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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:	Final Period, from 01/04/2016 to 31/03/2017
Place of review meeting:	Heraklion, Crete
Date of review meeting:	23-24 May 2017
Experts:	Tor BLOCH Henry KANOUI Jorge MARTINEZ de HURTADO Pirkko NYKANEN Elena TSIPORKOVA
Project Officer:	Stefanos GOUVRAS

Individual report	☐
Consolidated report	☒

European Commission
Information Society and Media

SEVENTH FRAMEWORK PROGRAMME

European Commission

Directorate-General Communications Networks, Content and Technology

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*

The objective for this final review was to ensure that the project demonstrates significant results, and presents comprehensive sustainability once the funding period ends, together with approval of the deliverables submitted, including important demonstrations and discussions about the future exploitation of the significant amount of results obtained.

The project objectives have been achieved and the reported work has been overall of high scientific quality. All milestones of this last period have been attained. The deliverables produced are excellent documentations of work. All are accepted.

The multiscale hypermodelling paradigm and its technological implementation on the CHIC platform (with extensive functionalities, visualisation and modelling tools, private cloud and integrated security framework) as well as the hypermodels of the four cancer types constitute major scientific innovations of this research project.

Demonstration of the project achievements constituted a major subject in the final review agenda. The four different cancer type scenarios in relation to the developed hypermodelling strategies have been presented and activated through the CRAFT clinical application environment.
The nephroblastoma hypermodel was discussed in length and convincingly demonstrated along different scenarios (combining different patients, different models, different treatment conditions, etc.) addressing the clinical question of tumor growth and reaction to treatment along time. Related imaging data were presented with the CCGVIS visualization tool that appears to be a promising and flexible system. The nephroblastoma hypermodel is very advanced and clearly orchestrated as a composition of several different physical models. The sustainability appears most realistic supported with concrete plans for future clinical trials and prospective studies. Umbrella protocol and ethical approval for nephroblastoma have been finalized already and patient recruitment will start in 2017. Once this phase is completed, it is envisaged that Philips, as partner, takes over on its own resources the development and long term exploitation of a clinical DSS, but this is still a matter of years.

For the lung cancer demonstrator, the clinical scenario focused on patients with a high risk of reoccurrence. The models shown were data-driven statistical models built upon machine learning methods with Bayesian and neural network classifiers. The demonstrator was quite restricted and simple and the very small number of patient data (9-15 patients) used to build the models are hardly statistically representative. Provisions for collecting larger data sets necessary to improve the models in order to start credible validation have been agreed among the consortium.

The glioblastoma demonstrator addressed the estimation of survival at the time of diagnosis using immunotherapy. The modelling approach is based on an elaborate statistical analysis of a sample of 134 patients with the aim to extract relevant features involving both the tumor and the immune system of the patient. This model could not be fully validated but relevant correlations have been detected. Clinical outcomes from this first experiment with immunotherapy for glioblastoma are promising. The work is planned to continue with a new cohort of patients to be analyzed and collect more evidence.

The prostate cancer demonstrator concerned the adjuvant androgen deprivation therapy effect on cancer progression. A hybrid, multilevel (pharmacokinetics, pharmacodynamics, molecular), continuous and discrete model of prostate cancer validated with over 3000 retrospective patients of Eureka1 study was demonstrated. This model simulates the ADT treatment and the post-treatment PSA value to assess the recurrence and progression accounting for patient specific genetic profile. A small number of patient cases were shown as examples of model outputs. Clinical validation is planned to be done in the future, with prospective patients.

The hypermodelling editor has also been demonstrated, with a quite naïve user interface to retrieve and create new hypermodels. Recommendations from previous reviews related to user friendliness, reasoning capabilities and consistency checking have been taken into account while developing new functionalities for the editor.

In summary, the demonstration session was very convincing and perfectly illustrated the work achieved, showing how different modeling approaches and different models developed by different teams can be combined into multiscale hypermodels. The clinical rationales behind the scenarios have been very convincingly demonstrated. From the four demonstrations, nephroblastoma and prostate cancer seem to be promising and advanced. Both lung and glioblastoma cancer cases are not sufficiently mature for advanced modelling approaches as there is still very little understanding of the underlying mechanisms behind the phenomena under study.

The clinical validation of hypermodels (including clinical validity and clinical value) has been a major topic discussed during the review. The developed models and hypermodels have been partially clinically validated with patient data and simulations. For the longer term, the proposed multi-phase methodology for the validation of hypermodels following the four phases in drug development has been further elaborated. However, scientific knowledge is evolving faster and faster and alternative validation paths better suited for taking this dynamicity into account should be considered. The importance of rigorous validation and demonstration of the clinical relevance has been well recognized by the consortium. Large efforts are needed to collect evidence on the clinical relevance and validity of the system and the partners have agreed to proceed with future validation and exploitation activities. The ways and possibilities for further funding are under exploration and a concrete sustainability plan as well as an exploitation plan have been formulated and agreed upon to ensure the continuation after the project end.

The results of the CHIC project can help to improve diagnosis and treatment of cancers. However, the deployment of this technology in clinical decision support systems needs clinicians to be educated in modelling to be able to understand and use these kinds of model-based systems that require that all necessary patient data are available.

The dissemination efforts are very intensive and covering a very broad range of activities and stakeholders all along the project. This effort is quite exceptional considering the quality of the contributions. Concrete and credible sustainability and exploitation plans have been developed and agreed upon.

The management has been very effective along the whole duration of the project and the consortium has been very reactive on the reviewers' recommendations. The recommendations from the previous review have been well and appropriately addressed by the consortium, in particular regarding the reorientation of the project towards clinical usage that lead to the design and development of the CRAF environment. Resources have been used according to the project needs and perfectly correspond to the work achieved.

Due to the potential clinical breakthrough knowledge in the VPH Cancer domain, it is suggested to consider applying for new applicable EU funding for the next phase, once products and services which can be, or will be, patented by the relevant partners, have been identified, as stated in the Project Final Report.

b. Recommendations concerning the period under review

NONE

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.

Due to the potential clinical breakthrough knowledge in the VPH Cancer domain, it is suggested to consider applying for new applicable EU funding for the next phase, once products and services which can be, or will be, patented by the relevant partners, have been identified, as stated in the Project Final Report.

All possibilities should be explored by the project to protect the results of CHIC in a way where further development work can continue driven by the need to reach clinical validation at some point in time. All avenues to advance towards clinical validation have to be explored. It is of utmost importance that the results of the CHIC project not be lost when the EU funding ends.

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.

The objectives have been very well achieved and the work is well in line with the DoW. There are excellent progress towards objectives in research and IT system development and implementation issues. Clinical relevance is high with potential breakthrough technology to be used in predefined clinical scenarios, in which actual knowledge remains uncertain. There is fruitful interaction and good integration across workpackages and between individual participants. An IPR memorandum of understanding has been completed to support future exploitation of project results.

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.

All the work packages have delivered according to the roadmap described in DoW Annex 1.

WP1: Project Management.
The project management is of excellent quality and led to the successful completion of the project activities within the foreseen budget.

WP2: User Needs and Requirements.
Focused on the further development of clinical scenarios and use cases. The consortium also invested further efforts related to gathering requirements for achieving acceptance of the hypermodelling approach by clinicians and patients.

WP3: **Clinical and Translational Science Scenarios.**
The activities related to collection of data for all four cancer types addressed continued. All developed hypermodels were evaluated by the appropriate clinical partners.

WP4: **Legal and Ethical Framework.**
The data protection framework of CHIC has been successfully deployed and the validated data is ready to be shared. A framework agreement for data retention during the project exploitation phase was prepared. An IPR memorandum was completed and signed to assist regulation of partner foreground exploitation. The quality of the deliverables in this area has been very high throughout.

WP5: IT Architecture.
The private cloud infrastructure of the project is fully functional including CRAF (Clinically Relevant Application Framework) component. The CHIC security framework has also been deployed and further developed.

WP6: Cancer Models and Hypermodel Design.
The WP advanced in the further development, focusing on the clinical relevance, of hypermodelling framework considering both mechanistic hypermodels and data-driven (machine learning) models. The development of all four CHIC hypermodels has been successfully completed. All four CHIC hypermodels have undergone several improvements and clinical adaptation and partial clinical validation. They have also been integrated into the CHIC platform.

WP7: Hypermodelling infrastructure.
The final version of the hypermodelling infrastructure has been completed. A continuous integration testing framework has been developed in order to ensure the quality assurance of new models added to the repository. Concurrent execution of hypermodels has also been made possible.

WP8: Model and Data Repositories.
New functionalities have been provided to the Model Repository including also new web services. These services have enhanced the integration of the Model Repository with the Hypermodelling Editor and the Hypermodelling Execution Framework. Additionally, all the models developed by the modelling partners have been registered within the Model Repository according to the guidelines provided.

WP9: **Image Processing and Visualization.**
CGGVis has been further developed. Promising results of nephroblastoma segmentation and an implementation of mobile app based visualization have been achieved. The performance of different approaches on imaging data sets has been evaluated.

WP10: **Integrated Platform.**
CRAF has been fully integrated with the backend services of the CHIC platform and is able to support four cancer types (Nephroblastoma, Small Cell Lung Cancer, Glioblastoma and Prostate Cancer) and the generation of cancer and clinical question specific reports. The joint effort made by FORTH and USAAR in getting the CRAF framework and the CHIC platform consolidated and guaranteeing its availability for the 20 months following the end of the CHIC project has been very impressive and has required a lot of effort.

WP11: **Clinical Adaptation and Validation.**
Partial clinical validation and acceptance of hypermodels have been performed during the reporting period. The obtained validation results for all four cancer types need to be further supported by the conduction of prospective clinical trials in order to eventually definitely prove the clinical credence and the clinical value of the developed hypermodels.

WP12: Dissemination and Exploitation.
The work package reported on an extremely broad range of different dissemination activities. The visibility of the project is well maintained both in the scientific and public space. The work package also developed a credible and well elaborated final exploitation plan.
It should be noted that the first educational impact of the work is now occurring: Specific exploitation of the CHIC platform for academic teaching purposes will take place within the framework of the globally first postgraduate course on *In Silico* Medicine (http://www.vph-institute.org/news/new-postgraduate-subject-on-multiscale-cancer-modelling-and-in-silico-medicine-mscm-ism.html), which is being taught by the CHIC coordinator, Res. Prof. G. Stamatakos in the affiliated School of Electrical and Computer Engineering, National Technical University of Athens. Other research and academic bodies of the consortium will exploit the CHIC platform in a similar way. As an example, TEI-C has introduced a subject called “Bioinformatics and Modeling of Biological Systems” into the curriculum of its undergraduate course on Informatics Engineering based, to a large extend, on the experiences and material developed in the context of the CHIC project.

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).

During the period, all deliverables where released on time. All are of very good scientific and technical quality, and are approved. However, it would have been desirable to obtain the final versions of the Final and the 4th Progress Reports prior to the actual review.

All milestones have been met.

STATUS OF DELIVERABLES			
No.	**Title**	**Status** *(Approved/ Rejected)*	**Remarks**
-	**Periodic Report #4 (01/04/2016 -> 31/03/2017)**	**Approved**	A detailed description of activities and achievements performed during the 4th year. Results obtained in by work packages and tasks are reported in details, as well as the role and contribution of individual partners. Project management meetings and events, dissemination activities and analysis of resources consumption are reported.
-	**Final Report**	**Approved**	A very accurate description of achievements with respect to the project context and objectives, reviewing also impact and exploitation of results. Concludes on the socio-economic impact and societal implications and financial summary.
D3.3	**Demonstration of the developed Meta- and Hyper-Multiscale Models and Repositories**	**Approved**	Presents the developed models in their clinical context, good report.
D5.1.3	**The final CHIC technical architecture (including the security tools and cloud infrastructure)**	**Approved**	The report presents the architecture from functional and deployment views. A detailed and comprehensive architecture description, good report.
D6.4	**Clinical adaptation and partial validation of hypermodels**	**Approved**	Presents the methods used for clinical adaptation and partial validation of the developed hypermodels and the results from these activities. A comprehensive and detailed report on preliminary validation activities.
D9.2	**A model and data visualization toolkit**	**Approved**	Presents the visualisation desktop tool CCGVIS, image segmentation algorithm for nephroblastoma, timeline visualisation of medical data and a mobile application for visualisation in prostate cancer care. A detailed and comprehensive report.
D9.3	**A multimodal and longitudinal brain tumour image analysis tool**	**Approved**	Describes the development, testing and validation of algorithms, methods and technologies for brain tumor image analysis with the glioblastoma case. Novel technologies have been developed and emphasis in validation has been on technical and clinical exploitation. Radiomics approach has been introduced, it has the purpose to combine imaging and non-imaging patient information with machine learning techniques to derive novel biomarkers to assess patient survival and tumor characteristics. Good report.
D9.4	**The integrated DrEye platform for image analysis and visualisation**	**Approved**	Describes the DrEye platform and its integration with the CCGVIS visualisation tool. The purpose has been to develop a unified imaging platform that can be used for analysis and visualisation and by both clinicians and researchers. DrEye is an open access platform. Good report.

D10.4	**The CHIC Hypermodelling Editor and orchestration environment**	**Approved**	Presents the design, development and architecture of the hypermodelling editor which integrates with the data, model and hypermodel repositories. Good and detailed document.
D10.5	**The CHIC Clinical Research integrated platform**	**Approved**	Describes the CRAF, that supports clinical research by integrating the CHIC components and repositories and offering a simple and smooth user interface. CRAF is accessible via Internet and it applies the CHIC security framework. The user acceptance/usability issues are not included in the report.
D11.4	**Validation of CHIC infrastructure as a whole**	**Approved**	Validation has been done by executing the three cancer models, nephroblastoma, lung cancer and prostate cancer, with the CHIC platform. The main aspects in validation have been reproducibility and execution time demands of the models. The workflow validation is presented as a step-by-step process of the clinician. The results are encouraging, they show that CHIC platform is table but more validation is needed on user acceptance and clinical validity. Good report.
D12.5	**Final Plan for the Use and Dissemination of Foreground**	**Approved**	Dissemination activities presented in detail. CHIC exploitable outputs have been defined: 14 IT/SW components, 12 models and the CHIC platform as a whole. An analysis of the identified outputs and their status and exploitation potential has been presented. Exploitation plans per partner are presented. A path to clinical validation has been explored to exploit the CHIC platform as a clinical decision support system. CHIC platform will be used after the project lifetime for hypermodelling the nephroblastoma in UMBRELLA protocol. The partners have agreed to maintain the infrastructure until the end of 2018 for further validation and to conduct research. It is estimated that clinical validation may take about 7 years to complete with prospective/retrospective/randomised clinical trials. Good report.

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.

Objectives have been relevant all along and they are considered to have been achieved within the project´s life. The value of the scientific approach and methodology has been demonstrated by the quality of the deliverables.

e. For Networks of Excellence (NoEs) only

Assess how the Joint Programme of Activities has been realised for the period and whether all the planned activities have been satisfactorily completed.

N/A

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.

The resources usage was presented in the review. The figure show slight underspending of the financial resources due to the lower direct costs of the partners. Person-months usage is above the plans. The resources have been used to achieve progress and with efficiency and effectiveness.

b. Deviations

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

No big deviations since the last review and the revised Technical Annex, some slight modifications between the partners.

[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.

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 project management (technical, administrative and financial) has been excellent and managed to steer the project activities to a successful completion of the defined project objectives.
Electronic communication means, e.g. skype, have been widely used.

b. Collaboration and communication

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

Collaboration and communication have been excellent, as shown by the quality of achievements gathering contributions from many different participants.

The consortium has worked well together; they have had a good team spirit and excellent cohesion and cooperation. During the reviews it has been clearly visible that all partners are committed to the project and they are aware of their shared vision and mission.

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.

All participants have been fully committed and the partners are highly skilled and very motivated towards the project goals. There is no evidence for underperforming beneficiaries and no changes in the consortium.

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 had excellent scientific progress and has the potential to advance further the state-of-the-art in the field. Potential scientific impact is high, both for clinical research and for cancer treatment. The technical hypermodeling infrastructure features important progress with many potential applications beyond the healthcare domain.

Clinical and social consequences could also become important with time in optimizing the diagnosis and treatment of cancer diseases helping thus to improve the patient's quality of life. The developed models, tools and services offer new ways and options to study cancer processes and develop new treatments and analysis methods. The clinical relevance of the developed modelling environment is also very convincing, but still requires further clinical validation to facilitate adoption in the medical practice

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.

The effective use of results for routine clinical practice is dependent on a full validation process that is beyond the scope of the project. The consortium has prepared itself well for the exploitation of foreground but real economic and clinical impact will only come after the validation has been properly carried out. It is estimated that clinical validation may take about 7 years to complete with prospective/retrospective/randomised clinical trials. Meanwhile, the sustainability of the achievements for nephroblastoma appears most realistic supported with concrete plans for future clinical trials and prospective studies. Umbrella protocol and ethical approval for nephroblastoma have been finalized already and patient recruitment will start in 2017.

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c. Dissemination

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

The project demonstrated excellent dissemination, supported by an impressively long list of dissemination activity e.g. journal articles and organisation and participation to conferences and workshops is reported. This is quite exceptional considering the quality of the contributions.

e. Involvement of potential users and stakeholders

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

Potential users and stakeholders are well involved, in particular through the organisation of dedicated conferences, presentations and studies. Re-orientation of CHIC during the current year to become more clinically guided has improved involvement of clinical and research stakeholders. The consortium has worked closely with the medical and research communities to raise awareness and to identify the needs and requirements for exploitation to the clinical practice. Users have been involved in partial clinical validation.

f. 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 project has had active collaboration and interaction with many EU VPH-projects, with scientific communities and associations as well as universities and research institutions. The Scientific Advisory Board has brought external expertise and interactions with many leading actors in the field.

6. OTHER ISSUES

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

NONE

Names of experts:	Signatures:
Pirkko NYKANEN	*[e-signed]*
Elena TSIPORKOVA	*[e-signed]*
Tor BLOCH	*[e-signed]*
Henry KANOUI	*[e-signed]*
Jorge MARTINEZ de HURTADO	*[e-signed]*
Date: 06.06.2017	