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TECHNICAL REVIEW REPORT

Information and Communication Technologies
ICT

Project acronym:	CHIC
Project title:	Computational Horizons in Cancer:Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology
Grant agreement number:	600841
Funding scheme:	Collaborative project
Project starting date:	01/04/2013
Project duration:	48 months
Coordinator:	Institute of Communication and Computer Systems National University of Athens (Greece)
Project web site:	http://www.chic-vph.eu

Period covered by the report:	Period No. 3, from 01/04/2015 to 31/03/2016
Place of review meeting:	Brussels
Date of review meeting:	1st June 2016
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SEVENTH FRAMEWORK PROGRAMME

European Commission
Information Society and Media

Individual report	☐
Consolidated report	☒

1. OVERALL ASSESSMENT

a. Executive summary

Please give your overall assessment of the project, commenting on the following:

- *main scientific/technological achievements of the project*
- *quality of the results*
- *attainment of the objectives and milestones for the period*
- *adherence to the workplan, any deviations (whether justified) and remedies (whether acceptable)*
- *take-up of the recommendations from the previous review (if applicable)*
- *contribution to the state of the art*
- *use of resources*
- *impact*

This is the fifth review of the project covering the 3rd annual period, assessing the project´s progress and the adherence to suggestions made at previous reviews.

The main emphasis of work performed during the reporting period was to demonstrate and validate the clinical relevance of the developed modelling environment. The majority of the project work in this period has been devoted to the further development and refinement of the cancer hypermodels and hypermodelling strategies, and further development and refinement of the clinical scenarios and use cases realisation.

An important effort has been done with respect to clinical drivers and concepts have been clarified. A rather significant change of direction following the recommendations of review #3 has been undertaken by the consortium.

The work reported is of good quality and has overall stayed in line with what has been suggested in previous reviews. Most of the technical achievements have been completed and delivered in conformance with the DoW. Objectives and milestones of the 3rd year have been globally reached in conformance with the workplan. The expected deliverables have been released on due date, and are well and clearly written, emphasizing the clinical needs that the CHIC project supports. The results are of high scientific quality, especially D4.4 on the legal framework. The analysis and recommendations are highly relevant, and their interest goes far beyond the project.

Collection of clinical, imaging and molecular data has continued. The clinical relevance has been further elaborated. Architecture development has continued with the focus on integration, private cloud finalisation and final technical architecture finalisation. CRAF web-version has been developed. The January 2016 Interim review recommendations have been sufficiently addressed

The review was informative but not really aligned with the WP or deliverable structure in the Technical Annex. Time pressure is omnipresent in reviews of big projects and more time should be allotted in the final review. The questions from the reviewers were answered by the project members present, involving a considerable amount of discussion. Project progress has been well demonstrated with clear oral presentations.

The very large gaps for some WPs between the early deliverables and the final ones is a handicap for the reviewers, although the project progress reports make a valiant effort to fill that gap. This particularity of the project strengthens the recommendation of having a two-day final review, so many results having not yet been presented.

The work reported confirms the clinical orientation of the project. This refocusing, already assessed during the interim review last January, is nicely featured by the provision of clinical scenarios and available data for the validation of CHIC environment for the types of cancer retained in the project and by further development of the CRAF framework for the clinician. The development of the semantic management infrastructure is also progressing and features a relevant and sound approach.

A web version of the CRAF environment was demonstrated and illustrated by simple scenarios consisting in building and running hypermodels for selected nephroblastoma and lung cancer clinical cases. The demonstrated hypermodeling scenario for lung cancer provided additional evidence that the software architecture and the computational environment enabling storage, querying, composition and execution of hypermodels is progressing adequately.

Demos were shown in the review on how a new hypermodel can be created on nephroplastoma cancer case. The hypermodel editor was not very user friendly and still with a quite simple and not very intuitive user interface. Furthermore, no validity checks were in place when combining models, creating new parameters or new relations between models.

The models seem to work appropriately, and give good prediction estimates. However, there is not yet validation data, evidence on the correct performance of the models, or explanation on which data the prediction is based on. Data missing strategy is not yet in place.

There was no demo on prostate cancer, though a deliverable D3.2 describes the CHIC infrastructure with the case of prostate cancer. A clinically driven scenario has been developed with the idea to predict with models the recurrence of prostate cancer after surgery

A significant effort has been made by the legal partner related to the European legal framework on patient's and researcher's rights and duties in eHealth related research, specifically elaborating on clinical validation issues, Intellectual Property rights, Patent issues and Data Protection policies.

IPR issues are in good progress with the signature of the MoU between partners. Legal and ethical issues are also properly addressed.

Potentially exploitable products in the clinical, technological/software and modelling categories have been analysed. The individual partners' exploitation plans and exploitation of the CHIC platform as a whole are in progress.

Technical achievements have been completed as expected and delivered in conformance with the DoW during the period. The deliverables are of expected scientific quality and are accepted.

Progress with dissemination activities has been explained and there is a sound strategy in place. Objectives are well targeted. Dissemination is still very strong. In total nearly 40 contributions in scientific journals or conference proceedings, presentations to conferences, workshops, exhibitions and training sessions are reported. Large public audiences are also addressed through the project web site and the annual newsletters.

Two workshops have been organised, in January 2016 Germany and in April 2016 in Canada. The first workshop was organised to study if the nephroblastoma hypermodels could be used as a decision support tool. The second workshop had the goals to study the clinical data repository (CDR) and two nephroblastoma hypermodels under the clinical research application framework (CRAF). Both workshops were successful with many participants and good feedback. Results are reported in D11.3. During these workshops questions were raised e.g on the clinical validation of the hypermodels, integration of the hypermodels, on the security of the data and models, on the sustainability and maintenance of the models and the CHIC platform, evaluation of the CHIC platform, integration of the technical components and hypermodels.

Resources consumption and costs reported are globally consistent with the work performed and results delivered. As requested, the partners put additional effort to development and integration tasks. An amendment to the DoW has apparently been delivered to the EC services, with WP and resource reallocations to be done until the end of the project and the remaining budget.

The management seems very professional and effective. The role of the participants and their mutual relationships are clearly stated, with good communication between partners.

In summary, the project has reviewed its workplan and governance structure in the directions necessary to implement the recommendations from previous reviews and is on track with all this work. Significant increases in manpower allocations overall has been made and changes in resource allocations between partners. Most of the recommendations from the previous review have been well and appropriately addressed by the consortium.

b. Recommendations concerning the period under review

Please give your recommendations on the acceptance or rejection of resources, work done and required corrective actions – e.g., resubmission of reports or deliverables, further justifications, etc.

The quality of the work done during the period is good, the stated objectives have been achieved. The use of resources has been modified slightly on the cost categories and tasks of the partners. There is still high potential for impact on the cancer research and treatment practices.

The recommendations from the January 2016 interim review have been implemented and their status was explained in the review.
The consortium should have considered to show the prostate cancer demo in the review, which could have been essential for reviewers understanding of the project achievements in the cancel modelling s a whole.

An updated version of D3.2 including the formulas missing p.16 should be delivered.

c. Recommendations concerning future work

Please give your recommendations – e.g., overall modifications, corrective actions at WP level, re-tuning of the objectives to optimise the impact or to keep up with the state of the art, better use of resources, re-focusing, etc. Where appropriate, indicate the timescale for implementation.

The project is coming to an end in March 2017. There is still much work to be done with the CHIC platform components, their integration, evaluation and validation of outcomes, improvement of the CHIC platform user interfaces, and with finalisation of the exploitation plans and their implementation.

Integration of the whole project remains a key issue for the coming period. It is essential to demonstrate the clinical effectiveness of the platform for the 4 types of cancers (including prostate cancer).

Comprehensive demonstrations of the whole system, bringing into play all aspects (repositories, security, hypermodel definitions, different failure modes, etc.) all seen from a clinician's point of view should be prepared **for the final review, recommended to be scheduled over two days**, so as to have enough time for all demonstrations and finalizing discussions, to be held at Iraklion, site of the Integration Coordinator (FORTH).

Clarification of the Prostate Cancer Commitments should be obtained and documented by the project management now - well in advance of the end of the project.

It is necessary to invest some time in developing a reasoning layer consisting of model composition consistency checking tools and repository of valid workflows in order to facilitate the usability of the hypermodelling framework

It appears that the **model adaptation** is very computationally expensive process. The consortium should consider strategies for optimizing the model adaptation process e.g.

- via grouping and profiling of similar patients and in this way being able to bootstrap the adaptation process
- via the construction of a population of virtual patients as developed by another VPH project PAEON (http://paeon.di.uniroma1.it/).

The model personalization is an issue and requires serious consideration in the remaining period of the project. This is really important in order to be able to validate in an objective fashion the generalization potential of the model.

The **user-friendliness** of the developed CRAF platform can be further improved by considering the development of visual, workflow-based interfaces, guiding the user through the selection and execution of different alternative hypermodelling strategies and providing support during the interpretation of the prediction results e.g. comparative evaluation of alternative treatment strategies.

The hypermodelling strategy should also develop dedicated processes for **conflict resolution** in situations when models originating from different sources (e.g. bio-physical vs. data-driven) produce conflicting results and thus cannot be further integrated. A sound strategy should also be put in place when incomplete data occur in individual patient settings.

Special attention should be paid during the coming period on the use of the resources. Use is below the plans by far. There is much work to be done and the resources should be used to complete all needed tasks and to strengthen the exploitation efforts and their implementation.

The consortium should consider the organisation of a larger dissemination event in order to spread the project results to a broader audience of stakeholders in order to insure higher visibility and guarantee sustainability of those results after the end of the project.

d. Assessment

☐ Excellent progress (the project has fully achieved its objectives and technical goals for the period and has even exceeded expectations).

☒ Good progress (the project has achieved most of its objectives and technical goals for the period with relatively minor deviations).

☐ Acceptable progress (the project has achieved some of its objectives; however, corrective action will be required).

☐ Unsatisfactory progress (the project has failed to achieve key objectives and/or is not at all on schedule).

2. OBJECTIVES and WORKPLAN

a. Progress towards project objectives

Assess to what extent the objectives of the project for the period have been achieved. In particular, please indicate if the project as a whole has been making satisfactory progress in relation to the Description of Work (Annex I to the grant agreement) and comment on the interaction between the work packages and the level of integration demonstrated.

During this period, the project has progressed as expected and the objectives set for the period have been met. The milestones have been attained; the contractual deliverables are of good quality and were issued on schedule.

The results are of expected scientific level and quality. There is fruitful interaction across work packages and good integration across individual participants.

Special mention is made to the work delivered by the legal partner, which transcends the project scenario and has a PanEuropean scope in eHealth related legal issues.

The change of emphasis to reach clinical relevant demonstrators with an attractive user interface before the end of the project is healthy and the project has progressed well in this direction. The revised Technical Annex submitted for approval by the project reflects this new emphasis.

b. Progress in individual work packages

For each work package (WP), assess the progress in relation to the Description of Work (Annex I of the grant agreement). Please also report and comment on any delays, reasons for them and any remedial action taken. Specify the work packages concerned.

<u>WP1 – Project management</u>

The 3rd periodic report is a detailed description of activities and achievements performed during the 3rd year of the project. Results obtained in by work packages and composing tasks are reported in detail, as well as the role and contribution of individual partners. Issues encountered and their resolution is commented. Project management meetings and events, dissemination activities (conferences and paper submission or publication in scientific journals) and analysis of resources consumption are reported. This report provides an excellent summary of the project performance during the period and demonstrates the effectiveness of the project management.

Almost all project activities are progressing according to the plan and the engagement and the motivation of the research partners is high. The consortium also managed to attract two new members to CHIC External Advisory Board and a Clinical coordinator has been nominated.

FORTH has taken a role as technical coordinator.

Several partners have adjusted their person month efforts to provide an updated budget distribution aligned with the project adjustments made over the last 6 months.

Budget has been used less than planned, only 62% of the total, but personal resources used over 70%.

Although the previous review (interim) was only 4 months ago, the recommendations have been acted upon by the management, with great energy as a demonstrated willingness of the project to implement the suggested and significant changes.

Amendment in process by the Commission (extension of some tasks, change of PM efforts etc.), new DoW provided.

WP2 – User needs and requirements

Focused on the clinical perspective and clinical relevance of the project. For that purpose, an additional deliverable D2.5 was produced and presented at the interim review last January. Further work regards acceptance of the system by clinicians and patients has been achieved.

Good work is being done, particularly concerning the data (anonymization of 1000 patients and annotation of 100). Some evaluation work has been done. No deliverables for this period. The focus during the reporting period was based on thorough analysis of necessary requirements to achieve acceptance of the hypermodelling approach by clinicians and patients. Scenarios and use cases have been also further developed. Interaction and collaboration with the p-medicine and MyHealthAvatar projects have continued. two workshops organised in 2016 to evaluate the models and collect user feedback.

The effort reported has been significantly (41%) less than budgeted. It is expected that the important participation in the International Conference and Exhibition on Paediatric Oncology in Toronto August 11-13.2016, as well as other activities, will correct this imbalance in the final reporting period.

WP3 – Clinical and Translational science scenarios

Selection and definition of a set of clinically relevant scenarios in the perspective of validating the CHIC infrastructure for the three types of cancer retained plus prostate cancer. Both the clinical cases and associated data have been taken from large clinical trials previously conducted. The performance of CHIC when running the considered cases will be assessed by the capacity of the system to answer a clinical question defined in advance.

D3.2 related to applicability to PCa relapse has been delivered.

A great amount of activity documented in D3.1 and D3.2 has taken place in this period. The effort has been 36% over the one budgeted - well in line with the review recommendations of the interim review in January 2016.

Making data available for research purposes is a major activity (still). As far as the use of the CHIC infrastructure for other cancer types, deliverable 3.2 describes in detail clinical scenarios for prostate cancer relapse after primary curative treatment, and the possible use of the various existing indicators but **does not, concretely, get to**

grips with the potential use of the CHIC infrastructure as it exists. It mentions where hypomodels are "..developed or in progress .. can integrate the clinical hypermodel for Prostate cancer." (page 37, Conclusions). This leaves rather open what the actual studies will contribute to the CHIC Project. Neither milestones (MS7) nor Deliverables (D3.3, Demonstration of the developed Meta- and Hyper-Multiscale Models and Repositories) in the revised Technical Annex submitted make any commitments for **real exploitation of the CHIC framework for Prostate Cancer.**

It is therefore recommended to the project management to ***clarify this prostate Cancer situation urgently***.

WP4 – Legal and ethical framework

Further research on data and copyright protection issues has been carried out.

Excellent work done reflected in D4.4 Whitepaper recommendations, to improve the European legal framework of eHealth for patients' and researchers' rights and duties (cf. D4.4).

After describing the traditional legal framework for research and clinical trials, patients' and researchers' rights has been analysed. The challenges are identified in patients' rights, privacy and data protection, and in researchers' rights and in IPR issues. New General data protection regulation (GDPR) is under development and the preliminary text (from December 2015) has been analysed in the report.

Processing of sensitive data is generally inhibited, only with the specific consent from the patient (consent for cancer research generally is not possible), can the data be processed. Pseudonymisation is also discussed. In silico model will likely qualify as a medical device, and as such would be subject to a set of premarketing testing and certification requirements. In silico cancer models would be classified as class IIB: medium high risk, testing and evaluation should be done by an independent entity, notified body.

Questions raised in the report, to be answered in the future:

- When would the existing validation rules be triggered and what concrete tasks do they impose on the model developers and testing clinicians?
- Should in-silico models be tested in the same way as pharmaceutical products? Regulations on the use of in silico decision tools in clinical practice are needed and how to handle informed consent, patient needs to be aware, doctor's ethical duty, event of adverse outcomes, personalised healthcare?
- How the researchers' IPR can be protected?
- How to prohibit data-siloing approach – keep the data confidential or license the use of data to collect profit?
- Are cancer models of CHIC protected by copyright laws, or as encoded into computer programs?

The IPR agreement between partners has been signed by all partners.

Excellent work overall with budget expenditure for the period exceeded by more than 30%, in accordance with earlier recommendations.

WP5 – IT architecture

The project has decided (in accordance with recommendations from previous reviews) to rely on the private cloud infrastructure and services from FORTH - extended to two virtual machines functionally separating out the in-silico trial repository. Re-identification of patients has been addressed - necessary because the CHIC framework is targeted at clinicians who need the feedback in case relevant clinical information is generated. Significant work on security (access control, auditing, etc.) has taken place.

The private cloud infrastructure of the project is fully functional. The CRAF (Clinically Relevant Application Framework) component has been introduced and is being further developed. The CHIC security framework has also been deployed and further developed.

Further development of security tools and services to accommodate data repository and other components in a unified security framework, has been attained. This work has been achieved in response to recommendations made at the previous review.

Demos in the review showed the private cloud working well

Budget for the period was exceeded by almost 25%, in full accordance with earlier recommendations.

WP6 Cancer Models and Hypermodel Design

For the 4 types of cancer, enhancement of existing simulation code for tumour growth and response to treatment. Further refinements, literature study, specification, early development and demonstration of the hypomodels. Part of the work is reported in D11.3.

A lot of activity and work to develop the clinically driven cancer models for the three "original" cancer types targeted has been made. In the absence of any planned deliverables the 3dr Project Periodic Report (pre-final version 25/05/16) describes this work and progress achieved in considerable detail.

A phenomenological model has also been developed in order to provide initial estimates of tumour response to treatment. Machine learning models have been being developed in order to address clinical questions for which the available data types are not sufficient from the development of mechanistic hypermodels perspective.

Clinical relevance has served as the driving force for the development and the adaptation of the hypermodels. Very early comparisons of the hypermodel predictions with biological reality and clinical experience support their potential to serve as clinical decision support systems in the future, however, this has not yet been done completely.

A small fly in the ointment was that the Nephroblastoma Hypermodel demonstration suffered from "demo"-effects and did not give a good overview of how the clinician would, in reality, proceed through the hypermodel design(?) to the actual result and its interpretation.

The revised technical annex submitted proposes an increase by about 40 person-months for WP6. This is fully aligned with the recommendations and the effort expended in period 3 reflects this new budget.

WP7 – Hypermodelling infrastructure

Technical development and implementation in line with planned.

Progressed as expected in the workplan. Hypermodels annotation functionalities are operational, basic functionalities for hypermodels execution are deployed, and the first release of the hypermodelling framework has been delivered. The definition of the hypermodelling language is completed. These achievements have been completed after an in-depth study and evaluation of available formalisms (Taverna and MUSCLE) which provided the basis of the final development.

D7.3 gives a good technical overview of the annotation services. It provides descriptions of the semantic infrastructure, deployable services and low-level services supported and a mechanism to extend these services and higher –level services geared towards the hypermodelling editor and model repository.

Semantic infrastructure provides services for hypermodelling editor, model repository and clinical data repository. The hypermodelling editor allows the user to view basic metadata information for each model: title, description, and model parameters description.

Clinical data repository builds a connection between RICORDO components, e.g. local ontology lookup service. Metadata can be extracted from clinical data automatically, processing is needed to store the metadata, it is stored in relational data base. For semantic metadata representation standardised ontologies are used and owl-format.

One of the project outcomes is a hypermodelling methodology.

The hypermodelling infrastructure has been deployed and integrated with the rest of the project IT infrastructure. Automated workflow wrapper generation, automated deployment and testing of models uploaded to the model repository have been also implemented.

VPH-HF has been modified for CHIC. This framework has been deployed and tested on both test and production nodes and integrated with the CHIC authentication system. All hypomodels and hypermodels supplied by the modelling partners have been successfully deployed and executed within VPH-HF.

The revised technical annex submitted proposes an increase by about 65 person-months for WP7. This is fully aligned with the recommendations, although the actual effort in Period 3 fell short (by 13 person-months - 18%) of this budget

WP8 – Models and data repositories

The prototypes and web services of the model/tool repository and the in-silico trial repository have been developed. In both cases, schemas and specifications have been updated according to the clinicians' requirements, and the interfaces improved as recommend at the previous review.

The clinical data repository has been extended to support additional clinical data format and integrated with the RICORDO framework in order to support advanced search queries. All

these developments were conducted with the objective to reinforce the clinical orientation of the project, as recommended. The prototype and the web services for the models and in silico trial repositories have been developed. The in silico trial repository has been moved to another virtual machine in the CHIC private cloud and it has been totally split from the model and the tool repository. The clinical data repository supports genetic, molecular and histopathology datasets. The semantics infrastructure has been developed to refine the hypo/hypermodel metadata schema, to create applications, to provide annotation (RDF) store and ontology DB Knowledge Base through RICORDO and to link RICORDO metadata management web services with the hypermodelling editor.

In the absence of any deliverables and specific demonstrations a significant amount of activities is reported upon in the progress report. The final deliverable (month 42) and demonstrations including a variety of these models and data repositories will be very important to document the outcome of all this activity to the reviewers.

WP9 – Image processing and visualization.

As decided by the consortium, DoctorEye has been further developed to be used as a single integrating platform for the whole WP, and is constantly updated to match the clinicians' needs.

Work on tumours segmentation using DortorEye has progressed with the study and evaluation of many imaging features for the considered cancer types and the implementation of semi-automatic methods. First clinical evaluations of these achievements have been started and several publications have been submitted.

The WP focused on the clinical evaluation of longitudinal tumour volumetry and on the extraction of imaging feature with discriminative potential for nephroblastoma response to preoperative chemotherapy.

The Project Progress Report reports satisfactory progress, the revised Technical Annex submitted has increased the amount of effort dedicated to this WP significantly (30% or about 25 person-months).

There are three deliverables scheduled for this WP in month 46. They will be important to judge the outcome of 40 months of effort since the initial deliverable in month 6.

WP10 – Integrated platform

Work on the Data Upload tool and the Hypermodelling Editor has been continued. Clinically Relevant Application Framework has been introduced and further developed.

The main achievements consist in the adaptation of the CHIC infrastructure for clinical research which results in the design of the CRAF environment, a suite of tools and end-users applications providing the clinicians with a full access to the CHIC infrastructure. A prototype of web-based CRAF was successfully demonstrated, the final product is under development. CRAF- evaluation and validation still remains open.

The effort has been increased by almost 40% (about 25 person-months) in the revised TA. Again the final review will have the crucial deliverables (month 44 and

month 46) making it possible to assess how much progress the project has made towards the outcome desired.

WP11 – Clinical adaptation and validation

The main result was the introduction of the CRAF component as a dedicated environment for the clinical researcher providing access to the full CHIC platform functionalities. The clinical orientation of the project thus achieved was assessed by the success of two evaluation workshops reported in D11.3. Other activities regard the provision of hypomodels and their integration into clinically oriented hypermodels. A first complete example for lung cancer has been defined and similar activities for nephroblastoma and prostate cancer hypermodels are in progress.

Report on 2nd workshop. Useful feedback obtained and correspondingly used to improve user interfaces

Two evaluation workshops have been successfully organised and reported, they were focused on collecting user opinions and feedback. Validation of models and tools not yet performed, usability has been tested. Validity of models, some validation activities would be needed to collect evidence, proof of concept, of the CHIC platform.

The activity report and D11.3 indicate a good and relevant level of activity with the introduction of the CRAF architectural component as part of the CHIC platform and general feedback from workshops. The emphasis on Prostate Cancer in the reporting raises the question of what is expected at the end of CHIC - the UNITO validation objectives are more indications of intentions than commitments (page 73 of the Project Progress Report):

" Firstly, we have to apply our models to the alternative treatments in external validation (surgery for RT nomogram and RT for the surgical model).
Secondarily, we have to develop therapeutic models including, for the surgical cohort, pathologic features and adjuvant RT, while, for the RT study, RT dose and adjuvant ADT.
Third, we should integrate the single hypo-models (to use conventional terms of the CHIC project) into a complete clinical hyper-model, that would take into consideration different clinical options and variable timing, starting from cancer staging and adding information along with therapeutic performances and follow-up."

Recommendation: Clarification of the Prostate Cancer Commitments should be documented by the project management now - well in advance of the end of the project.

WP12 – Dissemination plan

The dissemination activity during year 3 has been very effective, addressing the scientific community as well as large public audiences. The visibility of the project is well maintained both in the scientific and public space.

The work package reported on a very broad range of different dissemination activities. The visibility of the project is well maintained both in the scientific and public space. Newsletters were edited and 134 dissemination events during the first 30 project months. Interfacing with other projects is active.

Regarding exploitation, a preliminary plan for the exploitation of the CHIC platform as a whole has been prepared and is presented in D12.4: information collected from partners, CHIC exploitable outputs have been identified; 23 altogether. For each output TRL levels are defined and information collected to understand sustainability.
Three potential exploitation paths have been identified for CHIC platform: as a clinical decision support system, generic research exploitation and educational exploitation. Exploitation will be further discussed in the consortium with the Innovation radar questionnaire.

Website updated. Newsletters delivered. Several dissemination items have been reported together with a large number of peer reviewed scientific papers and contributions to conference proceedings.
Discussion of the sustainability and maintenance of the CHIC has continued in the consortium and a plan is under consideration.
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Exploitation planning requires attention and resources during the last project year, and thinking of what are the exploitable results, how they are hosted, who are exploitation partner(s), it is possible to find funding from industry, or public funds, or cross-border funding.

Therefore, the most important task of the work package for the remaining period of the project will be the development and implementation of realistic exploitation strategies for the project outputs

c. Milestones and deliverables

Indicate whether the planned milestones and deliverables have been achieved for the reporting period (please give more detailed comments first and then fill in the summary table below).

Three milestones (MS17, MS20, MS29) were planned during the period. All have been reached on due date. All deliverables have been released as planned. They are of overall good quality, substantial and informative. All are accepted.

STATUS OF DELIVERABLES			
No.	**Title**	**Status** *(Approved/Rejected)*	**Remarks**
Project Periodic report	**3rd Project Periodic report (Draft)**	**Approved**	Comprehensive report, some repetitive sections on work done
D3.1	**Report on scenarios and data from defined patients**	**Approved**	Definition of the clinical scenarios and available data relevant for the validation of CHIC environment for the three types of cancer retained in the project (glioblastoma, nephroblastoma and non-small cells lung cancers). The purpose is to enable IT developers and other basic scientists to get a good understanding of the clinical aspects when building the hypermodels and the associated simulation software. All

			models are developed on the basis of clinical data available from previous trials. The clinical relevance of the scenarios will be assessed by the capacity of the system to answer a particular clinical problem formulated as a "question to CHIC" for each of the three cancer types above. The approach is relevant, with clear and concise presentation.
D3.2	**Report on scenarios and data from prostate cancer for usage by the CHIC infrastructure**	**Approved**	The case of prostate cancer is investigated in order to test and assess the usability of the CHIC infrastructure for cancer types other than the ones retained in the project. The introductory part presents the clinical network of the Piedmont region (12 hospitals) where the model activities were evaluated and validated. The second part is devoted to the design of hypomodels used to assess the response to treatment and predict the evolution and possible recurrence of the disease after surgery, radiotherapy and hormonal therapy respectively. For each therapeutic approach, the underlying mathematical formulation and the statistical validation of the model are provided. The results and conclusions are commented in good details and limitations are indicated. The document concludes on further work needed to complete the assessment and exploitation possibility including the provision of serious games for the patient to support prevention and rehabilitation of collateral effects after surgery. The deliverable is of very good value with clear arguments and convincing explanations. Remark: missing math formulas p.16 **To be resubmitted (as docx3.2-version) with the formulas on page 16 presented in a readable format**
D4.4	**Whitepaper Recommendations for an amended European legal framework**	**Approved**	Focusses on the legal and ethical issues raised by the revolutionary role of in silico-based medical research and its consequences on the medical practice. It is a very acute analysis on the disruption introduced by the in silico-based approach whose objective is to establish and integrate mathematical models of biological processes and use such simulation models for the diagnosis and treatment of real patients. Considered as medical devices, these new computer-based decision-support tools raise big challenges regarding their certification and medical

			validation as well as the associated IPR in the perspective of a widespread use in current medical practice. The last part of the document investigates the limitation of the current (and under adoption) regulations with respect to this new context and concludes by a series of recommendations in order to take on board these new conditions in future reforms of the health legal framework. This document is of high value. It provides a deep insight and an acute analysis of the new challenges raised by the in silico approach, with relevant recommendations to deal with.
D7.3	**Hypermodels and annotation services**	**Approved**	Describes the semantic management infrastructure based on requirements from the hypermodel editor, the model repository and the clinical data repository. The semantic information includes metadata for annotations of CHIC objects (hypo/hypermodels and their parameters and clinical data objects). Annotations denote semantic relationships between objects and their parameters. Terms occurring in annotations refer to ontologies depicting a formal representation of the medical domain. Annotations are represented and stored as RDF triples. Ontologies are stored and retrieved in OWL knowledge bases. The semantic-based services consist in services for interaction with the RDF store, semantic reasoning services for interaction with the OWL knowledge bases and terminology services. The implementation is supported by the RICORDO environment including modules as RDFStore 2.0 for querying the RDF database and OWLKB 2.0 for ontology management and reasoning. The approach that is adopted appears relevant and sound. Issues are conveniently addressed and the technical solutions are well assessed. The results described in this deliverable are of high quality and interest from both the methodological and the implementation points of view.
D11.3	**Report on the second evaluation workshop round**	**Approved**	The 1st workshop (Jan. 2016 – Germany) had the objective to evaluate the relevance of the nephroblastoma hypermodel as a decision support tool for paediatric oncology. The 2nd workshop (Apr. 2016 – Canada) evaluated the clinical data repository and the nephroblastoma hypermodels operated under the CRAF environment. In both cases, there was significant

			feedback and encouraging results. The findings and conclusions of the two workshops should greatly help to improve and enhance the CDR and the CRAF. Following the workshops findings, the consortium has decided to build a virtual web-based CRAF platform for end-users interested in evaluating the CHIC infrastructure and hyopermodels. A pre-release of this evaluation platform is presented in the report.
D12.4	**Draft Plan for the Use and Dissemination of Foreground**	**Approved**	A refinement of the communication model is presented. Target groups, communication channels and messages to be delivered with contents and corresponding actions are very comprehensively defined and investigated. Exploitable outputs are discussed in length with status of technology readiness and requirements (SW, HW, dependencies with other components). The conditions of exploitation are also mentioned: status of IPR's, owners, licensing and a short introduction to the exploitation plan of the individual partners. As for previous periods, the dissemination activity during year 3 has been very effective The document is of very high quality and gives an excellent insight into the dissemination and exploitation strategy of the consortium.
D12.6	**Periodic Newsletters – Issues #2 and 3**	**Approved**	The editorial part stresses the recent evolution of the project, particularly the focus put on the clinical relevance. Other contributions are presentations of CHIC components (the Model and tools repository and the In-silico trials repository) by consortium members and a reminder of recent publications and forthcoming events. The letter of congratulations by a member of the External Advisory Board and the short discussion on the connection with MyHealthAvatar may look out of the scope of the newsletter.

d. Relevance of objectives

Indicate whether the objectives for the coming periods are (i) still relevant and (ii) still achievable within the time and resources available to the project. Assess also whether the approach and methodology continue to be relevant.

The project objectives are still highly relevant and achievable within the available time and resources. The scientific approach and methodology are relevant as demonstrated by

the quality of the deliverables and by presentations and demonstrations given at the review meeting.

After the refocusing of the project, objectives are still highly relevant but achieving them will require a lot of coordination over the last 12 months of the project. Furthermore, the feasibility of achieving all of the project objectives will depend on the development of realistic integration strategies guaranteeing the composition of robust, accurate and reproducible hypermodel environment.

The proposed Technical Annex changes will make it more likely that the objectives can be achieved. It is not possible, from the deliverables submitted for this period and the demonstrations made at the review, to make a complete assessment of whether the original considerable ambitions of the project will be met.

The scientific approach and methodology are relevant as demonstrated by the quality of the deliverables supplied.

3. RESOURCES

a. Assessment of the use of resources

Comment on the use of resources, i.e. personnel resources and other major cost items. In particular, indicate whether the resources have been utilised (i) to achieve the progress and (ii) in a manner consistent with the principle of economy, efficiency and effectiveness[1]. Note that both aspects (i) and (ii) have to be covered in your answer. The assessment should cover the deployment of resources overall and by each participant. Are the resources used appropriate and necessary for the work performed and commensurate with the results achieved? Are the major cost items appropriate? In your assessment, consider the person months, equipment, subcontracting, consumables and travel.

Several CHIC partners have adjusted their PM efforts in order to provide a more realistic budget breakdown. As far as possible, the partners balanced increased effort in one work package with reduced effort in another work package or shifted free resources in other cost categories to balance additional budget needed for increased personnel hours. The usage of project resources is below the plans, 62% used, but personnel resources have been used, over 70%.

The other expenditures are detailed and adequately justified for every partner. In total, the principles of economy, efficiency and effectiveness have been respected.

The project has submitted a revised Technical Annex in line with the changes in emphasis implemented during period 3. Effort spent in period 3 indicates that the revision to meet the new clinical emphasis may succeed.

[1] "The principle of economy, efficiency and effectiveness refers to the standard of “good housekeeping” in spending public money effectively. Economy can be understood as minimising the costs of resources used for an activity (input), having regard to the appropriate quality and can be linked to efficiency, which is the relationship between the outputs and the resources used to produce them. Effectiveness is concerned with measuring the extent to which the objectives have been achieved and the relationship between the intended impact and the actual impact of an activity. Cost effectiveness means the relationship between project costs and outcomes, expressed as costs per unit of outcome achieved." Guide to Financial Issues, Version 02/04/2009, p.33.

b. Deviations

If applicable, please comment on major deviations with respect to the planned resources.

Only minor deviations without significant impact on the project progress are reported.

4. MANAGEMENT, COLLABORATION AND BENEFICIARIES' ROLES

a. Technical, administrative and financial management of the project

Assess the quality and effectiveness of the project management, including the management of individual work packages, the handling of any problems and the implementation of previous review recommendations. Comment also on the quality and completeness of information and documentation.

The management has implemented the reorientation of the project in accordance with previous recommendations. It is very professional from the global perspective as well as at the workpackages level. The deliverables are of expected quality and very informative. They reflect an effective work organisation, and a suitable coordination between all involved parties.

The consortium satisfactorily addressed the remarks and recommendations made at the last interim review. There are obviously significant efforts and results regarding the focus on clinical orientation, integration and clinical validation.

There is, however, still limited progress regarding the hypermodelling strategies and the elicitation of best practices and guidelines in building hypermodels.

The recommendations made at the previous review were explicitly summarised and all implemented - even where it implied substantial changes.

b. Collaboration and communication

Comment on the quality and effectiveness of the collaboration and communication between the beneficiaries.

There is good coordination between the participants. Evidence of collaboration and communication is exemplified by the work done in the deliverables which gathers expertise and contribution from many different participants.
Coordination between the participants is good, with high evidence of collaboration and communication between participants.
The consortium is in permanent contact between partners through different means and quite a few meetings have been organised. All partners seem to be well aware on the project status and plans. Good team spirit in the consortium.

c. Beneficiaries' roles

Give an assessment of the role and contribution of each individual beneficiary and indicate if there is any evidence of underperformance, lack of commitment or change of interest.

There seems to be no lack of commitment or underperformance of any partner. All have contributed to deliverables and meeting materials and performed their tasks.

All partners, except the Italian one, have attended the review and were very reactive to experts' questions. The review was well prepared. Presentations and demonstrations were effective.

5. USE AND DISSEMINATION OF FOREGROUND

a. Impact

Is there evidence that the project has so far had, and is it likely to have, significant scientific, technical, commercial, social or environmental impact (where applicable)?

The project has a still a great potential for scientific, technical and medical impact. The approach proposed is a breakthrough regarding the assessment of tumour evolution in controlled scenarios, and response to treatment. The expected scientific impact should improve with the focus on clinical orientation.

In technical terms, the hypermodeling infrastructure, the associated tools and services and the methodological approach are important progress with many potential applications beyond the healthcare domain.

Large scale hypermodeling is a real challenge and the demonstration of a feasible approach would be a decisive progress. Clinical and social consequences should also be important in optimizing the diagnostic, assessment of evolution and treatment of cancer diseases helping thus to improve the patient's quality of life.

Results from evaluation workshops and consultations of the clinicians should be carefully collected and used to guide the ongoing work and results.

The project has excellent scientific progress and has the potential to advance further the state-of-the-art in the field. The major focus in the reporting period was on the demonstration of the clinical relevance of the developed modelling environment, which appears to be very convincing.

It has even already influenced cancer research, both at the treatment level and on education of medical professionals on cancer domain. The translational medical research impact is most likely, although the commercial impact is still to be ascertained.

b. Use of results

Comment on whether the plan for the use of foreground, including any updates, is still appropriate. Comment also on the plan for the exploitation and use of foreground for the consortium as a whole, or for individual beneficiaries or groups of beneficiaries, and its progress to date.

Potentially exploitable products in the clinical, technological/software and modelling categories have been analysed. The individual partners' exploitation plans and exploitation of the CHIC platform as a whole are in progress in line with the workplan, although very

general by now and need refinement and concrete actions, and not sufficiently concrete to be credible.

Discussion on the sustainability and maintenance issues of the CHIC project via the proposed Study Trial and Research Centre (STaRC) have been started, project outcomes identified and their sustainability are under analysis.

The innovation questionnaire was completed by the project in this period and the draft plan for the use and dissemination of foreground (D12.4) was submitted on time and accepted.

c. Dissemination

Assess whether the dissemination of project results and information (via the project website, publications, conferences, etc.) has been adequate and appropriate.

Dissemination is still very active: 15 peer-reviewed scientific papers published in journals or conference proceedings; 24 presentations to conferences, workshops, exhibitions and other training sessions addressing larger scientific audiences and 4 online contributions are reported. Large public audiences are addressed through the project web site and the annual newsletters.

Scientific dissemination has been intense and has raised interest in the specialised community targeted.

d. Involvement of potential users and stakeholders

Indicate whether potential users and other stakeholders (outside the consortium) are suitably involved (if applicable).

User organisations are involved as consortium members and are playing an important role for the integration work of all the system elements required to have a comprehensive demonstration to clinicians of the potential of the hypermodelling approach.
Contacts with other potential customers have taken place in the frame of the dissemination activity.
Some specific events could be organised, e.g. one for cancer researchers and one for cancer clinicians, to collect feedback and use experience from them in this kind of dedicated event on the CHIC tools and platform. This would extend the group of potential users and stakeholders involved.

e. Links with other projects and programmes

Comment on the consortium's interaction with other related Framework Programme projects and other national/international R&D programmes and standardisation bodies (if relevant).

The consortium is well linked and networked with other EU projects and initiatives in the VPH-domain. The project utilises also well earlier work and builds connections to research community. Interaction with the standardisation bodies is not evident.

Fruitful interactions with other on-going or completed European projects as p-Medicine, MyHealthAvatar, DrTherapat and AVICENNA and agreements for re-use of results have been signed.

6. OTHER ISSUES

If applicable, comment on whether other relevant issues (e.g. ethical issues, policy/regulatory issues, safety issues) have been handled appropriately.

An interim review is recommended to Nov/Dec 2016 to assess progress of the work by then and to ascertain the successful completion of the different tasks. The milestones for the coming period are MS2, MS 4, / D2.4 / hypermodels to be accepted by users, MS7, MS 10, MS 13, MS14, MS18, MS 21 and MS26: Chic integrated platform in the clinical environment.

The interim review could be organised around these two milestones:

- MS4, Hypermodels are accepted by users, at month 42 (Sept 2016), deliverable D2.4,
- MS10, Final version of the CHIC Architecture, at month 44 (Nov 2016), deliverables D5.1.2, D5.1.3, D5.2.2, D5.3.

A two day final review is recommended (as mentioned in Section 1. c. (**Comprehensive demonstrations of the whole system**, bringing into play all aspects (repositories, security, hypermodel definitions, different failure modes, etc.) all seen from a clinician's point of view should be prepared **for the final review, recommended to be scheduled over two days**, so as to have enough time for all demonstrations and finalizing discussions, to be held at Iraklion, site of the Integration Coordinator (FORTH))

Name(s) of expert(s):

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Signature(s): *[e-Signed]*

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