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1 Executive Summary

As more work is done within the consortium, more exploitable results will be attained. But at this stage many consortium members can readily identify the area of the project that will produce results which they will wish to exploit.

CO01: Siemens research is mainly involved in the areas of the project which are focused on decision support systems based on knowledge discovery. More specifically, Siemens is developing a comprehensive set of new applications in the area of knowledge-based imaging, combining it to a holistic approach for clinical decision support systems leading to a new personalized health-care paradigm. A first technology developed in this direction is the "CaseReasoner", where similar data sets based on a pre-selected feature ranking are returned. The CaseReasoner is expected to be at the base of new applications providing clinicians with fast search and retrieval of similar cases in distributed databases. Such concepts will enrich the decision making process by bringing distributed knowledge to the point of care. The work on the pulmonary trunk quantification pioneered by HeC has inspired Siemens to develop truly innovative applications for the characterization of the aortic and mitral valve, for adult cardiology.

P02: Lynkeus is seeking to exploit the knowledge and expertise it has gained in project creation, consortium building and project management, offering its services to organizations seeking to apply for EC funding in a wide range of research areas. Lynkeus will highlight the added value of the model it has developed, based on de-coupling the functions of global coordination and of Project Management. Lynkeus will also highlight how it can be especially beneficial if the Project Management system is designed with "vision management" as a central tenant, entwining it with the leadership of the dissemination work. To these ends, Lynkeus will continue enhancing the use of online management platforms and will strive to ensure that the Learning Objects prepared within the Training and Dissemination WPs of Health-e-Child will continue to be available online beyond the conclusion of the project.

P03: IGG is interested in exploiting the new techniques that allow the early detection of bone damage in patients with juvenile idiopathic arthritis. These techniques will be useful in clinical trials for the early detection of the disease possibly leading to new assessments of the potential efficacy of new tested drugs. The data collected and analyzed with new IT instrument developed by Health-e-Child will allow the future identification of new markers which may be capable of acting as appropriate predictors of the disease course. Additionally IGG is also interested in participating in the Intelligent Information Management/Medical Digital Library system currently being discussed with UCL and OPBG, with a specific interest to a possible rheumatology extension of it, oriented towards putting into being the tri-dimensional atlas of normal and diseased joints in children.

P04: UCL is looking to build on the integrated HeC experience by developing an Intelligent Information Management system for Congenital Heart Diseases. The development of such a system will include a variety of data, including Morphology, providing anatomical descriptions from post-mortem specimens, imaging via echocardiography, magnetic resonance, computed tomographic imaging, cardiac catheterisation and video clips of surgical procedures. Such a system will be as a unique resource for teaching, not only for professionals such as cardiologists, imagers, and surgeons, but also for those in Universities, such as anatomists and those undergoing undergraduate medical training, but also for patients and their parents,

who will be able to learn more about the conditions they have, and the options available for treatment. Validation of clinical images and data will be a crucial concern, and close cooperation with the International Nomenclature Society, and with other clinical and technological partners within Health-e-Child, and also beyond the Consortium, will be pursued.

P06: CERN's exploitable knowledge comes from the expertise it will gain in the EGEE gLite deployment, support operation and management. This will indirectly lead to a collection of EGEE gLite software focused on monitoring, operation tools and support tools which will be able to be applied to any application that requires a controlled environment to manage distributed computational and storage resources for a virtual organisation.

P09: The University of the West of England, Bristol has a long-term interest in pursuing the research and development effort related to the Health-e-Child project. The primary exploitation interest of the university concerns grid technology, advanced database management and knowledge representation, and is academic: the accumulated knowledge and expertise shall be capitalized on an exploited in ongoing and future research projects, just like in Health-e-Child UWE has been building on the expertise carried over from previous projects in developing and managing medical grid infrastructure, medical database management, ontology engineering and alignment techniques.

P10: UOA plans to exploit the knowledge discovery tools that they have developed during the Health-e-Child project, such as AITON, the scalable data mining platform for medical applications developed under WP13, and ACL (AITON Clean-up), a tool for data curation and quality control of clinical data. UOA is also planning to continue the development of these tools, past the end of the Health-e-Child project, and carry on providing support for current users. Building on the results of Health-e-Child and the developed tools, UOA will be able to provide state-of-the-art solutions for knowledge discovery, data analysis and validation, outcome analysis and risk certification for larger Intelligent Information Systems.

P11: Some of the results achieved in developing Health-e-Child have enabled DISI to enter the exploitation phase, supporting the spin-off of a new company, CAMELOT srl (Computerized Analysis of MEDical data with Learning and Optimization Technologies) in which the plan is to devise solutions to biomedical problems in the area of Computer Aided Diagnosis and Decision Support Systems. The expertise of CAMELOT relies on the ability to study solutions tailored to doctors' needs and based on state-of-the-art computer vision and machine learning technologies. CAMELOT is currently seeking partnership for developing innovative software products in areas and image modalities different from the ones explored in Health-e-Child.

P12: INRIA will study the possibility of licensing all the elements of its technology that can support the exploitation of the results obtained within the HeC consortium. In particular, the geometric models of the heart and the brain, along with the registration tools relating generic anatomies (atlases) to patient-specific images and data or images in longitudinal studies. A second set of methods that could potentially be transferred is related to the modelling of the physiology, for instance models of evolving tumours and electro-mechanical models of the heart contraction. INRIA will also investigate the possibility to exploit the models developed in the paediatric domain in other medical domains (e.g. general cardiology or neurology) or in other disciplines, e.g. in neuroscience.

P13: EGF will develop future training and educational courses based on the dissemination and training activities performed in the project, this will allow Health-e-Child materials to be exploited by a larger community and contribute to EGF's patrimony of teaching materials and online courseware to be offered to the wider medical community which will in turn attract further students and lecturers. All of the training courses which have taken place and are planned to take place as part of Health-e-Child will be offered as an e-learning service in order to allow courses to be consumed post factum by the Health-e-Child community and other interested parties via the internet on the EGF website, irrespective of the state of the Health-e-Child website.

P14: ASPER will seek to exploit the work done in conjunction with EGF, Siemens and IGG. Its exploitation activities will focus on the DNA testing microarray for detection of mutations that are connected to (paediatric) pilocytic gliomas. The contribution by partners will be to compile a scientifically relevant mutation list to ensure the commercial success of this test.

P15: MAAT expects to deliver an advanced healthgrid platform conforming with the European regulations related to personal data protection, and plans to progressively open access to the sources of this platform to the community. A model is being studied which will leverage existing mechanisms in Europe to widely spread the technology.

P17: OPBG sees the tools developed within Health-e-Child as having exploitation potential to improve the efficiency of clinical practices. The tools, among other things, have demonstrated the ability to track varied patient data from different applications and perform similarity searches on the diverse data across four different clinical Institutions. OPBG is devising an Intelligent Information Management system based on the work of Health-e-Child which will be able to be utilized in large institutions such as OPBG to connect medical relevant databases. The system will exploit the tools developed in Health-e-Child to perform patient similarity search, outcome analysis, cost analysis, and risk stratification, leading to a more efficient hospital.

Appendix 1: additional common exploitation goals, shared by some of HeC's partners, referring to the possibility of jointly developing an Intelligent Information Management/Medical Digital Library System

The goal is the creation of an Intelligent Information Management/Medical Digital Library System capable of handling massive data. Education facilities would be provided on top of it not only for physicians but also to patients/parents. Automated computing tools shall be provided for:

- automatic validation of data and imaging
- analysing the data, allowing for epidemiological studies, outcome analysis, and risk stratification
- similarity search
- knowledge discovery aiming at creating a system capable eventually of:
 - attracting ever more images and related datasets requiring validation
 - offering a fee-for-service facility for similarity search and knowledge discovery.

2 Exploitation Plan/Activities

2.1 CO01 Siemens

Disclaimer

The HeC consortium does not develop any products. The prototypes generated during the course of HeC are not to be used for clinical routine. Systems developed in parallel or after the HeC project will of course strictly follow the European Medical Device Directive and will undergo all necessary tests and validation procedures, e.g., CE labeling, FDA approval, etc. Siemens has large experience in medical in-vivo and in-vitro fields and in clinical IT systems and plans to exploit the results from HeC in the following directions.

Applications

For the duration of HeC, Siemens is mainly involved in the areas of decision support systems based on knowledge discovery. Furthermore Siemens interests lie in the modeling aspects of data, its visualization, and primarily its longitudinal, vertical and horizontal integration across modalities and data origin also taking into account new emerging data sources, e.g. proteomics. New important visualization techniques are tree maps, nearest neighborhood graphs, and heat maps. Here we provide a new integrated view on large medical data sets from different data sources.

Siemens is developing a comprehensive set of new applications in the area of knowledge-based imaging. In this context the advanced research pursued in HeC complements nicely with the Siemens internal development efforts. For example:

- the prototype used in HeC for the automatic analysis of the left and right ventricle of the heart based on MRI data sets is currently being productized by Siemens;
- the work on the pulmonary trunk quantification pioneered by HeC has inspired Siemens to develop truly innovative applications for the characterization of the aortic and mitral valve, for adult cardiology;
- automatic 3D parsing of the carpal bones for erosion quantification in arthritis is another example of an application that could be brought to market in the near future.

HeC demonstrates the in-vivo and in-vitro integration of data, i.e. integration of laboratory, "omics" data with the traditional imaging examinations. This integration leads to a holistic approach for clinical decision support systems leading to a new personalized health-care paradigm. A first technology in that direction is the "CaseReasoner" where similar data sets based on a pre-selected feature ranking are returned. It is expected the CaseReasoner to be at the base of new applications providing clinicians with fast search and retrieval of similar cases in distributed databases. Such concepts will enrich the decision making process by bringing distributed knowledge to the point of care.

Platform

The HeC platform has been developed as a forward looking research platform facilitating the implementation of a new vision for pediatric healthcare, in which the huge amount of distributed knowledge available in participating hospitals is properly exploited. While Siemens recognizes the research nature of the HeC platform, it will further pursue efforts to bring such knowledge platforms to market, with a focus to improve the quality of care in pediatrics while reducing its cost.

Ontologies

Ontologies have been studied in HeC for semantic modeling of clinical data. While the use of ontologies in clinical routine at this stage is still mainly a research topic Siemens will further pursue the integration of medical ontologies in future knowledge applications.

The experience gained in HeC enabled Siemens to lead a 5 year effort to apply semantic technologies to medical imaging. This particular use case MEDICO is funded by the German Ministry of Economics (BMWi) under the umbrella of the lighthouse project THESEUS. (URL: <http://www.theseus-program.de/en-US/home/default.aspx>)

Data

The data collection and its annotation are important inputs for the development and testing of new algorithms in the areas of knowledge discovery and clinical decision support systems. Those integrated data sets can further be used to verify and fine-tune the prototypes developed during the HeC project. Therefore clinical data is an important asset of the project.

Regulations

The work package dealing with the collection and distribution of data across hospital boundaries and country borders will generate important knowledge about how to deal with the European regulations and country specific laws. This knowledge will provide in-depth guidance for all partners for distributed data collection and its remote or centralized analysis.

Visibility

Siemens Healthcare sector increases its visibility in the pediatric sector and community while doing research in this area. Here new technologies from data integration towards clinical decision support systems are applied to children's personalized medicine. HeC expands its biomedical platform in this area. One further step is the new sister project "Sim-e-Child" (funded by the EC within FP7) which primarily connects the Johns Hopkins University hospital in Baltimore, U.S.A to the HeC grid network.

2.2 P02 Lynkeus

Lynkeus will seek to exploit the specific skills developed in the last five years, since it gave birth to what has proved to be an original model of Project Management of complex integrated projects, involving partners from many countries with diverse scientific, technological and clinical backgrounds.

Lynkeus will seek to exploit the experience gained by creating the initial proposal that led to HeC, by adding some of HeC's key industrial, clinical and technological partners to the consortium, by project managing the Consortium, by disseminating HeC's vision and results, and finally by adding OPBG to the consortium's clinical partners. A further example of "strategic management", helping to build up ad hoc consortiums, is shown by the Sim-e-Child proposal, submitted in April 2009 by Siemens (coordinator), partnering with other 8 American and European institutions (among which Maat GKnowledge, OPBG, and Lynkeus as Project Manager) in response to an FP7 call on International cooperation on VPH (Objective ICT-2009.5.4), which is currently under negotiation with the EC.

Lynkeus will endeavour to offer similar services to organizations that are seeking EC funding for innovative research projects. Lynkeus will highlight the added value from an approach which operates with a separation of functions between global coordination, for which the leading industrial or clinical partner is responsible, and a professional (and multilingual) Project Management, closely integrated into the decision making structure of a Consortium and strongly supporting its coordination – but not infringing of the Coordinators legal responsibilities to the Commission. This is believed to be especially beneficial if the Project Management system has been designed with "vision management" as a central tenant, because this way the Project Management can better strategically support the Coordinator and can also be usefully entwined with the leadership of the dissemination work within the project.

Lynkeus will seek to further develop the use of specific management tools like Project NetBoard (in cooperation with Vitamib, Grenoble, France), a professional Internet-based collaborative platform for time effective and cost efficient management of EC FP7 projects, consistent with the use of a project website. The designing of project portals, based on a Plone/Zope platform which facilitates collaborative work among partners, the management of content (CMS) and allows access rights to be managed by separate different working areas will also be offered by Lynkeus for EC funding based projects. The approach will be that of developing such portals as effective dissemination tools, capable of covering the project's goals, objectives, accomplishments, background information and partners' role and contribution, and running in parallel with the project's evolution, through constant updating and maintenance, providing timely and appropriate information.

Lynkeus will also seek to exploit the Learning Objects which, within Health-e-Child, are being developed in cooperation with UWE and EGF. This will involve ensuring that the knowledge about the use of the HeC's platform and the tools continue to be available after

the end of the project. This will be done by both maintaining their presence on the EGF website and devising a way of retaining the HeC website. These learning objects will be used to train new users of the platform at the current clinical sites and at potentially new clinical partners.

Finally, Lynkeus will also seek to support the consortium's exploitation of its integrated nature by investigating and promoting future research activities that complement the skills set and the relationships that have been developed during the course of the Health-e-Child.

2.3 P03 IGG

IGG is confident that the Health-e-Child project has provided new relevant techniques that will allow the early detection of bone damage from the follow-up meeting of patients with juvenile idiopathic arthritis. Moreover, these same techniques will be useful in clinical trials for the early detection of the disease possibly leading to new assessments of the potential efficacy of new tested drugs.

Further data collection can be instrumental to create a magnetic resonance based, tri-dimensional atlas of normal and diseased joints in children, constituting the premise for the development of new techniques that will allow the quantitative biochemical analysis *in vivo* of the of the articular cartilage.

Indeed, in addition to a morphologic study, it will also be possible, as an element of particular interest, to identify through the use of appropriate MR techniques macromolecular changes in the articular cartilage at stages when the damage induced to the cartilage is still potentially reversible. Two techniques, in particular, appear promising: the dGEMRIC technique, which provides *in vivo* quantitative information about the fixed charged density of the articular cartilage that is closely related to the glycosaminoglicane (GAG) concentration; and the T2-relaxation mapping technique, that provides information on distribution and integrity of type II collagen-based fibrillar network. This will make it possible to detect early, and potentially still reversible, biochemical changes of the cartilage matrix components (before macroscopic changes have occurred), which are susceptible to evolve towards morphologic cartilage changes (thinning, erosion).

Finally, the data, analyzed with new IT instrument developed by Health-e-Child will allow the identification of new markers capable of acting as appropriate predictors of the disease course.

Beyond these clinical directions of further exploitation of Health-e-Child's outcomes, IGG is also interested in participating into the Intelligent Information Management/Medical Digital Library system currently being discussed with UCL and OPBG, with a specific interest to a possible rheumatology extension of it, oriented towards putting into being the tri-dimensional atlas of normal and diseased joints in children.

2.4 P04 UCL

UCL is looking to build on the integrated HeC experience by developing an Intelligent Information System for Congenital Heart Diseases (CHD) for the following conditions:

1. Atrial Septal Defects within the oval fossa
2. Sinus Venosus Venoatrial Communications
3. Atrioventricular Septal Defect
4. Ventricular Septal Defect
5. Aortic Valvar Stenosis
6. Aortic Valvar Incompetence

7. Coarctation of the Aorta
8. Interrupted Aortic Arch
9. Aortic Vascular Rings
10. Left Pulmonary Arterial Sling
11. Marfan's Syndrome
12. William's Syndrome
13. Mitral Stenosis
14. Mitral Regurgitation
15. Hypertrophic Cardiomyopathy
16. Dilated Cardiomyopathy
17. Noncompaction Cardiomyopathy
18. Tetralogy of Fallot with pulmonary stenosis
19. Pulmonary Stenosis
20. Tetralogy of Fallot with pulmonary atresia
21. Transposition
22. Congenitally Corrected Transposition
23. Common Arterial Trunk
24. Double Outlet Right Ventricle
25. Double Inlet Left Ventricle
26. Hypoplastic Left Heart Syndrome – Norwood Stage 1
27. Tricuspid Atresia
28. Anomalous Coronary Arteries
29. Anomalous Left Coronary Artery from Pulmonary Trunk
30. Kawasaki Disease
31. Totally Anomalous Pulmonary Venous Connection
32. Partially Anomalous Pulmonary Venous Connection
33. Ebstein's malformation
34. Right Isomerism
35. Left Isomerism

The development of such a system will include a variety of data, including Morphology, providing anatomical descriptions from post-mortem specimens, imaging via echocardiography, magnetic resonance, computed tomographic imaging, cardiac catheterisation and video clips of surgical procedures. All the data types needed are available at UCL though not in sufficient quantities for a state of the art system since at UCL there is data for roughly only 50,000 patients. UCL is willing to contribute clinically to the development of tools aiming at providing automatic validation of data and imaging. Additionally tools along the same lines as those which have been successfully developed by HeC could be utilised for similarity searching and knowledge discovery.

A process of validation will be needed for creating a clinically relevant Intelligent Information Management system, and UCL can build on its ongoing cooperation with the International Nomenclature Committee (<http://www.ipccc.net/>) (INC) so that the morphology, images, and surgical videos could be checked for validation taking advantage of the world class expertise accrued through the INC and the CTSNet (<http://www.ctsnet.org/>). The system will be able to provide examples of lesions to demonstrate unequivocal phenotypic morphology which would naturally assist the INC's work towards developing universally acceptable definitions and collating archives whereby examples of the agreed definitions can be displayed for general consumption. In this way, the work will promote the worldwide acceptance of a workable system for describing and categorising congenitally malformed hearts.

An integral function of an operational Intelligent Information System for CHD using morphology, clinical images, and video recordings of surgical operation, will be as a unique open-access resource for teaching, not only for professionals such as cardiologists, imagers,

and surgeons, but also for those in Universities, such as anatomists and those undergoing undergraduate medical training, but also for patients and their parents, who will be able to learn more about the conditions they have, and the options available for treatment. Eventually UCL hopes to be able to create a system capable of, and advanced enough, to attract more images and related datasets from other Hospitals.

Further areas of exploitation:

Besides the aforementioned developments in cardiology, UCL is interested in exploiting the imaging results to inform clinical practice also in rheumatology, where Prof. Karen Rosendahl is coordinating the scores which are being developed together for MRI and radiographs, as well as for ultrasound, by the radiology group formed from the 4 centres.

The radiology group met in Genoa, Paris and London during 2008/2009, and will meet again in Rome during mid-September 2009, to finalize the MRI scoring system for JIA of the wrist. In collaboration with colleagues in Norway, the group has established a normative dataset for wrist MRI and radiography based on 80 healthy children aged 6 to 14 years. The group is at present working on 12 different papers, of which three are led from each centre, addressing the accuracy and validity of the different imaging modalities. Similar work will be done for hip imaging.

Rheumatology at UCL will be also focusing, under the direction of Prof. Patricia Woo, on the search for genes associated with disease progression and damage, using the candidate gene approach rather than genome-wide association because of the small numbers and heterogeneity of the patients. This process will involve production of an appropriate candidate gene list, construction of tagging SNPs for these genes, and production of a chip to analyse these SNPs and the analysis of all samples from the participating centres. Association analyses will be made with groups divided according to whether the disease has progressed or not according to clinical (including drug treatment) and imaging criteria. These will form an initial gene list to predict progression of disease in JIA. A further cohort will then be needed, in a future study, to validate/refine this first Health-e-Child list. The final hope is to be able to produce, at the end of the next study, a list of genes that would predict worsening of the disease.

2.5 P05 APHP

The HeC project has allowed APHP to develop a living database of clinical, biological (and samples for further genetic analyses) and modern imaging data with a prospective collection of data including follow-up data for patients with different diseases including juvenile idiopathic arthritis. One of the aims of the project is to facilitate the development of algorithms to better predict the patient's prognosis and help deciding of the best treatment approach.

In parallel, preliminary work has been performed in some excellent research units, including the Baylor Institute for Immunology in Dallas, in order to develop gene array analyses as a tool to help early diagnosis of several diseases (infectious, inflammatory, malignant diseases, with a particular focus on auto-inflammatory diseases which ranges from familial recurrent fevers to systemic-onset juvenile idiopathic arthritis, Crohn's disease, gout and type 2 diabetes).

Hereafter are indicated three relevant publications produced by the Dallas team:

- Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med*. 2005;201:1479-86.
- Allantaz F, Chaussabel D, Stichweh D, et al. Blood leukocyte microarrays to diagnose systemic onset juvenile idiopathic arthritis and follow the response to IL-1 blockade. *J Exp Med*. 2007;204:2131-44.
- Chaussabel D, Quinn C, Shen J, et al. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. *Immunity*. 2008;29:150-64.

The Necker-Enfants Malades hospital has been collaborating since 2006 with the Baylor Institute for Immunology through a phase 2B therapeutic trial using an IL-1 inhibitor in systemic-onset juvenile idiopathic arthritis (ANAJIS trial, Clinical trials registration number: NCT00339157, Abstract winner from the 2008 EULAR meeting, submitted for publication) and extremely informative information has been obtained from gene array analyses.

In the future we plan to develop gene array profiling as an almost real time tool for providing help for accurate diagnosis and also for the choice of the appropriate treatment approach. This could be analyzed prospectively on the cohort of HeC's patients and on a new cohort of patients in several inflammatory, infectious or malignant diseases.

APHP is also be interested in the ongoing discussion, within Health-e-Child, concerning the possible extension to rheumatology of the Intelligent Information Management/Medical Digital Library System already being proposed by UCL and OPBG for the cardiology sector. We need however to check attentively what would be the organizational implications of such a development with the radiology department of Necker-Enfants Malades.

2.6 P06 CERN

Cern will exploit its results from HeC as follows:

Exploitable Knowledge:

-Expertise in EGEE gLite deployment, support, operation and management.

Exploitable product(s) or measure(s):

-Indirectly: EGEE gLite software stack; monitoring and operations tools; user support tools.

Sector(s) of application:

-Any application that requires a controlled environment to manage distributed compute and storage resources of virtual organization(s).

Patents:

-Indirectly: The EGEE software license can be found here: <http://egee-jra2.web.cern.ch/egee-jra2/license.html> .

Owners & Other partners:

-Indirectly: for what concerns ownership, refer to the EGEE software license <http://egee-jra2.web.cern.ch/egee-jra2/license.html> .

2.7 P09 University of Western England

The University of the West of England, Bristol has a long-term interest in pursuing the research and development effort related to the Health-e-Child project. The primary exploitation interest of the university is academic and the accumulated knowledge and expertise shall be capitalized on an exploited in ongoing and future research projects. Our

experience in accumulating, reusing and exploiting knowledge has been successful just like in Health-e-Child we are building on expertise carried over from previous projects.

The University of the West of England's main interest is in the research and development concerning grid technology, advanced database management and knowledge representation. We shall be exploiting our experience in building and managing medical grid infrastructure, medical database management, we shall exploit the ontology engineering and alignment techniques in future research.

We have also experience with contributing to the commercial exploitation of project results by industrial project partners. We are interested and shall be contributing to commercial exploitation by industry partners of the Health-e-Child project, subject to carefully validating and observing intellectual property rights.

2.8 P10 University of Athens

National and Kapodistrian University of Athens as a high level public educational institution has two aims: to support knowledge and to produce research. The collaboration with other institutions, organisations and business, and especially the participation in EU-funded projects, fosters the achievement of this mission. The results of this participation will be exploited by the University in the following ways:

New inputs for research will be gained, in our aim to advance the state-of-the-art in biomedical query processing and data mining, and obtain solutions that can be put into practical use.

Existing infrastructures in the UoA can be assessed and improved in the context of international know-how.

The knowledge transfer regarding e-Infrastructures and the grid can be evaluated. This will open new directions in the educational process and will influence on improvement of this process.

New schemes to encourage and facilitate collaborative research between academia and industry can be developed and applied.

New contacts can be made with partners and people from many countries around the world and valuable experiences about the work in such projects and the state of the art in e-Infrastructures, ontologies, biomedical query processing, decision support systems, and mining of complex integrated data can be gained. Moreover, further collaboration with these people can be developed and sustained, even after the closing of the project.

Finally, as an academic, research institution, UoA will exploit the technological results of the project via the traditional route of articles in the professional and technical press and scientific journals, communications and presentations at conferences, trade shows and professional exhibitions.

More specifically, we plan to exploit the knowledge discovery tools that we have developed during the Health-e-Child project such as AITION, the scalable data mining platform for medical applications developed under WP13, and ACL (AITION Clean-up), a tool for data curation and quality control of clinical data.

AITION is a user-friendly tool, designed to run on grids, clouds or ad-hoc clusters alike, that allows doctors to investigate clinical, imaging, genetic and other patient data to find relationships between different medical variables. AITION is based on generative state-of-the-art causal-probabilistic algorithms to generate graph-based “knowledge models” that doctors can interactive explore to answer diagnostic and predictive questions. It differs from traditional data mining, since it provides ways to present, navigate, visualise, and interact with knowledge models. The end result is that users not only understand the process that led to a statistical conclusion, but also the impact of that conclusion on their medical hypotheses. Furthermore, since AITION users can easily “experiment” with alternative hypothesis, models and parameters – something very rare with traditional data mining approaches or tools – AITION is a real boon for discovering new medical leads.

Based on all the aforementioned benefits of the AITION system, we are planning to continue its development, past the end of the Health-e-Child project, and carry on providing support for current users. UoA has already used AITION for teaching purposes and it is currently being used on a number of student projects with practical assignments in which students can explore further applications of AITION and continue its development by expanding its suite of data mining algorithms. In this way, we are also able to secure AITION’s continued development.

Furthermore, early on, we realised the power of the AITION platform for knowledge discovery in other fields and applications beyond the medical field. That is, AITION has the flexibility to be used as a generic data mining platform and can be applied to a number of domains that could benefit from knowledge discovery tools; it does not need to be restricted to processing medical variables only. Its ease of use and user-friendliness can benefit not only clinicians by also other professionals. Based on this, we have already begun applying AITION for processing structured questionnaires of Greek Medical School students in order to investigate their career decisions, location preferences and speciality selection criteria. The questions cover a wide spectrum of socioeconomic data including career choices, influential factors and satisfaction rates on education and training issues. In a totally different context, we are exploring the application of AITION for assessing financial risk analysis in relation with signs of bankruptcy.

Similarly, the ACL system – which is able to get patient data from the Health-e-Child database, validate it, resolve many of the missing/null values, check for outliers and inconsistencies or mistakes in the data, compute scores, aggregates and other derived variables, and perform attribute discretizations – is not restricted to clinical data. The same tool can be adapted for any problem of data curation and quality control.

In addition to AITION, UoA has developed the Medical Processing Engine (MPE) in the context of Workpackage 8. MPE is an extensible data flow engine that can be used to solve complex scientific problems using a powerful language and optimizer. MPE has been used by HeC applications, and has been demonstrated in EU reviews. Also, MPE has been used as a core component of AITION.

Our plan for MPE include the development of "Athena Distributed Processing Engine" (ADP for short), which is a next generation data flow language engine. ADP will be used by other UOA EU funded projects, which demand high performance parallel processing. In addition, MPE and ADP will be extended to support the Amazon Cloud (S3), and other cloud technologies, in addition to grids and ad-hoc clusters. MPE will also be used as a core engine for large scale knowledge discovery, in the context of AITION. Finally, we are planning to use MPE & ADP in relevant distributed processing and advanced databases courses at the University of Athens.

Thus, AITION, ACL, and the other tools and technologies developed during this project can be exploited and integrated with on-going or future projects. For example, in collaboration with a number of Health-e-Child partners, we are currently considering continuing our collaboration in a future project, where we will be proposing the design of tools for Intelligent Information Management of a very large digital library of cardiovascular data from multiple modalities. Building on the results of Health-e-Child and the tools we have developed, we will be able to provide state-of-the-art solutions for knowledge discovery, data analysis and validation, outcome analysis and risk certification. This way, the knowledge gained and the tools created during the lifetime of the Health-e-Child project will continue to evolve and be fully exploited in supporting further knowledge and producing new research.

2.9 P11 DISI

From the start, by participating to the Health-e-Child project, DISI was led to expand the scope of its research in biomedical data analysis. The research competences in the final year of the project have spun from the mathematical foundation of machine learning methods capable of extracting information from data to the design, implementation and testing of learning algorithms applied to biomedical images, high-throughput data, clinical data and their integration.

Some of the results achieved in the project have enabled DISI to enter the exploitation phase. A few months ago, two post-docs involved in the project started a spin-off company, CAMELOT srl (Computerized Analysis of MEDical data with Learning and Optimization Technologies) in which they plan to devise solutions to biomedical problems in the area of Computer Aided Diagnosis and Decision Support Systems. The expertise of CAMELOT relies on the ability to study solutions tailored to doctors' needs and based on state-of-the-art computer vision and machine learning technologies. The experience acquired through Health-e-Child played a central role in this. CAMELOT is currently seeking partnership for developing innovative software products in areas and image modalities different from the ones explored in the project.

We believe that, thanks to Health-e-Child, DISI is now in a position to pursue its research interest in the e-health area from a more mature perspective. The channelling of the technological lessons learned in HeC in CAMELOT sees DISI ready to start new projects aiming at advancing the scientific state-of-the-art in the area of machine learning applied to knowledge discovery from biomedical data.

2.10 P12 INRIA

INRIA will study with the Health-e-Child partners the possibility to license all the elements of its technology that can support the exploitation of the results obtained within the Health-e-Child consortium. In particular, this may concern the geometric models of the heart and the brain, along with the registration tools relating generic anatomies (atlases) to patient-specific images and data or images in longitudinal studies. A second set of methods that could potentially be transferred is related to the modelling of the physiology, for instance models of evolving tumours and electro-mechanical models of the heart contraction. INRIA will also investigate the possibility to exploit the models developed in the paediatric domain in other medical domains (e.g. general cardiology or neurology) or in other disciplines, e.g. in neuroscience. The knowledge created through the Health-e-Child project will also be used to improve the models and potentially impact clinical practice in the long term by making some of the models and imaging tools accessible to clinical research.

2.11 P13 EGF

Health-e-Child (HeC) has acquired a central place in the business model of the European Genetics Foundation (EGF). Developing future courses based on the dissemination and

training activities performed in the project will allow HeC materials to be exploited by a larger community and contribute to EGF's patrimony of teaching materials and online courseware to be offered to the wider medical community which will in turn attract further students and lecturers. Reusable multimedia material will be exploited in future courses and in future research projects. Agreements will be made to allow the content developed in HeC to be put on web-based content databases.

EGF is a not for profit organisation whose core business is to provide advanced training to medical professionals and researchers, and to coordinate international research projects as a bridge between the Research (University) and Healthcare (Hospital) settings. EGF's mission is focused on:

1. Promoting the scientific and professional training of young European geneticists in fields related to genetic applications in the field of preventive medicine. The courses of the European School of Genetic Medicine train young scientists from all over the world, expanding their knowledge in the field of medical genetics helping them to acquire important skills in the treatment and prevention of genetic diseases.
2. Creating and managing a European centre of advanced training in genetics and genomics in Ronzano Italy which hosts a genetic tele-counselling centre, a Statistical Genetics Laboratory and be a home to the training activities that are central to our mission.

In the course of furthering these goals EGF has actively published didactic material, scientific books and journals and has been a vehicle for Awarding young graduates with many international scholarships in genetics and genomics. It has represented a physical venue and legal organization to attract and carry out a number of research projects in the field of Genetics. HeC has represented a chance to show the convergence of these ambitious goals. During the course of the project EGF has carried out some applied research in one WP and by the end of the project EGF will have hosted three training courses. The first was on the genetic components of rheumatic and auto-inflammatory diseases, the second was on utilising HeC's models in clinical practice and the third will be in September 2009 on the Genetic Basis of Brain Tumours.

Beyond the course itself several activities will be based around the exploitation of results from HeC. All of the courses will be offered as an e-learning service in order to allow HeC courses to be consumed post factum via the internet by the HeC community and other interested parties. They will also be offered as a Hybrid Courses, in conjunction with the Learning Objectives which are being produced by Lynkeus and UWE, which will combine e-learning with traditional learning. The Ronzano courses will also be broadcast to a network of Remote Training Centres across Europe Africa and the near East. After the end of the project this multimedia materials will continue to be available "On-Demand" after a participant has registered, as has been the case during the course of HeC. Courses and lectures authorized by the speakers have been recorded (audio and video), post-processed (editing, graphics etc.) and uploaded on public servers in order to create multimedia products available on the EGF website, irrespective of the state of the HeC website. Being on the EGF website will allow the courses to continue to be available irrespective of the state of the HeC website long after the conclusion of HeC.

Further more the materials produced with HeC will also be made available to other research projects and exploited as content and learning sources for their own educational concerns. Public materials have already been made available through the HeC site and that of EGF to

interested parties. In particular some of the materials which have public releases have been put on the content repository of the Eurogene project. Proactive interaction with international projects will continue try to increase the level at which the material shared.

The project has given EGF the chance to gain a lot of experience on how to extract learning packages from scientific exploits and transform them into courses, e-learning packages and diversified multimedia content items that can be combined or integrated in many different educational and research oriented activities. The courses performed with the HeC project have all been considered successes with participation extending beyond the HeC user community. EGF expects to benefit from these relationships through greater clinical attendance at future courses and the further development of the faculty thanks to the willingness to return and teach of those who lead the courses at Ronzano.

2.12 P14 ASPER

The exploitable result of the work done in Asper in co-operation with EGF, IGG, Siemens, and in case of need other partners, will be a DNA testing microarray for detection of mutations that are connected to (paediatric) pilocytic gliomas. The contribution by partners will be to compile a scientifically relevant mutation list to ensure the commercial success of this test. The test will be ready for the second quarter of 2009.

2.13 P16 MAAT

MAAT expects as a result to the work carried out in work packages WP4, WP5, WP7 and WP14 to deliver an advanced healthgrid platform conforming to the European data protection regulations and complying with the community technical standards for Grid and database technologies integration. MAAT has expressed willingness in Open Sourcing parts of it for enabling a useful return to the Scientific Community and in a second stage, new business models and opportunities. Thus, by the end of the project, MAAT plans to make a proposal to the IPR committee in order to progressively open access to the sources of this platform to the community. A model is being studied, which will leverage existing mechanisms in Europe to widely spread the technology.

Meanwhile, MAAT's interest mainly lies in the Gateway and Grid innovative new technologies as supporting pillars of its Platform as a Service (PaaS) and Software as a Service (SaaS) offering for different market sectors, packaged under code name GaaS. The latter has been recently unveiled at the Linux Days 2009 conference in Geneva and will be presented at the up-coming EGEE'09 conference as well.

2.14 P17 OPBG

The HeC project has developed a number of tools that have seldom, if ever, been applied in the medical field, though tools such as the "Case Reasoner", "Tree Maps" and "AITION" still require proper validation before their benefits can be fully realized in the medical domain. It is these tools which OPBG sees as having the greatest exploitation potential to improve the efficiency of clinical practices.

Each year millions of data pieces are generated in the clinical practice of a large Paediatric Cardiac and Surgical Department. Frequently they are stored in different databases located on independent servers; it is therefore complicated to track patient's varied data from different applications or to perform similarity searches utilizing parameters that pertain to different stages of the diagnosis or treatment process. The tools that have been developed within the HeC project have demonstrated the ability to perform such tasks across four different clinical Institutions. It is therefore conceivable that a platform like HeC's might be utilized in a large institution such as OPBG to connect all the relevant databases.

Grid technology has developed an infrastructure where distributed computing capacity can be leveraged to provide the resources necessary to carry out the large-scale computations that would be needed to develop a clinical Intelligent Information/Digital Library system. It is foreseeable that this or another applicable system for distributed computing such as cloud computing could be utilized to provide the resources needed to both manage the system and run tools similar to those developed within HeC for similarity searching, knowledge discovery and decision support on a much larger test bed encompassing a variety of data types, such as morphology, imaging and video.

The purpose is to provide a powerful system for patient similarity search, outcome analysis, cost analysis, risk stratification leading to a more efficient hospital. Also a computed-aided tool for diagnosing the various cardiac lesions from the morphology and images provided would lead to better verification of the different conditions, and also will act to help those less experienced to enhance their diagnostic skills, as well as potentially providing more appropriate treatment for individual patients.

When such a system is successfully implemented and validated it could then be extended to other hospitals to form a network generating much larger data loads adding to the complexity and clinical relevance of the system. In the long run the possibility exists of offering such a system to other hospitals for a fee. Potential client hospitals would benefit from advanced distributed computing solutions for validating their data and the use of the tools which will have been tested by having been run on massive amount of data.

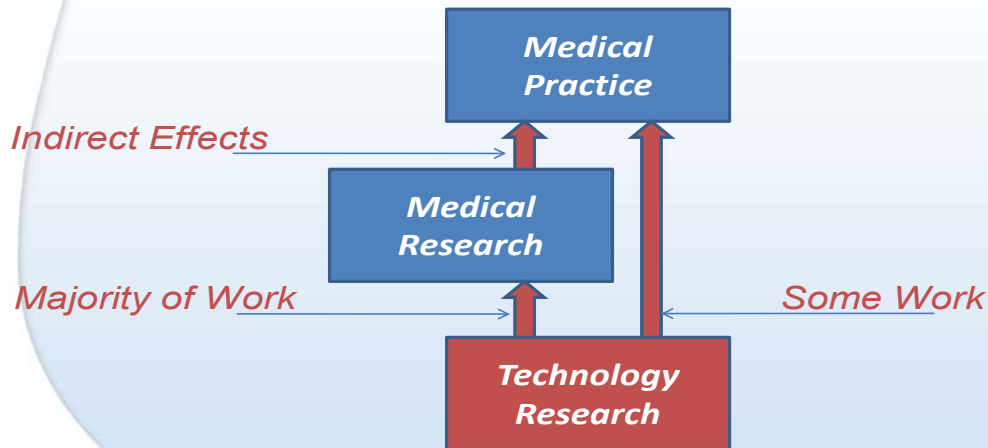
Appendix 1 Additional common exploitation goals shared by some of HeC's partners

The preceding pages [the individual sections of the Exploitation Plan] represent a detailed and updated outlook of the exploitation plans put forward by most of the partners involved in Health-e-Child.

The Consortium is however aware that the Exploitation plan which was delivered to the Commission in December 2008, and of which the current one constitutes a completion and an updated version, was deemed to be insufficiently detailed. This point was verbally highlighted at the Annual Review held in Brussels in March 2009, and in written form in the final Consensus Report, issued following the review. In his accompanying letter, transmitting the Consensus Review, Health-e-Child's Project Officer at the ICT for Health Unit within the EC, Mr. Benoît Abeloos, stated that the project was "performing satisfactorily", but that it could only continue if three conditions were met", and specifically one was that the consortium "develop a detailed exploitation plan taking into account not only the different components of the system being developed, but also the integrated nature of the project".

Furthermore it was made clear that the European Commission is especially interested in the clinically exploitable results of the project, and that the new plan should pay particular attention to this area. The recommendations specifically referred to "making the results of the project more exploitable, utilisable by the current hospitals, and more suitable for the potential expansion of clinical partners in the future." These considerations have led the Consortium to agree on a global understanding on how to pursue relatively short-term integrated goals, capable of driving together at least some, if not all, of the technological and clinical partners, towards potentially jointly exploiting some of the Health-e-Child developments which seem nearest to access a marketable phase. A concise definition of the variety of outcomes which can be envisaged was illustrated during the presentation made on this subject during the course of the Annual Review in March 2009; the approach taken into account has been the following:

HeC Exploitation: Grand Scheme



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HeC Exploitation: Academic Interests

- **Education**
 - HeC will provide a rich vein of case studies
 - Technological know how
- **Research**
 - Journal and conference publications
 - Follow-up research and development based on current momentum and achievements (seeking funding opportunities)
- **Technology transfer**
 - Academia-industry collaboration for commercializing HeC research results
 - Spin-off companies based on current research programmes (e.g., DISI spin-off)

1

HeC Exploitation: Platform for IT Transfer

- **Clinical workflow: HeC as infrastructure for data sharing across hospitals**
- **Intelligent integration of medical/clinical databases**
 - Clinical data and annotations
 - Images and imaging results
 - Relevant publications (possibly)
- **Integration of additional information and knowledge**
 - VPH models and databases
- **Advanced services**
 - Uniform digital library services
 - Data mining and other data analytics
 - Intuitive visualization and visual data mining

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HeC Exploitation: Platform for IT Transfer

- **Tool sharing**
 - HeC exposing, sharing and diffusing advanced tools and knowledge at the clinical research level
 - HeC distributed platform supplying computational power for modeling and knowledge discovery
 - Raising awareness about new technologies thanks to user-friendliness of tools
 - Easy upgrade of functionality modules thanks to web services
- **VPH initiative**
 - Disease models and predictive models
 - Multi-scale patient models, patient similarities
 - Decision support and knowledge discovery
 - Data storage and delivery

10

HeC Exploitation: Exploitation Models

- HeC functionality as a service
- HeC tools as a deployable products
- HeC knowledge as consulting service
- ...

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The pages which follow are examples of how some technological and clinical partners within Health-e-Child are planning to implement projects leading to developments which are in line with those more broadly indicated in March.

Health-e-Child's foreground

As an early member of the VPH research community, Health-e-Child (HeC) has been working since 2006 on building an integrated healthcare platform for paediatrics. It integrates innovative predictive disease models, complex data visualization and knowledge discovery applications, with the ultimate goal of supporting clinical decision making in rare paediatric diseases. The platform, which is securely and anonymously hosting the health records enrolled for the HeC clinical studies in cardiology, rheumatology and neuro-oncology, has been demonstrated in major international conferences and tested by its end-users through a growing 10 sites grid network.

The HeC platform is based around the development of a Service Oriented Architecture (SOA), providing information as a service to the clinical partners, by integrating transactional, analytical, and unstructured information, making it available and consistent, and offering access to complex, heterogeneous data sources as services which can be reused across processes and can be independently maintained to enable flexibility and increase IT resource productivity. HeC's SOA collects, checks, validates and makes clinical data accessible, reduces costs and risks, increases overall agility by providing reusable information services, spanning structured and unstructured information that can be plugged into applications, clinical processes, and portals. It encompasses Information integration, Content management, Clinical Intelligence, Master Data Management, Database Services, and Implementation Services through its Grid platform and related applications.

Examples of particularly useful services on the HeC Grid platform

The CaseReasoner, developed by Siemens, is the tool which interacts with HeC's Gateway to extract the necessary patient data from the underlying grid database. It provides clinicians with a flexible tool for operations such as data filtering and similarity search from anonymous patient records from anyone of the partner hospitals, and also for the exploration of the resulting data sets. Other innovative techniques for patient similarity visualization are combined distance/heatmaps, treemaps and neighbourhood graphs. Similar cases are detectable both in the whole integrated case database, and in some subsets of interest, defined in the form of a simple filter. This allows clinicians to compare recorded diagnoses, treatments and outcomes — helping prescribe treatment more confidently.

The AITION application is an Integrated Ontology Driven Causal Probabilistic Network Framework for BioMedical Knowledge Discovery, Feature Selection, Vertical Integration and Semantic Modelling under Uncertainty, developed by the University of Athens, providing a simplified, yet powerful, knowledge discovery system aimed at being user-friendly for clinical researches, with a good and functional GUI. AITION is complemented with ACL (AITION Clean-up), a tool for data curation and quality control of clinical data, and it is designed to run on grids, clouds or ad-hoc clusters alike. It differs from other traditional data mining tools, since it provides ways to present, navigate, visualise, and interact with knowledge models. The end result is that users not only understand the process that led to a statistical conclusion, but also the impact of that conclusion on their medical hypotheses. Furthermore, making it easy to “experiment” with alternative hypotheses, models and parameters, AITION is a real boon for discovering new medical leads.

A paediatric-targeted semi-quantitative MRI and US scoring system for the assessment of the inflammatory and erosive changes in the wrist and hip of children with JIA has been developed by DISI. This is the result of testing and improving image segmentation algorithms to measure the synovial membrane volume and bone erosion in MRIs, and of investigating variational methods for foreground/background separation in image processing, and segmentation using machine learning techniques for voxel classification. Image annotation tools have also been developed and tested for establishing the ground truths for learning, and what is now available is a specific tool for JIA allowing knowledge discovery from biomedical data through regularization methods.

Other developments in cardiology concern the development by INRIA of Patient-Specific Computational Models, which will eventually lead to multi-scale generic models. The image analysis aims at building a 3D volumetric mesh of the patient's heart from clinical images, and the electromechanical (EM) model personalisation adjusts the parameters to the individual patient's physiology, allowing a much more feasible study of therapy planning. The next goal is to make some pre-computed simulations available on HeC's Grid platform (disease-specific, closest patient, previous exams, etc...), developing personalised EM simulations, based on exam-related results and user interactions, where the Computational Anatomy is integrated through the MedINRIA software, providing the clinician with linear/non-linear registration tools allowing for the mapping of a pre-computed atlas of a patient.

The goal of “active clinical dissemination”

Since its beginning the HeC consortium has been fully aware that the more data the project would have, the more accurate its integrated models and knowledge discovery tools would be. In order to pursue this objective, an initial strategy followed by the consortium has been based on an “Active Clinical Dissemination” approach - that is, on seeking the active involvement and inclusion of a growing number of paediatric centres.

2007 and 2008 saw the implementation of this strategy leading firstly to the welcoming of OPBG into HeC, and latterly to exploration of whether there could be sufficient IT and clinical compatibility to enable the Johns Hopkins University to join the consortium.

Further steps in the direction of an “active clinical dissemination” became possible at the beginning of 2009, and indeed were taken by some consortium members (Siemens AG, Lynkeus, Maat GKnowledge, OPBG), leading to a joint proposal between them and some leading external American and European institutions (the American College of Cardiology, the Johns Hopkins University Hospital, Siemens Corporate Research, and the Technische Universität München). All together, these 9 partners submitted to the FP7 call on International cooperation on VPH (Objective ICT-2009.5.4) a well-received project, now under negotiation with the EC.

The Sim-e-Child (SeC) project – this is its name - is a follow up STREP which aims to strengthen the impact of Health-e-Child by:

- establishing an international cooperation for developing a grid-enabled platform for large scale simulations in paediatric cardiology,
- providing a collaborative environment for constructing and validating multi-scale and personalized models of a growing heart and vessels,
- advancing the state-of-the-art by providing comprehensive and patient specific models for the dynamic and longitudinal interactions occurring in the left heart, with a focus on the congenital aortic arch disease and repair.

SeC intends to enhance the Health-e-Child cardiac models by establishing an international collaboration beyond the European research area in order to validate the models on additional data (1400 cases). If funded, the project will allow the American College of Cardiology and the Johns Hopkins University Hospital to validate the developed heart modelling capabilities using ongoing clinical trial databases, i.e. the Coarctation of the Aorta Stent Trial [COAST] and the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions [GenTAC], in collaboration with OPBG in Italy.

In addition, SeC plans to expand HeC’s models by integrating the existing Siemens Corporate Research models of the aorta, aortic valve and mitral valve, together with blood flow modelling and flow visualization from the Technical University of Munich. The new and comprehensive heart model will be applied to congenital aortic disease, thus enriching the portfolio of applications available in HeC and broadening its end-user community.

To support all these activities, SeC aims to integrate HeC’s Gateway and Case Reasoner with powerful tools for simulation workflow composition and sharing of scientific experiments, deriving advanced clinical measurements and models for personalized predictions of optimal therapy.

Possible future developments of Health-e-Child

A long term goal of the consortiums’ is to be able to create and validate tools which are commercially interesting and have the potential to be marketable. Since HeC has created a relatively strong brand and received a significant amount of critical acclaim in both the technical and clinical fields, with the end of the project under 10 months away, the opportunity exists to focus some of the remaining time on establishing how some well received tools and applications could be turned within a reasonable lapse of time into possible “products” with some commercial appeal which would deserve to be marketable. In working towards these objectives, however, the partners will of course have to take into due account all the complex

legal, ethical and regulatory requirements that may be relevant, and the appropriate investment decisions which can ensue from working towards making a prototype into a marketable product.

Particular attention has been paid to the section of the recommendations in the EC Reviewers' Consensus Report which referred to the general theme of making the results of the project more exploitable, utilisable by the current hospitals, and more suitable for the potential expansion of clinical partners in the future. The specific recommendations in question requested that the consortium:

- 'work on a coherent service model for the end clinical user including a business model for this users institution and a service model for "after sales services"'
- 'produce a model for knowledge feedback to the patients (as part of the service model)'
- 'Since medicine is performed in teams – a plan for incorporating methods for computer supported clinical work and clinical communications would enhance the clinical uptake'
- Produce 'focused objectives for the daily clinical use and the training of clinical users'

Keeping these recommendations in mind, some partners within HeC have agreed, as already mentioned, on the idea of trying to develop together a relatively short-term plan for follow up work which would have the potential to further refine the platform, tools and applications, validate the results, and facilitate a wider use by clinical end-users, with the longer term goal of producing tools and applications which both go beyond the state of the art and are marketable.

The approach on which these partners have agreed considers it to be sensible to develop an intelligent information management/medical digital library system that expands not only on the data already collected by HeC (and possibly also on the data which will be collected by SeC, if the negotiation phase with the EC, to which the project will now be submitted, will prove to be eventually successful), but that is based on the large numbers of data and imaging scans available within the clinical partners who will be involved in such a work plan, and believe that this would be an excellent field within which to validate the results to date and improve the saleability of the tools developed so far.

In this spirit, a number of clinical/technological objectives have been selected:

- The creation of an underlying digital library capable of handling massive data
- Education facilities to be provided on top of it not only for physicians but also to patients/parents
- Automated computing tools to be provided on top of it for:
 - automatic validation of data and imaging
 - analysing the data, allowing for epidemiological studies, outcome analysis, and risk stratification
 - similarity search
 - knowledge discovery
- Creating a system capable eventually of
 - attracting ever more images and related datasets requiring validation
 - offering a fee-for-service facility for similarity search and knowledge discovery

Outline of the proposed Intelligent Information Management/Medical Digital Library System

At this level of abstraction certain simplifications have had to be made; so far only one disease type has been included. The particular choice of Congenital Heart Disease (CHD) was made because of the extensive experience of a subset of the clinical partners dealing with it as members of the HeC project and the availability of nontrivial amounts of digital content representing interesting and reliable clinical outcomes. At least two of these partners have explicitly expressed a deep interest in specific developments leading to an Intelligent Information Management/Medical Digital Library System in the area more broadly of paediatric cardiology, while two other clinical partners would be highly interested in a similar development in the area of rheumatology, but have not had the time yet to analyse sufficiently in depth the organisational implications of such a choice.

The development of an intelligent information management/medical digital library presents the opportunity to investigate several challenges which are particularly evident in the cardiac domain. These include the following:

- (i) a great variety of content types, e.g., images resulting from particular medical procedures, which are extremely valuable to scientists but, unlike traditional publications, they have not been available to the community in an organized fashion through some digital library (i.e., there is no PubMed for images),
- (ii) an anthropocentric nature of research, which is mostly based on individual patients and their clinical behaviour instead of projects with experiments or observations,
- (iii) particular concerns about patient privacy, which are in theory contrary to the spirit of Open Access

The specimens and imaging archives of UCL and OPBG constitute a sufficient amount of morphology, imaging and surgical video data necessary to create a digital library containing massive amounts of cardiovascular data. However, it would certainly be beneficial to include a larger number of clinical partners, thus increasing the amount of data available and therefore the size and complexity of the intelligent information system/medical digital library.

The idea is to build a system aiming at making it possible to have regular epidemiological studies, outcome analysis, and risk certification, together with decision support tools based on similarity search and knowledge discovery and capable of dealing with data and outcomes of the following wide range of conditions:

1. Atrial Septal Defects within the oval fossa
2. Sinus Venosus Venoatrial Communications
3. Atrioventricular Septal Defect
4. Ventricular Septal Defect
5. Aortic Valvar Stenosis
6. Aortic Valvar Incompetence
7. Coarctation of the Aorta
8. Interrupted Aortic Arch
9. Aortic Vascular Rings
10. Left Pulmonary Arterial Sling
11. Marfan's Syndrome
12. William's Syndrome

13. Mitral Stenosis
14. Mitral Regurgitation
15. Hypertrophic Cardiomyopathy
16. Dilated Cardiomyopathy
17. Noncompaction Cardiomyopathy
18. Tetralogy of Fallot with pulmonary stenosis
19. Pulmonary Stenosis
20. Tetralogy of Fallot with pulmonary atresia
21. Transposition
22. Congenitally Corrected Transposition
23. Common Arterial Trunk
24. Double Outlet Right Ventricle
25. Double Inlet Left Ventricle
26. Hypoplastic Left Heart Syndrome – Norwood Stage 1
27. Tricuspid Atresia
28. Anomalous Coronary Arteries
29. Anomalous Left Coronary Artery from Pulmonary Trunk
30. Kawasaki Disease
31. Totally Anomalous Pulmonary Venous Connection
32. Partially Anomalous Pulmonary Venous Connection
33. Ebstein's malformation
34. Right Isomerism
35. Left Isomerism

Validation of the data included in the Intelligent Information Management/Medical Digital Library System

As UCL stated in their individual exploitation plan a secondary “process of validation will be needed for creating a clinically relevant Intelligent Information Management system, and UCL can build on its ongoing cooperation with the International Nomenclature Committee (<http://www.ipccc.net>) (INC) so that the morphology, images, and surgical videos will be able to be checked for validation, taking advantage of the world class expertise accrued through the INC and the CTSNet (<http://www.ctsnet.org>).” The INC was established to develop and maintain an internationally acceptable system of nomenclature to enhance global communication and facilitate care of patients, teaching, and research into paediatric congenital cardiac disease across disciplines.

Medical Benefits

Congenital heart disease (CHD) has been the first disease area where to look into as a sensible testbed, but in the finalised project plan it is very likely that CHD will only be one of a selection of diseases. CHD is however particularly significant as the incidence of congenital cardiac malformations remains relatively constant and because of improvements in diagnosis, with major advances made recently in foetal echocardiography, post natal echocardiography, magnetic resonance imaging, and computed tomographic imaging, and important improvements made in surgical correction, the number of patients who survive into adulthood has increased dramatically over the last 50 years. In the 1950's, most children with a congenitally malformed heart would die in early childhood. We now expect virtually all such patients to survive.

Underpinning these advances in patient care has been a thorough understanding of cardiac morphology. And though there have been many advances, simplifications, and attempts to unify the descriptions of the congenital cardiac lesions themselves over the last 2 decades, differences in opinion still exist. Furthermore, because of the often-complex anatomical

arrangements, not all paediatric cardiologists, surgeons, and imagers have the level of expertise to define the lesions present in all the patients that present to them.

Three essential goals

The Intelligent Information Management/Medical Digital Library System which is considered as a promising common exploitation project by a number of partners within HeC will aim to:

1. Provide a link for all congenital cardiac malformations:
 - a. Morphology, providing anatomical descriptions from post-mortem specimens – see www.cardiacmorphology.com
 - b. Imaging via echocardiography, magnetic resonance and computed tomographic imaging, and cardiac catheterisation – see <http://publish.heartit.com/2475-1000-1928-1591>
 - c. Surgical operations via video clips of operative procedures
2. Validation of the system through the International Nomenclature Committee to ensure the unification of diagnostic descriptions
3. Development of automated computerised methods to interpret morphological slides, or images of specimens, and diagnostic images. Such computer-aided diagnosis would potentially enable inexperienced users to diagnose conditions more accurately, and hence provide appropriate management for individuals

International Nomenclature Committee partnering benefits

In 2000 the European Paediatric Cardiac Code was published by the European Association for Paediatric Cardiology. At the same time another committee of surgeons and paediatric cardiologists was working in parallel in North America, under the joint aegis of the Society of Thoracic Surgeons and the European Association of Cardiothoracic Surgery, to produce a similar system for coding patients with congenitally malformed hearts. When the STS/EACTS coding system was also published in 2000, the multiple conflicts between the systems were readily apparent. In the same year it was decided that the approaches needed unification and the International Nomenclature Committee was established and subsequently became legally constituted in Canada.

Over the subsequent 8 years, members of the committee have met on numerous occasions, and have succeeded in cross-mapping the two systems, producing the International Classification of Congenital Cardiac Malformations, and retaining the unique numbers for coding contained within the European Paediatric Cardiac Code. The process of cross-mapping was supposed to provide the required world-wide consensus for describing and cataloguing congenital cardiac malformations. However, problems were encountered with the most common lesions, such as holes between the ventricles. This was because the very terms used in the 2 systems could not always be cross-mapped with accuracy. The International Nomenclature

Committee, therefore, established 2 working groups, one concerned with definitions, and the other with archives. These groups are currently seeking to provide universally acceptable definitions, and to collate archives whereby examples of the agreed definitions can be displayed for general consumption. Their work is proving harder than was initially imagined. The Intelligent Information Management/Medical Digital Library System will play a role in this work by being able to provide examples of lesions to demonstrate unequivocal phenotypic morphology which would assist the INC in developing universally acceptable definitions. Additionally the system will be able to act as a collating archive whereby examples of the agreed definitions can be displayed for general consumption. In this way, the work will promote the worldwide acceptance of a workable system for describing and categorising congenitally malformed hearts.

Joint exploitation potential

As stated by OPBG, on a system-wide level the technical goal for the Intelligent Information Management System is to provide seamless access to validated medical research results as each year millions of data pieces are generated in the clinical practice of a large Paediatric Cardiac and Surgical Department. Frequently these data are stored in different databases located on independent servers; it is therefore complicated to track patient's varied data from different applications or to perform similarity search utilizing parameters that pertain to different stages in diagnosis or treatment. The tools that have been developed within the HeC project have demonstrated the ability to perform such tasks across four different clinical Institutions. The system will build on these developments by providing access to a number of applications and tools from a single platform which will be accessible from multiple locations at multiple sites. It will support medical researchers in executing several distinct scenarios related to depositing, reviewing, accessing, and otherwise manipulating scientific results.

Several technical approaches have been examined and recognised as being suitable for providing the system with the resources required. The experience gained using Grid systems during HeC will be very beneficial and the potential that cloud computing holds will also be utilised where necessary. Further thought and consultations will be needed, together with the EGI in conjunction with the EuroBioImaging ESFRI roadmap, in order to assess whether a Grid/Cloud approach would be feasible in parallel with the GEANT2 network.

The system will be populated with medical data, harvested from the clinical partners' appropriate hospital repositories - though the numbers of clinical centres is not fixed. It is estimated that through the two clinical partners having already shown a strong interest in this development, the system will have access to at least 100,000 scans of children's hearts, to the related anonymised health records and underlying datasets, and possibly also to relevant scientific literature from major journals in the field.

There are four interlinked objectives to this integrated exploitation activity.

Firstly, and this applies primarily to UCL, the Intelligent Information Management system based around congenital cardiac malformations using morphology, clinical images, and surgical video recordings will act as a unique resource for teaching, not only for professionals such as cardiologists, imagers, and surgeons, but also for those in Universities, such as anatomists and those undergoing undergraduate medical training, and also for patients and their parents, who will be able to learn more about the conditions they have, and the options available for treatment.

Secondly, and this applies mainly to OPBG, there is a strong interest in utilising the system as a tool to increase hospital efficiency. As is stated in OPBG's Exploitation Plan, on top of the system "a computed-aided tool for diagnosing the various lesions from the morphology and images provided will lead to better verification of the different conditions, and also will act to help those less experienced to enhance their diagnostic skills, as well as potentially providing more appropriate treatment for individual patients."

Connecting these two objectives are the tools which UOA will be providing for the system. As UOA stated in their exploitation plan, they would like to adapt their "ACL system – which is able to get patient data from the HeC database, validate it, resolve many of the missing/null values, check for outliers and inconsistencies or mistakes in the data, compute scores, aggregates and other derived variables, and perform attribute discretization" to work on the much larger testbed that the Intelligent Information Management System would provide. Additionally UOA's AITION tool which "is a user-friendly tool, designed to run on grids, clouds or ad-hoc clusters alike" could be used to enable "doctors to investigate clinical, imaging, genetic and other patient data to find relationships between different medical variables" within the data sets held on the system. These services will go beyond the typical keyword-based textual interaction with the system, but will also include specialized features that take advantage of the rich forms of the underlying data. Possibly, access based on image or health-record similarity, or provision of packaged objects that include publications together with their related health records could also be some of the key services offered.

It is hoped that the tools developed by UOA work sufficiently well on the datasets provided by OPBG and UCL that the system will be able to be expanded to include more datasets, possibly in a variety of disease areas. This third objective would test the scalability of the system and test both the technical qualities of the system and the tools which are built on top of it.

Should the applications work well enough on a greatly enlarged testbed, the fourth long term goal is for the system to be offered to hospitals for a fee. The potential client hospitals would not only be offered the possibility of validating and adding their data to the system, enjoying advanced Grid/cloud computing solutions, but would also gain access, on a fee-for-service basis, to decision support tools, based on knowledge discovery and on similarity search capacities, which will have been running on a massive amount of previously validated data.

It is in the pursuit of these four objectives that UOA, UCL, OPBG, MAAT, and LYNKEUS have already agreed to bring their efforts together, with possibly APHP and IGG also being willing to develop in parallel a comparable approach for rheumatology. The long term goal is to provide marketable products to the clinical community, though the partners are open to exploring possible avenues of funding for the development of the tools and of the Intelligent Information Management system.