently[29]. Already a great diversity of cancer related models exist, focusing on various aspects of this complex phenomenon at different scale levels. Several mathematical techniques[30] and approaches have been proposed. These include continuous, discretized continuous and discrete[31] methods as well as hybrid approaches. Hybrid approaches combine the benefits of continuous and discrete mathematics and offer the possibility of integrating phenomena of different time and length scales. Within this context and in order to address concrete clinical questions the idea of the "oncosimulator" has emerged[32],[33]. Efforts on an international and even intercontinental level

26 *Y. Boykov, V. Kolmogorov. An experimental comparison of min-cut/max-flow algorithms for energy minimization in vision. IEEE Trans. PAMI, 26(9):1124–1137, 2004*

[27] *Q. Yang, L. Wang, N. Ahuja, A Constant-Space Belief Propagation algorithm for stereo matching, In CVPR, 2010*

[28] *V. Kolmogorov, Convergent tree-reweighted message passing for energy minimization, IEEE Trans. PAMI, 28(10):1568-1583, 2006*

[29] *T. Deisboeck and G. S . Stamatakos Eds. Multiscale Cancer Modeling. CRC Press 2010. Pp. 407–436. Print ISBN: 978-1-4398-1440-6, eBook ISBN: 978-1-4398-1442-0. DOI: 10.1201/b10407-19*

[30] *HM Byrne (2010). Dissecting cancer through mathematics: from the cell to the animal model. Nature Reviews Cancer.10(3): 221-230*

[31] *D.D.Dionysiou, G.S. Stamatakos, N.K.Uzunoglu, K.S.Nikita, A. Marioli , A Four Dimensional In Vivo Model of Tumour Response to Radiotherapy: Parametric Validation Considering Radiosensitivity, Genetic Profile and Fractionation , J. theor. Biol. , 230 , 1-20 , 2004*

[32] *G.Stamatakos "In Silico Oncology Part I: Clinically Oriented Cancer Multilevel Modeling Based on Discrete Event Simulation" In T.Deisboeck and G. Stamatakos Eds 407-436 2011-01-01 CRC Press, Print ISBN: 978-1-4398-1440-6 eBook ISBN: 978-1-4398-1442-0 DOI: 10.1201/b10407-19 Boca Raton, Florida, USA, 2011*

[33] *http://cordis.europa.eu/fetch?CALLER=PRINT_OFFR&SESSION=&ACTION=D&RCN=6061*

have been initiated, in order to both promote the multi-scale character of cancer modeling and intensify the interaction among modelers, experimentalists, clinicians and other specialists so as to develop advanced mutually hybridized models of cancer development and response to treatment. Within this framework the European Commission, in collaboration with the National Cancer Institute, National Institute of Health of the United States, funded the 1st Transatlantic Workshop on Multiscale Cancer Modeling as a component of the ICT 2008 event[34]. Research group leaders from both coasts of the Atlantic presented their modeling approaches and an important intercontinental interaction was established and subsequently a transatlantic book was published[35]. Although in order to understand cancer and optimize its treatment in the patient individualized context all its aspects are important, it appears that models that are directly driven from actual clinical problems and questions, preferably formulated by clinicians, may lie more closely to the clinical translation path. Therefore, if the utilization of a model as a decision support tool is envisaged, then a direct involvement of clinicians in the model development and validation process should be considered.

Contribution of CHIC

Due to the hypercomplexity of cancer it appears that no single modeler or modeling research group has developed models that optimally describe every single aspect of the cancer phenomenon and its interactions with a vast number of particular medical treatment schemes. Additionally, despite the progress made so far, there have not been any standards regarding both the description of each model and its internal architecture. This renders the eventual hybridization of different models extremely difficult. Therefore, in order to facilitate the development of composite and "custom" made comprehensive models (hypermodels) aiming at addressing concrete medical and biological questions and eventually leading to their transformation into patient individualized decision support and treatment design systems, a model description standardization through a metalanguage will be developed and proposed to the broader cancer modeling community. Generic strategies and hypermodelling infrastructure that will enable the mutual fitting together of elementary models will be developed by CHIC. The special tumour types considered by the proposal (i.e. nephroblastoma, glioblastoma, lung cancer, colon cancer and prostate cancer) will serve as guiding paradigms. A number of exemplary hypermodels based on the previous paradigms will be developed and validated. Subsequently, a more generic version of the Oncosimulator[36], a multiscale cancer modeling concept and system will emerge. The new Hypermodel Oncosimulator will be clinically adapted by exploiting the clinical studies and multiscale data to be provided by the CHIC clinical partners (concerning nephroblastoma, glioblastoma and non-small cell lung cancer). A new multiscale and continuum model of early colorectal cancer and vascular tumour growth will also be developed and validated against data obtained by experimental and clinical partners. Regarding prostate cancer, 'traditional' growth models will be enhanced by assuming that the tumour carrying capacity may vary throughout development, promoting organ invasion, near (and far) metastasis, etc. Hybrid biomechanical-biological models of glioblastoma will undergo further hybridization with additional small spatial scale biomechanisms. A model, a data and an *in silico* trials repository will be developed, in order to store both the standardized models (hypomodels, models and hypermodels) and relevant data for their validation. These repositories will be made accessible to the wider cancer modeling community under the legal constraints applicable. It is pointed out the hypemodeling infrastructure/software tools will be fairly generic so as to be usable for other multiscale domains of the VPH initiative apart from cancer.

[34] *http://ec.europa.eu/information_society/events/ict_bio/2008/docs/200811cancer-model-wkshp-report.pdf*
[35] *http://www.crcnetbase.com/isbn/9781439814406*
[36] *G.S.Stamatakos, E.Ch.Georgiadi, N.Graf, E.A.Kolokotroni, and D.D.Dionysiou, "Exploiting Clinical Trial Data Drastically Narrows the Window of Possible Solutions to the Problem of Clinical Adaptation of a Multiscale Cancer Model", PLoS ONE 6(3), e17594, 2011*

B1.2.9 MULTISCALE CANCER MODELLING: Systems biology

State of the art

Human genome-sequencing has enabled the creation of an exhaustive parts-list in mammalian cellular systems. The primary challenge has now shifted towards functional relationships between the parts and mechanistic description of how the parts function as modules and as a whole. Systems biology lies at the heart of addressing this grand challenge and focuses mainly on synthesizing these relationships when they are considered together. Pathways have long represented a convenient way of summarizing the results of many hundreds of experiments. The past decade has prompted the creation of several databases of metabolic and signaling pathways (e.g Kyoto Encyclopedia of Genes and Genomes, BioCarta, Signal Transduction Knowledge Environment). In general, these resources represent the relationships between molecules in a cell either as reactions or as activation or inhibition events. The specificity of cellular responses is decoded by spatial and temporal signals propagating through intracellular signaling pathways. Computational models[37,38] and network analysis tools continue to provide insights into the complex relationships between the stimuli, cellular responses, and cell fate.

Contribution of CHIC

CHIC will be engaged in multiscale modeling of altered functional interactions in oncogenic signaling networks through multiscale hybrid physical/systems approaches relevant to non-small-cell lung cancer, glioblastoma, and nephroblastoma. The aims include: (1) an in-house developed multiscale strategy for constructing models of intracellular signaling networks with the ability to encode molecular resolution of key nodes; (2) extensive molecular modeling of the effect of mutations on protein function in order to differentiate driver mutations from passenger mutations; (3) physical biology approaches to study sub-cellular localization and trafficking using mesoscale models and linking altered trafficking to signaling and cell fates.

B1.2.10 CLINICAL MEDICINE: The nephroblastoma clinical study

State of the art

Almost all patients with nephroblastoma are treated within prospective, randomized multicentre trials conducted by either the SIOP Society in Europe or by the COG group in North America. The SIOP trials use preoperative chemotherapy without proven histology[39]. The management of nephroblastoma consists of a combination of chemotherapy, surgery and, selectively, radiotherapy. To date, chemotherapy is risk-stratified according to histological subtype and tumour stage alone. So far, there are no diagnostic and prognostic biomarkers for pre-treated tumours. Because of this, improving treatment is only possible by identifying new biomarkers and a deeper understanding of the biology of nephroblastoma. In the SIOP 2001 study, the majority of patients are protocol patients receiving preoperative chemotherapy followed by surgery and postoperative chemotherapy. Postoperative treatment is based on local stage and histology after surgery.

Contribution of CHIC

Medicine is undergoing a revolution that is transforming the nature of healthcare from *reactive to preventive*, based among others on a new systems approach, which focuses on integrated diagnosis, treatment and prevention of disease in individuals and envisages to achieve personalized predictive

[37] *A. J. Shih, S.E.T., R. Radhakrishnan, Analysis of Somatic Mutations in Cancer: Molecular Mechanisms of Activation in the ErbB family of Receptor Tyrosine Kinases. Cancers, 2011. 3(1): p. 1195-1231*

[38] *R. Radhakrishnan and Tamar Schlick, Orchestration of cooperative events in DNA synthesis and repair mechanism unraveled by transition path sampling of DNA polymerase beta's closing. Proc. Nat. Acad. Sci. 05/2004; 101(16):5970-5. DOI: 10.1073/pnas.0308585101*

[39] *Graf N et al.: The role of preoperative chemotherapy in the management of Wilms' tumour. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 27:443-454, 2000*

treatment[40]. Multi-level data collection within clinico-genomic trials and interdisciplinary analysis is becoming mandatory. There are many problems related to the disparate nature of the data sources. Several partners of the CHIC consortium have great experience in VPH, which serves as a solid background showing that collaboration between different stakeholders caring for cancer patients in the area of VPH leads to better patient outcome. Clinical data processing procedures and computer technologies play an important role in this context. Following clinical adaptation and validation within the framework of clinico-genomic trials, models, hypermodels and oncosimulators are expected to enhance individualized treatment optimization[41] and help in finding new targets for treatment. Moreover, provision of insight into tumour dynamics and optimization of clinical trial design and interpretation constitute short- and mid-term goals and are only possible in such IT infrastructures that are provided by CHIC. CHIC will allow the efficient secure sharing and handling of large and heterogeneous personalized data sets coming from different sources distributed around Europe. The CHIC approach will serve as a proof of concept for other cancer types.

Clinical Baseline

Blastemal subtype after preoperative chemotehreapy is one of the most important clinical parameters predicting a poor outcome. Therefore, the seamless integration of data generated through CHIC will enhance the Oncosimulator for decission making.

Advance and aimed results by CHIC

Based on the integration of the Oncosimulator in the CHIC infrastructure and a closed workflow results from the Oncosimulator will be provided from 100 patients. The workflow will be tested on retrospective data and validated on prospected data.

Criteria of performance / research indicators

Inclusion of 100 patients with complete clinical, imaging and molecular data for individual patients will be provided. A validation of the result generated by the Oncosimulator with the corresponding imaging data of the patient will be done.

B1.2.11 CLINICAL MEDICINE: The glioblastoma multiforme clinical study

State of the art

Glioblastoma Multiforme (GBM) is the most frequent and malignant high grade glioma. Despite the improvement in treatment techniques, the prognosis of patients with GBM remains poor. Even after maximal treatment with surgery, radiotherapy and chemotherapy, relapse is universal, and there is an obvious need for more effective new therapies. Preclinical research is focused on alternate approaches, such as more selective therapies, which specifically target intracellular signalling pathways or surface molecules, anti-angiogenesis strategies and especially immunotherapy. Immunotherapy for HGG has been reviewed extensively in the last couple of years[42]. Results from children with relapsed HGG have also been published[43]. In the HGG-2006 trial full integration of DC-based tumour vaccination into standard postoperative radiochemotherapy is studied in 77 patients. Results from the HGG-2006 protocol were used to power the recently initiated prospective placebo controlled double blind phase IIb randomized clinical trial (EudraCT 2009-018228-14).

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[40] http://www.cra.org/ccc/initiatives

[41] *Graf N, Hoppe A, Georgiadi E, Bellemann R, Desmedt C, Dionysiou D, Erdt M, Jacques J, Kolokotroni E, Lunzer A, Tsiknakis M, Stamatakos G: 'In Silico' oncology for clinical decision-making in the context of nephroblastoma. Klin Pädiatr 2009; 221:141-149*

[42] *Van Gool SW, Maes W, Ardon H, Verschuere T, Van Cauter S, De Vleeschouwer S. Dendritic cell therapy of high grade gliomas. Brain Pathol 2009;19:694-712*

[43] *Ardon H, De Vleeschouwer S, Van Calenbergh F et al. Adjuvant dendritic cell-based tumour vaccination for children with malignant brain tumours. Pediatr Blood Cancer 2010;54(4):519-525*

Contribution of CHIC

Immunotherapy for malignant glioma is an emerging modality to treat patients. Remarkable clinical results have been observed by different research teams independently over the whole world. The team at KU Leuven has gained long-standing experience in developing this combined modality for patients with relapsed malignant glioblastoma multiforme (GBM) as well as patients with primary diagnosis of GBM. However, as the production of the vaccines requires special good manufacturing practice facilities and is labor-intensive for highly specialized technicians, the need of predicting which patient would benefit from such a treatment is obvious.

Clinical Baseline

Patients in the placebo group function as baseline for the treatment efficacy upon addition of immunotherapy. To our knowledge, there are no integrated data available for patients with GBM to assess potential efficacy of immunotherapy. Therefore, the data generated through CHIC will form the first step towards integrated patient profiling in order to predict .

Advance and aimed results by CHIC

Based on the integration of clinical, immunological and tumour biological data generated by the currently running randomized clinical trial in KU Leuven, CHIC is expected to provide important analytical knowledge through the cancer hypermodels to be developed that could support and foster immunotherapy as a treatment option for those patients who would really benefit from such an advanced innovative treatment.

Criteria of performance / research indicators

Inclusion rate as foreseen in the trial: 146 patients over 2.5 years
Availability of complete data sets on clinical, radiological, immunological and tumor biological aspects for an individual patient. It is aimed to have all data available in at least 65% of the patients (100/146 patients) equally distributed in both arms of the randomized trial in order to make appropriate conclusions.

B1.2.12 CLINICAL MEDICINE: The lung cancer clinical study

State of the art

Lung cancer is the leading cause of cancer for women and men. Non small cell lung cancer (NSCLC)[44],[45] accounts for more than 80% of all lung cancer cases. Due to limited success of systemic chemotherapies up to now, the 5-Year Survival Rate amounts to 15%. New molecular-based "personalized" therapies focus on inhibition of signal transduction pathways. After selection according to sequencing data or DNA FISH, the first trials could be finished showing the effectiveness of these drugs based on molecular tests from tumour tissue after sequential molecular testing for second or third line therapies.

Contribution of CHIC

In the near future, it will be necessary to know the tumor-specific pathways very early after tumor diagnosis to choose the most promising therapy. For that purpose a system biology model will be

[44] *Y.-T. Kim, T.-Y. Kim, D.-S. Lee, S.-J. Park, J.-Y. Park, S.-J. Seo, H.-S. Choi, H.-J. Kang, S. Hahn, C.-H. Kang, S.-W. Sung, and J.-H. Kim; Molecular changes of epidermal growth factor receptor (EGFR) and KRAS and their impact on the clinical outcomes in surgically resected adenocarcinoma of the lung, Lung Cancer 2008; 59: 111-118*

[45] *Linxweiler M, Linxweiler J, Barth M, Benedix J, Jung V, Kim YJ, Bohle RM, Zimmermann R, Greiner M., Sec62 bridges the gap from 3q amplification to molecular cell biology innon-small cell lung cancer., Am J Pathol. 2012 Feb;180(2):473-83. Epub 2011 Dec 21*

developed based on the transcriptome analysis of up to 100 tumour specimens. This data will form the basis for the bottom-up approach of the *in silico* model for NSCLC, thus improving the accuracy of the developed *in silico* Hyper-Multiscale Models. In USAAR, all relevant clinical data, tumour typing, as well as radiological, macroscopic, quantitative microscopic data, proliferation data and angiogenesis data have been retrieved or collected prospectively. Genetic profiles of the relevant pathways, miRNA data, and deep sequencing data of at least a limited number of well-defined NSCLCs, will be added for comprehensive analysis. For small biopsy specimens of lung cancer, manual dissection, laser-microdissection, quantitative few cell PCR approaches, DNA sequencing, biochip reverse-phase hybridization, mRNA preamplification and whole genome amplification are available, as well as epidemiological and follow-up parameters from the Saarland tumour center. All this will be integrated into the hyper-multiscale models for *in silico* oncology in order to support therapy-related clinical decisions.

Clinical baseline

Most of the NSCLC lung cancer cases are detected at high TNM stages (IIIB and IV). One of the most important parameters for the length of survival at these stages is the response to therapy. Thus, it is important to determine the best and fastest way how to find out which therapy is most likely to induce partial remission of the tumour. Data generated through CHIC will focus on decision making in a multiparameter setting.

Advance and aimed results by CHIC

The CHIC infrastructure will focus on macromorphological, histopathological and molecularpathological data analysis mainly derived form tumour biopsies, as these specimens are most frequently used for diagnosis of NSCLC at high stages. From tumour DNA and RNA molecular analysis will be performed with respect to personalized therapy procedures. These data and classical prognostic and predictive data will be integrated into the CHIC platform for 100 lung cancer patients with advanced stages.

Criteria of performance / research indicators

For these 100 NSCLC patients with high TNM stages, complete clinical, imaging, morphological and molecular data will be provided with respect to therapy response and survival. The results will compared with the results of conventional combined radio-/chemotherapy and results generated by the Oncosimulator.

B1.2.13 LAW AND ETHICS: Processing patients' medical data and intellectual property rights regarding the amalgamation of models

State of the art

The processing of patients' medical data is governed by legal and ethical rules. Ethical and legal frameworks are set up to guarantee compliance with existing rules in the corresponding research field. Such frameworks as the one that will be set up for the needs of the eventual CHIC project help researchers to process data on valid legal grounds. The reuse and/or amalgamation of models and data result in intellectual property issues. Researchers are concerned about the possible loss of economical and scientific interest as a consequence of sharing models and data.

Contribution of CHIC

CHIC will 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. It is unclear whether and to which extent amalgamations of models can be protected by intellectual property rights. In many cases they cannot be protected by patents, as they are either non-technical or could be considered as non-patentable software "as such"

(see art. 52 of the European Patent Convention). There is also the risk of no copyright protection, as such models could be seen as mere ideas (not protected). If they have to be regarded as protected works, it is further doubtful whether such amalgamations can be seen as computer programs and/or databases in the European protective frameset. Therefore, 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 work developed will be provided. Furthermore, legal research will be done 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.

Baseline & Performance indicators

Relevant baseline work (topic description)	Background / Source of evidence (patent, publication, related project)	Related Partner(s)	Expected Progress beyond state of the art / new work in CHIC	Related specific objective(s)	Comments/ clarifications (optional)
Cancer modelling and the oncosimulator	Models and oncosimulators already developed or under development in ACGT, CONTRA CANCRUM, p-medicine and other projects worldwide	ICCS, FORTH, UPENN, UOXF, UNITO, UBERN, PHILIPS	Main new work: • Development of new models or adaptation of existing ones • Decomposition of existing and new CHIC models into their elementary component models • Fitting together of standardized elementary tumour bioprocess modules to create hypermodels • Creation of multi-modeller hypermodels and the hypemodel based oncosimulator • Numerical study of the resultant hypermodels	Development of the CHIC component models and hypermodels.	
Hypermodelling supportive technologies	VPHOP	USFD, ICCS, FORTH, BED, UCL, CINECA, USAAR	Main new work: Development of the ICT hypermodelling infrastructure, intended as a set of services and technologies that will make possible to build and execute integrative models, formed by component models and relation models, coherent with the vision of VPH.	Development of the generic hypermodelling infrastructure.	
The CHIC architecture	ACGT, TUMOR, p-medicine	FORTH, CUSTODIX, PHILIPS, UBED, TEI-C	Main new work: • Develop a complex architecture that will allow the definition of hypermodels from interoperable existing and new cancer models.	The CHIC interoperable integrated platform.	

			• Enhance the security issues with respect to the multi-user nature of the proposed hyper modelling framework. • A Private cloud solution for CHIC that will deal with storage/ compute power and exposing CHIC tools as reusable REST/SOAP web services in this community cloud.		
Cancer modelling standardization	TUMOR, VPHOP	ICCS, FORTH, UPENN, UOXF, UNITO, UBERN, PHILIPS, USFD, BED, UCL, CINECA, USAAR	Main new work: • Model input, output and description standardization according to the hypermodelling metalanguage of WP7	Standardization of the CHIC cancer hypermodels.	
Clinical adaptation and partial validation of models	Initial clinical adaptation results and strategies derived from ACGT, CONTRA CANCRUM, p-medicine	ICCS, FORTH, UPENN, UOXF, UNITO, UBERN, PHILIPS, USAAR, BED	Main new work: • Partial experimental and/or clinical adaptation and validation of hypermodels, based on clinical data provided by the clinical partners	Clinical adaptation and partial validation of CHIC hypermodels.	
Development of ObTiMA	Work done on ObTiMA within ACGT and p-medicine.	USAAR, CUSTODIX, FORTH	Main new work: 1. Integration in the CHIC framework 2. Integration of DrEye and other tools in the ObTiMA framework	Use of ObTiMA in a prospective clinical trial and	

			3. Development of closed workflows with the integration of ObTiMA 4. Enhancing the Certification process of ObTiMA 5. Making ObTiMA a real modular software Describing interfaces for the connection with external modules	as a data provider for hypermodels.	
Initial Analysis of the ethical and legal requirements on the reuse of pseudonymized and anonymized data within CHIC	ACGT, Deliverables D10.1, D10.2, D10.3; p-medicine deliverable D5.1; EURECA deliverable D7.1; Linked2Safety deliverable D2.1	LUH, ICCS, USAAR, UPENN, CUSTODIX	• The legal and ethical rules governing the processing of patients' medical data for purposes of CHIC will be analyzed. An appropriate legal analysis is a precondition for achieving the project's goal. • Furthermore the framework guarantees that researchers are able to do their research without being detained by legal limitations. Especially the development of the ICT tools, services and secure infrastructures may cause legal and so far unsolved problems in the field of intellectual property law which have to be resolved.	The CHIC legal and ethical framework.	
Initial analysis of the copyright-related legal requirements for the sharing of data and amalgamation of models	p-medicine deliverable D5.2	LUH, ICCS, USAAR, UPENN, CUSTODIX	Legal requirements for an amalgamation of models as needed in CHIC are widely unexplored in the lagal litterature. This exercise will help to understand in how far traditional concepts of intellectual property can foster the amalgamation of models needed for CHIC.	The CHIC legal and ethical framework.	

within CHIC					
WP-leader in the FP7-project p-medicine (270089)	p-medicine, Deliverable D5.1	LUH, CUSTODIX	Project is from the theme "Dealing with data warehouses and the access to biobanks" No relevant dependencies with CHIC		
Development of model/tool repository	TUMOR	ICCS, FORTH, CUSTODIX, USAAR, PHILIPS, UPENN, UCL, UBERN	Main new work: • Develop a generic model/tool repository able to host the variety of components needed to construct hypermodels. • Develop the interfaces (services) to allow the Hypermodel Editor and Hypermodel Executional Framework to interact with the model/tool repository.	Development of the CHIC repositories and the semantic metadata management tools.	
Development of patient data repository	p-medicine	ICCS, FORTH USAAR, UBERN, UCL	Main new work: • Develop the interface (services) that will allow content to be imported in and exported from the CHIC data repository.	Development of the CHIC repositories and the semantic metadata management tools.	
Development of in-silico-trial repository		ICCS, UBERN, FORTH USAAR, UPENN, UCL	Main new work: • Develop an in-silico-trial repository. • Develop a web-based interface (GUI) to enable users to interact with the in-silico-trials repository. • Develop the interface (services) that will allow the Hypermodel Executional Framework to store the outcome of a simulation in the in-	Development of the CHIC repositories and the semantic metadata management tools.	

			silico-trial repository.		
Semantic Metadata Management	RICORDO	UCL ICCS, USAAR, FORTH	Main new work: • Carry out a requirement analysis to find the core set of ontologies that are relevant to the CHIC community. • Further developing and adapting RICORDO software interfaces for querying and editing the core knowledge base. • Develop a distributed RDF repository solution to store metadata. • Develop software interfaces for querying and editing metadata. • Develop a graphical user interface (GUI) to enable users to interact with the annotations.	Development of the CHIC repositories and the semantic metadata management tools.	
Image segmentation & registration tools	Research in energy minimization based segmentation techniques , including those based on graph cut, belief propagation and tree reweighted message passing;	BED, UBERN, FORTH	Main new work: • Combination of various approaches for optimized outcome in clinical context • Clinical relevant brain tumor image analysis framework that enables automatic segmentation of high grade glioblastomas brain tumors making use of the entire set of information and the biomechanical tumor growth model • A software platform for the assessment of Tumor treatment response	Development of Visualization and Image processing toolkits.	

Multiscale visualization	MSV (Multiscale Spatiotemporal Visualisation – FP7 248032)	BED	Main new work: • Effective filtering techniques for large scale data and models • Effective aggregation techniques allowing for hierarchical information display • Effective subspace clustering techniques supporting the search for data patterns in subspaces. • Effective display of uncertainty information via the abovementioned means	Development of Visualization and Image processing toolkits.	
The CHIC Integrated platform	ACGT, VPHOP, p-medicine	FORTH, CINECA, PHILIPS, ICCS, USAAR, UBERN	Main new work: • 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	The CHIC interoperable integrated platform	

Specific objectives and performance indicators

Specific Objective	Related WPs	Related milestone(s) and due months(s)		Objectively verifiable indicators	Source of verification (Deliverable; Demonstration)	Comments/ clarifications
Scientific and technical objectives						
Development of the generic hypermodelling infrastructure	**7**	**MS15** **MS16** **MS17** **MS18**	**12** **24** **36** **48**	The final hypermodelling framework has been deployed on test mode	D7.4	
Development of the CHIC component cancer models	**6**	**MS11** **MS12**	**6** **20**	The component models have been described. Numerical and clinical experience-based checks of the models completed.	D6.1, D6.2	
Development of the CHIC cancer hypermodels and the CHIC hypermode based oncosimulator	**6**	**MS13**	**40**	Description of the CHIC hypermodels	D6.3, D7.4	
Clinical adaptation and partial validation of CHIC cancer hypermodels and the CHIC hypermodel based oncosimulator	**6**	**MS14**	**46**	CHIC hypermodels have been quantitatively clinically adapted	D6.4	WP11 deliverables and milestones are relevant as well
Standardization of the CHIC cancer hypermodels	**6**	**MS13**	**40**	Hypermodels for all clinical scenarios conformal to WP7 guidelines are provided.	D6.3, D3.3 (Demonstration of the developed	WP7 and WP3 deliverables and milestones are relevant as well

					Meta- and Hyper-Multiscale Models)	
Definition of scenarios and evaluation criteria supported by CHIC	**3, 11**	**MS5 MS27 MS28 MS29**	**24 12 18 36**	At least 10 scenarios are defined coming from all 3 nephroblastoma, lung cancer and glioblastoma with a list of evaluation criteria for each scenario	D3.1, D11.1, D11.2, D11.3	The work of WP11 and WP12 are taken into account despite this work lasts longer than the first 36 months
Availability of data from nephroblastoma, lung cancer and glioblastoma patients	**3**	**MS5**	**24**	Retrospective data of at least 50 patients with Nephroblastoma, lung cancer and glioblastoma are available for the use in test scenarios for tools under development	D3.1	Integrated databases are not needed at M12 as M3.1 is due to M24, but retrospective data need to be available for testing of developed tools
Use of ObTiMA in a prospective clinical trial	**3**	**MS5**	**24**	ObTiMA is used in the prospective multicenter and randomized trial for nephroblastoma	D3.1 and Demonstration	
Development of the CHIC repositories and the semantic metadata management tools.	**8**	**MS20 MS21**	**28 42**	CHIC repositories and semantic metadata management tools are deployed.	D8.2, D8.3 and Demonstration of the CHIC repositories and the semantic metadata management tools.	MS20 will take into consideration the work of task 8.2 despite the fact that D8.2 is due to month 30. MS21 demostrates the integration with security and ethical framework.
Development of Visualization and Image processing toolkits	**9**	**MS23 MS24 MS25**	**18 24 24**	• Visual analytics techniques are verified by technical experiments on the data	D9.1 and Demonstration of the initial version of the	

				used within the project. • Image segmentation and registration techniques are verified by technical experiments on the data. • Initial version of the tumor response quantitative platform is ready.	tumor response quantitative platform	
The CHIC interoperable integrated platform.	**10**	**MS25**	**24 26**	The overall design of the orchestration platform as well as the related components and interfaces will be concluded by PM18 ensuring a smooth implementation strategy.	D10.1, D10.2, D10.3, D10.4deal with all aspects of the integrated CHIC platform	MS25 will ensure that the integration strategy and components are in place.
The CHIC legal and ethical framework	**4**	**MS8**	**14**	The legal and ethical implications of the project are defined and structured.	D 4.1, D 4.2, D 4.3.1, D4.3.2	The consortium will receive the legal guidelines needed to keep the project legally compliant.

B1.3 S/T methodology and associated work plan

B1.3.1 Overall strategy and general description

In order to optimize both the implementation and the expected final outcome of CHIC we have structured the proposal as is described in detail in Tables 1.3d and is visually depicted in the (additional) subsection 1.3f.

All scheduled activities are structured in a way so as to produce a coherent and integrated work plan. CHIC consists of several innovative and interrelated components that will be integrated to form the CHIC environment. The R&D work will be continuously influenced by the interaction between the research and verification components of the project. CHIC will actively seek to re-adjust its research activities and objectives based on evidence as a result of a quality assurance process. In more detail, the major project component clusters are the following:

I. **User requirement Analysis and Specifications.** As a prior condition for the development within the CHIC framework this component will identify and assess the user needs, the state of the art, key technological opportunities and issues of trust and security. The initial output of this work package will cover all major research and development topics of the project. CHIC will be driven by clinicians. It will fully take into account ethical and legal constraints. This project component cluster is further divided into the following two workpackages (WPs) (WP2): User Needs and requirementsa and WP4: legal and ethical framework.

II. **Clinical trials/studies and Cancer Models** This component includes the activities related to the driving clinical trials and the cancer (hyper-) models to be developed as trial simulators. The workpackages involved are WP3 (Clinical and Translational Science Scenarios), WP6 (Modelling and Hypermodelling Design) and WP11 (Clinical Adaptation and Validation). Clinical trials/studies will drive cancer (hyper-)modelling who in turn will drive the development and testing of the hypermodelling infrastructure.

III. **The CHIC Technologies and Services.** The aim of this project component cluster is to provide the necessary technology to support the project vision and objectives. This component will be continuously fed by the user requirements and evaluated with the objective of identifying additional generic tools and services to be developed as part of the CHIC technological framework. This project component cluster is made up of the following workpackages: WP5 (IT Architecture), WP7 (Hypermodelling Infrastructure), WP8 (Model and Data Repositories), WP9 (Image Processing and Visualization) and WP10 (Integrated Platform).

IV. **Trust and security.** The aim of this component cluster is to provide the required trust and security infrastructure for the CHIC services. This component is responsible for specifying and implementing the overall trust and security infrastructure, and for integrating it into the CHIC framework. The activity will be undertaken by WP4 (Legal and ethical framework) and WP5 (IT Architecture).

V. **Horizontal Activities.** These span the lifetime of the project and provide support to all other project components. They include specifically activities in WP1 (Project management) and WP12 (Exploitation and Dissemination). The Project management workpackage will provide the effective and professional management and services required, so that all other project components run unobstructed for delivering their objectives and hence making sure that CHIC as a whole does meet its stated objectives. The work breakdown is based on the envisioned research activities covering the aspects of the project from management through to dissemination and exploitation of the results. Each work package carries out a set of coherent,

related and manageable tasks to achieve the objectives of CHIC. The project components are presented and discussed in more detail in the following sections.

B1.3.2 Timing of work packages and their components

	Task	Lead	Start	End	year 1				year 2				year 3				year 4			
					1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48
WP1	**Project Management**	**EURICE / ICCS**	**1**	**48**	MS1	MS2		MS2		MS2		MS2		MS2		MS2		MS2		MS2
T1.1	Decision making management	EURICE	1	48																
T1.2	Administrative and financial coordination	EURICE	1	48																
T1.3	Contractual management	EURICE	1	48																
T1.4	Assessment of progress and results	ICCS	6	49																
WP2	**User Needs and Requirements**	**USAAR**	**1**	**42**			MS3											MS4		
T2.1	State of the Art of Knowledge for building hypermodels	FORTH	1	8																
T2.2	Scenario based user needs and requirements	USAAR	1	8																
T2.3	Requirements for enhancing hypermodels beyond the domain of cancer	PHILIPS	1	18																
T2.4	How to get acceptance of hypermodels by patients and physicians	USAAR	12	42																
WP3	**Clinical and Translational Science Scenarios**	**KU Leuven**	**1**	**48**								MS5				MS6				MS7
T3.1	Wilms tumor	USAAR	1	48																
T3.2	Glioblastoma multiforme	KU LEUVEN	1	48																
T3.3	Non small cell lung cancer	USAAR	1	48																
T3.4	Applying the CHIC infrastructure to other cancer types	UNITO	12	36																
WP4	**Legal and Ethical Framework**	**LUH**	**1**	**42**					MS8											
T4.1	Initial analysis of the ethical and legal requirements on the reuse of pseudonymized and anonymized data within CHIC	LUH	1	6																
T4.2	Initial analysis of the copyright-related legal requirements for the sharing of data and amalgamation of models within CHIC	LUH	1	9																
T4.3	Development of a data protection and copyright framework for CHIC	LUH	1	42																
T4.4	Whitepaper preparation	LUH	14	28																
WP5	**IT Architecture**	**TEI-C**	**1**	**42**						MS9								MS10		
T5.1	Reference Architecture Definition	TEI-C	1	42																
T5.2	Security tools and services	CUSTODIX	1	28																
T5.3	Private cloud infrastructure	BED	1	27																
WP6	**Cancer Models and Hypermodel Design**	**ICCS**	**1**	**46**		MS11					MS12						MS13		MS14	
T6.1	Cancer hypomodelling & hypermodelling strategies & elementary models	ICCS	1	36																
T6.2	Subcellular cancer modelling	UPENN	1	36																
T6.3	Biomechanics enhanced tumour modelling	UBERN	1	36																
T6.4	Clinical modelling paradigms of nephroblastoma, glioblastoma, lung cancer	ICCS	6	46																
T6.5	The colon cancer modelling paradigm	UOXF	6	46																
T6.6	The prostate cancer modelling paradigm	UNITO	6	46																

WP7	**Hypermodelling Infrastructure**	**USFD**	**1**	**48**	MS15 MS16 MS17 MS18
T7.1	Models execution	ICCS	1	27	
T7.2	Metamodels annotation	BED	7	36	
T7.3	Hypermodels execution	CINECA	7	42	
T7.4	Metahypermodels annotation	UCL	25	48	
T7.5	Hypermodelling infrastructure	FORTH	7	42	
WP8	**Model and Data Repositories**	**ICCS**	**1**	**48**	MS19 MS20 MS21
T8.1	Development of repositories	ICCS	1	48	
T8.2	Infrastructure for Semantic Metadata Management	ICCS	1	48	
T8.3	Integration with the security and the legal/ethical framework	UCL	1	48	
WP9	**Image Processing and Visualization**	**BED**	**1**	**46**	MS23 MS22 MS24
T9.1	User requirement analysis	BED	1	6	
T9.2	Scalable visualisation techniques	BED	3	18	
T9.3	Uncertainty data visualisation	BED	9	24	
T9.4	Visual analysis Suites for the model / data repository	BED	13	46	
T9.5	A general image processing dvelopment toolkit	UBERN	6	18	
T9.6	Image registration tools	UBERN	3	36	
T9.7	Multimodal and longitudinal brain tumor image analysis	UBERN	9	46	
T9.8	Multimodal and longitudinal brain tumor image analysis	FORTH	8	42	
WP10	**Integrated Platform**	**FORTH**	**1**	**44**	MS25 MS26
T10.1	Portal	FORTH	1	8	
T10.2	Interoperable interfaces for retrieving model and hypermodel descriptions	PHILIPS	1	18	
T10.3	Data management and computational infrastructure	CINECA	7	36	
T10.4	Data and hypermodel orchestration	FORTH	7	44	
WP11	**Clinical Adaptation and Validation**	**USAAR**	**1**	**48**	MS27 MS28 MS29
T11.1	Formulate evaluation & validation criteria to enhance clinical adaptation of hypermodels	USAAR	1	12	
T11.2	Coordinate evaluation activities by partners	UNITO	6	18	
T11.3	Clinical adaptation of the CHIC infrastructure as a whole	USAAR	12	48	
T11.4	Validation of the CHIC infrastructure as a whole	ICCS	36	48	
WP12	**Dissemination and Exploitation**	**CINECA**	**1**	**48**	MS30 MS31 MS32 MS33
T12.1	Dissemination activities	EURICE	1	48	
T12.2	Exploitation and IPR issues	CINECA	1	48	
T12.3	Training activities	ICCS / USAAR	12	48	

B1.3.3 Overall project structure

Figure 1.3.3-a shows the work package structure of the proposal and the inter-work package major interactions in a visual way.

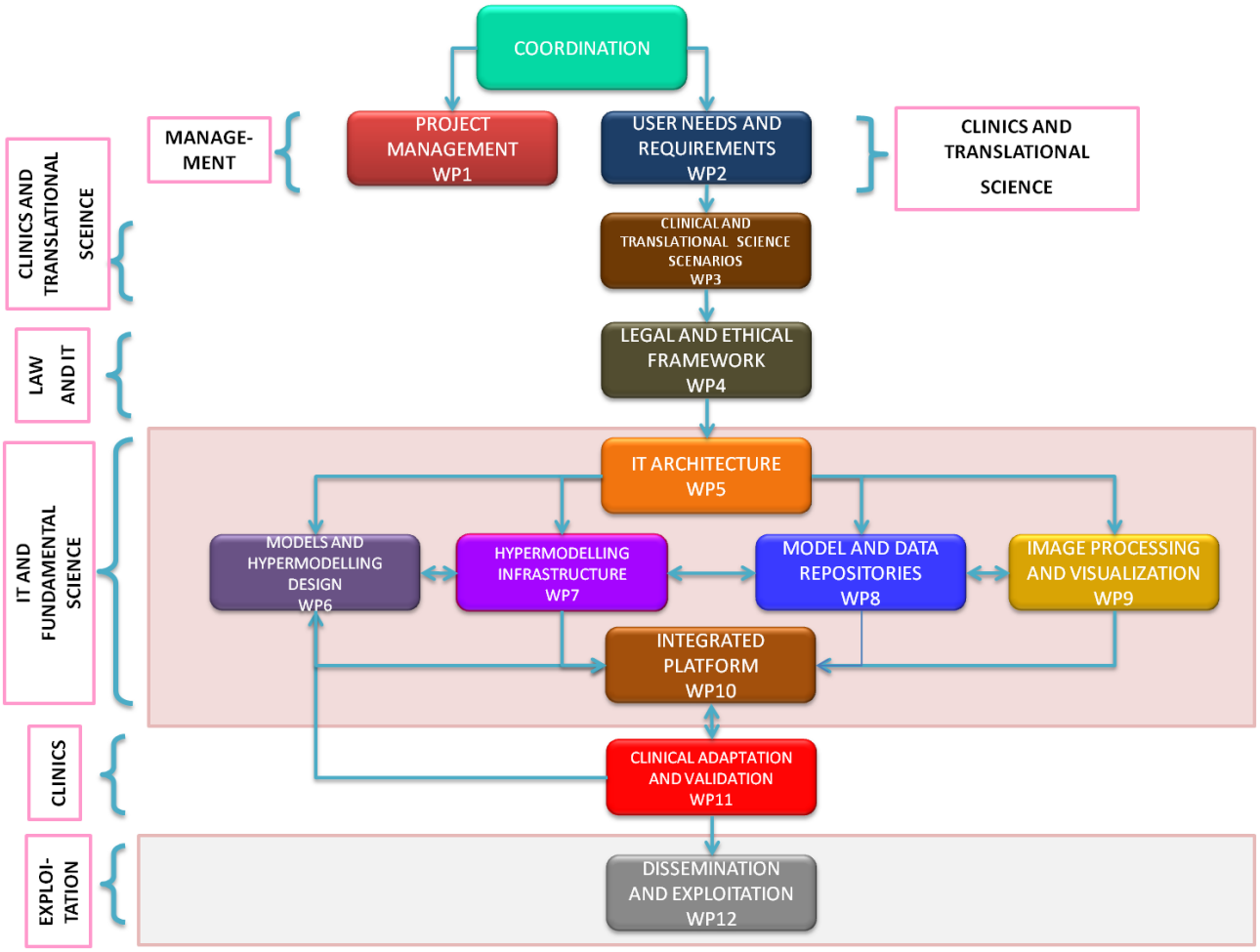


Figure 1.3.3-a Overall project structure

1.3.4 Risks and contingency plans

The CHIC project presents a certain number of risks that are inherent to the nature of an international collaborative project and to our ambitious objectives and the work planned by the partners. The general approach of the project to make risks manageable is its modular composition reflected in the work plan, the availability of fallback solutions in each work package and for each system component, as well as the involvement of clinical experts and end users for assessments in each phase of the system development. Even if a system module fails to be completed, which is not very likely, the remaining ones still produce valuable results. During the course of the project, the risks will continuously be reassessed at regular intervals to reflect any changes in the threat level or to monitor the emergence of risks unforeseen as the project moves towards completion. All efforts will be made to address the issues before they arise, implementing pre-emptive measures. During the lifespan of CHIC the Management Board will be able to identify potential risks soon enough, thanks to a Quality Assurance plan, that will be established soon after the start of the project. The following table gives an overview of the identified risks and the contingency plans to be adopted. According to the nature of the risk, we distinguish between scientific and technological risks, consortium related risks and

resources and financial risks. Where possible, the work package(s) from which the risk arise(s) is given in the table.

Table 1.3f: Risks and contingency plans

Risk No.	Risk	Nature[1]	Contingency Action
1	The overall architecture does not meet the requirements after first experiences.	STR	Immediately a review process will be invoked. WP leaders agree on such corrective modifications in the system architecture which minimize the adaption efforts for already existing components.
2	Project concepts are not acceptable from the perspective of the potential user community.	STR	The engagement of end users in all phases of the project serves as a preventive measure for this risk. End user consultation events will be held during the project.
3	Regulatory and ethical issues will require more time than expected and will postpone the delivery of data.	STR	The risk is minimized as part of the data is already available by the funded EU projects p-medicine and ContraCancrum. In addition many partners of CHIC are aware of and adhere to the legal and ethical framework developed in ACGT and further elaborated in p-medicine. A WP dealing with this issue will further reduce this risk.
4	The user requirements identified for the scenarios are not feasible within the scope of the project	STR	The project will manage the user requirements process in order to ensure that expectations are realistic. The scenarios will be defined in close collaboration with the CHIC technical partners to ensure that the user expectations are met. It will also clearly prioritise those functions that will be essential for piloting and identify any longer term priority requirements, which could be incorporated at a later date into potential products brought to market.
5	There is a failure of evaluation feedback	STR	Both the evaluation criteria and testing and validation plan will be rigorously specified before the pilot implementations commence. This means that any variations in the feedback received should provide valuable information about real differences in the potential of CHIC within each of the scenario arenas.
6	Complex interdependencies among the different WPs in CHIC may affect the coherence and the validity of results.	STR	Good communication among workpackages to identify all dependencies and to avoid ignoring relevant dependencies will be fostered and coordinate decisions that may affect other parts of the work will be done.
7	End-users may find the system difficult to use	STR	The system will be validated by end-users at different stages during development, and not only in the validation phase. Usability

			will be emphasized. Users' comments will be taken into account and newly identified requirements incorporated into the next versions. A workshop dealing with this issue will be held.
8	Possible change of European legislation throughout the project	STR	To assure CHIC's enduring accordance with European data protection legislation, a permanent observation of changes in the European legislation throughout the project is of high importance. If the EU modifies data protection regulation, this modification process will be studied by in order to guarantee compliance with future European legislation.
9	Integration problems for multiple data from different technical platforms	STR	Early proof-of-principle analyses to recognise the risk and adapt or exclude certain data formats or platforms.
10	Low attractiveness because CHIC has not addressed the appropriate stakeholders	STR	Efforts will also be made to contact other categories of stakeholders, which are not currently represented in the consortium. The goal is to attract their support/interest without the compensation of making them members of the consortium. The intention of CHIC is to expand the platform to other domains and thus engage end-users outside of CHIC. This will minimize this risk.
11	The project is too ambitious and unrealistic to succeed	CR	As clinicians from several institutes are enrolled in the project, realistic and clinically useful scenarios and use cases can be expected.
12	One or more partners are not able or not willing to perform their duties at all, in part or in time. The quality of a result of a task is not sufficient.	CR	The Coordinator specifies a clear and fair time limit for improvement after consulting the WP leaders. In case of failure, the conflict resolution procedure will be applied and all consequences as described in detail in the consortium agreement.
13	One partner withdraws from the project	CR	The partner will be replaced as soon as possible with capacities from other partners in accordance with the Commission. If the partner's responsibilities cannot be delegated to other partners in the consortium a new partner will be included in the consortium applying the respective procedure of the Commission
14	Overspending or under-spending by a partner	RFR	In both cases the coordination will ensure that the corresponding institutes give proper justification. Failure, for a given institution, to justify the over- or under-spending may result in a budget reallocation of its resources to other partner institutes in the project, in accordance with the general rules defined in the consortium Agreement.

[1] **CR**: Consortium related Risk; **STR**: Scientific and Technological Risk; **RFR**: Resources and Financial Risk

B2 Implementation

B2.1 Management structure and procedures

The management structure of the CHIC project is based on experience from previous projects under Framework Programme 7 involving large numbers of partners from both academia and industry. The consortium has designed a structure that clearly defines the management activities, tasks and responsibilities as well as the decision-making and financial procedures.

B2.1.1 Management structure

The CHIC management structure is illustrated in Figure 2.1.1-a

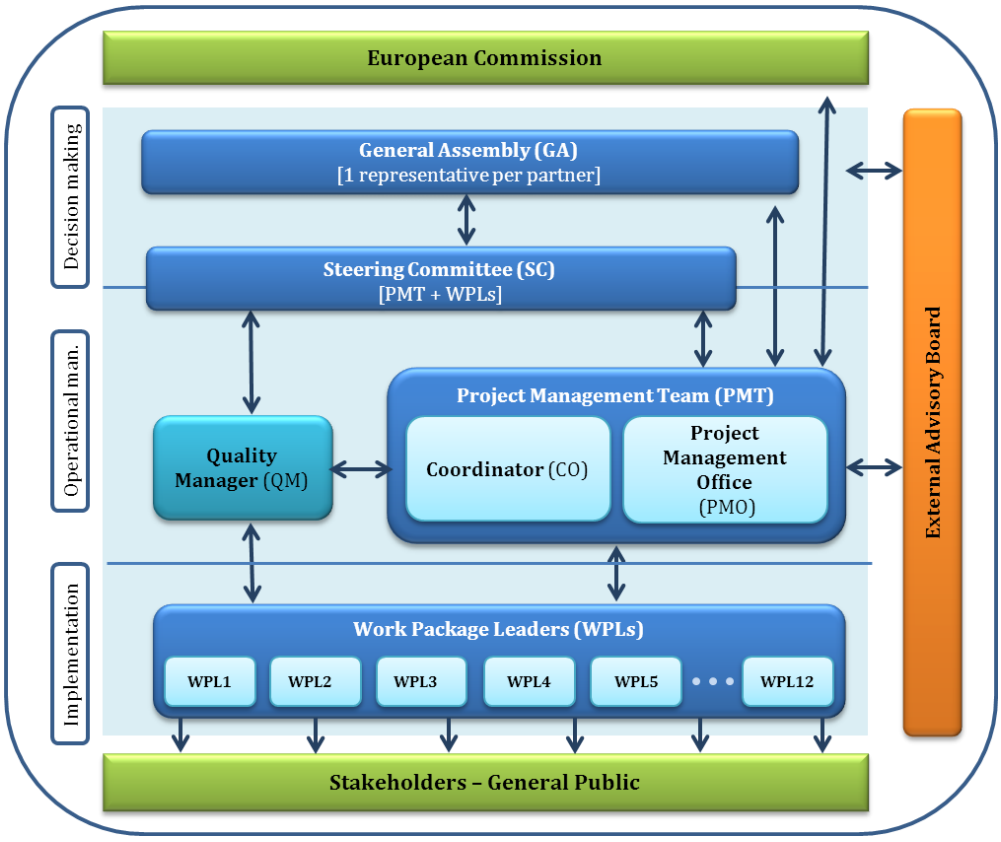


Figure 2.1.1-a Management Structure of CHIC

The following levels of management are defined:

Level 1: *Decision making*	At this level the management is coordinated by the General Assembly (all partners)
Level 2: *Operational management*	At this level two groups are responsible: the Steering Committee and the Project Management Team
Level 3: *Implementation*	At this level the management is supervised by the WP Leaders

The following section briefly describes the tasks and responsibilities of these management levels. Their tasks and responsibilities will be laid down in detail in the consortium agreement to be agreed upon before the start of the project.

Implementation level

Work Package Leaders (WPL)

The Work Package Leaders (WPL) will be responsible for the scientific coordination of their respective WPs, including the coordination of the workflow between their WP and the others. They will arrange for the timely execution and submission of the deliverables to assure the attainment of the goals of each technical application and will regularly report to the PMT on research development and progress status (see reporting mechanisms). A decentralized organization of the scientific work in which the WPL acts as interface between the partners of his respective WP and the PMT will assure maximum efficiency for project implementation.

Operational level

The Project Management Team (PMT)

The Project Management Team (PMT) is composed of the overall scientific project coordinator (CO) and the Project Management Office (PMO) that work closely together and stay in constant contact via e-mail, the web-based management tool as well as via regular meetings. The PMT will establish a sound legal, administrative and communication basis that will enable the partners to work efficiently and in accordance with general formal requirements as well as the requirements set forth in the CHIC workplan.

Overall scientific project coordinator (CO)

Georgios S. Stamatakos[46] is Research Professor of Analysis and Simulation of Biological Systems at the Institute of Communication and Computer Systems (ICCS) - National Technical University of Athens (NTUA) where he has founded and leads the *In Silico* Oncology Group (www.in-silico-oncology.iccs.ntua.gr). He holds a Diploma degree in electrical engineering from NTUA, an MSc degree in bioengineering from the University of Strathclyde, Glasgow, Scotland and a Ph.D. degree in physics (biophysics) from NTUA. The focus of his research group is on *in silico* oncology and multiscale cancer modelling. He has proposed the notion and the system of *oncosimulator*. He has led the development and clinical adaptation of the oncosimulators of the European Commission (EC)-Japan co-funded ACGT integrated project and other EC funded projects (ContraCancrum, TUMOR, p-medicine). G.Stamatakos has co-initiated and co-organized a number of international research workshops, including the series of International Advanced Research Workshops on *In Silico* Oncology and the First Transatlantic (EU-US) Workshop on Multiscale Cancer Modeling (ICT 2008, Brussels 2008). The latter was co-funded by EC and NCI. He has been co-editor, contributor and reviewer of the transatlantic multi-author textbook entitled "Multiscale Cancer Modeling" and published by CRC Press (2010). He is a member of the Editorial Board of Cancer Informatics, the Technical Chamber of Greece, the Institute of Electrical and Electronics Engineers (IEEE) and the Center for the Development of a Virtual Tumor (CViT) supported by the US NIH-National Cancer Institute through the Integrative Cancer Biology Program (CA113004). He will be in charge of the overall monitoring and coordination of all technical, knowledge- and innovation-related activities at consortium level. Furthermore, he will carry out the risk assessment activities verifying the fulfilment of defined milestones and the coordination of any actions required to reduce potential risks together with the WPL and the PMO. In detail, his tasks are as follows:

- Act as interface between the consortium and the European Commission together with the PMO
- Represent the project in relation to the outside world
- Transfer the EC payments to the project partners

[46] *http://www.la-press.com/spotlight-on-cancer-informatics-georgios-s-stamatakos-phd-article-a120*

- Monitor compliance of the partners with their obligations
- Collect, review and submit reports and other deliverables to the European Commission with the support of the PMO
- Chair the meetings, prepare the minutes of the meetings and monitor the implementation of decisions taken
- Transmit relevant documents and information to the partners concerned

Project Management Office (PMO)

The scientific coordinator will be assisted by a Project Management Office (PMO), EURICE. Externally, the PMO will assume the role of an interface between the project consortium and the European Commission together with the CO. Internally, EURICE will assist the CO in administrative, financial, formal and organisational matters, including conflict and intercultural management. The PMO provides and maintains an up-to-date communication and information structure (e.g. website service and web-based project management tool). The main tasks of the PMO include:

- Organisation of meetings of members of the Consortium including the preparation of minutes and the agenda
- Helpdesk for the partners concerning all administrative, financial and EC regulatory questions
- Coordination of report preparation including all financial reports and certificates on financial statements, if applicable, as well as the documentation of deliverables
- Coordination of the dissemination and innovation-related activities with the help of the task leaders in WP12

Quality Manager (QM)

The Quality Manager (QM) will be responsible for the overall quality assurance of the project. He/she will thus be in charge of the continuous follow-up of the work performed and propose suitable corrective action to the WPL concerned in case of any non-conformities with quality guidelines and subsequently review the effectiveness of such corrective action. He/she will closely cooperate with the WPLs, the Project Management Team and the Steering Committee and will offer them his/her support wherever needed. The quality of the project's results (deliverable and milestones) will be monitored at every stage of the project's development. The Quality Manager will be appointed on the occasion of the kick-off meeting.

The Steering Committee (SC)

The Steering Committee (SC) – composed of the WPL, the Quality Manager and the PMT – will monitor the progress in the WPs and thus supervise the overall implementation of the project. The SC does not have any decision-making power. However, based on reports and information from the WPLs the SC will prepare proposals for decisions for the General Assembly thereby ensuring the fast and efficient processing of relevant issues.

Decision-making level

General Assembly (GA)

The General Assembly (GA) is composed of one representative of each partner institution. Each representative is responsible for the proper utilisation of the contractor's resources allocated to the project and for the attainment of the objectives assigned to his institution. Each representative will further name a deputy who has the necessary knowledge and authorisation to represent the respective institution in the framework of the CHIC project. The GA will be chaired by the CO and will serve as the ultimate decision-making forum for all vital issues of the project such as:

- Changes in the overall project plan including the re-allocation of tasks and budget, technical objectives and project management
- Assessment of the technical progress and the results achieved
- Resolving conflicts that could not be settled according to the procedures described below
- Actions with regard to a defaulting party

External Advisory Board

The partners have decided to establish an external advisory board to provide advice and support concerning the strategy and progress of the project and to ensure that the project is always heading in the right direction. The board will have an advisory role only and will specifically take into account the ethical and legal issues relevant to the project. It will be composed of representatives of expert groups who have a special interest in various fields of the project, such as the Virtual Physiological Human, IT, data security and biobanking. A special emphasis will be laid on the involvement of patient groups as the compliance with ethical requirements is of primary importance to the project. The experts will review the key results and progress reports and will provide feedback and comments. The following experts have announced their participation in the external advisory board:

- David Ingram, Professor of Health Informatics and Director of the Centre for health Informatics and Multiprofessional Education, University College London
- Metin Akay, Professor of Biomedical Engineering, University of Houston, Texas, USA and IEEE Press Series Editor for the IEEE Press Series in Biomedical Engineering,
- Francoise Meunier, Director General of the European Organization for Research and Treatment of Cancer (EORTC)
- Trachette Jackson, Professor of Mathematics at the University of Michigan, USA. Senior Editor of Cancer Research
- Yuri Nikolsky, Chief Executive Officer GeneGo (a Thomson Reuters Company)

The members of the external advisory board shall sign non-disclosure agreements before obtaining access to any confidential project-related information. The specific provisions of the non-disclosure agreement to be signed will be agreed on with all CHIC beneficiaries during the first months of the project.

B2.1.2 Management procedures

Monitoring project progress and reporting

The WPLs will monitor the status of the deliverables and milestones of their respective workpackages. They will report to the PMT regularly (on a 6-monthly basis) and on the occasion of the regular SC and GA meetings. In turn, the PMT will be responsible for the elaboration, assessment and submission of reports and will make sure that the partners are informed about the requirements of the European Commission.

Reports will help to assess project progress on the basis of the activities carried out (on a task and WP basis), the resources spent (overview per partner), the deviations from the initial work plan and their implications including adjustments of the plan, if necessary, the status of deliverables and milestones and dissemination and innovation activities

The reports will be structured in accordance with the reporting guidelines provided by the European Commission. All reports will be submitted via the web-based management tool and will be archived and used as reference and basis for further reports and controlling tasks.

Inter-partner Communication

Transparent and continuous communication will ensure that the partners will be kept fully informed about any development of the project. Automated e-mail forwarding and a project website for file sharing will facilitate the day-to-day communication and the distribution of intermediate results. The website – divided into a public and a restricted area – will also serve as a structured document repository and as a contact point and dissemination tool for the different partner institutions, providing contact details, project details, related publications, conferences, recent highlights and updates on activities.

External Communication

WP12 will be responsible for the communication with external bodies through activities such as workshops and publications. Together, WP1 and WP12 will coordinate both inter-partner communication and the planning of exploitation issues (see below).

Meetings

The Meetings of the different project bodies will be scheduled as follows:

- Meetings of the General Assembly: twice a year
- Meetings of the Steering Committee: twice a year (on the occasion of the meetings of the General Assembly) and additional tele- or videoconferences as necessary (approx. every three months)
- Review meeting: depending on EC requirements
- WP meetings: as necessary

The meetings will be hosted by different partners. Additional meetings or video conferences will be held as necessary, e.g. for the preparation of major reports or in case of a major risk situation. Whenever possible and appropriate, the meetings will combine meetings of different project bodies in order to save resources.

Decision making

The detailed rules for decision making and conflict resolution will be laid down in the consortium agreement to be concluded and signed before the Grant Agreement. This will include the rights and responsibilities of the different consortium bodies, the voting rules and the scope of the consortium bodies' decision-making power.

The basic decision-making mechanism in this project can be summarized as follows (following the principles laid down in the DESCA consortium agreement model, version 3.0):

- Each consortium body has a quorum and may deliberate only if two-thirds (2/3) of its members are present or represented.
- Each member of a consortium body present or represented in the meeting has one vote.
- Defaulting party members may not vote.

Conflict resolution

The decision-making procedures are aimed at finding a consensus among the partners and at avoiding any adverse effects of one partner's activities on those of another partner. In the event that a dispute arises which cannot be settled amicably between the partners concerned, the following procedures apply:

- Each partner will report immediately and in writing to his respective WPL and the CO any risk situation that may conflict with the successful achievement of the project objectives.
- The Steering Committee will assess the impact that the conflict might have on the work progress/project activities in the different work packages.
- At first, the WPL shall try to resolve the conflict with the help of the partners of the work packages concerned. In the event that no consensus can be reached at this level, the CO will act as mediator between the partners.
- If the conflict is not resolved, the CO will present the issue to the Steering Committee for discussion.
- If an agreement is not reached with the help of the SC, the dispute will be passed on to the General Assembly
- Disputes that could then still not be settled finally will be subject to arbitration in Brussels pursuant to mediation in accordance with the WIPO Mediation Rules. The award of the arbitration panel will be final and binding.

B2.2 Beneficiaries

Participant 1	**Institute of Communication and Computer Systems (ICCS)**
Organisation	The Institute of Communication and Computer Systems (ICCS) is an academic research body affiliated to the National Technical University of Athens (NTUA). It is the research host of the School of Electrical and Computer Engineering of NTUA. It has participated in and coordinated numerous large scale research and development projects funded by the European Commission in both FP6 and FP7 frameworks.
Main Tasks	Role: Project Coordinator, WP6 and WP8 leader, involvement in all workpackages Main tasks in the project: • Scientific coordination of the project • Design, devevelopment and testing of meta- and hypermodelling based oncosimulators and infrastructures • Development of hyper-model and data repositories
Relevant Previous Experience	*In Silico* Oncology Group (ISOG), Laboratory of Microwaves and Fibre Optics, ICCS-NTUA is a world leader in the field of the emergent discipline of *in silico* oncology. **Indicative publications:** [1] G.S.Stamatakos, E.Ch.Georgiadi, N.Graf, E.A.Kolokotroni, and D.D.Dionysiou, "Exploiting Clinical Trial Data Drastically Narrows the Window of Possible Solutions to the Problem of Clinical Adaptation of a Multiscale Cancer Model", PLoS ONE 6(3), e17594, 2011 [2] G.Stamatakos "*In Silico* Oncology Part I: Clinically Oriented Cancer Multilevel Modeling Based on Discrete Event Simulation" In T.Deisboeck and G. Stamatakos Eds 407-436 2011-01-01 CRC Press, Print ISBN: 978-1-4398-1440-6 eBook ISBN: 978-1-4398-1442-0 DOI: 10.1201/b10407-19 Boca Raton, Florida, USA, 2011 [3] G.S.Stamatakos, E.A.Kolokotroni, D.D.Dionysiou, E.Ch.Georgiadi, C.Desmedt. An advanced discrete state - discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study. J. Theor. Biol. 266, 124-139, 2010
Staff Members Involved	**Georgios S. Stamatakos** is Research Professor of Analysis and Simulation of Biological Systems at the Institute of Communication and Computer Systems (ICCS) - National Technical University of Athens (NTUA) where he has founded and leads the *In Silico* Oncology Group (www.in-silico-oncology.iccs.ntua.gr) . He holds a Diploma degree in electrical engineering from NTUA, an MSc degree in bioengineering from the University of Strathclyde, Glasgow, Scotland and a Ph.D. degree in physics (biophysics) from NTUA. The focus of his research group (www.in-silico-oncology.iccs.ntua.gr) is on *in silico* oncology and multiscale cancer modelling. He has proposed the notion and the system of Oncosimulator. He has led the development of the Oncosimulators of the European Commission (EC) and the Japan co-funded ACGT integrated project and other projects. G. Stamatakos has co-initiated and co-organized a number of international research workshops, including the series of International Advanced Research Workshops on *In Silico* Oncology and the First Transatlantic (EU-US) Workshop on Multiscale Cancer Modeling (ICT 2008, Brussels 2008). The latter was co-funded by EC and NCI. He has been co-editor, contributor and reviewer of the transatlantic multi-author textbook entitled "Multiscale Cancer Modeling" and published by CRC Press (2010). **Dimitra D. Dionysiou** is a Senior Researcher. She holds a diploma degree in electrical and computer engineering and a PhD on *in silico* oncology, both from the National Technical University of Athens (NTUA), and an MSc in bioinformatics from the University of Athens. Dr. Dionysiou has worked for the development of several clinically-oriented multiscale oncosimulators and has published more than 50 peer-reviewed articles in journals, books and conference proceedings.

Participant 2	**European Research and Project Office GmbH (EURICE)**
Organisation	Eurice is a spin-off company of Saarland University, founded in 2000 in order to assist and consult scientists, researchers and innovative companies in the area of EU research and project management. Today, Eurice is the largest EU project management office with a team of about 35 academic experts with different scientific and non-scientific backgrounds, such as law, medicine, biology, chemistry, communications, information sciences, or computer sciences.
Main Tasks	Role: WP1 leader Main tasks in the project: • Administrative assistance: Eurice will be in charge of administrative and legal aspects of the CHIC project in close cooperation with the scientific coordinator. • Project Management Office (PMO): Eurice will provide a fully equipped Project Management Office to assist the coordinator in administrative, financial, formal and organisational aspects, including conflict and intercultural management as well as the financial management. The PMO will assume the role of an interface between the project consortium and the European Commission together with the coordinator. Its facilities include an up-to-date communication and information structure (e.g. website service, communication tools).
Relevant Previous Experience	Eurice has been involved in EU Framework Programmes since FP4 and has been in charge of the management of more than 80 EU-funded projects, both as a management and dissemination partner, with an overall budget of over € 200 million. It is currently managing nearly 30 international research projects with partners from more than 40 countries and an overall budget of over € 130 million. Eurice is a partner in the IPR helpdesk project which offers basic assistance in Intellectual Property Rights issues and is co-funded by the European Commission. Eurice has successfully participated in several ICT projects over the years with the most relevant being the current EU project p-medicine (FP7).
Staff Members Involved	**Corinna Hahn** is Senior Programme Manager and has experience with EU-funded research projects since 2000. **Project assistant**: Julia Petry. **Jörg Scherer** is Senior Programme Manager with more than 15 years of experience in international collaborative RTD projects. He has held over 100 training workshops, lectures and has published numerous articles on international research and project management.

Participant 3	Universitaet des Saarlandes (USAAR)
Organisation	Saarland University was founded in 1948 in co-operation with France. Today the University counts 15.500 students of whom 7 percent are foreign students. Saarland University has 8 faculties and provides the broad spectrum of disciplines typical of a classical universitas litterarum. At the Faculty of Medicine (University Hospital), located in Homburg / Saarland more than 1800 people are studying medicine. There are 36 hospitals or institutions treating more than 54.000 inpatients and nearly 190.000 outpatients each year. **Participants from Saarland University are on the one hand the department of Paediatric Oncology and Haematology and on the other hand the department for Pathology**. These two departments are part of the Comprehensive Cancer Centre of the University Hospital and responsible for the care of patients in the Saarland and the surrounding area. The focus in research of the Department of Paediatric Oncology and Haematology is nephroblastoma (clinical study and trial and basic research in cooperation with different institutes) and brain tumour. The Department of Pathology has significant expertise in the treatment of patients with lung cancer (in cooperation with the departments of radiotherapy and thoracic surgery). Part of activities is supported by the Institute of Human Genetics relating to tumour immunology and gene expression analysis works.
Main Tasks	USAAR is leading WP2 (User Needs and Requirements) and WP11 (Clinical Adaptation and Validation). Main tasks are: • to investigate the state-of-the-art of knowledge to build hypermodels, • to define scenario based user needs and requirements, • to formulate evaluation criteria, and • to enhance validation and clinical adaptation for hypermodels. USAAR is a partner in WP3 (Clinical Translational Science Scenarios). Main tasks • Transcriptome analysis of tumor, staging, grading to be used for the development of a system biology model
Relevant Previous Experience	**Relevant projects:** **USAAR** has been involved in EU Framework Programmes for many years. In FP7, USAAR is a partner in the ContraCancrum, CONTRACT, EURECA and TUMOUR projects. In addition, the department of Paediatric Oncology and Haematology is the coordinator of the p-medicine, which is a large-scale integrating project, which aims to build an IT infrastructure for personalized medicine. **Relevant publications (Prof. Bohle**) 1. Linxweiler M, Linxweiler J, Barth M, Benedix J, Jung V, Kim YJ, Bohle RM, Zimmermann R, Greiner M. Sec62 bridges the gap from 3q amplification to molecular cell biology in non-small cell lung cancer. Am J Pathol 2012;180:473-83 2. Goeckenjan G, Sitter H, Thomas M, Branscheid D, Flentje M, Griesinger F, Niederle N, Stuschke M, Blum T, Deppermann KM, Ficker JH, Freitag L, Lübbe AS, Reinhold T, Späth-Schwalbe E, Ukena D, Wickert M, Wolf M, Andreas S, Auberger T, Baum RP, Baysal B, Beuth J, Bickeböller H, Böcking A, Bohle RM, Brüske I, Burghuber O, Dickgreber N, Diederich S, Dienemann H, Eberhardt W, Eggeling S, Fink T, Fischer B, Franke M, Friedel G, Gauler T, Gütz S, Hautmann H, Hellmann A, Hellwig D, Herth F, Heussel CP, Hilbe W, Hoffmeyer F, Horneber M, Huber RM, Hübner J, Kauczor HU, Kirchbacher K, Kirsten D, Kraus T, Lang SM, Martens U, Mohn-Staudner A, Müller KM, Müller-Nordhorn J, Nowak D, Ochmann U, Passlick B, Petersen I, Pirker R, Pokrajac B, Reck M, Riha S, Rübe C, Schmittel A, Schönfeld N, Schütte W, Serke M, Stamatis G, Steingräber M, Steins M, Stoelben E, Swoboda L, Teschler H, Tessen HW, Weber M, Werner A, Wichmann HE, Irlinger Wimmer E, Witt C, Worth H; German Respiratory Society; German Cancer Society. Prevention, diagnosis, therapy, and follow-up of lung cancer: interdisciplinary guideline of the German Respiratory Society

	and the German Cancer Society. Pneumologie 2011; 65:39-59 3. Fink L, Kwapiszewska G, Wilhelm J, Bohle RM. Laser-microdissection for cell type- and compartment-specific analyses on genomic and proteomic level. Exp Toxicol Pathol 2006; 57 Suppl 2:25-29 4. Fink L, Bohle RM. Laser microdissection and RNA analysis. Methods Mol Biol 2005; 293:167-185 5. Fink L, Kohlhoff S, Stein MM, Hänze J, Weissmann N, Rose F, Akkayagil E, Manz D, Grimminger F, Seeger W, Bohle RM. cDNA array hybridization after laser-assisted microdissection from nonneoplastic tissue. Am J Pathol 2002;160:81-90
Staff Members Involved	**Prof. Dr. Norbert Graf** is Professor of Paediatrics and Director of the Clinic for Paediatric Oncology and Haematology and a member of the Faculty of Medicine. He is the chairman of the Renal Tumour Study Group of the International Society of Paediatric Oncology (SIOP-RTSG) and the Principal Investigator of the current Trial for Kidney Tumours within SIOP. He is an Associate Member of COG (Children's Oncology Group, North America) and closely cooperating the COG Renal Study Group. He is the coordinator of p-medicine and has more than 25 years of experience with clinical trials. **Prof. Dr. Rainer M. Bohle** is Professor of Pathology and Director of the Department of Pathology, current head of the Department of Neuropathology and a member of the Faculty of Medicine since 2006. He is the chairman of the Saarland Tumor Center, member of the International Association for the Study of Lung Cancer and member of the Certification Committee for Lung Cancer Centers of the German Cancer Society. He has more than twenty years of experience in molecular pathology. **Prof. Dr. E. Meese** is Professor of Human Genetics and Head of the Department of Human Genetics of the Faculty of Medicine of the University of the Saarland in Germany. Prof. Meese is a member of the German Society of Human Genetics, German Society of Genetics, and the American Society of Cancer Research. He was board member of the European Conference on Cytogenetic and Molecular Genetics, chairman of the core grant „Molecular Pathology of Proliferation", founding member of the Centre for Human and Molecular Biology of the University of Saarland, and vice dean of the Medical Faculty. He is presently Member of Steering Committee of Center of Bioinformatics at the University of Saarland. Since 1991 his work is continuously supported by Grants form the DFG (German Research Foundation) and German Cancer Foundation.

Participant 4	**Katholike Universiteit Leuven (KU Leuven)**
Organisation	KU Leuven is the oldest and largest university of the region and belongs to the League of European Research Universities (LERU). The University Hospital Leuven belongs to KU Leuven and has an international reputation in combining translational and clinical research with optimal patient care.
Main Tasks	Leader of WP3: Clinical and Translational Science scenarios. Trials for Wilms' tumor, glioblastoma multiforme en non-small cell Lung Cancer are conducted, and data will be collected for evaluation and validation of the Meta- and Hyper-Multiscale Models and Repositories using existing models from VPH. The data sets will also be used for the integrated Oncosimulator and will subsequently be validated via clinical and oncologic outcome.
Relevant Previous Experience	Immunotherapy for GBM is a successful translational research project through which KU Leuven plays a major role in the neuro-oncology community worldwide. Currently 5 PhD students perform preclinical research, and 3.4 FTE technicians produce the vaccines in the GMP laboratory. We drain patients from 23 different countries in- and outside Europe for immunotherapy in our institution. There is an exponential increase of patients. We run trials for patients with relapsed HGG in the cohort comparison trial HGG-IMMUNO-2003. The HGG-2010 trial is recruiting patients with primary diagnosis of GBM from 19 participating neuro-oncology centers linked to the University Hospital Leuven. This phase IIb prospective double-blind placebo-controlled randomised clinical trial is recruiting on schedule. The data from this trial are the focus of CHIC.
Staff Members Involved	**Stefaan Van Gool**, MD, PhD, is a pediatric neuro-oncologist at the University Hospital Leuven, and initiator of the HGG-IMMUNO translational research program. Full Professor at KU Leuven. Senior clinical investigator at the Fund for Scientific Research – Flanders. **Steven De Vleeschouwer**, MD, PhD is a neurosurgeon in the University Hospital Leuven, trained and subsequently involved in the immunotherapy program. Associate Professor at KU Leuven. **Femke Pauwels** holds a master in biomedical sciences and is the clinical coordinator of the immunotherapy trials.

Participant 5	**University of Bedfordshire (BED)**
Organisation	The University of Bedfordshire has expanded rapidly in the last few years and now has approximately 25,000 students on two main campuses, in Luton and in Bedford. The Department of Computer Science and Technology is one of the largest departments in the University and regularly enrols over 500 postgraduate students a year across several Masters courses. The Department also offers a range of undergraduate courses and has strong formal links with numerous universities around the world for teaching and research purposes.
Main Tasks	Role: WP9 Leader Within WP9, BED will be responsible for coordinating the work across the wide range of visualisation and image processing tasks BED also has significant roles in *WP5: IT Architecture* and *WP7: Hypermodelling Infrastructure*.
Relevant Previous Experience	The **Centre for Computer Graphics and Visualisation (CCGV**) has 3 professors and 10 postdoctoral research fellows. It has a long history of involvement in international projects, in which it has specialised in developing visualisation and modelling solutions to real-world problems. CCGV has been particularly active in the area of medical applications and has been involved in 9 projects within the 7th Framework Programme. These include the successful ContraCancrum project in which CCGV worked closely with a number of partners in the CHIC consortium. **Recent Publications** M Viceconti, G J Clapworthy, D Testi, F Taddei and N J B McFarlane, *Multimodal Fusion of Biomedical Data at Different Temporal and Dimensional Scales*, Computer Methods and Programs in Biomedicine, Elsevier, Vol 102, No 3, pp 227-237, 2011 N J B McFarlane, X Lin, Y Zhao, G J Clapworthy, F Dong, A Redaelli, O Parodi, D Testi, *Visualisation and Simulated Surgery of the Left Ventricle,* Interface Focus, Royal Society, Vol 1, No 3, pp 374-383, 2011 B Liu, G J Clapworthy and F Dong, *Multi-layer Depth Peeling by Single-Pass Hardware Rasterisation for Faster Isosurface Raytracing on a GPU*, Computer Graphics Forum, Vol 29, No 3, pp 1231-1240, 2010
Staff Members Involved	**Feng Dong** is Professor of Visual Computing and has been involved in European projects for 14 years and had been the recipient of several project awards from the UK Research Councils. His research interests cover image processing, visualisation, visual analytics and the use of the GPU. He is currently Project Coordinator of the GPSME project working on the automatic translation of code into GPU format (FP7-286545) **Gordon Clapworthy** is Professor of Computer Graphics and Head of the Centre for Computer Graphics and Visualisation. He has been involved in 27 European projects over the last 16 years, in 9 of which he was Project Coordinator. He has published 200 peer-reviewed articles, and his research interests cover computer graphics, biomedical visualisation and fundamental computer graphics algorithms. **Enjie Liu** is a Senior Lecturer in the Department of Computer Science & Technology. Her research interests include web services and ontologies in which she has been involved within 4 EC-funded projects during FP7. She also has a research interest in wireless technologies, with research council projects in femtocells.

Participant 6	**University of Sheffield (USFD)**
Organisation	The University of Sheffield (USFD) is the Times Higher Education UK University of the Year in 2011. Official independent research assessments confirm its reputation as a centre for world-class research in many disciplines; in particular, more than two thirds of our technological research has been ranked either "internationally excellent" or "world leading". It has more than 25,000 students from 128 countries, and over 5,500 staff. The University has recently made ~3M pounds investment in Virtual Physiological Human (VPH) research, with the establishment of the INSIGNEO Institute on Biomedical Imaging & Modelling, a new Institute spanning the Faculties of Engineering and Medicine and the Sheffield Teaching Hospitals NHS Foundation Trust.
Main Tasks	Role: WP7 leader Main tasks in the project: 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.
Relevant Previous Experience	Among USFD senior members there are today some of the academics that most contributed to the shaping of the VPH initiative: co-authors of 2005 VPH white paper and Editors of the 2007 VPH Research Roadmap, co-coordinators of the STEP support action, of the VPH pillar in the ARGOS observatory, and of the VPH-FET action, core members of the VPH Network of Excellence, and members of the Board of Directors of the VPH Institute. **Publications** Cristofolini L, Taddei F, Baleani M, Baruffaldi F, Stea S, Viceconti M. Multiscale investigation of the functional properties of the human femur. Philos Transact A Math Phys Eng Sci. 2008 Sep 28;366(1879):3319-41. Viceconti M, Taddei F, Van Sint Jan S, Leardini A, Cristofolini L, Stea S, Baruffaldi F, Baleani M. Multiscale modelling of the skeleton for the prediction of the risk of fracture. Clin Biomech. 2008 Aug;23(7):845-52.
Staff Members Involved	**Marco Viceconti** is full Professor of Biomechanics at the Department of Mechanical Engineering at the University of Sheffield and Scientific Director of the Insigneo Research Institute. Before this he was the Technical Director of the Medical Technology Lab at the Rizzoli Orthopaedic Institute in Bologna, Italy. He is currently President of the European Alliance of Biomedical Engineering (EAMBES). His main research interests are related to the development and validation of medical technology, especially that involving simulation. He has published over 200 papers, mostly indexed in Medline, and serves as reviewer for many international funding agencies and peer-reviewed journals. Marco Viceconti is one of the key figures in the emerging Virtual Physiological Human (VPH) community. Co-author of the first white paper on VPH, scientific co-ordinator of the seminal VPH research roadmap, "VPH ambassador" for the VPH Network of Excellence, Co-ordinator of one the VPHOP integrated project, he is also currently chairing the Board of Directors of the VPH Institute.

Participant 7	Foundation for Research and Technology – Hellas (FORTH)
Organisation	**The Foundation for Research and Technology – Hellas (FORTH)** is one of the largest research centres of Greece with well-organised facilities and a highly qualified staff. The research and technological focus of the foundation is centered on selected areas of great scientific, social, and economic interest. **The Institute of Computer Science (ICS) with the Computational Medicine Laboratory (CML)** will be involved and contribute to the current project. ICS, since its establishment in 1983, is a pioneering contributor towards the deployment and adoption of Information Society Technologies in Greece and plays a leading role in worldwide efforts towards the development of an Information Society accessible and acceptable by all citizens. The CML lab at FORTH-ICS has established a tradition of internationally acknowledged excellence in conducting high-level R&D work and in developing innovative systems and services. Its research activities focus on the development of innovative computer methods and tools in the area of medical and biomedical informatics, ehealth, m-Health, medical imaging and bioinformatics. Recently the lab is also focusing its R&D activities on biomedical modelling and simulation in the wider VPH research context.
Main Tasks	FORTH will lead WP10 on Integration of CHIC. FORTH will significantly contribute to WP7 (Hypermodelling infrastructure) and WP9 (Image processing and Visualisation). Being the integrator of the project, FORTH will participate in WP2 (User Needs). Finally, FORTH will contribute to a lesser extent to WP6 (Model and hypermodels design) and WP11 (Clinical Adaptation and validation) as well as WP12 (dissemination and exploitation).
Relevant Previous Experience	The laboratory has been involved in several projects and initiatives related to CHIC topics. In particular the group coordinated the **ACGT project**- an IST Integrating project aiming at the development of the European Biomedical Informatics Grid for cancer research, the **ContraCancrum project** – an FP7 STREP project focusing on multi-level cancer modelling, and is currently coordinating the **TUMOR project** – an FP7 STREP project focusing on model interoperability for cancer research (international collaboration with MGH). It is also involved in 2 FP7 STREP projects: **INTEGRATE** focusing on model and collaborative tools development**,** and **ENCCA (European Network for Cancer Research in Children and Adolescents**). Finally, FORTH is leading the architecture and integration work in the FP7 IP project **p-medicine,** and is also strongly involved in the recently started **EURECA** IP project.
Staff Members Involved	**Dr. Kostas Marias** holds a Principal Researcher position at ICS-FORTH and has been involved in numerous projects in the field of Medical Image Analysis. Currently, he is the coordinator of 2 EC projects on cancer modelling (ContraCancrum and TUMOR) and is actively involved in providing open access image analysis/modelling tools in the clinical setting for the promotion of predictive oncology. **Dr. Vangelis Sakkalis** holds an Associate Researcher position at ICS-FORTH. He is currently the Technical Coordinator of TUMOR. **Mr. Stelios Sfakianakis** has joined ICS-FORTH's Computational Medicine Laboratory (CML) in 2000. His interests include the semantic integration and composition of services in state of the art computational environments such as the Grid and the Semantic Web. Additionally, he is interested in the design of programming languages and their various paradigms. **Prof. Constantine Stephanidis** is Professor at the Department of Computer Science of the University of Crete, teaching Human – Computer Interaction. He is also the Director of the Institute of Computer Science (ICS) of the Foundation for Research and Technology – Hellas (FORTH), Head of the Human - Computer Interaction Laboratory, and Head of the Ambient Intelligence Programme. He has been engaged as the Scientific Responsible in more than 50 National and European Commission funded projects in the field of Human - Computer Interaction. Currently, Prof.

	Stephanidis is coordinating multidisciplinary and cross-thematic activities aiming to conceptualize, design and develop in vitro, and deploy in vivo, pioneering, innovative technologies and applications for interacting with smart environments, capable of "understanding" and proactively addressing individual human needs, following a human-centred approach. He has published more than 500 technical papers in scientific archival journals, proceedings of international conferences and workshops related to his fields of expertise. In 2010, Prof. Stephanidis was elected member of the Informatics Section of the Academia Europaea, a functioning European Academy of Humanities, Letters and Sciences. **Mr. Georgios Zacharioudakis** (BSc in Computer Science and a MSc in Distributed Systems has expertise in the integration of heterogeneous and distributed services, the design of health care telematics applications, ambient intelligence components and applications, using SOA architectures and open technologies and protocols. **Mr. Georgios Manikis** (MSc) have expertise on medical image processing, modelling of biological processes, biostatistics and pattern recognition with applications in classification, feature extraction, and data integration.

Participant 8	**Leibniz Universitaet Hannover (LUH)**
Organisation	The Institute for Legal Informatics of Leibniz University of Hannover, involved in CHIC, was established in 1983 and is the first Institute dedicated to this goal at a German University. The project will be set into the organizational framework of the Institute for Legal Informatics (IRI) and the Learning Lab Lower Saxony at LUH (www.l3s.de). The principal investigator, Prof. Dr. Nikolaus Forgó, is director of the IRI and member at L3S. The the Institute for Legal Informatics of the Leibniz University of Hannover (www.iri.uni-hannover.de) at the Law School of the University of Hannover is the oldest establishment dedicated to scientific research on legal problems of Information and Communication Technologies at a German University and with currently more than 40 people staff one of Europe's largest institutions in the field. The institute is actively involved in about 10 European research projects with a focus on issues of data protection data security and intellectual property. The L3S Research Center focuses on fundamental and application-oriented research in all areas of Web Science. In the context of a large number of projects, the L3S explores numerous issues covering the entire spectrum of challenges in Web Science as a field of research.
Main Tasks	LUH is WP leader of WP4 "Legal and Ethical Framework". It's major tasks in CHIC comprise: • In-depth analysis of the existing European rules on data protection • Definition of the legal, ethical and security requirements and guidelines • Design of the CHIC Legal Framework • Design and analysis of the CHIC-intellectual property framework guiding patients, researchers and research organisations on their respective right on data, algorithms and software developed in the project and after the project's end. • Development of a Data Governance and Business Model. • Assisting the Consortium with upcoming legal questions during the project • Development of recommendations on an amendment of the existing European normative framework for European stakeholders such as the European Commission.
Relevant Previous Experience	The Institute of Legal Informatics is involved in the following FP7 projects: • EURECA, EU-project, *running* • p-medicine, EU-project, *running* • PONTE, EU-project, *running* • SMART, EU-project, *running* • Linked2Safety, EU-project, *running*.
Staff Members Involved	**Prof. Dr. Nikolaus Forgó** has studied law, philosophy and linguistics in Vienna and Paris. In 1997 he got his Dr. iur. (Dissertation in legal theory). Between the years 1990-2000 he has been an Assistant Professor at the University of Vienna (Austria). From 2000 he is a full Professor for Legal Informatics and IT-Law at the University of Hanover. He has many publications, and has carried teaching and consulting in all fields of IT-law, legal informatics, civil law, legal history and legal theory. **Dr. Tina Krügel,** LL.M. has studied law in Hanover and completed her legal clerkship in Hanover/Johannesburg (SA). In 2002 she attended the LL.M.-Programme EULISP in Hanover/Oslo. In 2005 she got her Dr. iur. (e-commerce law). Since 2004 she is an attorney at law and works for the IRI as a research associate with the main focus on data protection law. She has several publications in the field of e-commerce law and data protection law. **RA Thorsten Heermann/Wolfgang Rottwinkel** (administrative matters)

Participant 9	**University of Pennsylvania (UPENN)**
Organisation	The computational molecular systems biology laboratory housed in the Departments of Bioengineering and Biochemistry and Biophysics at the University of Pennsylvania is involved in developing and applying multiscale modelling techniques for molecular and cellular processes regulating signal transduction in cancer cells. The laboratory focuses on physically based techniques such as molecular dynamics and coarse-grained models of protein/lipid assemblies as well as network techniques to model emergent properties in signalling cascades.
Main Tasks	UPENN is primarily involved in WP6 in the following tasks: • Computational network models relevant to cellular signalling in glioblastoma, non-small-cell lung cancer, and nephroblastoma • Molecular models to identify driver versus passenger mutations in oncogenic signalling proteins relevant to the above cancer types • Development of patient/cohort specific networks by combining whole genome sequencing data with the network modelling techniques.
Relevant Previous Experience	We have prior experience in leading US National Science Foundation and in playing active roles in US National Institutes of Health funded projects in developing multiscale modelling techniques including those for multiscale cancer modelling. Key representative publications highlighting the scientific impact from these projects and their relevance to cancer modeling, are listed below: * Analysis of Somatic Mutations in Cancer: Molecular Mechanisms of Activation in the ErbB family of Receptor Tyrosine Kinases, A. J. Shih, S. E. Telesco, R. Radhakrishnan, Cancers, 2011, 3(1), 1195-1231; doi:10.3390/cancers3011195. Pubmed ID: 21701703 * A Multiscale Modeling Approach to Investigate Molecular Mechanisms of Pseudokinase Activation and Drug Resistance in the HER3/ErbB3 Receptor Tyrosine Kinase Signaling Network, S. E. Telesco, A. J. Shih, F. Jia, R. Radhakrishnan, Molecular Biosystems (RSC Journal), 2011, 7 (6), 2066 - 2080. DOI: 10.1039/c0mb00345j. Pubmed ID: 21509365. * Systems Biology and Physical Biology of Clathrin-Mediated Endocytosis: An Integrative Experimental and Theoretical Perspective, V. Ramanan, N. J. Agrawal, J. Liu, S. Engles, R. Toy, R. Radhakrishnan, Integrative Biology (RSC Journal), 2011, 3(8), 803-815. DOI: 10.1039/c1ib00036e. Pubmed ID: 21792431. * The ErbB3/HER3 Intracellular Domain is Competent to Bind ATP and Catalyze Autophosphorylation, F. Shi, S. E. Telesco, Y. Liu, R. Radhakrishnan*, M. A. Lemmon*, Proceedings of the National Academy of Sciences, 107, 7692-7697, 2010. Pubmed ID: 20351256; *Co-corresponding authors. * Molecular Dynamics Analysis of Conserved Hydrophobic and Hydrophilic Bond Interaction Networks in ErbB Family Kinases, A. Shih, S. E. Telesco, S. H. Choi, M. A. Lemmon, R. Radhakrishnan, Biochemical Journal, 2011, **436**(2), 241-251. Pubmed ID: 21426301.
Staff Members Involved	**Ravi Radhakrishnan**, Principal Investigator, Computational Molecular Systems Biology Lab, has vast training and experience in developing multiscale modelling techniques relevant to cellular signalling and to cancer. Computational Molecular Systems Biology Laboratory Lab Members will participate under the direction of the Principal Investigator.

Participant 10	**The Chancellor, Masters and Scholars of the University of Oxford (UOXF)**
Organisation	The University of Oxford is a world-class center of excellence in research and teaching, with over 21,000 students and 1,600 academic staff. Its Mathematical Institute and Department of Computer Science enjoy strong international reputations for excellence in research, with particular strengths in mathematical and computational biology.
Main Tasks	Oxford's primary role will be in WP6: In this WP Oxford's main tasks will be to develop new multiscale and continuum models of early colorectal cancer and vascular tumor growth. The new models will be implemented into the CHIC software using the hypomodelling framework to be developed in WP7 and will be validated against data obtained by experimental and clinical partners. The Oxford team will also contribute to the activities of WP 12.
Relevant Previous Experience	Oxford has a strong track record of securing EC funding. For example, during the University financial year from August 2009 to July 2010, 107 new EC awards worth £36.1M were granted. Of particular relevance to this proposal is the involvement of Prof Byrne and Dr McKeever in four separate EC proposals funded under FP6 and FP7. These include three projects focused on developing new models and software for studying tumor growth and a Marie Curie Research Training Network (awarded to University of Nottingham where Byrne was based until recently) designed to provide multidisciplinary training to mathematicians and statisticians working at the Life Sciences Interface. **Publications:** 1. H. M. Byrne (2010). Using mathematics to dissect cancer. *Nature Rev Cancer* 10(3): 221-230. 2. M.R. Owen, I.J. Stamper, M. Muthana, G. W. Richardson, J. Dobson, C. E. Lewis, H. M. Byrne (2011): Mathematical modelling predicts synergistic anti-tumor effects of combining a macrophage-based, hypoxia-targeted, gene therapy with chemotherapy, *Cancer Research 71:2826-2837* 3. D. Johnson, J. Cooper and S. McKeever: "Markup Languages for In Silico Oncology", In Proc. 4th Int. Adv. Res. Workshop on In Silico Oncology and Cancer Investigation (4th IARWISOCI). Pages 108-110. September, IEEE (2010).
Staff Members Involved	**Professor Helen Byrne** is an applied mathematician with 20 years' experience of developing and solving continuum and multiscale mathematical models that describe different aspects of solid tumor growth and its treatment. She has a track record of successful collaboration with biologists and experience of participating in and leading large multidisciplinary projects. **Dr Steve McKeever i**s a lecturer in Software Engineering specializing in domain specific languages. Over the last 10 years he has applied techniques from programming language theory to physiological modeling of both the heart and cancer. He has a track record of collaborating with hardware engineers, mathematical modelers and biochemists.

Participant 11	**Università di Torino (UNITO)**
Organisation	The University of Torino is one of the most ancient and prestigious Italian universities. It has about 70,000 students and 4,000 academic, administrative and technical staff. The Medical School is involved with several clinical centers, including the IRCC (Institute for Cancer Research and Treatment).
Main Tasks	UNITO is involved in several work packages. In WP3 "Clinical and Fundamental Science Scenarios) UNITO will provide: • Epidemiological data and effectiveness of standard/innovative therapies to the researcher in order to better focus mathematical models on practical goals • An open database relating the selected pathologies to their natural history and/or diagnostic parameters • Detailed info on therapies. Data will be available from IRCC- Candiol0 (TO), Italy. In WP6 "Models and Hypermodel Design" UNITO will contribute to task 6.4 The prostate cancer paradigm. In WP11 (Clinical Adaptation and Validation)UNITO will be involved in the: • Development of a mathematical model specifically focused on prostate cancer, and aiming at giving a quantitative indication about how safely the ACTIVE SURVEILLANCE strategy may be applied in specific cases. • Quantitative validation of the effectiveness of standardized therapies (mainly radiotherapy, chemotherapy and hormonal therapy) Vs. innovative ones. WP12 (Dissemination and Exploitation) and WP13 (Education and Training): Stages opportunity at IRCC linking modeling activity and experimental/clinical experiences.
Relevant Previous Experience	Experience in modelling tumour growth and therapies is documented in several scientific papers, e.g.: • Tumor growth instability and its implications for chemotherapy, P. Castorina D. Carcò, C. Guiot, T.S. Deisboeck, Cancer research (1538-7445) 69: 8507-15, 2009. • Physical aspects of cancer invasion, C. Guiot, N. Pugno, P.P. Delsanto, T.S. Deisboeck, Phys. Biol (1478-3967) 4: 1-6, 2007. • Growth laws in cancer: implications for radiotherapy, P. Castorina, T.S. Deisboeck, P. Gabriele, C Guiot, Radiation research (0033-7587) 168: 349-56, 2007. • An elastomechanical model of tumor invasion C. Guiot, N. Pugno, P. P. Delsanto, Applied Physics Letters (0003-6951) 89: 233901-3., 2006. • A growth model for multicellular Tumor Spheroids, P.P Delsanto, C.Guiot, P.G. Degiorgis, C.A. Condat, Y. Mansury, T.S. Deisboeck, Applied Physics Letters (0003-6951) 85: 4225-4227, 2004.
Staff Members Involved	**Caterina Guiot PhD** is assistant professor in Applied Physics experienced in modelling growth phenomena and published around 100 scientific papers in the area. **Pietro Gabriele MD** is the Director of the Radiation Therapy division at IRCC, **Elisabetta Garibaldi MD** is a staff member of the Radiation Therapy division at IRCC.

Participant 12	**University of Bern (UBERN)**
Organisation	The Institute of Surgical Technology and Biomechanics at the University of Bern is one of the pioneers and world leading centres in the field of computer-assisted surgery (especially for orthopaedic applications) and a reference site for research on spinal biomechanics. The institute comprises 6 research groups specialised on surgical navigation, medical image analysis, smart surgical instruments, experimental biomechanics, computational bioengineering and tissue mechanobiology.
Main Tasks	UBERN will be responsible for the simulation of cancer biomechanics, including macroscopic level simulation of the tumor, the biomechanical environment and its impact on tumor growth. We will also contribute to tumor imaging and visualization, developing advanced methods for image fusion, segmentation and automatic analysis. Contribution to data repository and IT infrastructure providing web-based access and related tools for basic data visualization, remote database queries and image processing.
Relevant Previous Experience	The ISTB has been active in computer assisted surgery and biomechanics research since its foundation in 1981 and has conducted several studies focused on the development and application of novel numerical methods in order to answer specific practical clinical questions. An important research field focuses on computational biomechanics. Advanced finite element models were developed and used to understand the degenerative processes, to evaluate different surgical reconstruction techniques or to provide pre-operative surgical planning. Experience has been obtained in solving complex contact mechanic problems as well as non-linear material constitutive laws. Another important research area focuses on the development of mathematical laws describing biological evolution. Over the past year, the institute developed competences on the macroscopic modeling of brain tumors. We proposed a macroscopic tumor model relying on biomechanical principles, which was integrated with a discrete entity-discrete event cellular level based simulator. Medical image analysis is also a strong focus of our work. Methodological research has focused on image segmentation and registration on multimodal brain tumor analysis studies, where novel atlas-based and multimodal segmentation techniques have been developed under the framework of the EU FP7 project ContraCancrum. There is also significant experience in building population-based computer models of anatomical and physiological processes, by automatic analysis of image datasets.
Staff Members Involved	**Dr. Philippe Büchler** received his MSc degree in physics from the Swiss Federal Institute of Technology, Lausanne, Switzerland in 1998 and the PhD from the same university in 2002. After working as a research scientist at the Swiss Federal Institute of Technology, he joined the MEM Research Center, University of Bern, and became head of the Computational Bioengineering group in 2006 and received his habilitation (venia docendi) in 2011. His research interests include the application of numerical methods to study skeletal biomechanics, cell metabolic activities in avascular soft tissues as well as the clinical application of biomechanical modeling in ophthalmology, for the treatment of spinal disorders and to predict tumor evolution. **Dr. Mauricio Reyes** has been head of the Medical Image Analysis group at the Institute for Surgical Technology and Biomechanics since 2007. He received his bachelor degree at the University of Santiago de Chile, Chile in 2001. During 2002-2004 he conducted studies to obtain his PhD degree from the University of Nice, France on the topic of lung cancer imaging and breathing compensation in emission tomography. In 2006 he joined the Medical Image Analysis group at the MEM Research Center as a postdoctoral fellow focusing on topics related to medical image analysis and statistical shape models for orthopaedic research.

Participant 13	**Custodix NV (CUSTODIX)**
Organisation	Custodix is a private limited company established in 2000 specialized in data protection solutions for eHealth and is today recognized in the sector as one of the most advanced and reliable Trusted Service Providers (TSPs) providing technical privacy protection solutions. Custodix offers products and services dealing with different aspects of modern (biomedical) data management, e.g. end-to-end solutions for data protection in e-Clinical Trials, disease management and other longitudinal studies. Custodix has an international customer-base including commercial companies and governmental research organizations.
Main Tasks	• Task leader Task 5.2: Security tools and services • Integration of Data Protection and Security Framework in CHIC
Relevant Previous Experience	Custodix has been involved as main security responsible and in some cases architecture responsible in the following EU projects which are (subject-wise) relevant to this proposal: • ACGT - Advancing Clinico Genomic Trials on cancer; FP6; 2006-2010 • p-medicine - From data sharing and integration via VPH models to Personalised Medicine; FP7, 2011-2015 • EURECA - Enabling information re-Use by linking clinical REsearch and Care; FP7, 2012-2015 The following publications demonstrate relevant experience: • BRIDGING THE GAP BETWEEN CLINICAL RESEARCH AND CARE - Approaches to Semantic Interoperability, Security & Privacy, R. Vdovjak, B. Claerhout, A. Bucur, Proceedings HEALTHINF 2012. • Ontology-Based Matching of Security Attributes for Personal Data Access in e-Health, I. Ciuciu, B. Claerhout, L. Schilders, R. Meersman, in Proceedings of OTM Conferences (2). 2011, 605-616. • A Data Protection Framework for Transeuropean genetic research projects, B. Claerhout, N. Forgo, T. Kruegel, M. Arning, G. De Moor (2008), in: De Clercq, E./De Moor, G./Bellon, J./Foulon, M./Van der Lei, J. (Eds.): Collaborative Patient Centred eHealth, Studies in Health Technology and Informatics Volume 141, IOS Press: Amsterdam, Berlin, Oxford, Tokyo, Washington, DC, pp. 67-72.
Staff Members Involved	**Elias Neri** holds a master degree in software development. He has participated in several European (IST) research projects (e.g. FP6 ACGT, FP7 TAS3, FP7 p-medicine), in which his focus has been on security and data protection related research topics. **Wouter Dhaeze** holds a master degree in software development. He has over 6 years of experience as software development consultant. He has joined Custodix in 2010 as a researcher focusing on security and data protection and has become a major contributor to the Custodix de-identification tool suite. He has been actively involved in the FP7 P-Medicine EU Project**.**

Participant 14	**Royal Philips Electronics (PHILIPS)**
Organisation	Royal Philips Electronics of the Netherlands is a diversified Health and Well-being company, focused on improving people's lives through timely innovations. As a world leader in healthcare, lifestyle and lighting, Philips integrates technologies and design into people-centric solutions, based on fundamental customer insights and the brand promise of sense and simplicity. Headquartered in the Netherlands, Philips employs approximately 116,000 employees in more than 60 countries worldwide. The company is a market leader in cardiac care, acute care and home healthcare. **Healthcare Information Management:** The department Healthcare Information Management of Philips Research Europe focuses on Information Management in Clinical Applications and in Home Care environments and on Clinical Decision Support Systems. The two main clinical domains currently addressed are oncology and cardiology, next to generic solutions regarding clinical information systems, information integration, domain modelling, medical imaging, standardization and interoperability.
Main Tasks	Role: Project partner Main tasks in the project: • Contribute to the definition of the architectural design of the CHIC system and the definition of the interfaces among modules to enable interoperability (part of WP5) • Contribute to the definition and implementation of the data management and computational infrastructure required by the CHIC system and to the design of the model repositories and of the interoperable interfaces enabling the management of models and hypermodels (WP10). • Contribute to the elaboration of the exploitation strategy and plan and to the dissemination of the project results. • Contribute to the requirements engineering in WP2.
Relevant Previous Experience	Beside carrying out industrial research projects for Philips Healthcare, the members of the Healthcare Information Management group have participated in and led numerous collaborative projects at National (Dutch-government funding) and European level. Our team has in-depth expertise in data management, information integration, high performance computing and solving computationally intensive problems, cloud computing, semantic interoperability and clinical decision support.
Staff Members Involved	**Anca Bucur** has been with Philips Research Europe since 2003 as senior scientist, and has lead and participated in several industrial research projects in the healthcare domain. She has carried out research projects in Clinical Information Systems, medical imaging, and computational genomics, having as main client Philips Healthcare. She has also led Philips' contribution to the Dutch-funded collaborative VL-e project and to the European FP6 ACGT project, where she was also responsible for the work package —Distributed data access, tools and application. She is currently the coordinator of the FP7 projects INTEGRATE and EURECA. **Richard Vdovjak** holds a PhD in computer science focusing on model-driven distributed ontology-based information systems, from the Technical University of Eindhoven, the Netherlands. He joined Philips Research Europe in 2005 as senior scientist. He has led several research projects dealing with issues related to distributed picture archiving and communication systems (PACS), as well as issues related to semantic interoperability in the context of clinical information systems in the domain of oncology. He was also involved in research on model-driven software development.

Participant 15	**University College London (UCL)**
Organisation	Centre for Health Informatics and MultiProfessional Education (CHIME), CHIME plays leading international roles in research on the design, implementation, evaluation and adoption of electronic health records (EHRs). CHIME has been a key player in successive EU Framework projects since 1992 and is recognised as one of the leading centres of expertise globally in the requirements, information modelling, clinical data specifications and privacy management for EHR. A major success of the department has been establishing and leading the openEHR foundation, a not-for-profit company which exists to promote and publish, via the Web, the formal specification of requirements for electronic health record information, supporting development of open specifications for health information systems. Since its establishment in 2001, it has grown to over 800 members in 80 countries, through Web resources hosted from CHIME. CHIME has led the development of one of the world's cornerstone health informatics standards: for the communication of electronic health records. This standard, which is in practice a series of five inter-related standards, was published as ISO EN 13606 Parts 1-5, between 2008 and 2010..
Main Tasks	Deployment and integration of an ontology-based semantic metadata infrastructure: 1) standardization of CHIC resource metadata, and its semantic interoperability with other metadata repositories in the VPH domain; 2) the provision of tools for metadata annotation and federated storage 3) the application of ontology-based inferencing for the classification and querying of metadata.
Relevant Previous Experience	Relevant EU projects and national initiatives, see below Relevant publications: 1. Wimalaratne, S.M., Grenon, P., Hoehndorf, R., Gkoutos, G.V., de Bono, B. An Infrastructure for Ontology-Based Information Systems in Biomedicine: RICORDO Case Study. Bioinformatics 1;28(3):448-50 (2011) 2. de Bono, B. et. al. The RICORDO approach to semantic interoperability for biomedical data and models: strategy, standards and solutions. BMC Research Notes 4:313 (2011) 3. Hoehndorf, R. et. al. Integrating systems biology models and biomedical ontologies. BMC Syst Biol. 2011 Aug 11;5(1):124
Staff Members Involved	**Dr Bernard de Bono** leads the development of semantic interoperability standards for biomedical resources and the application of ontology-based metadata management based on such standards. de Bono directs the RICORDO VPH project that developed a computational infrastructure for the ontology-based annotation, sharing and inferencing over VPH resource semantic metadata. This infrastructure is now being applied in practical support of interoperability between biomedical resources in a number of settings ranging from a repository framework for the CellML modeling community to a modeling pipeline for an Innovative Medicines Initiative (IMI) consortium of pharmaceutical companies (DDMoRe). **Prof. Dipak Kalra** plays a leading international role in research and development of electronic health record architectures and systems, including the requirements and models needed to ensure the robust long-term preservation of clinical meaning and protection of privacy. Prof. Kalra is a Director of the openEHR Foundation and Vice President for research of the EuroRec Institute. **Prof. Peter V Coveney** holds a Chair in Physical Chemistry, is Director of the Centre for Computational Science (CCS) and the UCL Computational Life and Medical Sciences network (CLMS), and is an Honorary Professor in Computer Science at UCL. Coveney is Chairman of the UK Collaborative Computational Projects (CCP) Steering Panel and is a member of the UK High-End Computing Strategy Committee, for which he chaired a Working Group that produced the new UK High-End Computing Strategic Framework in 2006.

Participant 16	**Consortio Interuniversitario Cineca (CINECA)**
Organisation	CINECA, established in 1969, is a non-profit consortium of 54 Italian Universities, the National Institute of Oceanography and Experimental Geophysics (OGS), the National Research Council (CNR), and the Ministry of Education, University and Research (MIUR). CINECA is the largest Italian supercomputing centre with an HPC environment equipped with cutting-edge technology and highly-qualified personnel which cooperates with researchers in the use of the HPC infrastructure, in both the academic and industrial fields. CINECA's mission is to enable researchers to use HPC systems in a profitable way, exploiting the newest technology advances in HPC. The Supercomputing, Application and Innovation Department in CINECA has a long experience in cooperating with the researchers in parallelising, enabling and scaling up their applications in different computational disciplines, covering engineering, mathematics and bioinformatics, but also "non-traditional" ones, such as biomedicine and data-mining. CINECA has a wide experience in providing education and training in the different fields of parallel computing and computational sciences. Thanks to the recent re-integration of CINECA's former spin-off SCS Srl., which focused on the exploitation of CINECA research results, the group involved in the CHIC project brings extensive commercial expertise to the consortium.
Main Tasks	CINECA will be mainly involved in the development of the hypermodelling infrastructure as part of WP7 and in dissemination and exploitation activities (WP12).
Relevant Previous Experience	The group has a long experience in the development of application for computer-aided medicine based on MAF. It has an excellent track record in participation in research and in development of components related to the VPH. CINECA has acquired several years of experience in EU projects since FP3. In FP7, besides coordinating HPC-Europa2 (www.hpc-eurpa.eu) and HPCWorld, participates in the following projects: PRACE-2IP, 3IP (www.prace-ri.eu), EMI (www.eu-emi.eu), EUDAT (www.eudat.eu), MMM@HPC, VMUST, VERCE, MONTBLANC, DEEP, RISC, EESI2 and some national and regional projects. Through their recently re-integrated spin-off company SCS, CINECA has previous experience in hypermodelling technology development as part of VPHOP and in the leading dissemination activities as part of MSV and VPH-Share projects.
Staff Members Involved	**Debora Testi** has an Electronic Engineering Degree from the University of Bologna (1997) and a PhD in Bioengineering from the University of Bologna (2002). She has published about 20 papers in international peer-reviewed journals. Most of her publications have been related to software for computer-aided software for the pre-operative planning of total hip replacement, and for the prediction of femoral neck fractures in osteoporosis patients. **Matteo Balasso** took his Computer Science degree from the University of Bologna in 2007. After the degree he worked for DataSensor spa in the research and development group on computer vision. From 2008 he is developer of web based application and services.

Participant 17	Technological Educational Institute of Crete (TEI-C)
Organisation	The Biomedical Informatics and eHealth (BMI and eHealth Lab) is a highly innovative and self-contained research unit which resides at the Dept. of Applied Informatics and Multimedia of the Technological Educational Institute of Crete (TEI Crete). The laboratory is strongly involved in R&D in the fields of Biomedical Informatics, Intelligent Health Information systems and Clinical Decision Support Systems. Although a relative young laboratory it has an internationally acknowledged excellence in conducting high quality scientific research and developing innovative Information Technology (IT) applications, products and services.
Main Tasks	WP5 Leader. Within WP5, TEI-C will be responsible for the definition of the CHIC architecture for subsequent implementation and integration. Particular emphasis will be given to the definition of appropriate interfaces among the modules to enable interoperability. TEI-C will also contribute to WP9, Task 9.2: Scalable visualization techniques Task 9.4: Visual Analysis Suites for the model/data repository, as well as in WP12 – Dissemination and Exploitation.
Relevant Previous Experience	Currently the Laboratory consists of 12 people, 3 of which hold a Ph.D. degree and 2 are Ph.D. candidates. A number of diploma theses and graduate thesis are developed per year under the supervision of the academic or other qualified staff of the laboratory. The laboratory is co-ordinated by Prof. Manolis Tsiknakis, who has recently joined the Department. Prof. Tsiknakis – as a principal researcher at FORTH - has an impressive record of state-of-art research at National and European level. He was the scientific coordinator of the ACGT FP6 project, and is a key participant in other relevant FP7 projects, such as p-medicine, EURECA and INTEGRATE. The main areas of expertise of the lab are (a) ontology based integration and analysis of multilevel biomedical data; (b) high performance computational approaches to demanding biomedical applications; and (c) the Semantic interoperability (SIOp) of health information systems.
Staff Members Involved	**Prof. Manolis Tsiknakis** is an Associate professor of Biomedical Informatics and eHealth and Head of the BMI and eHealth lab of the department. He has coordinated many collaborate EU funded research projects, and has been the technical coordinator of a large scale national effort for the development of HYGEIAnet, the regional health information network of Crete. Recently, Dr Tsiknakis has been the scientific coordinator of an EU funded integrated project (ACGT - Advancing Clinico-Genomic Trials on Cancer) focusing on the development of innovative ICT solutions supporting large scale translational research on Cancer. He is also involved in a series of R&D projects in the domain of cancer biomarker discovery and translational medicine. He has been a key note speaker in important IEEE conferences, and also acts as a regular reviewer for a number of scientific journal and conferences. He has been a member of the Advisory Board in several FP6 and FP7 projects. His current research interests are in the areas of biomedical informatics, service oriented architectures, semantic information integration, and service platforms for pervasive eHealth and mHealth service. **Dr Manolis Spanakis**, is a post-doctoral researcher at the BMI lab of TEI-C. His expertise, specialization and research lies in the wider scientific domain of computational medicine and wireless communication networks, and in particular on high performance computing, biomedical informatics; wireless medical sensors; performance and analysis of mobile ad-hoc routing protocols; and wireless network measurements analysis. **Dr Mathaios Pediaditis**, is a Postdoctoral Research Assistant at the BMI lab of TEI-C. His domain of expertise and research interests lie in the areas related to network and IS security, processing and analysis of biomedical signals (e.g. ECG, EMG), images and video and affective computing.

B2.3 Consortium as a whole

B2.3.1. Consortium composition, expertise and complementarities of the CHIC participants

Collaboration is an indispensable prerequisite for any complex and multidisciplinary scientific endeavour. CHIC has recruited 16 leading organizations from 7 European countries and one organization from the USA, based on their outstanding and complementary expertise, in order to develop, verify and demonstrate the proposed solutions and to guarantee maintenance, sustainability and a wide use of the resulting tools and services. All members of the CHIC consortium share the vision and principles of the proposed project, with regards to shared infrastructures, shared data, interdisciplinary team work and focus on innovative cross-discipline research.

The idea for the CHIC project has evolved over a significant period of time, as a result of a) experiences, collaborations and R&D activities from previous or running National and EU projects - like ACGT, ContraCancrum, TUMOR, p-medicine– and b) priorities regarding the urgency to fight cancer and improve current treatment management. Subsequently, a suitable interdisciplinary research team has been built for starting up the project and extending partnership. The team contained relevant basic science researchers (cancer modelers) from ICCS, IT researchers from FORTH (Institute of Computer Science), BED and ICCS, and clinical researchers from USAAR, which worked thoroughly on the formation of the partner selection criteria.

The successful completion of the CHIC workplan and realization of its objectives requires the concurrent presence, and obviously successful collaborative work, of a diverse set of expertise.

More specifically:

1. At the core of the project lies the development of multiscale cancer hyper models. This core activity corresponds well within the skills and expertise of ICCS, UOXF, UPENN, UNITO, FORTH and UBERN. Of course, numerous other outstanding institutions have been lately active in the vast research field of cancer modeling, and could contribute to this endeavor, but formulating a consortium of a manageable size, constituting the initial “critical mass” needed to accomplish the envisaged research, has been considered an important aspect of the whole endeavor.
2. Innovative multi-level data analysis that is very important for models is the core domain of expertise of our partners UBERN, FORTH and BED.
3. An important goal for CHIC is that of translational clinical research advancement through the adoption of cancer models in the clinical practice. The most important criteria for the selection of the clinical partners have been possession and willingness to share and study relevant data, commitment to innovative cross-discipline research, focus on innovative methods for knowledge discovery, as well as adherence to and compliance with legal and ethical issues.
   The relevant expertise of our clinical partner USAAR is unparalleled, while KU Leuven has an international reputation in combining translational and clinical research with optimal patient care.
4. In the modelling infrastructure development activity, the project requires knowledge and expertise in semantic interoperability, markup languages and ontologies-related standards. Our partners USFD and UCL have a proven record of expertise both from their academic achievements and their involvement in projects such as VPHOP, VPH-NoE, and RICORDO. They are also strongly linked and contributors to key standardisation activities, while Marco Viceconti from USFD is one of the key figures in the emerging Virtual Physiological Human (VPH) community and will assist the project in aligning its translational research plan with the wider VPH initiatives. In addition,

our partner CINECA has significant experience in hypermodeling technology development thanks to the hired staff previously working on the hypermodeling technology of VPHOP project, whereas ICCS will build on previous model repository development experience gained in the context of TUMOR project.

5. Another main area in which the project needs to move beyond current state-of-the-art is the domain of service-oriented science and virtualization technologies. Taking into consideration that our ambition is not to define and propose new solutions for the healthcare IT systems or new clinical research systems but to develop bridges that enable the semantic interoperability of these two worlds, and modules/software services that provide added-value to these worlds by making use of existing data collected in either of these domains, the obvious architectural choice is a "service oriented approach". A number of CHIC partners have demonstrable experience in developing state-of-the art SOA compliant solutions in healthcare. PHILIPS, FORTH and CUSTODIX, are such partners.
6. In the Healthcare ICT section, the project requires knowledge and expertise in healthcare information technology, and healthcare related standards. A number of such organisations have been selected with a proven track record of involvement in such R&D activities. PHILIPS, FORTH, UCL, TEI-C USFD and CUSTODIX, have a proven record of healthcare IT development. They are also strongly linked and contributors to key standardisation activities, such as CEN, HL7, IHE.
7. In addition we expect that legal issues, currently unsolved, with respect to the compliance of our proposed solutions in this area with the existing legal regulations and ethical framework of Europe, in particular with respect to "seamless access and analysis" of patient clinical data, need to be addressed by CHIC. In responding to this need, we have brought into our partnership the University of Hannover. They are undisputable experts in scientific research on legal problems of Information and Communication Technologies with application in Healthcare.
8. Closely related to the above legal issues are the obvious data protection solutions required by the project. CUSTODIX specializes in data protection solutions for eHealth and is today recognized in the sector as one of the most advanced and reliable Trusted Service Providers. CUSTODIX has been involved as main security responsible in ACGT, p-medicine and EURECA.
9. Realizing the huge exploitation potential that lies behind the CHIC scientific and technological objectives has also been at the centre of our concerns. In maximizing this potential we have selected specific industrial and commercial partners such as PHILIPS or partners with extensive expertise in these areas, such as CINECA, to undertake this important task. PHILIPS and CINECA consider the CHIC project as a strategic initiative and have concrete exploitation plans.

Figures 2.3.1-a and 2.3.1-b graphically depict the areas of expertise relevant to the CHIC workplan, which are also presented in more detail in the previous section and in Table 2.3a, which clearly highlights their roles and responsibilities within the CHIC framework.

Table 2.3a: Consortium Overview

Participant No.	Participant short name	Type	Country	Expertise	Role in the project
1	ICCS	RES	Greece	In silico oncology. Development of clinically-	Scientific coordinator. Coordination of

				oriented multiscale cancer models. Clinical adaptation and validation of cancer models. Cancer model repository design and development.	models and hypermodel design. Coordination of model and data repositories. Contribution to validation and clinical adaptation; hypermodeling infrastructure; integrated platform; dissemination and exploitation
2	EURICE	SME	Germany	EU RTD Project Management, Exploitation and dissemination	Day-to-day management; communication, website services; dissemination
3	USAAR	HE	Germany	Translational clinical research. Clinical care, clinical trials and clinical research in paediatric oncology. Clinical trial management systems. In silico oncology.	Coordination of user needs and requirements. Coordination of clinical adaptation and validation. Data collection. Contribution to Clinical Translational Science Scenarios. Dissemination and exploitation
4	KU Leuven	HE	Belgium	Clinical care, clinical trials translational and clinical research	Coordination of clinical and fundamental science scenarios; data collection, clinical adaptation and validation
5	BED	HE	UK	Visualisation and modelling solutions	Coordination of visualisation and image processing tasks; contribution to IT architecture and hypermodelling infrastructure
6	USFD	HE	UK	VPH technologies, modelling and simulation of human physiology and diseases	Coordination of the development of ICT hypermodelling infrastructure

7	FORTH	RES	Greece	Post-genomic research and innovative computer methods and tools in the area of medical informatics, ehealth, m-Health, medical imaging and bioinformatics. Biomedical modelling and simulation.	Coordination of IT architecture and integration. Contribution to hypermodeling infrastructure, image processing and visualization, user needs, model and hypermodels design, dissemination and exploitation
8	LUH	HE	Germany	Legal and ethical problems of ICT in the healthcare domain.	Ethics, legislation, privacy and security, legal framework
9	UPENN	HE	USA	Multiscale modelling techniques, computational molecular systems biology	Computational network models, molecular models, development of patient/cohort specific networks
10	UOXF	HE	UK	Multicsale mathematical modelling of solid tumour growth and its treatment	Development of new multiscale and continuum models of early colorectal cancer and vascular tumour growth
11	UNITO	HE	IT	Modelling Tumour Growth	Data provision, development of mathematical models, quantitative validation
12	UBERN	HE	Switzerland	Computer-assisted surgery and biomechanics research, population-based computer models of anatomical and physiological processes	Simulation of cancer biomechanics, tumour imaging and visualisation
13	CUSTODIX	SME	Belgium	Privacy protection and e-security	Ethics, legislation, privacy and security.
14	PHILIPS	IND	Netherlands	Clinical technology, clinical information systems, information integration, domain modelling, medical imaging, standardization and interoperability	Definition of architectural design, and interfaces among modules; definition and implementation of data management and computational infrastructure,

					exploitation strategy, dissemination
15	UCL	HE	UK	Electronic health records, clinical knowledge management	Deployment and integration of an ontology-based semantic metadata infrastructure
16	CINECA	RES	IT	Development of applications for computer-aided medicine	Development of the hypermodelling infrastructure; coordination of dissemination & exploitation activities
17	TEI-C	HE	Greece	Biomedical informatics, intelligent health information systems and clinical decision support systems	CHIC architecture definition for subsequent implementation and integration
[1]Type: **IND**: Industry, **HE**: Secondary and Higher Education Establishment, **RES**: Research Organisation, **SME**: Small or Medium sized Enterprise, **PB**: Non-profit Public Body, **OTH**: All other organisations					

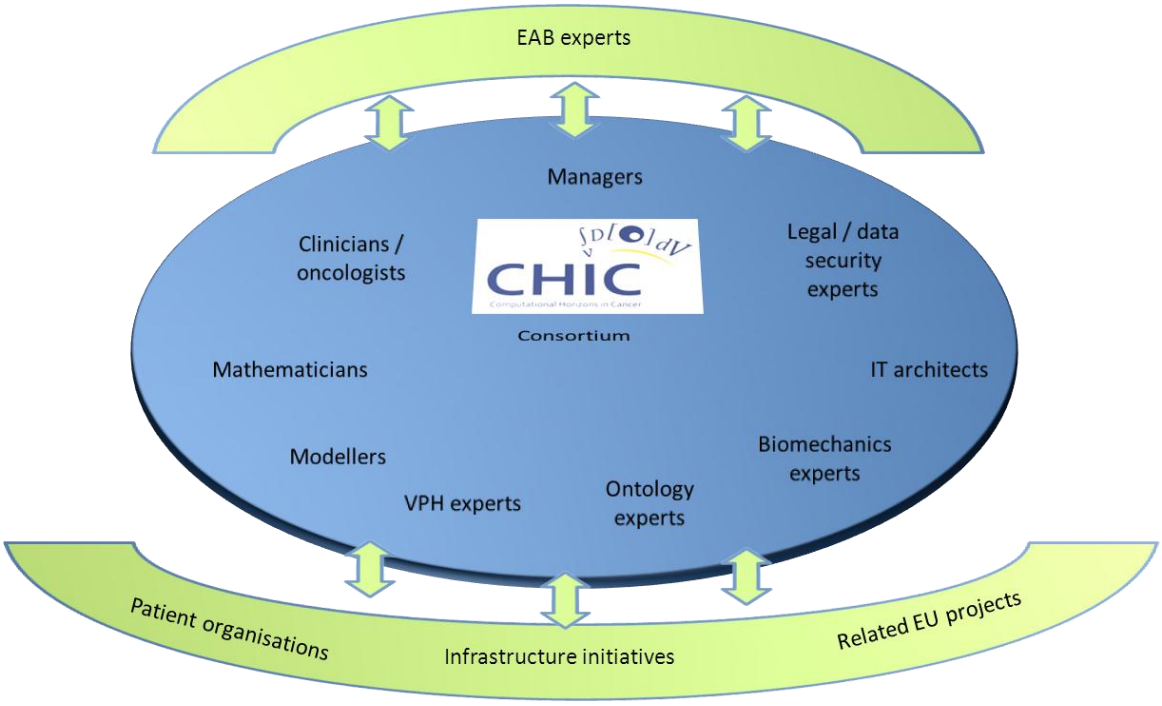


Figure 2.3.1-a Areas of expertise of the various partners relevant to the CHIC workplan

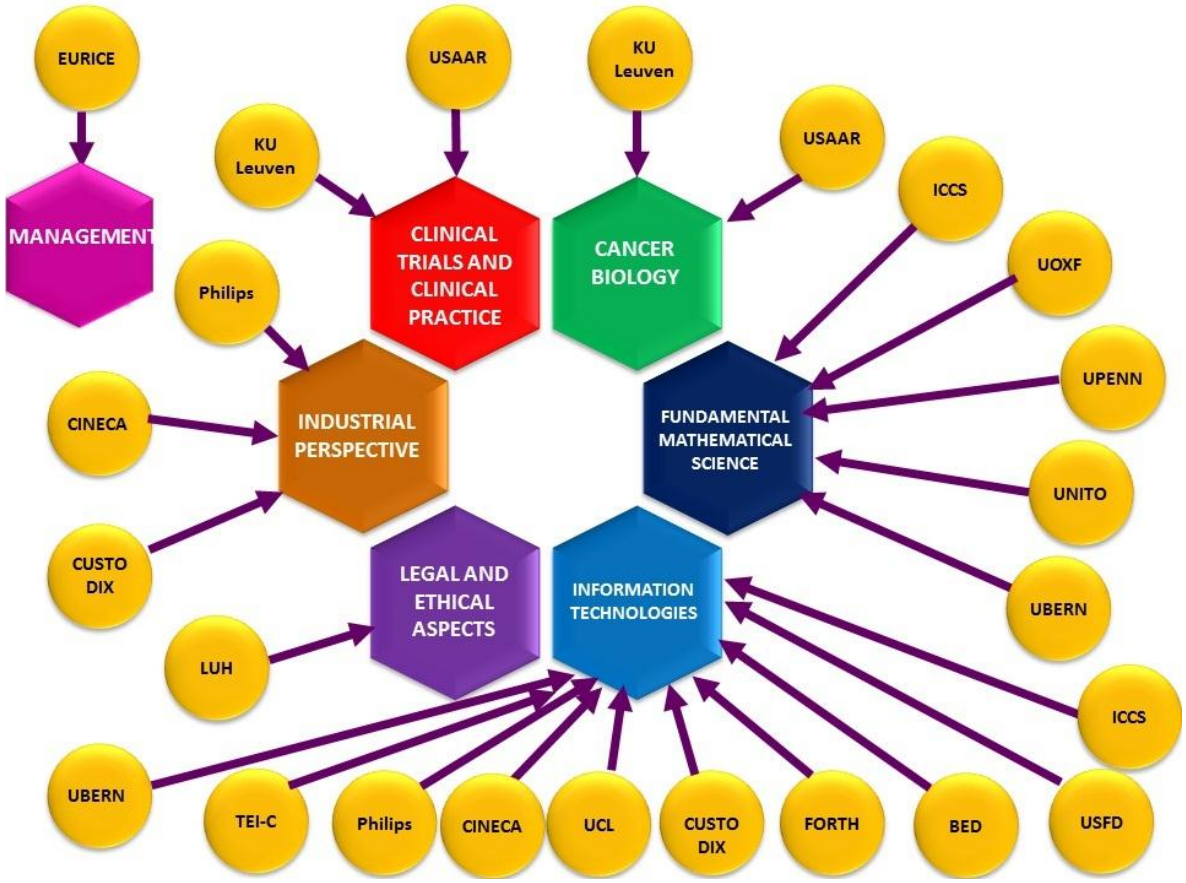


Figure 2.3.1-b Major expertise of the partners that will be brought to and exploited by CHIC. Any given partner may also be involved to a lesser extent in other CHIC domains. In case that the contribution of a given partner in more than one domain is major, the partner appears linked to more than one domain.

At this point a special mention must be made to the **CHIC Coordinator**. In close collaboration with a core group of partners, ICCS has been the driving force in gathering partners possessing the required skills and expertise, for the successful completion of the project. ICCS will have close interaction with all the CHIC partners and provide all the necessary scientific guidance for all work packages to carry out their work and collaborate extensively among themselves. EURICE will carry out the administrative coordination of the project and support the coordinator in the execution of financial tasks, while ensuring all exchanges with the representatives of the European Commission. ICCS and EURICE will have close interaction with all the CHIC-partners and provide the entire necessary framework to carry out their work and collaborate extensively among them. Their past experience in large and complex collaborative projects is a reassurance for the complex endeavour of CHIC.

Another important aspect, which has been taken into account by the CHIC partners, is the **cooperation with partners from the US**. There is a long-standing cooperation between the scientific coordinator and partner UPENN in the cancer modelling research field. UPENN perfectly qualifies to add to the modelling arsenal of the consortium the important dimension of cancer modelling at the molecular level. The already established interaction between the Coordinator and UPENN has been considered as a major asset facilitating the required collaboration. Further **links with US** will be established via the External Advisory Board.

B2.3.2 Linking with major stakeholder groups

Provisions have been made for linking to other pools of expertise and with major stakeholder groups and, thus, relevant expertise. This is ensured by the establishment of the **CHIC External Advisory Board** as well as by further experts, who have expressed their interest in the project (see attached letters of commitment).

The CHIC External Advisory Board will consist of recognised experts as presented in Part B2.1 (please see letters of commitment in the Annex):

- David Ingram, Professor of Health Informatics and Director of the Centre for Health Informatics and Multiprofessional Education (Annex, page 108)
- Metin Akay, Professor of Biomedical Engineering, University of Houston, Texas, USA and IEEE Press Series Editor for the IEEE Press Series in Biomedical Engineering (Annex, page 109)
- Francoise Meunier, Director EORTC (Annex, page 106)
- Trachette Jackson, Professor of Mathematics, University of Michigan, Senior Editor of Cancer Research (Annex, page 107)
- Yuri Nikoslky, Chief Executive Officer, GeneGo (a Thomson Reuters Company , USA (Annex, page 110)

Further clinical and research personalities and organizations, patient organizations as well as **representatives of EU funded projects and infrastructures** have expressed their interest not only in the results of the CHIC project but also to cooperate with CHIC during the project implementation. These are (please see letters of support and commitment in the Annex):

- National Cancer Institute, Division of Cancer Biology, USA (Annex, page 112)
- ECRIN, European Clinical Infrastructures Network, represented by INSERM, France (Annex, page 113)
- Imperial College London, Department of Surgery and Cancer, UK (Annex, page 114)
- Boston University, Department of Biomedical Engineering, USA (Annex, page 115)
- The European Platform for Patients Organisations, Science and Industry, Belgium (Annex, page 116)
- Brainstrust, national brain cancer charity, UK (Annex, page 118)
- International Confederation of Childhood Cancer Parent Organisations, The Netherlands (Annex, page 119)

Links to these organisations, which represent major dissemination targets and channels, have already been or will be established and maintained during the project period using a sophisticated dissemination strategy and tools (see chapter 3.2). Such activities will increase the impact of the project on the one hand and at the same time will help the consortium to refine strategies during implementation.

Of particular note is the statement made by Jennifer Couch, Chief, Structural Biology and Molecular Applications Branch, Division of Cancer Biology, **National Cancer Institute, National Institutes of Health, USA** according to which in case that CHIC is funded there will be new and continuing

opportunities for direct and multifaceted transatlantic interaction and potential for cooperation in the domain of multisacle cancer modelling and *in silico* oncology (Annex, p. 112).

B2.3.3 Consortium member involvement in other relevant EC funded projects and intercontinental initiatives

Members of the CHIC consortium are/were also key participants/co-ordinators in the following VPH related projects funded by the European Commission: p-medicine, ACGT, ContraCancrum, TUMOR. These four projects address the cancer domain in particular. Other highly relevant projects are: VPH-NoE (Virtual physiological human network of excellence), VPH Share, RICORDO (Interoperable anatomy and physiology), EURECA, Integrate, Discipulus (Roadmap for the Digital VPH Patient), Contract (Consent in a Trial and Care Environment). The following table presents highly-relevant projects to CHIC and the corresponding linking partners.

Table 2.3b: EC projects relevant and linked to CHIC through common core partners

Relevant projects to CHIC	CHIC partners linking to relevant related projects	Collaboration and re-usability
ACGT	PHILIPS, LUH, CUSTODIX, FORTH, ICCS, USAAR, TEI-C	CHIC will exploit and further develop several tools developed in ACGT including CAT, ObTIMA, as well as security components and legal/ethical framework components.
CONTRACANCRUM	ICCS, FORTH, USAAR,UBERN, UCL, PHILIPS	CHIC will utilise models and workflows that have been demonstrated in ContraCancrum as well as multimodal image analysis tools.
TUMOR	FORTH, ICCS, USAAR,UOXF	Through the participation of Massachusetts General Hospital (MGH), US in the TUMOR consortium, the establishement of tumour model repository interoperability on a transatlantic level is sought. CHIC, in which a new US partner (UPENN) participates, will further develop the model interoperability architecture developed in TUMOR as well as the initial versions of model repositories.
RICORDO	UCL	CHIC will built upon the RICORDO multiscale ontological framework in support of the Virtual Physiological Human community to improve the interoperability amongst its Data and Modelling resources.
p-medicine	FORTH, ICCS, USAAR, UCL, PHILIPS, LUH, EURICE, CUSTODIX, UOXF	CHIC will work closely with p-medicine in developing a collaborative environment facilitating clinically driven multiscale VPH modelling leading to personalized medicine by exchanging developments and sharing and running VPH simulations for clinical decision support problems. CHIC will utilise the p-medicine data warehouse for the secure storage and sharing of heterogeneous data in order not to dublicate effort in this respect. CHIC will also re-use the p-medicine workbench exploiting the available tools, models, and workflows.
VPH-SHARE	PHILIPS, UCL, CINECA	CHIC aims to offer complementary to VPH-SHARE workflows on cancer modelling and to achieve this it will take into consideration the processes by which VPH share model are formulated, analysed and annotated for integration into workflows that are able to exploit the VPH infostructure. CHIC will also exploit the concepts for a patient avatar as the information representation at the

		centre of a personalised simulation workflow.
INTEGRATE	PHILIPS, FORTH	CHIC will link to INTEGRATE in order to exploit solutions related to its dynamic infrastructure for storing, managing and sharing biomedical data, models, tools, methodologies, and knowledge. Important complementarity to CHIC work will be the standard-based interfaces and services enabling users to store, query and manage heterogeneous multi-scale data, predictive models, annotations and other types of metadata preserved in the repositories.
EURECA	PHILIPS, USAAR, CUSTODIX, FORTH	CHIC will utilise parts of the expected research outcome of EURECA especially regarding linking data, models and information from repositories with clinical care information in the EHR systems and with research data in the clinical trial systems. CHIC will exploit the potential to adopt complementary components such as canonical models of the sources leveraging on existing standards and vocabularies, models describing the data and information in EURECA repositories as well as their semantic interoperability layer.
DISCIPULUS	UCL, USFD	CHIC will strongly interact with the DISCIPULUS project offering its expertise on cancer modelling, in order to develop the vision and sound ICT research agenda around the Digital Patient. To this end, a two way interaction will be set up in order to consolidate the roles that predictive models might play in healthcare in the future.
VPH-NoE	UCL,BED, FORTH	CHIC will exlpoit and enhance at the same time, the VPH ToolKit mainly in the area of cancer predictive models and workflows that in this way, will be disseminated to the wider VPH community. CHIC will also exploit the VPH-NoE channels for interdisciplinary training activities and dissemination.
CONTRACT	LUH, CUSTODIX, USAAR, TEI-C	CHIC will take significant input from CONTRACT relaed to the appropriate legal and ethical framework since CONTACT is expected to shed light on the impact of EU legislation on informed consent (Clinical Trials Directive, Data Protection Directive) on translational research.

Other more broadly relevant research projects in which participants of the consortium are (or have been) involved are: VPH2 (Virtual Pathological Heart), MSV (Multiscale Spatiotemporal Visualization), VPHOP (The osteoporotic Virtual Physiological Human), ENCCA (European Network for Cancer Research in Children and Adolescents), RT3S (Real Time Simulation for Safer vascular Stenting), NMS Physiome (Tools to develop the NeuroMusculoSkeletal Physiome), Aneurist (Integrated Biomedical Informatics for the management of cerebral aneurysms), LHDL (Living human project: Interactive digital library services to access collections of complex biomedical data on the musculo-skeletal apparatus).

In addition, two members of the consortium (ICCS, USAAR) are also participants in the US NCI funded project "**Center for the Development of a Virtual Tumor" (CViT)**[47]. The same members have also participated in the "**1st Transatlantic Workshop on Multiscale Cancer Modeling**"[48,49] co-organized and co-founded by the European Commission and the US National Institutes of Health - National Cancer Institute. Additionally they are contributors to (and co-editor of) the book entitled "**Multiscale Cancer Modeling**", CRC press, ISBN: 9781439814406 that has its roots in the previously mentioned strategic event.

[47] *https://cvit.org/teampages*
[48] *http://ec.europa.eu/information_society/events/ict_bio/2008/ta-cancer-wkshp/index_en.htm*
[49] *http://ec.europa.eu/information_society/events/ict_bio/2008/docs/200811cancer-model-wkshp-report.pdf*

Members of the consortium (ICCS,FORTH) have also been co-organizers of the series of workshops entitled "**International Advanced Research Workshop in In Silico Oncology and Cancer Investigation (IARWISOCI)**"[50] and the "**First Summer School in Computational Oncology"**[51], which took place in Heraklion, Crete, in June 2011 and was co-organized by FORTH. The next IARWISOCI workshop will take place in Athens in September 2012 and is co-funded by the European Commission through the TUMOR project.

B2.3.4 Involvement of SMEs

1. **CUSTODIX:** This Belgian SME has extensive **expertise in data protection**, with a strong emphasis on Privacy Enhancing Technology for medical data collection. Custodix is today recognized in the sector as one of the most advanced and reliable Trusted Service Providers (TSPs) for technical privacy protection solutions. Custodix offers products and services dealing with different aspects of modern (biomedical) data management, e.g. end-to-end solutions for data protection in e-Clinical Trials, disease management and other longitudinal studies. Custodix has been involved as main security responsible and in some cases architecture responsible in the following EU projects which are (subject-wise) relevant to this proposal:
    - ACGT - Advancing Clinico Genomic Trials on cancer; FP6; 2006-2010
    - p-medicine - From data sharing and integration via VPH models to Personalised Medicine; FP7, 2011-2015
    - EURECA - Enabling information re-Use by linking clinical REsearch and Care; FP7, 2012-2015

2. **EURICE:** Eurice is a spin-off company of Saarland University, founded in 2000 in order to assist and consult scientists, researchers and innovative companies in the area of EU research and project management. Today, Eurice is the largest EU project management office with a team of about 35 academic experts with different scientific and non-scientific backgrounds, such as law, medicine, biology, chemistry, communications, information sciences, or computer sciences.

B2.3.5 Other countries

The University of Pennsylvania is a partner of the CHIC consortium. The **cooperation with partners from the US** represents an important aspect, which has been taken into account by the CHIC partners. There is a long-standing cooperation between the scientific coordinator and partner UPENN in the cancer modelling research field. UPENN perfectly qualifies to add to the modelling arsenal of the consortium the important dimension of cancer modelling at the molecular level. The already established interaction between the Coordinator and UPENN has been considered a major asset facilitating the required collaboration. Further **links with US** will be established via the External Advisory Board. It is noted that three members of the External Advisory Committee (see Annex) namely Professor Metin Akay, Professor Trachette Jackson and Dr Yuri Nikolsky are from the United States. Of particular importance is the written commitment of NCI (Structural Biology and Molecular Applications Branch, Division of Cancer Biology) for direct interaction and cooperation (Annex, p. 147). An additional letter of support from Boston University further strengthens the international character of the endeavour.

[50] *http://www.4th-iarwisoci.iccs.ntua.gr/*
[51] *http://computationaloncology.org/*

B2.3.6 Conclusion: The CHIC consortium as a whole

Each CHIC partner has an impressive track record in their respective domains of expertise. The CHIC partner selection criteria, described in the previous sections, have ensured that the full range of skills and expertise required for carrying out the proposed project are available. All partners included in the consortium add enormous value to it. Their expertise and experience is endorsed also by the extensive participation of the members of the consortium in previous EU framework programmes. The extensive partner profiles and the short CVs of the involved key personnel further highlight the outstanding composition of the consortium.

Equally importantly, the ability of the consortium to build cooperative working teams has been confirmed, as most of the partners have successfully collaborated in a number of research projects. This is of critical importance because only high-level collaboration can add a surplus to such ambitious and demanding research projects. The collaborative capacity of the consortium will be further enhanced by the strong leadership of the project by ICCS and EURICE, and the scientific and technical support of the procedure by highly-experienced key personnel in the consortium, such as Prof. Norbert Graf (coordinator of p-medicine), Prof. Manolis Tsiknakis (coordinator of ACGT) and Dr. Kostas Marias (coordinator of ContraCancrum and TUMOR projects).

Concluding, it should be reemphasized that the current highly motivated and committed consortium a) consists of partners with outstanding quality and experience, b) possesses all the required skills and expertise in the highest possible level, and c) demonstrates an impressive record of collaborative and innovative work. It is our strong belief that this consortium will respond successfully to the challenges of the proposed work.

B2.3.7 Sub-contracting

No subcontracts are foreseen within the framework of the technical WPs, but only under the WP Management relating to the issuing of Certificates on the Financial Statements: For partners with an individual amount of requested funding that exceeds the 375.000 Euro limit, compulsory audit certificate costs are accounted for and, if needed, registered under the management activity. The total estimated costs of certificates on the financial statements amount to 64.584€.

B2.3.8 Additional partners

Not applicable to the CHIC project.

B2.3.9 Third Parties

Not applicable to the CHIC project.

B2.4 Resources to be committed

Further to forms A3.1 and A3.2 as presented in SEP, the planned budget distribution by partner and **cost category** for the CHIC project is given in the table below. All budgets listed in this table reflect the estimated costs expected to be incurred in carrying out the project and were calculated according to the accounting principles of the partners, which are subject to formal annual financial audits.

Table 2.4a: CHIC budget distribution by partner and cost category

Partner short name	Personnel	Travel	Durable equipment	Consu-mables	Other direct costs	Subcon-tracting	Indirect costs	Total costs	Requested EC contribution
ICCS	636,000	40,000	5,000	62,000	120,000	6,000	517,800	1,386,800	1,128,800
EURICE	324,500	19,173	0	0	20,000	6,000	275,825	645,498	645,498
USAAR	725,498	47,000	38,764	181,000	60,000	5,682	631,357	1,689,301	1,282,996
KULeuven	340,000	25,000	30,000	52,500	60,000	2,000	304,500	814,000	625,000
BED	484,000	26,000	0	8,000	15,000	5,000	319,800	857,800	659,800
USFD	679,296	28,001	30,000	20,000	0	4,000	454,378	1,215,675	941,825
FORTH	412,800	26,500	33,670	30,000	20,000	6,000	359,136	888,106	688,031
LUH	350,622	25,000	3,000	0	0	3,000	227,172	608,794	474,928
UPENN	391,564	24,982	22,473	4,060	11,986	5,000	282,140	742,206	573,282
UOXF	289,078	50,526	2,774	0	5,884	3,902	208,956	561,120	446,591
UNITO	270,000	25,000	15,000	50,000	10,000	5,000	222,000	597,000	462,998
UBERN	465,000	30,000	0	30,000	0	4,000	315,000	844,000	651,000
CUSTODIX	180,000	28,000	0	5,000	0	0	90,000	303,000	245,375
PHILIPS	398,466	25,000	0	0	0	3,000	592,650	1,019,116	566,120
UCL	497,978	25,000	100,000	36,000	0	6,000	395,387	1,060,364	804,156
CINECA	228,000	29,400	0	25,008	0	0	313,899	596,307	325,560
TEI-C	37,400	10,000	1,900	0	0	0	29,580	78,880	60,040
Totals	**6,710,202**	**484,582**	**282,581**	**503,568**	**322,870**	**64,584**	**5,539,580**	**13,907,967**	**10,582,000**
% of total	**48,25%**	**3,48%**	**2,03%**	**3,62%**	**2,32%**	**0,46%**	**39,83%**	**100,00%**	

Travel (approx. 3,5%): Travel costs will be used to finance the following meetings:

- 13 general project meetings (kick-off, two progress meetings a year and review meetings);
- An appropriate number of WP meetings as well as visits to partner sites
- the participation of partners in selected and highly relevant conferences to present the project and its results (mainly in year 3 and 4);

Wherever possible, the partners will strive to make use of tele- or videoconferences and try to combine conference participation and meetings. Part of the travel costs will be needed to organise the integration and validation of tools and services, which requires the attendance of several partners over a period of several days.

Durable equipment (approx. 2%): several partners need to purchase laptops, servers as well as infrastructure-related hardware, such as a GPU enhanced compute cluster for executing simulations. In WP3 sequencing tasks require the acquisition of an automated slide handling system, whose costs will amount to approx. 25000€.

Consumables (approx. 3,6%): Consumable costs can be divided into three main groups corresponding to main project activities:

- IT and modelling activities: purchase of software and licenses, fees for the use of computing facilities and server infrastructure
- Materials related to clinical work and data provision: It is envisaged to collect and analyse data from 300 patients, which requires the purchase of material related to DNA sequencing, molecular analysis of tumours, lab materials, chemicals.
- Materials related to production of dissemination and training materials (Dissemination kit), materials related to the organisation of workshops and summer schools

Other direct costs (approx. 2,3%): 75.000€ have been allocated to the coordinator's budget to finance expenses of the Advisory Board members and an Ethical Committee that might be established (see

further information in Chapter 4.4); 40.000€ for the organisation of the summer schools to be organised within the framework of WP12; ICCS reserves 35.000€ for the organisation of the planned workshop. Further 120000€ are allocated to clinical partners USAAR and KU Leuven for data collection, analyses and provision. In addition, partners have included in their budgets costs for publications and innovation-related activities.

Personnel costs: The main part of the costs will be personnel costs used to finance 1.177 person months. The distribution of person months and percentage of the total workload is shown in the following diagram:

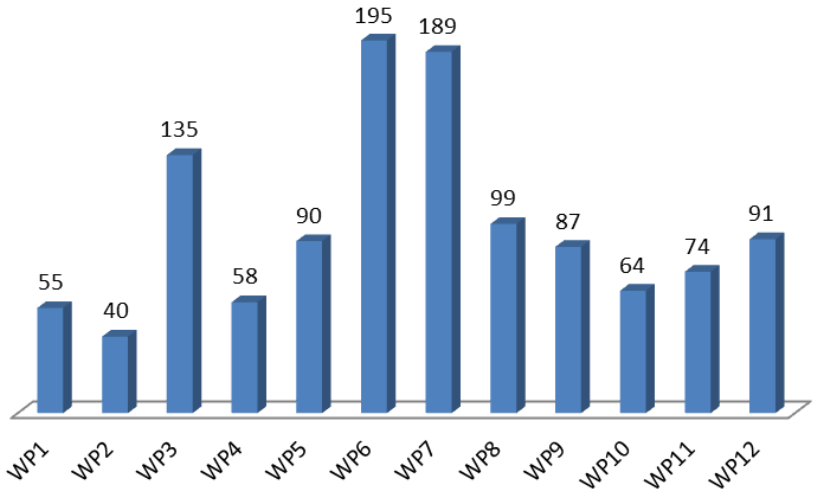
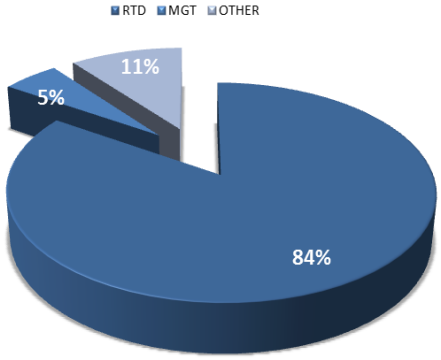


Figure 2.4.1-a CHIC workload in different WPs (number of person months)

The work packages 6, "Cancer model and Hypermodel Design", as well as WP7, "Hypermodelling infrastructure", represent the core work packages of the project and, thus, require the highest workloads.
It should be noted that WP1, "Management", efforts do not include the efforts needed for the technical and scientific coordination of the planned RTD activities. Such efforts are included in the RTD work packages as stipulated by the FP7 financial regime.
The consortium will invest considerable resources in WP12 (Dissemination, Training and Exploitation). Corresponding plans are outlined in Chapter 3.2. Costs in this WP will also comprise costs of the members of the External Advisory Board and workshop organisation costs.

Resources in different activity types



RTD activities (WP2 – WP11) represent the largest share in the overall activities and consequently make up for the largest part of the total budget (84%); 5% of costs will be used to efficiently manage the project (WP1). The activity "Other" (11% of total costs), to carried out under WP12, comprises considerable efforts on dissemination, training and exploitation activities, which are considered essential to obtain the objectives of the project.

Resource efficiency through use of synergies

The CHIC project will continuously follow up existing synergies with related projects. The partners will promote synergies between CHIC and other running EU projects as well as nationally funded projects wherever possible. The contacts between these projects will prevent redundant work and guarantee the effective use of the CHIC financial resources.
Subcontracting – please refer to chapter B2.3

B3 Impact

B3.1 Strategic Impact

B3.1.1 Contribution to expected impact

B3.1.1.1 More predictive, individualised, effective and safer healthcare

The most recent genomic and post-genomic studies suggest that every cancer is different in very many substantial ways, which is why almost no cancer type responds equally well to a treatment in each patient. So if there is a clinical domain where individualised medicine is mandatory, this is oncology.

The biggest barrier to a complete individualisation of diagnosis, prognosis, and treatment planning is that the vast majority of complex diseases are systemic in nature, involve multiple organ systems at multiple space-time scales, and require multiple bodies of knowledge (clinical, biological, biophysical, etc.) to be properly investigated. In other words, it is too much for any single individual no matter how skilled he or she can be. It is from this analysis that the prime motivation for the whole VPH initiative stemmed: information technology can be developed that makes possible to capture into predictive models disparate knowledge produced by different experts, and then compose these models into integrative models capable of predicting such complex systemic interaction, and ultimately provide a predictive and individualised decision support for any clinical activity.

So far this vision has been interpreted primarily as small groups collaboration. In each project funded by the VPH initiative a relative small group of experts (typically between 5 and 20) developed a complex integrative model tackling a specific disease. What CHIC aims is a quantum leap: we want to develop a hypermodelling environment where hundreds of experts can contribute with their portions of knowledge, compose their knowledge with that of the others, and slowly develop extremely sophisticated integrative models of cancer. **We claim this is the core goal of the VPH agenda**.

Multiscale hypermodels that are validated based on experimentation and clinical trials will have a profound impact in rationally optimizing conventional and targeted therapy protocols. In particular, the cost as well as the time to arrive at an optimal clinical protocol for therapy can be significantly reduced, thereby positively impacting the precision of therapy regimens as well as improving the quality of life for patients.

Hypermodels can also serve to significantly reduce human errors in choosing various options in personalized medicine, as we enter a data rich path for diagnosis and treatment. Realistic hypermodels can lead to more refined decision trees for disease.

CHIC is expected to have a crucial impact on the emergent discipline of *in silico* oncology and in the future in the real clinical domain. The technology to be developed by CHIC will be generic in nature, but the application target will be oncology. The prediction of the response of tumours and normal tissues to treatment dictates an efficient combination of a host of advanced models focusing on different aspects of the natural phenomenon of cancer (biochemical, biophysical, biomechanical etc.) so as to realistically simulate the spatiotemporal course of the expected tumour response to treatment. Simulation hypemodels are envisaged to be used as treatment optimizers through conducting patient individualized experiments *in silico* (=on the computer) via hypermodel oncosimulators. Following their strict prospective clinical validation, such elaborate hypermodels are expected to significantly contribute to the improvement of cancer treatment outcome by avoiding unnecessary treatment.

Realistic large scale hypermodelling is expected to have a significant effect of the reduction of costs for healthcare. It is anticipated that a better stratification of treatment and enhanced targeting of drugs for patients with cancer will be made possible in the future through the utilization of validated complex hypermodels. Such expectedly realistic entities will have an impact on the occurrence of serious late effects, such as kidney failure followed by kidney transplantation, cardiomyopathy with subsequent

need for heart transplantation, rehabilitation programmes, which will ultimately lead to a reduction in medical consumption and costs. Furthermore, preventing more relapses in cancer patients would save costs for relapse treatment that is more expensive than initial correct and best treatment options.

VPH hypermodels are also anticipated to foster and improve translational medicine through the development of future clinical trials. Through the collaboration with other European Commission funded projects such as p-medicine, TUMOR, VPH-Share and others, harmonised and standardized approaches in the VPH domain will be exploited and further developed. Through this cooperation a common approach to translational medicine will be promoted and will further contribute to the standardization of VPH projects. Such collaborations will enhance the development of future clinicogenomic trials in the domain of cancer and beyond.

There is a widening knowledge gap between the care provided in top clinical sites and community care sites, resulting in large differences in treatments and outcomes. The need to bring the latest therapy options to each and every hospital must be addressed before being able to significantly reduce the numbers of patients that receive suboptimal treatment, or the wrong treatment. Validated models are an important source of input for clinical decision support systems and would facilitate the development of future-proof and scalable tools that can easily incorporate new knowledge and can be updated with the latest validated research results.

Smart use of clouds, which are highly distributed, scalable and virtualized environments that offer availability, accessibility and sharing of data at low cost, have the potential to increase efficiency and effectiveness of care, reduce costs, and improve sharing of data, collaboration and knowledge dissemination.

B3.1.1.2 Reinforced leadership of European industry and strengthened multidisciplinary research excellence in supporting innovative medical care

European industry is faced with significant pressure to reduce costs and improve efficiency in order to stay competitive in today's markets. This is also true of course for healthcare informatics where the costs of development, deployment and maintenance of solutions need to be strongly controlled. At the same time, the volume and variety of data collected for a patient in the context of care and the amount of clinical knowledge that needs to be accessed has increased tremendously and new knowledge becomes available at a rapid pace. In this context, solutions that rely on models that are scalable and build by making use of widely adopted standards have a significant advantage. Additionally, the use of new technologies such as cloud computing enables applications to be run remotely reducing the cost of deployment and maintenance. Clouds also offer cost-effective and efficient use of resources, instead of being responsible for maintaining own hardware repositories.

Our partner CINECA will provide the commercial expertise to help maintaining a supported version of the hypermodelling environment that can be deployed on a commercial basis to organizations that need to have an hypermodelling facility not publicly available (i.e. within hospitals, or in healthcare industries in relation to products development).

Other organizations might deploy internally a version of the hypermodelling technology to be used for internal research or to provide consulting and/or on-demand simulation services to hospitals, clinical research organizations, and industries.

The CHIC project will have an impact on the further development of the VPH initiative as it transits towards its second stage of maturity, the vision of the so-called ***in silico*** **medicine** that will be the primary target of Horizon 2020. CHIC already includes some elements in its design that anticipate this vision, and will provide a test bed for some of the most challenging concepts.

B3.1.1.3 Improved interoperability of biomedical information and knowledge

The VPH hypermodelling environment that will be developed in CHIC, starting from an advanced prototype developed in the VPHOP project, will expose by the end of the CHIC project a set of features so advanced and sophisticated to be easily identified as the **leading solution worldwide** for this specific problem.

The improved interoperability and adherence to the established standards in the identified areas is an essential prerequisite for successful commercial deployment of healthcare informatics solutions such as clinical decision support systems. In the absence of an interoperability solution, any deployment may require significant effort with customization and interfacing to each hospital's infrastructure. Building complex models and aggregating valuable clinical datasets to be accessed and used at a global scale would provide large benefits in terms of the cost-effective and efficient use of resources.

B3.1.1.4 Increased acceptance and use of realistic and validated models that allow researchers from different disciplines to exploit, share resources and develop new knowledge

The primary impact of the CHIC project will be in the realization of a generic distributed and collaborative hypermodelling environment, which will make possible for researchers working on different aspects of a clinically relevant problem, with different backgrounds, and observing the phenomenon at different space-time scales, to compose their efforts into a systemic representation of the human body capable of predicting very complex systemic interactions so important in many diseases including cancer.

At the end of the CHIC implementation the hypermodelling environment should be deployed as a service infrastructure to serve the VPH research community worldwide. Initially the portfolio of modeling components will include primarily musculoskeletal and oncological resources, as a legacy of the parent projects, but we expect that it will quickly expand to all other VPH research domains, because of its neutrality and generality.

B3.1.1.5 Accessibility to existing knowledge by bio-medical researchers through the VPH repositories linking data with models will prove the large scale benefits of having both the data and models readily available.

The repositories, the hypermodelling editor, the hypermodel execution framework, the semantic annotation, image processing, visualization and software execution tools and services to be developed by CHIC within a security framework in an open access setting are expected to much facilitate the reuse of existing models and the hypemodels to de developed.

B3.1.2 Steps to bring about the impact

Expected Impact	Steps to bring about this impact
More predictive, individualised, effective and safer healthcare	Development of the CHIC hypermodels and oncosimulators driven by the CHIC clinical studies. The hypermodels will be clinically adapted and partially clinically validated using data from the same studies (WP6 in collaboration with WP3 and WP11).
Reinforced leadership of European industry and strengthened multidisciplinary	The hypermodelling infrastructure to be developed (WP7 in collaboration with the rest of the workpackages) is to be exploitable by the European industry active in innovative clinical care. The three industrial partners of CHIC are interested in exploring the possibility for integrating it into their

research excellence in supporting innovative medical care	main products and services in order to be better positioned in the personalized and highly sophisticated era of medicine. The hypermodelling infrastructure will have primarily a long-term sustainability problem to be addressed after the end of CHIC. One possibility is to transfer the operations to the VPH Institute that would leverage on internal funding from its members, external funding from various agencies and charities, and pay-per-use contracts with the various VPH research consortia, to sustain it. The commercial exploitation will require a solid business model. One good candidate is that used in other complex software frameworks, where the framework in itself is distributed freely as an open source project, but the company sells the support and consulting for industrial quality deployments of the framework. This approach would be compatible with the development of other business opportunities for consultants and on-demand simulation services. The two types of business would not be in competition, but on the contrary that could slowly form a business environment where industries and healthcare organizations buy a deployed and supported infrastructure to run their hypermodels, and hire consultants to develop new models, or deal with workload exceeding the internal manpower.
Improved interoperability of biomedical information and knowledge	The proposed ontological annotation of models and data essentially based on the previous RICORDO project and the standardization of the VPH hypermodel development process are key steps to bring about improved interoperability of biomedical information and knowledge within the CHIC framework (WP7).
Increased acceptance and use of realistic and validated models that allow researchers from different disciplines to exploit, share resources and develop new knowledge	As a first step the consortium clinicians in collaboration with the consortium cancer modellers will define the requirements for the hypermodels to be developed, tested, clinically adapted and partially retrospectively validated (WP2). An IT infrastructure will be set up to allow sharing patient data and provide computational resources to develop the hypermodels (WP5, WP7, WP8, WP9, WP10). Based on the final outcome of the CHIC project (WP11) a prospective clinical trial aiming at clinically validating cancer hypernodels could be implemented but this lies beyond the CHIC timeframe. Transferring the technology developments to the industrial partners will facilitate the involvement of industry in the process of translating multiscale hypermodeling and *in silico* oncology/medicine to the clinic. The composition of the CHIC consortium perfectly matches this translational scenario since they represent information technology (IT), fundamental mathematical science, biology, clinics, industry and biomedical and IT legislation (WP4).
Accessibility to existing knowledge by bio-medical researchers through the VPH repositories linking data with models will prove the large scale benefits of having both the data and models readily available.	The development of a hypermodel repository, a hypermodelling driven clinical data repository, a distributed metadata repository and an *in silico* trial repository for the storage of executed simulation scenarios (WP8) within a semantically annotated clinical environment (WP3, WP11) will serve as an ideal demonstrator of the benefits of having both the data and (hyper) models readily available.

B3.1.3 Why a European (rather than a national or local) approach is needed

The scale of ambition involved is huge, and only at the European level it is imaginable to find the level of excellence required.

Also, any exploitation scenario will be targeting niche markets, and businesses will be profitable only if operated on the global market.

B3.1.4 Interaction with other national or international research activities

The hypermodelling technology we plan to develop in CHC is accumulative in nature, so it will be naturally develop with contributions from research groups spread all over the world. Also, national research initiatives within member states will of course leverage on the existence of this European technological infrastructure.

The CHIC consortium and its partners are historically at the centre of a network of international relationships that will be continued and expanded during this project. The hypermodelling technology will be developed keeping a close watch on other European and international initiatives that can strengthen or complement it, first of all those emerging form the two VPH infostructure projects, VPH-Share and p-medicine.

Detailed information on the interaction with other research projects is provided in Section 2.3.3. Of particular importance is the interaction of CHIC with the transatlantic project TUMOR (Transatlantic Tumour Model Repositories) whose all EU partners are also CHIC partners. Since an US partner (UPENN) is also a member of the CHIC consortium, the efforts for transatlantic interoperability of models and repositories will be intensified. Additionally the US National Cancer Institute (NCI-NIH) has expressed their interest to interact and collaborate with the CHIC consortium (see letter of support in the Annex)

The technologies and outcomes of the VPHOP, RICORDO and Physiomespace will be used as a basis on which CHIC will be deployed. Moreover, the database system provided within the CHIC project will be linked to exiting cancer databases of other projects such as ContraCancum and p-medicine. Collaboration with the Swiss National Centre of Competence in Research (NCCR) Co-Me regarding data storage activities will be established via the Swiss partners of the CHIC consortium.

B3.1.5 Assumptions and external factors that may determine whether the impacts will be achieved

The primary assumption is that VPH research and its clinical and industrial applications will expand in the next few years. VPH research started in 2006 and in only six years has raised roughly €200m of direct funding at the European level with dozens of running projects which we estimate involve at least 2000 researchers in Europe from both public and private organizations. Given that there is a clear development roadmap for the VPH vision which suggests that it will be extensively adopted in the next framework programme Horizon 2020 we think that this assumption is reasonable.

B3.2 Plan for the use and dissemination of foreground

CHIC will put a significant effort to disseminate its achievements and cancer modelling technology in order to maximise early clinical adoption and attract other modelling researchers to participate in the CHIC cancer modelling paradigm. To achieve this, a careful dissemination and exploitation plan will be central to the project targeting primarily the relevant scientific and clinical communities. Further, since industrial exploitation of CHIC's results is also an important step towards adoption, European industry is another important target group. Last, it is important to stress that the hypermodelling approach planned in CHIC requires a very detailed and careful plan concerning the management of the intellectual property and the joint intellectual property that will be the result of the combination/unification of models under the CHIC guidelines.

B3.2.1 Dissemination strategy

The following sections reflect the plan of the consortium decisions on creating an effective project dissemination strategy concerning: (1) the dissemination targets and objectives, (2) the CHIC dissemination target groups, (3) the dissemination methods, tools and activities, and (4) the dissemination plan and consortium responsibilities.

(1) Dissemination targets and objectives: The overall target of the CHIC dissemination strategy is to spread information about CHIC results to specific target groups for dissemination actions that are directly or indirectly related to the cancer modelling and its clinical translation, as well as the modelling community as a whole, since a number of the ICT technologies/end results developed/achieved in CHIC will be of general use for any VPH research on cancer.
The main goals related to the dissemination of CHIC include a) the dissemination of its objectives, its approaches and results, b) the exchange information with other initiatives and projects relevant for tumour modelling, c) the promotion of the use of tools and methods created by CHIC in clinical practice, d) the establishment of communication with stakeholders, clinicians, industry, and academic groups for dissemination of CHIC results and e) the interaction with the industry. More specifically, the CHIC consortium plans to disseminate information concerning:

- Applications of new technologies for analysis of complex, multi-source data in oncology for modelling,
- Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology,
- Meta- and Hyper-Multiscale workflow execution software environment,
- Strategies for optimisation of cancer treatment and for enhancement of prognosis of patients suffering from cancer as a whole
- Clinical translation and wider adoption of models and hypermodels
- The use of the models/hypermodels and the associated tools as a decision support mechanism for optimising individualised cancer treatment

To achieve a significant dissemination of the above the consortium will a) create and/or formalise tools for a continued flow of information from the project consortium to the main stakeholder groups, b) ensure a considerable impact of the project within targeted communities through establishment of links with various stakeholder networks, and c) increase and maintain the stakeholders' interest in the project results in terms of awareness, understanding and action.

(2) Target groups: The consortium has identified a number of stakeholder groups who will be continuously informed about the progress, as well as intermediate and final results of the project, using a wide range of different tools as described later in this section. The identification of the target groups was based on the type of the stakeholders' involvement in the project (internal, external and connected). Consequently, three stakeholder groups have been identified as shown in the following figure:

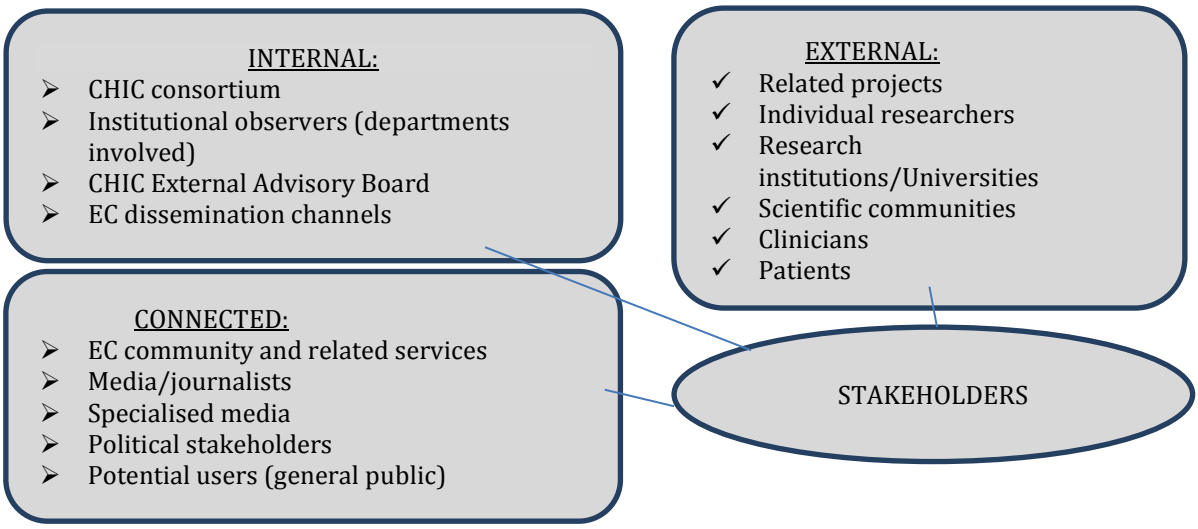


Fig.3.2.1-a CHIC stakeholder groups

An analytical description of the stakeholder group will be reported in D12.1: "Dissemination Plan". However it is worth mentioning that **CHIC has already started developing an international dissemination network** (see the letters of support in the Annex) through the collaboration with a number of high impact organisations including:

- National Cancer Institute, Division of Cancer Biology
- European Clinical Research Infrastructures Network (ECRIN)
- The European Platform for Patients Organisations Science & Industry (EPPOSI)
- The Meg Jones Crain Cancer charity (brainstrust)
- International Confederation of Childhood Cancer Patient Organisation
- IEEE

This network will form a unique opportunity to promote the goal of dissemination of the cancer modelling achievements to the wider cancer community, in order to enhance awareness and accelerate clinical translation and adoption.

Last, it is important to stress that industry is a crucial target for dissemination from the CHIC perspective. Since CHIC's results can be implemented in software especially as part of decision support systems, the medical informatics industry will be the first to be targeted. PHILIPS being the main industrial partner of CHIC will assess these possibilities and guide the whole consortium towards the industry needs from the very beginning of the project.

(3) Dissemination methods, tools and activities: These dissemination types have become the main reference for classifying the identified stakeholder groups (as shown in the paragraph below) and for choosing dissemination methods, tools and activities within the project while considering the following issues: A range of different dissemination tools will be used to ensure the highest visibility of the project progress and its results. The dissemination tools can be grouped according to the type of dissemination activities they are used for, as is shown in the following table:

Table 3.2a Overview of CHIC dissemination tools and activities

Type of activity	Dissemination tool
Oral dissemination	Presentation on external scientific conferences/exhibitions/ workshops, project conference, summer schools/ workshop/meeting/briefing, report, face-to-face communication
E-based oral dissemination	Webinar, E-based consultancies, online video tutorials
Paper-based written	Report, scientific article/paper, set of promotional materials (fact

dissemination	sheet, flyer, leaflet, brochure, posters, roll outs), information package
E-based written dissemination (e-newsletters)	Project website, links to other websites, E-newsletter, mailing list, E-bulletin, E-form of a set of promotional materials, information database
Dissemination via mass media	Press-release, interview, panel discussion, project video

(4) Dissemination plan and consortium responsibilities: According to the dissemination types described above, the identified stakeholders have been classified into three main target groups. A special set of appropriate dissemination methods/tools and benefits from the dissemination activities to be applied are summed up in the table below. Moreover, the table contains information on planned CHIC partners' contributions as well as on possible dissemination channels. The implementation dates as far as can be planned at this stage of the proposal are outlined in WP12. The Project Management Team will set up actual implementation dates on the occasion of the Kick-Off-Meeting of the project and update them every 12 months in order to provide the project with a reasonable and achievable dissemination programme.

Table3.2b CHIC Dissemination plan and consortium responsibilities

Target group	Tools	Channel/network/ project/body	CHIC partner in charge
Political stakeholders	*Online:* webinar E-bulletin, presentation, consultancy, promo-materials, website, panel discussion,	Patient organisations	USAAR, KU Leuven
General public			
European Commission	Online: E-bulletin, info-package, website, project video, Face-to-face: EC organised meetings Written: report, factsheet, newsletter		Project Management Team, Diverse
Institutional observers (departments involved)	Online: website, project video face-to-face: presentation, consultancy, Written: reports, newsletter		All partners
Users and end users			
Patients	*face-to-face*: presentation, workshop, set of oncological conferences[52], CHIC summer school *online:* webinar, consultancy, promo-materials, info-package, website, e-links, e-newsletter, mailing list, *written:* peer-reviewed publications; Scientific journals[53] and clinical journals[54]	Patient organisations	USAAR, KU Leuven
Clinicians		e.g. CIRM, ISS, INSERM, SCReN, AEMPS, EORTC, MRC, KKS, ECRIN: e.g. Vinnova, TEKES, EFGCP, TMF e.V.	USAAR, KU Leuven
Scientific communities			
VPH technology	*Online:* website, e-links, E-newsletter, mailing list, webinar, promo-materials, info-package, project video *written:* peer-reviewed publications; Scientific journals *Face-to-face*: workshops, CHIC	VPH NoE; VPH-Share, Biomed Town	USFD, UCL, ICCS, FORTH, BED, UOXF, CINECA, TEI-C
Healthcare ICT			PHILIPS, FORTH, UCL, BED, USFD, CUSTODIX,

[52] *E.g. Congresses and conferences of the European Cancer Organization (ECCO); Annual SIOP Conferences; Conferences of the American Society of Clinical Oncology (ASCO) in North America; International Breast Cancer Conferences; Meetings of I-BFM, Annual meeting of the UK's National Cancer Research Institute*

[53] *E.g. International Journal of Radiation Oncology Biology Physics; Cancer Informatics; Journal of Theoretical Biology; Methods of Information in Medicine; Computers in Biology and Medicine, Plos One, IEEE Transactions on Biomedical Engineering, Multiscale Modeling Simulation, Journal of Theoretical Biology*

[54] *E.g. Cancer Research; Journal of Clinical Oncology; Pediatric Blood & Cancer; Blood*

	summer school, contributions to international scientific conferences		CINECA, TEI-C
Mathematical modelling		TUMOR	ICCS, UPENN, UOXF,UNITO, UBERN
Clinical Research Systems		ESFRI	USAAR, FORTH
Clinical research		KKS, EATRIS	USAAR, UOXF, KU Leuven
Oncology		GPOH, SIOP, COG, EORTC,	USAAR, KU Leuven
ICT Legal & ethical aspects, data protection		CDP	LUH, CUSTODIX
Biobanking		BBMRI; BIOMEDBRIDGES	USAAR, ICCS, UCL
Ontologies			USAAR, UCL

Central to the dissemination plan is the envisaged organisation of a scientific workshop on topics related to CHIC. The workshop will be part a series of workshops under the title International Advanced Research Workshop on *In Silico* Oncology and Cancer Investigation. The previous workshop took place in Athens on September 8-9,2010 and was hosted by ICCS. Apart from the sponsoring of the European Commission Directorate-General for Information Society and Media Virtual Physiological Human initiative, the workshop was also endorsed by the International Federation for Medical and Biological Engineering (IFMBE) and technically co-sponsored by the Institute of Electrical and Electronics Engineers (IEEE), Engineering in Medicine and Biology Society (EMBS) (for more information see http://www.4thiarwisoci.iccs.ntua.gr/index.html).

B3.2.2 Exploitation strategy

In terms of exploitation strategy, we can distinguish between internal and external exploitation. Internally, all partners will use all project outputs to a major or minor extent in their sub-sequent development activities. Externally, the major impact will be made by the shared and global project results following the industrial guidance provided by PHILIPS and the commercial expertise provided by CINECA. However, the achieved results can be exploited also independently.

In general, CHIC proposes the development of clinical trial driven tools, services and infrastructure that will support the creation of multiscale cancer hypermodels (integrative models). CHIC aspires to make a breakthrough in multiscale cancer modelling through greatly facilitating multi-modeller cancer hypermodelling and its clinical adaptation and validation. Standardization of model description and model "fusion" will be two of the core means to achieve this goal. The creation of such elaborate and refined hypermodels is expected to sharply accelerate the clinical translation of multiscale cancer models and oncosimulators following their prospective clinical validation (*in silico* oncology). Addressing intellectual property issues in multi modeller modelling will foster the community spirit in the VPH domain.

Even if the complete exploitation strategy both at project and partner level will be defined as soon as the first CHIC results will be available, some individual partners have already identified possible exploitation plans, which are here presented:

ICCS is very much interested in all three aspects of hypermodelling, hypermodelling infrastructure and *in silico* oncology, i.e. basic science, engineering and clinics, and therefore the process of coordinating CHIC and participating in most of the CHIC activities including the development of hypermodel oncosimulators will be an excellent opportunity for it to capitalize on the extremely fruitful interactions among the members of the consortium.

USAAR who is a clinical partner of the consortium is committed to the advancement of *in silico* oncology through the ab initio clinical orientation and thorough clinical validation of the simulators. Therefore, following clinical validation/optimization, it will make a multifaceted exploitation of both the CHIC end results/product and the process of its implementation. Its plans are to use the CHIC platform as a clinical decision support and treatment planning system, an educational tool and a research environment.

FORTH contributes to the economic, social and technological development in Greece and is therefore interested to exploit the results of the project and disseminate VPH research culture in Greece. In this effort, FORTH-ICS will place special emphasis on education and training related to the outcome of the project, by providing a significant number of scholarships to undergraduate and postgraduate students and by training numerous professionals in cancer modelling technologies.

UCL will collaborate closely with the VPH Network of Excellence and RICORDO projects to ensure that software and tools developed in this project are disseminated through the VPH NoE toolkit. It is also planned to use several toolkit components in UCL's technical infrastructure. We will also use the compute allocations provided by the NoE to gain access to the DEISA (which will become PRACE) and EGEE (which will become EGI) computing platforms.

USFD considers a number of possible scenarios, with respect to the end of the project including: (a) use of the hypermodelling technology in clinical trials supported by clinical research funding bodies (immediately after the end of the project), (b) hypermodelling technology is deployed on a service infrastructure and sold as service to Clinical Research Organisations that run large-scale multicentric sponsored clinical trials (2-3 years after the end), (c) deployment and support of the hypermodelling technology in a limited number of research hospitals, which will use personalised modelling on most of the patients entering a specific clinical pathway (3-5 years after the end) and d) embed the hypermodelling technology into products and or services that are sold onto the healthcare technology market worldwide (5-8 years after the end).

CINECA plans to exploit the hypermodelling technology and infrastructure that will be generalised within CHIC by: selling pre-configured services deployment, hosting and calculation time to non ICT users; selling of consultancies and maintenance services to ICT groups willing to use the software framework in their activities; re-using the hypermodelling technology into internal products and or services that are then sold.

PHILIPS is committed to deliver healthcare solutions that enable continuous improvement in patient care, delivering better healthcare for all at lower costs. In complex diseases such as cancer, access to relevant clinical research information, such as complex models and validated results of clinical trials, will become essential in future clinical decision support systems. Solutions like CHIC will help to improve patient safety as well as overall results of the healthcare delivery process. Philips plans to exploit the CHIC results by transfers to appropriate business units in Philips Healthcare.

UBERN The institute for surgical technology & biomechanics at UBERN has an interest in the clinical application of computational biomechanics for patient-specific planning systems. Therefore, UBERN will exploit the results and methods developed within the scope of this project to enable technology transfer towards clinical application of biomechanical simulations and corresponding image analysis. Exploitation concerns both methodological developments applied to other clinical disciplines (orthopedics, ophthalmology etc.) and the planning of optimized cancer therapy based on the expected tumour shrinkage. Another exploitation plan concerns the database system that will be developed to share the patients' data within the CHIC project. The development will be based on an existing system, funded by the Swiss National Science Foundation. During the CHIC project, common resources will be used to improve the system and adapt it to the specific needs of cancer research. UBERN are also planning to offer an open storage system for the medical image datasets beyond the framework of this project.

B3.2.3 Management of Intellectual Property

The Consortium is convinced of the innovation potential of the expected results and will invest in their development and subsequent exploitation by taking the appropriate steps in the course of the project. CHIC will elaborate an intellectual property research plan to ensure that the IP generated within this collaborative, multidisciplinary environment will be properly managed. This will be ensured by the guidance of The Institute of Legal Informatics (IRI) of the Leibniz University of Hannover (Partner 8 of CHIC) which will develop a concrete plan for managing joint IPR since the early beginning of the project. This is also an important milestone of the project (MS8 The CHIC Data protection and intellectual property framework).

Additionally, the Consortium Agreement will be another legal basis for dealing with intellectual property rights and exploitation issues within and beyond the project implementation period. The latter in particular offers the possibility of agreement on project-specific, individual rules for the dissemination and exploitation of project results. As a general rule, foreground generated will become intellectual property of the partner(s) who generated it. All project partners will grant each other free access rights in order to carry out the project, the conditions for access to results necessary for the exploitation of own results (beyond the project) will be determined in the Consortium Agreement and separate agreements as appropriate.

Apart from the general legal conditions, proper management structures and decision-making processes will be designed as described in Section 2, in order to avoid problems with intellectual property protection when it comes to exploitation. Is important to stress that Knowledge Management activities in the first months of the project will address the detailed description of the background the partners bring into the project and a common agreement on the methodologies to be applied in the R&D work. These activities are covered by WP12 Task 12.2 **Exploitation and IPR issues**. During the implementation of the project, Foreground generated and scientific project results with high innovation potential will be identified and documented through the yearly and interim reports as well as the project deliverables. All project knowledge and documents will be stored in a password-protected website for continuous reference. Protection of innovative results will be a priority – the WPL of WP12, together with the Coordinator and WP4 as legal supporter, will monitor this aspect closely and will initiate suitable actions in cooperation with the individual partners as well as the lawyers and technology transfer offices of the partner institutions.

All this will be done jointly by all partners, under coordination of the Coordinator and the Project Management Office, and will be laid down in the Plan for the Use and Dissemination of Foreground (PUDF) which will be set up after the second project year and updated yearly until the end of the project. In more detail the PUDF will include the following three sections:

- Foreground and its Use: in this section, contractors are asked to identify all the scientific results arising from the project and their intentions for use.
- Dissemination of Foreground: in this section contractors are asked to list all the actions carried out in order to make their research results known to the public.
- Publishable results: in this section, contractors should provide a summary description of each exploitable result.
- This work is done in WP12, Task 12.2 and will be elaborated through the deliverables D12.4 Preliminary Plan for the Use and Dissemination of Foreground (M24), D12.5 Draft Plan for the Use and Dissemination of Foreground (M36) and D12.6 Final Plan for the Use and Dissemination of Foreground (M48).

B4: Ethical Issues

CHIC will involve research on cancer patients. It is the aim of **CHIC** to share, join and analyse heterogeneous clinical, imaging and research data, including genetic and molecular data of patients, under the guidance of a legal and ethical framework to foster Meta- and Hyper-Multiscale Models and repositories for *In Silico* Oncology within VPH. The use of clinical and research data entails several legal and ethical implications:

1. Health data in general and particularly genetic data contain a large amount of very sensitive information about the person concerned. A person's genetic data provides information about his descent, ethnic origin, and, with a certain probability, also about future diseases and possibly about their healing chances and much more.

2. The core idea of **CHIC** is the development of Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology. The access to and joining of large amounts of patient data collected in clinical trials or hospital information systems are needed to evaluate and validate these models before they can be part of future clinical practice.

As a result these models will be generated to use them by physicians in their routine care for patients. This will result in:

- Gaining new knowledge about diseases by developing Meta- and Hyper-Multiscale Models and Repositories based on system biology and using clinical and molecular data from patients

- Increasing the efficiency and effectiveness of treatment for patients

The merging of health data collected for therapeutic or diagnostic purposes within or without clinical trials on the one hand and health data collected for research purposes on the other raises ethical and legal issues. **For ethical reasons this will be addressed in the context of the patients' informed consent, particularly their right of withdrawal.**

From a legal point of view, it needs to be considered that a change of the purpose of processing personal data is in many cases prohibited. Data that were collected for one purpose may not be used without legitimation for another purpose. Therefore, a Data Protection Framework will be of paramount importance. CHIC will cooperate with p-medicine where a legal and ethical framework will be developed that is compliant to all legal and ethical requirements. This Framework is relying primarily on de-facto-anonymisation, pseudonymisation of personal data, a security framework, binding contracts and the procurement of appropriate informed consent. The legal and ethical framework of p-medicine relies on that of from ACGT[55, 56, 57, 58] that is extended to the access to data warehouses, biobanks and to tools and models for decision support for physicians. CHIC will extend this framework to Meta- and Hyper-Multiscale Models and Repositories (WP6) and will therefore add new aspects of the European concept of personal data.

Clinical trials that serve as use cases to test and validate the developed Models in CHIC will not be conducted unless approval by local/national ethical review committees. For approval informed consent is mandatory. Collection of data will follow the rules in the different countries. Informed consent will be obligatory in the prospective collection of data. All studies, also those built on previously collected data will be the subject of ethical reviews. Personal identifiers of data will be protected by pseudonymization in any case, meaning that the data subject's identity is protected on the one hand, but the providing centre will always be able to go back and identify the patient, if new

[55] *ACGT: D10.1: Production of informed-consent form in compliance with the clinical trials, post-genomic research and genetic data handling requirements. 15.03.2007*
[56] *ACGT: D10.2: The ACGT ethical and legal requirements. 13.03.2007*
[57] *ACGT: D10.4: Production of contracts regarding data protection, data security and ethical issues. 15.03.2008*
[58] *ACGT: D11.4: Finalized ACGT security architecture. 17.03.2010*

information is expected to be of benefit for the patient on the other hand.

B4.1 Patient informed consents

The participation of a patient in CHIC is always voluntary. Extraordinary care will be taken to receive appropriate and legally valid informed consent to the collection of, access to, joining of and analysing the patients' health data in prospective studies. In particular, such research will only be carried out with the prior, free, informed and expressed consent of the person concerned. This will be done in accordance with all applicable international laws and ethical guidelines related to the protection of personal data as well as internationally accepted rules on bioethics and human rights. For ethical reasons it is vital that each participant of this project is informed and is able to decide what is done with his or her data according to the principle that autonomy needs consent. All decisions and/or interventions to be made will be made with respect to the privacy of the persons concerned and the confidentiality of such personal data subject to applicable national and international data protection laws. Data of patients coming from data sources already existing will be analysed in terms of the validity of existing consent. Such patients will be asked to give their consent again where appropriate. If refreshing consent is not possible, for reasons of the patient's death, a lack of contact details or otherwise, data will only be used if the existing consent is valid. Clinicians involved in CHIC will always handle all informed consent issues. Results from the FP7 project CONTRACT[59] of the EU will be taken into account. Templates of informed consents will be provided in the respective deliverables. If informed consent will not be achievable for legal or practical reasons, a careful and proper legal and ethical analysis will clarify whether the data may be however used due to national exceptions from informed consent principle, in particular due to art. 8 par. 4 Directive 95/46/EC.

B4.1.1 Right of withdrawal

The CHIC consortium acknowledges the international debate underpinning the importance of a transparent system for withdrawing consent in biomedical research. For this purpose, patients and participants, having given their consent to the processing of their data, shall be able to withdraw such consent at any time and for any reason without any disadvantage or penalty on the same basis as proposed by other large-scale research undertakings. CHIC will adhere to the guidelines given by CONTRACT.

B4.1.2 Patients not able to give consent

For patients unable to give consent, due to their age or mental disability, CHIC will provide information sheets and obtain consent from their legal representatives. For patients who are minors at the time of obtaining consent, agreements will be provided, informing them about their rights upon reaching majority and asking them for additional ascent whenever they are sufficiently able to understand the implications of their declaration. The CHIC consortium is fully aware of and acknowledges the ethical and legal difficulties of conducting research with patients unable to give consent and will reduce such research as much as possible and adhere to internationally accepted standards in relation to such research. In any doubtful cases the CHIC consortium will not include such participants in their research. As patients with nephroblastoma are mainly young children their data will only be used if either parents or all legal representatives have given prior and freely their informed consent. The informed consent for taking part in CHIC has to be separated from the informed consent of taking part in a corresponding prospective clinical trial. Criteria to accept legal representatives are specified in the respective clinical trials and will be accepted by CHIC. In this patient group awaited results from CONTRACT will be used.

[59] *http://contract-fp7.eu/*

B4.1.3 Protection of privacy

Sharing heterogeneous data from multiple sources can be a threat to personal integrity, which shall be minimised. All partners need to ensure compliance with their national laws and will be supported in achieving this goal by the legal/ethical WP10 in CHIC. Only pseudonymized or anonymized datasets will be used. Software and tools will be further used so that no scientist working with the data will ever know the true identity of the study subjects. Privacy will also be protected when results or data are presented. Again, the general rule will be to restrict all presentation of data to aggregations, or to line listings deprived of personal identifiers so that the identity of the study subject cannot be deduced by anybody but the providing institution (no backward identification). After completion of the project, all assembled datasets will be destroyed if the individual patient will not give an informed consent to maintain the data for further analyses in a succeeding project. This informed consent needs to provide all information about the further usage of the data. This procedure has to comply with each partner's national legal and ethical guidelines for preserving raw data and guidelines for post-analysis (irreversible) data destruction.

B4.2 Enrolment of children in clinical trials

A new Paediatric Regulation entered into force in the European Union (EU) (Regulation (EC) No 1901/2006) on 26 January 2007. We do not expect any specific impact of this regulation on CHIC.
The objective of the Paediatric Regulation is to improve the health of children in Europe by[60]:

- facilitating the development and availability of medicines for children aged 0 to 17 years,
- ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately,
- improving the availability of information on the use of medicines for children without:
  - subjecting children to unnecessary trials,
  - or delaying the authorisation of medicines for use in adults.

The Paediatric Regulation dramatically changes the regulatory environment for paediatric medicines in Europe. The new legislation comprises:

- Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use[61]
- Regulation (EC) No 1902/2006 an amending regulation in which changes to the original text were introduced relating to decision procedures for the European Commission[62]

The main elements of the finalised Regulation include:

- the establishment of a new body, the Paediatric Committee, sited at the European Medicines Agency (EMA)
- for new products and certain changes to the marketing authorisation for products still covered by patent protection
  - a requirement for paediatric data based on a paediatric investigation plan (PIP)
  - a six-month extension of the supplementary protection certificate (SPC) if information arising from a completed PIP is incorporated into the Summary of Product Characteristics (SmPC)

[60] *http://www.ema.europa.eu/htms/human/paediatrics/regulation.htm*
[61] *http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf*
[62] *http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf*

- for orphan medicinal products
  - a two-year extension of market exclusivity if information arising from a completed PIP is incorporated into the Summary of Product Characteristics (SmPC)
- for off-patent products
  - a new category of marketing authorisation called the paediatric use marketing authorisation which will be associated with a ten-year period of data and market protection
- a European database of paediatric clinical trials, part of which will be publicly accessible
- a requirement to submit data from paediatric clinical trials to the regulatory authorities
- coordination of a European Paediatric Clinical Trials Network.
- funding for the study of off-patent medicines provided through the Community framework programmes
- an identifying symbol on the package of all products authorised for use in children.

B4.3 Processing of personal data

The CHIC project will deal with highly sensitive healthcare data. Personal data processing requires a higher level of protection and is subject to numerous regulations. Furthermore, because of the therapeutic or scientific implications, such data processing has to absolutely minimise the potential of medical errors or erroneous scientific results. All relevant legal sources (legislation, case law, studies, surveys prior to legislation) at National and International level will be reviewed and examined thoroughly to identify the applicable policies and rules to be adopted. The sources considered for the purposes of this exercise include, but are not limited to:

European level:

- Art. 3, 7, 8 of the Charter of Fundamental Rights of the European Union
- The Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
- Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components

- Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices
- Art. 8 of the Convention of the Council No. 5 for the protection of human rights and fundamental freedoms
- Convention No. 108 of the Council of Europe for the protection of individuals with regard to automatic processing of personal data
- Proposal for a Regulation on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation), COM(2012) 11 final

Recommendations:

- Council of Europe, Recommendation No. R(97)5 on the protection of medical data adopted of 13 February 1997
- Council of Europe, Recommendation on human rights and biomedicine, concerning biomedical research, Strasbourg 25th of January 2005

Relevant International Instruments and Documents:

- World Medical Association Declaration of Helsinki
- Convention No. 164 of the Council of Europe for the protection of human rights and dignity of the human being with regard to the application of biology and medicine (Convention on Human Rights and Biomedicine)Additional Protocol to the Convention on human rights and biomedicine concerning biomedical research
- UNESCO Universal Declaration on Human Genome and Human Rights
- UNESCO International Declaration of Human Genetic Data
- UNESCO Declaration on Bioethics and Human Rights

Article 29 Data Protection Working Party:

- Working Document on Genetic Data (WP 91)
- Opinion 6/2000 on the Human Genome and Privacy
- Opinion 4/2007 on the concept of personal data
- Working Document 1/2008 on the protection of children's personal data

Other relevant documents:

- Opinion of the European Group on Ethics in science and new technologies to the European Commission, No. 11, 21 July 1998
- International Guidelines for biomedical research involving human subjects (prepared by the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization)

B4.3.1 The CHIC legal and ethical framework

In case a problem arises with new legislation relating to health/genetic data collection, data access or patient rights, the WP leader of the legal and ethical framework (WP4) will evaluate the situation and take appropriate actions, supported by the Center for Data Protection (CDP)[63],[64]. The CDP will support CHIC wherever needed on an informal, non-funded level. No subcontracting will be needed. The legal responsibility will always remain within the consortium. Special attention will be given to the following legal and ethical issues directly related to the research performed by CHIC:

- Patient's prior, free, express and informed consent
- Evaluation, analysis and renewal where appropriate of the informed consent of already existing patient data that will be made available
- Procedures of withdrawal in case a patient wishes to quit at any time
- Design and implementation of legally compliant anonymisation and pseudonymisation tools
- Lawful process, transfer, transmission and storage of health data codified in the **CHIC** ethical and legal policies
- A feedback procedure to the patient where necessary and agreed on in the informed consent
- The CHIC Data Protection Framework:
    - Anonymisation/double-pseudonymisation of health data;
    - Linkage / Contracting
        - Conclusion of binding contracts with all research units with respect to the internal data protection and data security
        - Authority to be addressed for necessary feedback to the patient
        - Central contact point for patients to claim their rights

B4.3.2 Feedback procedure

The WP4 leader will be the central contact point for patients and participants with respect to rights resulting from the processing of their data within CHIC. In order to make unauthorised re-identification of a patient substantially more difficult, the integration of a Trusted Third Party will be evaluated, acting as data custodian holding the key necessary for re-identification. In case there is a need to give feedback to patients, and the patient concerned agreed to receiving feedback as part of the consent provided, the procedure to be followed will be:

1. The CHIC data protection officer (DPO) is to be informed.
2. DPO will initiate the re-identification procedure by sending the specific pseudonymised data set to the Trusted Third Party (TTP) for re-identification. The TTP is custodian of the key and is able to assign the data set to the treating physician or hospital, who is in the best position to assess and divulge the clinical data as well as to decide on further action, if necessary.

[63] *www.privacypeople.org*

[64] *Forgó N, KollekR, Arning M, Kruegel T, Petersen I: Ethical and legal Requirments for Translational Genetic Research. Published by Verlag C.H. Beck oHG, München, Germany; Co-published Hart Publishing, Oxford United Kingdom, 2010*

3. The treating physician or hospital thereafter gives feedback to the patient.

This procedure will also take place in case of incidental findings in patients. The local physician is responsible to inform the patient about the incidental finding, as he is the only person in charge for the patient.

Animal experimentation

There will be no data from animal experiments used in CHIC.

B4.4 Practical management of CHIC legal and ethical issues

The CHIC consortium acknowledges that many other ethical issues that are not foreseeable at this moment may arise as a result of the innovative design of the project. To ensure that at any point in time throughout the project, all ethical, legal, social and safety issues raised by any of the activities of CHIC are evaluated in a timely, accurate and careful fashion from the perspective of all stakeholders involved, WP4 will closely interact with all WPs involved in research on personal data. The leader of WP4 will be designated as the Data Protection Officer of the project and will serve as a central contact point for all privacy related requests coming from inside and outside the project. In any case privacy of clinical data will be ensured building on the guidelines developed in ACGT, p-medicine and CONTRACT. The deliverables of WP11 of ACGT and of WP of p-medicine will serve as a master for the technical security infrastructure.

Secondly, the clinical beneficiaries' institutional ethics committees will be contacted and involved to provide the maximum available safety.

Finally, the necessity of establishing an ethical committee will be discussed at the kick-off meeting. Such an External International Ethical Committee (IEC) would consist of leading academics in the relevant field, providing a consultative function. Members of the IEC would be invited to consortium meetings and be contacted for advice whenever needed. They would support the DPO and the legal/ethical WP in their work and report to the coordinator whenever appropriate.

It has to be mentioned that all clinical trials providing data for CHIC will be funded outside of CHIC. All these trials have approval or will be approved according to GCP criteria and the EU regulations. Ethical approval for these trials is mandatory in any case.

The duration of data storage is depending on the regulations of each of these trials. This is specified in the trial protocols. If data are used in CHIC all these data are pseudonymized or anonymized and no personal data will be stored within the framework of CHIC. After the end of the funding period of CHIC all data will be destroyed within the framework of CHIC, if the project will not sustain. The storage of the data within the respective clinical trials is regulated by the trials themselves and independent of CHIC.

Ownership of models and IP issues will be regulated during the runtime of CHIC and guidelines will be provided by WP4 (Deliverables D4.2, D4.3.1 and D4.3.2).

Copies of local national ethical approvals for clinical trials will be provided to the consortium, before entering data into the infrastructure of CHIC.

In summary the CHIC framework will be based on the p-medicine framework and built according to the European legal and ethical requirements that will guarantee the compliance of researchers with the European Legal framework. This is based on contracts between providers and users of data, tools and services, informed consent and respective tools developed for pseudonymization of data. The

access to the **CHIC** framework will be regulated by a roles and rights management system via a portal. Unauthorized access will therefore be avoided and the risk of misuse of data is restricted to people legally bound by contracts to data providers.

ETHICAL ISSUES TABLE

Table 4.1a: Ethical Issues

	YES	Page
Informed Consent		
• Does the proposal involve children?	**X**	22-26
• Does the proposal involve patients or persons not able to give consent?	**X**	22-26
• Does the proposal involve adult healthy volunteers?		
• Does the proposal involve Human Genetic Material?	**X**	22-26
• Does the proposal involve Human biological samples?	**X**	22-26
• Does the proposal involve Human data collection?	**X**	22-26
Research on Human embryo/foetus		
• Does the proposal involve Human Embryos?		
• Does the proposal involve Human Foetal Tissue T Cells?		
• Does the proposal involve Human Embryonic stem Cells?		
Privacy		
• Does the proposal involve processing of genetic information or personal data (e.g. health, sexual, lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	**X**	22-26
• Does the proposal involve tracking the location or observation of people?		
Research on Animals		
• Does the proposal involve research on animals?		
• Are those animals transgenic small laboratory animals?		
• Are those animals transgenic farm animals?		
• Are those animals cloned farm animals?		
• Are those animals non-human primates?		
Research Involving Developing Countries		
• Use of local resources (genetic, animal, plant etc)		
• Impact on local community		
Dual use		
• Research having direct military application		
• Research having the potential for terrorist abuse		
ICT Implants		
• Does the proposal involve clinical trials of ICT implants?		
I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL		

B5 Consideration of gender aspects

All partners in the consortium are committed to a work environment in which all individuals are treated with respect and dignity. It is believed that each person has the right to work in a professional atmosphere that promotes equal employment opportunity and prohibits discriminatory practices, including harassment. Equal Employment Opportunity (EEO) and non-discrimination has been – and will continue to be – a fundamental principle within the consortium, where assignments and advancement are based upon personal capabilities and qualifications, without regard to race, colour, sex, language, religion, political or other opinion, national or social origin, property, birth or other status. The consortium recognizes the need to attract and retain talent, and that must encompass doing a better job of recruiting and developing women - traditionally less visible in the technology sector. In view of the low percentage of women active in technical jobs, it is the consortium's policy to strive for women working in the project. The type of work is equally suited for women and men. In CHIC several women are already active at key positions:

1. Corinna Hahn (EURICE) is Senior Programme Manager and has experience with EU-funded research projects.
2. Helen Byrne (UOXF) is Professor of Mathematics.
3. Caterina Guiot (UNITO) is Professor in Applied Physics.
4. Dimitra Dionysiou (ICCS) a Senior Researcher at ICCS.
5. Anca Bucur (PHILIPS) is a Senior Scientist at PHILIPS.
6. Debora Testi (CINECA) is an R&D Manager at CINECA.
7. Enjie Liu (BED) is a Senior Lecturer at the Dept. of Computer Science and Technology.
8. Tina Kruegel (LUH) is a Research Associate with main focus on data protection law.

At the scientific level the project will be even more gender balanced, since among the younger research community in this field there is a strong involvement of female students and PhD students. The project leader Georgios Stamatakos will monitor any related issues in the CHIC project.

B5.1 Actions to be taken

Within CHIC we will promote gender equality in several ways. Education is in this respect important.

- When publishing project job vacancies, urge women to apply, especially in fields where males usually dominate. Aim should be that the project is comprised of at least 40% women.
- To make projects even more attractive to women, offer part-time positions whenever possible.
- Offer the opportunity for parental leave.
- Positively encourage women to become involved in management roles in the Consortium. One possibility is to substitute single managers with a management groups, with equal numbers of females and males represented. The aim should be that at least 40% of project staff, including Principal Investigators are female.

- Offer specialised vocational training and gender training for females, including career management, communication, rhetoric techniques, and conflict management.
- Create a network of women scientists within the project linked to other European networks of female scientists.
- At consortium conferences, the number of sessions chaired by women should equal the numbers chaired by men.
- Women scientists should be encouraged to be responsible for dissemination of results and in communication activities.
- Workshops and conferences within the project should preferably be short and intensive and held during weekdays. Overnight stays should be minimised. Evening and weekend meetings should be avoided when feasible for family and economic reasons. Video conferencing should be encouraged. Offer conference child care if possible and necessary.

B6 Annex: Letters of Commitment to serve as External Advisory Board (EAB) members and letters of support and/or intent to collaborate with the CHIC consortium

A.

LETTERS OF COMMITMENT TO SERVE AS MEMBER OF THE EXTERNAL ADVISORY BOARD (EAB)

EORTC
European Organization for Research and Treatment of Cancer
International Association under Belgian Law

Françoise MEUNIER, MD, PhD, FRCP
Director General
EORTC

Pr. Georgios S. Stamatakos
Institute of Communication and Computer Systems
National Technical University of Athens
9, Iroon Polytechniou
GR-157 80 Zografos, Greece

Brussels, 19 March 2012

Re: Member of the External Advisory Committee

Dear Pr. Stamatakos,

I am pleased to confirm hereby the willingness of the EORTC to become member of the External Advisory Board of the project **"CHIC - Computational Horizons In Cancer: Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology"** to be submitted to EU within the framework of the FP7-ICT-2011-9 call.

I would like to express EORTC's interest in such ambitious project aiming to the development of a technological platform allowing the collection, integration and use of heterogeneous biomedical datasets for the sake of efficient and personalized treatment selection for cancer patients.

Sincerely yours,

Pr. Françoise Meunier
EORTC Director General

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Georgios S. Stamatakos
Research Professor, PhD
Leader, In Silico Oncology Group
Laboratory of Microwaves and Fibre Optics
Institute of Communication and Computer Systems
National Technical University of Athens
9, Iroon Polytechniou

March 20th, 2012

Dear Dr. Stamatakos:

Thank you for the invitation to serve on the External Advisory Board (EAB) for the Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology initiative. I am happy to accept this invitation and confirm that I will be able to serve for the full duration of the project. As part of my duties as an EAB member, I will be happy to provide comments and suggestions concerning specific aspects of the project implementation, as they relate to my expertise and to attend board meeting as requested.

The CHIC proposal describes the creation of an impressive, multinational consortium that is poised to rapidly and significantly advance individualized treatment of cancer by creating the tools and infrastructure necessary to develop, adapt and validate hyper-models of the disease. I look forward to participating on the EAB.

Sincerely,

Trachette Jackson

Dr. Trachette L. Jackson
Professor of Mathematics
Co-Director, Mathematical Biology Research Group
Department of Mathematics
University of Michigan

UCL

Georgios S. Stamatakos
Research Professor, PhD
Leader, *In Silico* Oncology Group
Institute of Communication and Computer Systems
National Technical University of Athens
9, Iroon Polytechniou
GR-157 80 Zografos, Greece

March 6th 2012

Dear Georgios

Re: Invitation to become a Member of the External Advisory Board (EAB) of the IP proposal entitled: "Computational Horizons in Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology"

Thank you for your kind invitation to become a Member of the External Advisory Board of your new Project. I am delighted to accept and will be happy to contribute as you request.

As you know from our discussions at the meetings of the ACGT and now the p-Medicine project, I have had a long-standing interest in mathematical methods in medicine and have followed the progress of *in silico* oncology, from the early era of radiotherapy treatment planning and associated models of dose fractionation through to your own extensive modelling of tumour responsiveness to chemotherapy. It is a pleasure to support the CHIC proposal. The research teams involved have demonstrated great ability and ingenuity in their quest to align their modelling methods with practical issues relevant to the management of patients.

Yours sincerely,

David Ingram
Emeritus Professor of Health Informatics,
University College London

UNIVERSITY of HOUSTON

Cullen College of Engineering
Department of Biomedical Engineering

March 11, 2012,

Dr Georgios Stamatakos,
Research Professor

Metin Akay, Ph.D.
Founding Chair

John S Dunn Endowed Chair Professor

3605 Cullen Blvd, Room 2027
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Letter of support for the research proposal "CHIC - Computational Horizons In Cancer: Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology" to be submitted to the European Commission

Dear Georgios,

I write this letter in support of the research proposal entitled "CHIC - Computational Horizons In Cancer: Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology" to be submitted to the European Commission. As the Founding Chair of the Biomedical Engineering Department at the University of Houston, USA and the IEEE (Institute of Electrical and Electronics Engineers) Press Series Editor for the IEEE Press Series in Biomedical Engineering. I am delighted to serve as External Advisor on this proposal.

Since I am a fervent supporter of the emerging biomedical engineering and clinical discipline of in silico oncology, which is one of the "key players" in the proposal you are coordinating, I will be delighted to provide my expertise on any bioengineering and bioinformatics aspects of the project which might benefit from it. Furthermore, being a devotee to the promotion of biomedical education in the world I will support the dissemination of the results of the project on the global biomedical engineering community as well as the maximization of its impact.

I wish you all the best for your application and very much hope that the importance of this initiative is recognised and supported.Letter of support for the research proposal "Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology" to be submitted to the European Commission

Best regards,

Metin Akay

THOMSON REUTERS

Yuri Nikolsky, Ph.D.
VP, Research & Development
Thomson Reuters, IP&Science
5901 Priestly Dr.
Carlsbad, CA 92008, USA

Prof. Georgios Stamatakos,
Institute of Communication and Computer Systems
National Technical University of Athens
9, Iroon Polytechniou
GR-157 80 Zografos, Greece

March 30, 2012

Dear Prof. Stamatakos,

I am pleased to confirm that I agree to serve as a Member of the External Advisory Board (EAB) for the integrated proposal (IP) entitled: "Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology" to be submitted to the European Commission (EC) for possible funding within the framework of the FP7-ICT-2011-9 call.

I would like to express my strong interest in such an ambitious project aiming at standardizing multiscale cancer modelling and developing and clinically validating advanced cancer hyper-models in order to individualize and optimize cancer treatment.

I anticipate a fruitful interaction with the CHIC partners and look forward for our collaboration.

Sincerely yours

Yuri Nikolsky

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B.

LETTERS OF SUPPORT AND/OR COMMITMENT FOR COLLABORATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Cancer Institute
Division of Cancer Biology
Executive Plaza North, Suite 5000
Bethesda, Maryland 20892-7380

1 April, 2012

Georgios S. Stamatakos
Research Professor
Leader, *In Silico* Oncology Group
Institute of Communication and Computer Systems
National Technical University of Athens
9, Iroon Polytechniou
GR-157 80 Zografos, Greece

Dear Dr. Stamatakos,

Thank you for sharing with me your planned project entitled "Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology" to be submitted to the European Commission (EC) for possible funding within the framework of the FP7-ICT-2011-9 call.
The scope of your proposed work is aligned with the interests of the National Cancer Institute, NIH in areas such as *in silico* biology, integrative cancer biology, and computational modeling of cancer. We support work of similar scientific focus within the Integrative Cancer Biology Program (http://icbp.nci.nih.gov/) and through the Inter-Agency Multi-Scale Modeling Consortium (http://grants.nih.gov/grants/guide/pa-files/PAR-11-203.html). If your proposal is funded, there will be new and continuing opportunities for direct and multifaceted transatlantic interaction and potential for cooperation in the domain of multiscale cancer modeling and *in silico* oncology. This kind of effort in the past has led to our joint effort on the 1st Transatlantic Workshop on Multiscale Cancer Modeling that took place in Brussels in 2008 as well as participation and interaction through webinars and at various scientific meetings.

I look forward to continuing to hear about your progress in cancer modeling. Please let me know if you have any questions.

Sincerely

Jennifer Couch, Ph.D.
Chief, Structural Biology and Molecular Applications Branch
Division of Cancer Biology
National Cancer Institute, National Institutes of Health

Paris, March 16th, 2012

Letter of support for the IP proposal entitled: "Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology"

The European Clinical Research Infrastructures Network (ECRIN, www.ecrin.org) is a research infrastructure designed to provide integrated services to multinational clinical trials in Europe, at a not-for-profit cost. ECRIN is an ESFRI-Roadmap, FP7-funded pan-European infrastructure, and in 2012 ECRIN will become a single international organisation with a legal status of European Research Infrastructure Consortium. Optimal use of clinical research and healthcare data is a major challenge for ECRIN, as a major tool for improving treatments.

Hereby ECRIN expresses its interest for the **"Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology"** that aims to simulate diseases (mainly several cancer types) in the computer in order to build models which will allow simulating in an individual patient how his tumour will respond to treatment. The main input of ECRIN to the CHIC project will be the validation in real-life clinical trials of the models for the development of personalised treatments. I am convinced that this project is of relevance in the future for patient care in better modelling and defining the best treatment available.

Jacques Demotes-Mainard
ECRIN Project Coordinator
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Imperial College
London

From: Roger G Dale, PhD, FInstP, FIPEM, FRCR
Professor of Cancer Radiobiology
Department of Surgery and Cancer
Faculty of Medicine
Imperial College
Charing Cross Hospital Campus
London W6 8RF UK.

To: Georgios S Stamatakos, PhD
Research Professor
Leader, *In-Silico* Oncology Group
Institute of Communication and Computer Systems
National Technical University of Athens
9, Iroon Polytechniou
GR-157 80 Zografos, Greece.

16th March, 2012

Dear Professor Stamatakos,

Re: IP Proposal "Computational Horizons in Cancer (CHIC): Developing meta- and hyper-multiscale models and repositories for *In-Silico* Oncology".

It is with pleasure that I write to offer my strong support for the above research proposal.

The emergent fields of *in silico* oncology and multiscale cancer modelling are proving to be valuable tools for identifying critical aspects of cancer progression and for the individualisation of cancer treatment through the process of *In-silico* experimentation. Your own group at the National Technical University of Athens has made extensive contributions in this field and has already identified the potential usefulness of exploiting multiscale biological data for individual patients.

A significant aspect of the new proposal is that it will examine the benefits of fusing together various bioprocess models, as already developed by NTUA and others, and which address various aspects of the natural phenomenon of cancer known to be of importance. The coherent integration of cancer growth and treatment models will help accelerate the testing and direct clinical application of personalised *In-Silico* modelling, a process which could help transform current approaches to cancer treatment.

My support for your proposal is based in part on the fact that I have enjoyed profitable collaboration with the NTUA *In-Silico* group at various times since 2002. My own area of interest is the application of theoretical radiobiology to the radiation treatment of cancer but the NTUA approach to simulating tumour growth and regression has potential application in many aspects of cancer treatment, not just radiation oncology. As an Invited Speaker at the First International Advanced Research Workshop on *In Silico* Oncology (1st IARWISO) in Sparta, Greece in 2004, I met with many other international researchers from a wide variety of scientific or medical backgrounds who routinely collaborate with NTUA and it was clear that the strong international links already established by NTUA provide a platform for developing a broad overview of treatment optimisation using single- or multi-modality therapies.

There is no doubt in my mind that *In-Silico* computer techniques will become a major tool offering the accelerated investigation of many aspects of the natural history of cancer, from first initiation through to ultimate demise following successful therapy. This process will require integration between already extant and separately-validated models of growth and response and identification of the dataset combinations (both both pooled and individualised) which best allow clinical exploitation of the *In-Silico* predictions. The NTUA group has an exemplary track record of pioneering work in this field and, through the above proposal, is uniquely poised to make further significant contributions to this fundamentally useful research area.

Yours sincerely,

Boston University
Department of Biomedical Engineering

44 Cummington Street
Boston, Massachusetts 02215
Muhammad H. Zaman,
Assistant Professor
617-358-5881. zaman@bu.edu

March 29, 2012

To

Georgios S. Stamatakos
Research Professor
Leader, *In Silico* Oncology Group
Institute of Communication and Computer Systems
National Technical University of Athens
9, Iroon Polytechniou
GR-157 80 Zografos, Greece

Dear Dr Stamatakos,
I am pleased to confirm that I fully support the integrated proposal (IP) entitled: "Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology" to be submitted to the European Commission (EC) for possible funding within the framework of the FP7-ICT-2011-9 call.
I would like to express my strong interest in such an ambitious project aiming at standardizing multiscale cancer modelling, and developing and clinically validating advanced cancer hypermodels in order to individualize and optimize cancer treatment.
I anticipate a fruitful interaction with the CHIC partners.
Sincerely,

Muhammad H. Zaman
Assistant Professor, BME.

Georgios S. Stamatakos
Coordinator, The CHIC Proposal
Research Professor, PhD
Leader, *In Silico* Oncology Group
Institute of Communication and Computer Systems
National Technical University of Athens
9, Iroon Polytechniou
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12th March 2012

TITLE OF THE PROPOSAL: "Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology".

ACRONYM: CHIC

To be submitted to the European Commission for possible funding in the framework of the FP7-ICT-2011-9 call

Dear Professor Stamatakos,

I write as Chair of EPPOSI (The European Platform for Patients Organisations, Science and Industry) in support of the above proposal. It is the view of EPPOSI that this project represents a very important and timely initiative. We hope that it is successful, as it has the potential to contribute significantly to a novel area of medicine, with consequent benefits for patients and families currently living with intractable conditions. There is considerable synergy between the aims of this project and those of EPPOSI, The possibility of feeding these into the ongoing development of EPPOSI's thematic programme of work on the management of chronic conditions by EU healthcare systems adapting to novel possibilities in the context of constrained resources and rising expectations.

The emergent field of ***in silico* oncology** and the role of **multiscale cancer modelling** for the capturing of critical aspects of cancer and the individualization and optimization of cancer treatment though *in silico*) experimentation have significant potential for the development of effective novel therapies for a wide range of cancers. To be successful this will be dependent on extensive exploitation of the individual patient data (molecular, histological, pharmacogenomic, imaging, clinical, previous treatment data) in conjunction with advanced multiscale cancer models.

Fusing different bioprocess models, referring to a wide range of aspects of the natural phenomenon of cancer, as envisaged in this proposal, would provide a coherent semantic description of cancer models. This is expected to dramatically

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epposi Partnering for Healthcare Policy

accelerate the integrative process necessary for the development of innovative therapeutic opportunities.

Of particular relevance is the 4th International Advanced Research Workshop on *In Silico* Oncology and Cancer Investigation (4th IARWISOCI) http://www.4th-iarwisoci.iccs.ntua.gr/. This workshop and further events in this framework will be tightly linked to this proposal. It provides both introductory and specialist research information on the emergent field of *in silico* oncology.

EPPOSI welcomes this proposal and looks forward to a productive engagement with your consortium should the application be successful.

Yours sincerely

Alastair Kent
Chair

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18 March 2012

Georgios S. Stamatakos
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Athens Greece

Dear Professor Stamatakoz

Re: Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology

brainstrust, a national brain cancer charity in the UK, is delighted to endorse the above proposal. The major clinical paradigms, which sit within the framework of the CHIC proposal, align very closely with *brainstrust's* ethos and core principles, which include empowering patients so that they can make informed decisions about their care pathway. Stratification of medicine for brain cancer patients is crucial when securing the best outcomes. The goal of this research, to translate the models and the corresponding oncosimulators to the clinic, will provide the clinician with the optimal treatment scheme based on the patient's individual imaging, histological, molecular, clinical and pharmacogenomic multiscale data.

We, at *brainstrust*, wholly endorse this research.

Warm regards

Dr Helen Bulbeck
Founder and Director of Services
brainstrust

Registered charity no: 1114634

INTERNATIONAL CONFEDERATION OF
CHILDHOOD CANCER PARENT ORGANIZATIONS

Georgios S. Stamatakos
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GREECE

March 30th, 2012

Dear Dr Stamatakos,

I am pleased to confirm that ICCCPO fully supports the integrated proposal (IP) entitled: "Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for *In Silico* Oncology" to be submitted to the European Commission (EC) for possible funding within the framework of the FP7-ICT-2011-9 call.

I would like to express the ICCCPO's strong interest in such an ambitious project aiming at standardizing multiscale cancer modeling, and developing and clinically validating advanced cancer hyper models in order to individualize and optimize cancer treatment.

The ICCCPO anticipates a fruitful interaction with the CHIC partners.

Sincerely yours,

Marianne Naafs-Wilstra
Secretariat leader

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