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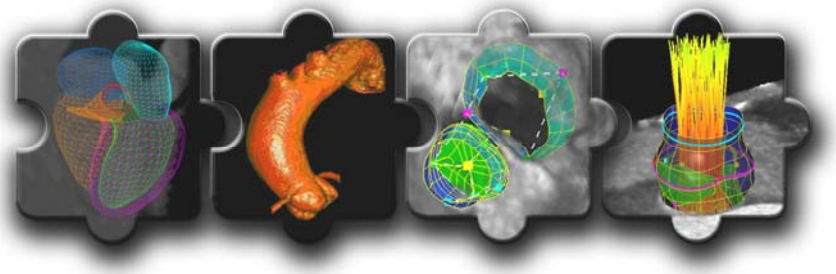

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Quality Assurance Guidelines

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1. Introduction

This document is designed to give guidance on quality planning, achieving, testing, and refining in the different areas of the project – mainly IT algorithmic research and development, clinical research, and project management. Although the three areas are closely linked together, the requirements and standard procedures are in many respects different.

1.1. Purpose

The Sim-e-Child collaborative project directly addresses all three expected outcomes of the cooperation call [SeC DoW]:

a) **Interoperability:** The clinical databases of JHU and Health-e-Child will be federated to increase the pool of available patients for clinical model validation. The Sim-e-Child platform will be built on open standards to ensure interoperability and reusability of the results.
b) **Tools and services:** New tools will be made available for global cooperation: the web- and grid-enabled Sim-e-Child platform will include components for modelling, simulation and collaboration. New and comprehensive heart models will be developed using this enabling facility.
c) **International validation environment:** The Sim-e-Child platform will provide components for joint verification and validation of models. Both existing and new heart models will be validated collaboratively by the clinical partners in the EU and US. In particular, as a first step, the modelling capabilities for the LV and RV developed in HeC are validated using cases stored at JHU (resulting in a deliverable D5.1, “Health-e-Child Heart Models Clinical Validation Report”). The final system will allow physicians to seamlessly collaborate in simulating and validating advanced cardiac models based on the large transatlantic virtual database sharing the results of their scientific experiments. This outcome will directly address the issues of quality control and assurance in modelling and simulation.

Sim-e-Child understands the fundamental importance of integrating research to achieving the overall goals, which requires the project to be able to leverage and extract new knowledge from several different scientific disciplines. The integration of competences from the biomedical, data analysis, modelling and simulation, and data and systems infrastructure domains will create significant management challenges.

The task of extracting and sharing the results, and integrating them into a larger picture, is complex, and can only be dealt with through an effective structure. For this reason the Project has placed integration at the centre of all its work packages, management bodies, committees and boards.

The Quality Assurance Guidelines (QAG) establish the approach to quality procedures to be followed by SeC. They aim to ensure that the results and deliverables of the project are of high quality and meet the specifications set out in the DoW [SeC DoW]. They will therefore be used by all partners, and particularly by WP leaders and all members of the Consortium responsible for approving the work (Management and Technical Coordination Board, Scientific Committee, Ethical and Legal Committee).

1.2. Overview of the document structure

The document is split into the following three main chapters: “Quality Assurance Guidelines for Information Technology”, “Quality Assurance Guidelines for Clinical Research and Practice”, and “Quality Assurance Guidelines for Project Management”.

These guidelines recognise that, with the diversity of the participating project partners, many different quality assurance and control systems are already in place - the guidelines do not, therefore, seek to override existing procedures. The QAG defines the minimum requirements to be followed during the project execution phases.

In large parts the document consists of references to existing quality systems. There is no intention to develop and establish a completely new quality framework. This document is largely a revision of the corresponding HeC deliverable D1.1a [HeC D1.1a].

1.3. Abbreviations

QA	Quality Assurance
QAG	Quality Assurance Guidelines
PM	Project Management
DoW	Description of Work
HeC	Health-e-Child
SeC	Sim-e-Child
MTCB	Management and Technical Coordination Board
WPL	Work Package Leader
GCP	Good Clinical Practice
SOP	Standard Operating Procedure
CRF	Case Report Form

2. Quality Assurance Guidelines for Information Technology

The complete development chain from requirements collection to the delivery of the prototype software to the end users has to be controlled and managed from a quality point of view. Therefore all partners are required to follow their internal procedures to ensure the high quality goals of the SeC project. On the other hand it is very difficult to implement a common unified framework within the consortium because of the (different) already existing quality frameworks. Therefore this document provides the users with a minimal set of tasks to be followed during all work package activities in the IT areas. For more detailed guidelines and best practice recommendations for quality assurance in software development, the reader is referred to [Feldman 2005; Almeida et al, 2007]. Some recommendations and QA guidelines specific to the design of modeling and simulation software, which is in the focus of the project, are provided in [Ören, 1984] and [Ören and Yilmaz, 2005].

The major procedural steps for the IT part of the project consist of:

- Requirements collection and analysis,
- Design of the software,
- Development of the software,
- Testing of the modules and integration test, and
- Deployment of the software prototype.

2.1. Requirements

The IT participants of the project recognise the importance of requirements analysis and documentation in successful software development and end-user satisfaction. To this end, a work package has been formed which is dedicated to the analysis and documentation of users' requirements, and especially interoperability requirements (WP 2) and in which both all IT and all clinical teams participate. The successful deliverables of this work package (first requirements analysis document (D2.1) after 10 months and its revision (D2.2) after 20 months) in itself are a quality measure, which pave the way for further development by distributed teams creating a coherent application, meeting the needs of the end-users. Further quality assurances are that on the one hand development teams observe the documented requirements and on the other that a review process allows for the evolution of the requirements documents to cater for changes during the project lifetime. Requirements analysis is largely addressed during the first phase of the project, Requirements Elicitation, Clinical Protocol and Assessment Procedures – which consists in analysing and aligning the requirements from a user and system standpoint between the available EU HeC infrastructure, the US COAST and GenTAC databases. A clinical protocol defining the criteria for the coding system, patient history, clinical finding, imaging and possibly genetics that are used by both clinical institutions for assessing the aortic arch is established and the clinical assessment procedure for validating the heart models and their extensions is defined [SeC DoW].

2.2. Design

Collaborative software development requires that the ideas behind developed program code are well documented. This facilitates maintainability, testing, requirements validation and most importantly integration of software components. SeC's IT partners shall adhere to the practice that the design of software components will be documented, especially of those features which are interaction points between components, like APIs. Again, the guidelines for assurance are partly built in our Description of Work [SeC DoW] via the first requirements analysis document (D2.1) after 10 months and its revision (D2.2) after 20 months that also describe the overall system design. We do not require – and the diversity of the project's research and development domains hardly allows for – that all teams follow a uniform design paradigm, but best design practices shall be guaranteed and supervised by work package leaders.

2.3. Development

All the IT participants have substantial expertise and experience with the software development process and all the institutes maintain their own development guidelines which are of high standard and are best suited to each institute's main profile: academic or enterprise. It is the responsibility of the work package leaders to synchronize and to supervise the adherence to commonly agreed development practices. Standard principles like full version control, attempt to minimize the number of different programming languages and runtime environments used, modular development, early testing, following a coding standard, adhering to release cycles, etc will apply.

2.4. Testing

The IT developers will follow a standard multi-tier testing plan. Within developer groups, unit testing will be performed parallel to development and a work package level integration testing plan will be in place. This will be the foundation for successful integration testing across the work packages, which will follow the release cycles. Unit tests will be designed and developed to validate the system functionality and accompanying system releases through the project's lifetime (addressed in Task T4.6 of the project, Month 7-30).

2.5. Deployment and Field (Clinical) Assessment

Phase 3 and Phase 4, the last phases of the process, are devoted to the deployment of the completely integrated software modules, interim prototype platform (due Month 20) and then model revision and extension and their final clinical assessment (due Month 30). These phases are planned and well defined in WP4 "Simulation and Collaboration Platform Development" of the DoW [SeC DoW]. End users will finalise the clinical validation of new models, using the simulation facilities (with a deliverable D5.3 as a result, "Left Heart Models Clinical Validation Report"), and the system will be made available to the wider VPH community, due at Month 30.

3. Quality Assurance Guidelines for Clinical Research and Practice

The Sim-e-Child project does not focus on enrolling new patients but rather intends to use existing data that has already been acquired in the context of other projects and clinical studies (HeC, COAST, etc). Nonetheless, the MTCB together with the ethical and legal committee will ensure that all data used in the project has been properly anonymised, are of an acceptable quality and that the local ethical committees have approved the sharing of the data.

3.1. Terminology

Maintaining accuracy and quality throughout a clinical study is a continual, dynamic process [Valania, 2006]. Although study requirements are carefully set forth initially in detailed documents such as an approved clinical protocol, a data management plan, and an accompanying project plan, expectations and requirements can change during a study. This ongoing process requires revising mechanisms and communicating these revisions clearly to all investigators and support staff.

Quality: the total set of characteristics of a product or service that affect its ability to satisfy a customer's stated or implied needs.

Quality system: the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

Quality assurance in clinical research: the systematic and independent examination of all trial-related activities and documents. These audits determine whether the evaluated activities were appropriately conducted and that the data were generated, recorded, analyzed, and accurately reported according to protocol, standard operating procedures (SOPs), and good clinical practices (GCPs).

Quality control in clinical research: periodic operational checks within each functional department to verify that clinical data are generated, collected, handled, analyzed, and reported according to protocol, SOPs, and GCPs.

3.2. Clinical Data Acquisition

Acquisition or collection of clinical data can be achieved through various methods that may include, but are not limited to, any of the following: paper or electronic medical records, paper forms completed at a site, interactive voice response systems, local electronic data capture systems, or central web based systems [Valania, 2006].

There is arguably no more important document than the instrument that is used to acquire the data with the exception of the protocol, which specifies the conduct of that clinical study. The

quality of the data collected relies first and foremost on the quality of that instrument. No matter how much time and effort go into conducting the clinical trial, if the correct data points were not collected, a meaningful analysis may not be possible. It follows, therefore, that the design, development and quality assurance of such an instrument must be given the utmost attention [Rondel and Varley, 1993].

The ICH guidelines on Good clinical practice (GCP) [ICH/GCP Guidelines] use the term 'Case report form' or 'CRF' to refer to these systems. No matter what CRF is utilized, the quality and integrity of the data is of primary importance. The following recommendations are meant to assist in the design, development and quality assurance of the CRF such that the data collected will meet the highest standards. They are meant to highlight some of the most important points to consider during the protocol design and data quality assurance and validation processes.

3.3. Minimum Standards

Design the CRF to collect the data specified by the protocol.
Document the process for CRF design, development, approval and version control.
Make the CRF available at the clinical site prior to the enrollment of a subject.
Document training of clinical site personnel on the protocol, CRF completion instructions and data submittal procedures prior to the enrollment of a subject.

3.4. Best Practices in Clinical Research

Design the CRF along with the protocol to assure collection of only those data the protocol specifies.
Keep questions, prompts and instructions clear and concise.
Design the CRF to follow the data flow from the perspective of the person completing it, taking into account the flow of study procedures and typical organization of data in a medical record.
Avoid referential and redundant data points within the CRF whenever possible. If redundant data collection is used to assess data validity, the measurements should be obtained through independent means.
Design the CRF with the primary safety and efficacy endpoints in mind as the main goal of data collection.
Establish and maintain a library of standard forms.
Make the CRF available for review at the clinical site prior to approval.
Use NCR (no carbon required) paper or other means to assure exact replicas of paper collection tools.

3.5. Best Practices in Paediatric Heart Diseases

The Paediatric Cardiology Units in SeC follow the international standards and guidelines established for the proper management of paediatric heart diseases.

To unify clinical nomenclature and terms, SeC plans to follow the diagnostic coding system for paediatric heart disease that was already referred to within HeC. The guidelines are known as the "European Paediatric Cardiac Code" by the Coding Committee of the Association for European Paediatric Cardiology (http://www.aepc.org/european-paediatric-cardiac-codi/).

The Association for European Paediatric Cardiology (AEPC) was founded in Lyon in 1963 and has subsequently created a network of specialists working in the same field encountering similar problems. The mission of AEPC is to promote the knowledge of the normal and diseased heart and circulation and exchange of knowledge and continuous education.

Over the years, ten working groups have been set up within this Association to bring together workers with similar interests in order to facilitate collaborative research, such as collaboration with paediatric cardiac surgeons, adult cardiologists and other scientists in closely related fields.

AEPC and its Working Groups aim to enhance collaboration amongst members for scientific research and professional development and to maintain high standards of professional practice. The Ordinary Members of AEPC originate from 32 countries in Europe, and each country is represented within the Association by an elected National Delegate.

An Annual Meeting and a Teaching Course are organised by the AEPC in the third week of May in collaboration with one of the member countries. Additional symposia and courses are usually a part of the annual meetings.

These meetings, courses, symposia are evaluated by EBAC (European Board for Accreditation in Cardiology) for continuous medical educational. EBAC is a joint board of ESC, UEMS-Cardiology Section and AEPC. Newsletters are sent regularly to all the members and are also available on the AEPC website and published in the journal "Cardiology in the Young". "Cardiology in the Young" is an international journal dedicated to paediatric cardiology and congenital cardiac malformations in adults, produced by Cambridge University Press. It is published 6 times per year and comes with two to three supplements per year, one of which is the abstracts book of the annual AEPC meeting.

The Italian Society of Paediatric Cardiology (SICP) is the national reference for producing guidelines and protocols and for promoting and exchanging knowledge on paediatric heart diseases (http://www.sicped.it).

The clinical databases to be used in the SeC project have been designed by different organizations and for different purposes, while hosting similar and complementary paediatric cardiology data for the scope of the present project. Data interoperability will therefore need to be established to enable a collaborative development of extended models and clinical assessment procedures to be followed. This will imply aligning the clinical data protocols and internal database structures, which is addressed by WP2, "Clinical Protocol and Data

Alignment, Ethical Clearance and Monitoring" [SeC DoW]. Prof. Giacomo Pongiglione, the head of the Department of Cardiology in OPBG, held in the past the same position within the Istituto Giannina Gaslini in Genoa, was the Clinical Coordinator of HeC IP and is now fulfilling the same role within SeC. Prof. Pongiglione is the WP leader for WP3 aligning the clinical protocol and collaborating with JHU in WP5 in the evaluation of the left heart model for congenital Aortic Arch disease. As the US leader in WP3, Prof. Allen Everett from JHU is responsible for aligning local case data to the HeC structure for validation of the HeC LV dilation model. The American College of Cardiology (ACC), a 39,000-member non-profit professional medical society and teaching institution, is the leading organization dedicated to advocating for quality cardiovascular care, through education, research promotion, development and application of standards and guidelines, and to influence health care and policy. ACC works with the two hospitals to define the clinical assessment procedure for validating the heart models and their extensions. ACC leads the effort to bring the HeC platform to the US beginning with the Helen B. Taussig Congenital Heart Center at JHU and supports the alignment and validation efforts in WP3 and WP5.

The project will be conducted according to Good Clinical Practice (GCP). Good Clinical Practice is a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials (EU Good Clinical Practice Directive - Brussels: European Commission, 2004).

4. Quality Assurance Guidelines for Project Management

Quality planning is an integral part of management planning. The quality of the Project Management of SeC is assured by the following components:

- Management structure
- Project planning
- Project controlling and reporting
- Deliverables quality (scientific validation)
- Risk control

4.1. Management Structure

The Sim-e-Child project management focuses on three primary managerial tasks [SeC DoW]:

- Decision Making, implemented by the Governing Board;
- Scientific and Technical Coordination, performed by the Management & Technical Coordination Board;
- Operational Management, also performed by the Management & Technical Coordination Board;
- Advisory, carried out by the Scientific Committee and the Ethical and Legal Committee.

The structures and specific roles of these bodies, and their interaction towards a coherent management structure, have been planned to reflect the nature of the project with the aim of enabling it to achieve its goals. They also reflect the experience accrued with HeC, in the belief that the outcomes from one modelling scenario should serve as specific input parameters for the next model.

The Management & Technical Coordination Board (including all the WP leaders) ensures both the project managing and the technical and scientific coordination of the project. It is responsible for: monitoring the planned progress of the activities; technical co-ordination and supervision; checking the financial consistency of the Project; evaluating the need for new contractors; supporting the Project Coordinator in interfacing with the European Commission; drafting and validating the project deliverables to be submitted to the Commission; responding to requests for information from the general external community.

The major decisions regarding the overall legal, contractual, ethical, financial, and administrative management are taken by *the Governing Board*, chaired by the Coordinator P1, Siemens.

The Scientific Committee ensures a high-level state-of-the-art scientific advice and check on all technological developments undertaken by SeC.

The Management & Technical Coordination Board (MTCB) will seek to control five variables:

- *Time* - The amount of time required to complete the project. Typically broken down for analytical purposes into the time required to complete the components of the project, which is then further broken down into the time required to complete each task contributing to the completion of each component.
- *Cost* - Calculated from the time variable. Cost to develop an internal project is time multiplied by the cost of the team members involved. When hiring an independent consultant for a project, cost will typically be determined by the consultant or firm's hourly rate multiplied by an estimated time to complete.
- *Quality* - The amount of time put into individual tasks determines the overall quality of the project. Some tasks may require a given amount of time to complete adequately, but given more time could be completed exceptionally well. Over the course of a large project, quality can have a significant impact on time and cost (or vice versa) [Pyzdek, 2003].
- *Scope* - Requirements specified for the end result. The overall definition of what the project is supposed to accomplish, and a specific description of what the end result should be or accomplish.
- *Risk* - Potential points of failure. Most risks or potential failures can be overcome or resolved, given enough time and resources. Of course, theoretically risk can also be negative, meaning that on principle also opportunities, for completing the project faster than expected, could also arise while tackling the different milestones.

Obviously quality in project management influences and is influenced by time and cost of the project tasks. MTCB is also responsible for the quality management in the different work packages.

The Ethical and Legal Committee ensures that all Consortium activities adhere to the ethical policy agreed upon by the project participants and are in line with European and US Directives.

4.2. Project Planning

Within the SeC project, Quality Assurance is focused on achieving an ongoing implementation activity aimed at facilitating a common understanding and agreement of key project issues such as the formulation of user requirements, the definition of project objectives, roles and responsibilities, critical success factors, risks, constraints and organisational impact, etc.

In particular, the following list includes the main quality assurance components taken into account in the project planning processes.

- Defined roles and responsibilities: identification of the roles having responsibility, accountability, and authority within the scope of the process.

- Minimum documentation requirements for the project have been established and archived for use and updating with the Communication platform.
- Common standards and processes for use in development of the project are being identified and benchmarked.
- Attention to QA aspects has been important in preparing and reviewing the project's development plan, standards, and procedures.
- Measures for tracking project progress and project quality have been indicated through the reporting mechanisms available within the Self Assessment Plan.
- Planned WP reviews, along with roles and responsibilities are being constantly updated.
- Functional configuration audit, to ensure deliverables match requirements and are consistent and ready for delivery at the end of the project.
- Timing and content of planned management reviews have been identified and are being addressed.
- Provision of necessary documentation for post-project review of the project is being ensured by the use of the PM and Communication platforms.
- All the partners of the project are aware of the roles, responsibility, authority, and value of the project.
- Deviations from the project's plan are being communicated to the project management team and effectively addressed.
- Management is notified when deviations and/or delays are not being addressed.
- Periodic reports of all ongoing activities are being provided to the project management team and highlighted relevant quality aspects are being gathered and reported. WP leaders will review the QA activities on a regular basis.

4.3. Project Controlling and Reporting

The controlling and reporting of SeC was undertaken by the Project Coordinator from Siemens, Michael Suehling, in conjunction with the Project Manager from Lynkeus, Edwin Morley-Fletcher. During the course of the first reporting period four in person meetings were organised and regular conference calls were held. From the beginning of the second reporting period monthly conference calls will be hosted by the Project Coordinator. As a result of this close cooperation, all deliverables were submitted on time.

In the fist reporting period Project Net Board was chosen as a suitable online collaborative management tool because a selection of the partners had used it during the HeC project. Due to its complexity some partners, especially those from the US, are being progressively instructed on how to use it with the aim of implementing its full range of tools in the second reporting period.

4.4. Deliverables Quality (Scientific Validation)

The Self-Assessment Plan (D1.2), one of the two first deliverables of SeC at Month 5 of the project, is considered as the first step towards deliverables quality. Both the Work Package Leaders (WPLs) and the Scientific Committee Chair have been involved in defining modes and characteristics for the self-assessment of the SeC project. It is the WPLs' common belief that the Self-Assessment Plan must be considered as a dynamic process, undergoing appropriate regular updating in order to validate/modify the chosen indicators, and taking account of the Scientific Committee's evaluation. The re-definition of the Self-Assessment indicators therefore represents a deliverable at the end of each Reporting period.

As the first input, each WPL was requested to clarify the main objectives each WP aims to achieve. They then provided a description of the measurement processes/methodologies which have been adopted. Finally, and on the basis of the previous inputs, a series of correlated indicators for measuring the outcomes of the various WP activities has been defined, associating them, as much as possible, to task-level details with an approximate numerical indication of the allowed threshold limits related to each WP objective.

More recently, the Project Management has proposed that the first draft of any deliverable should be uploaded three weeks after the end of the month specified for delivery, in order to let all the partners have a thorough look and possibly suggest amendments.

4.5. Risk

The risks that may potentially affect the SeC project are continuously monitored in order to elaborate the corresponding contingency plans. The *Management and Technical Coordination Board* of the project will specifically address risk issues at each meeting. All Consortium Partners are concerned with risk detection. When a risk is detected, it is reported to the WP Leader concerned, who assesses the risk. Risks that are serious, affecting the critical path of the project, are further reported to the Project Coordinator. In each WP, risks must be evaluated by the WP Leader, together with their possible impact and the required action. Risk analysis can be recorded on the administrative software platform. The risks are estimated using a numeric scale from 1 to 3, where 3 represents a risk that is almost certain on the likelihood scale, or a risk that is very serious, affecting the critical path of the project, on the risk impact scale.

Each identified risk will have an owner who is responsible for its risk mitigation, monitoring and reporting. In addition, the risk owner proposes preventive and corrective treatment, consisting of suitable actions to reduce the severity and probability of occurrence of the risk.

As stated in the DoW [SeC DoW], the analysis of the activities to be carried out in the SeC Project lists some risks potentially threatening the achievement of project goals. The preliminary list of potential risks is presented below. The results from this analysis will be monitored and updated during the overall lifetime of the project (Task T1.9 "Risk Management").

Risks related to data privacy, security, legal, and regulatory requirements: The requirements related to data privacy and security must be reconciled with applicable legislation. Therefore task T3.4. “Ethical Clearance and Monitoring” has been introduced to address this issue already early in the project. (Estimated risk level: 2)

Management Risks:

A) Consortium heterogeneity. The project brings together clinicians and scientists with very diverse expertise and background. The integration of the project team presents a risk that will be constantly monitored. The project coordinator will have a very important role in establishing an open communication channel between the clinical and computer science world. In an attempt to reduce the difficulty of the project integration, to limit any potential technical conflicts of interest and to ensure the centralisation of the project’s decision making, the Sim-e-Child consortium has been designed to be comprised of partners with complementing skills and expertise with only limited technological overlap. (Estimated risk level: 2)

B) Underestimation of the required effort. This risk is handled by the WP leaders monitoring the planned versus actual effort required by each task. Indicators and statistics will be included into periodic progress reports to the project coordinator. (Estimated risk level: 1)

C) Turnover of key-personnel. This risk is managed by standardizing the way of working across the various teams and by defining a backup policy, so that in case of unexpected departure, remaining personnel can temporarily compensate for the absent ones, while waiting for a permanent replacement. (Estimated risk level: 1)

Technical Risks:

Diversity of medical procedures and complexity of problem domain. For the scope of the project we will focus on one specific simulation task (congenital aortic arch disease) which is sufficient to demonstrate the main technical objectives (setting up a simulation portal). (Estimated risk level: 1)

The HeC project has already been successfully completed in April 2010, so that the related risks identified in DoW are no longer existing (**Risks Related to the conclusion of HeC**).

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