SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

Call: H2020-SC1-DTH-2018-2020 (*Digital transformation in Health and Care*)

Topic: SC1-DTH-06-2020 (*Accelerating the uptake of computer simulations for testing medicines and medical devices*)

Grant agreement No: 101017578

Deliverable 1.5

Quality assurance guidelines

Due date of delivery: 31 August 2021

Actual submission date: 14 June 2021

Start of the project: 1 January 2021
End date: 31 December 2023

This project has received funding from the European Union's Horizon 2020 research and innovation programmeunder grant agreement N° 101017578

Reference

Name	SIMCor_D1.5_Quality assurance guidelines_LYN_14-06-2021
Lead beneficiary	Lynkeus (LYN)
Author(s)	Mirko De Maldè (LYN)
Dissemination level	Public
Type	Report
Official delivery date	31 August 2021
Date of validation by the WP Leader	14 June 2021
Date of validation by the Coordinator	14 June 2021
Signature of the Coordinator	Titus Kuehne Digital unterschrieben von Titus Kuehne Datum: 2021.06.14 09:58:24 +02'00'

Version log

Issue date	Version	Involved	Comments
26/03/2021	1.0	Mirko De Maldè (LYN)	First draft by LYN
19/04/2021	2.0	Anna Rizzo (LYN)	Internal review and integrations by LYN
27/05/2021	3.0	Jan Bruning (CHA), Mirko De Maldè, Anna Rizzo (LYN)	Integration of PC's review and all Consortium partners' indication on internal review partners
11/06/2021	4.0	Andreas Arndt (BIO), Maria Panagiotopoulou (ECRIN), Thomas Czypionka (IHS), Michael Stiehm (IIB), Valentina Lavezzo (PHI), Wouter Huberts (TUE), Malte Rolf-Pissarczyk (TUG), Lucian Itu (UTBV), Claudio Capelli (UCL), Liesbet Geris, (VPH), Raphaelle Lesage (VPH)	Consortium partners' review
11/06/2021	5.0	Mirko De Maldè (LYN), Anna Rizzo (LYN)	Final review and formal checking by LYN
14/06/2021	Final	Jan Brüning (CHA), Grischa Gabel (CHA)	Submission by PC

Executive summary

This deliverable outlines the set of guidelines that the SIMCor consortium adopted for ensuring the highest quality in the execution of the project, as a framework of procedures, standards and rules to guarantee the quality of project outcomes. The document outlines the project management procedures adopted for monitoring project activities and mitigating risks and addresses the procedures for the preparation and quality control of project deliverables, reports and software.

Table of contents

List of figures

List of tables

Acronyms

Acronym	Full name
4T	Tolerate, treat, terminate, transfer
AD	Ahead deadline
D	Deliverables
DoA	Description of Action
IQPR	Internal quarterly progress report
PC	Project Coordinator
PM	Project Manager
PR	Project reports
ROM	Reduced order modelling
WG	Working group
WP	Work package

Introduction

The purpose of this deliverable is to outline the set of guidelines and standards that the SIMCor consortium adopted for ensuring the highest quality in the execution of the project, to serve as a framework of procedures, standards and rules to guarantee the quality of project outcomes (e.g., deliverables, periodic reports, software, infrastructure).
In the first section, *'Project management and risk mitigation'*, the document outlines the project management procedures adopted by the consortium for monitoring project activities, ensuring timely completion of project tasks, mitigating any potential risk identified during the project implementation, and maximising the efficiency of cooperation among partners.
In the second one, *'Deliverables and reporting'*, the document specifically addresses the procedures to be followed for the preparation and quality control of projects deliverables and reports, as means for assessing intermediate project outcomes.
The third one, *'Software implementation'*, provides best practices for software implementation.

This framework will facilitate the consortium in making sure that:

1) The project is running smoothly, and risks are taken into account and timely mitigated with proper strategies;
2) Reports and deliverables are complete, self-containing, clear, and properly presented;
3) The outcomes of the project, as described in relevant deliverables, are coherent with the project scope, overall implementation approach, plan and expectations, as set forth in the *Description of Action* (DoA);
4) Partners have considered current state-of-the-art and established best practices in their respective fields, and their outcomes are indeed novel and based on solid scientific and technological grounds, also assessing reproducibility and validity of the models and methods produced within the project;
5) The outcomes, in particular software and new procedures, take into account requirements and constraints of the intended operational scenarios in which they are going to be adopted.

While this document has not the purpose of providing detailed guidelines for the consortium in the assessment of each of the above-indicated aspects of the project execution and delivery, these principles are meant to inform quality assurance procedures as described in the following paragraphs. It is worth also noting that the present guidelines are not intended to overrule the current practices adopted internally by each partner, but to provide a common minimum framework of quality assurance for the project, to be adopted by the whole consortium.

Project management and risk mitigation

The SIMCor consortium adopted a basic set of management procedures aimed at facilitating a smooth cooperation between partners, a clear common understanding of the project objectives, and a prompt reaction to unforeseen issues. This will enable the consortium to make the most effective choices moving toward the project goals, while at the same time allowing to identify the major threats to the achievement of these objectives, making it possible to put in place appropriate mitigation strategies.

The rationale of the **overall management structure and the specific role and interaction of the different management bodies, described in *D1.3 - Project handbook (LYN, M4)***, have been conceived to secure a smooth and effective leadership of the project. Together with an effective ongoing **monitoring and self-evaluation, to be described in *D1.4 - Self-assessment plan (LYN, M6)***, they will ensure an effective double-check on the single partners' work in light of the different aspects (i.e., technical, formal, ethical, legal) to be taken into account, constantly keeping on track the day-to-day management, keeping it in line with the scientific vision of the project and ensuring the timely achievement of its goals at the highest quality level.

The main elements of the management structure are **the Governing Board, the Steering Committee, the external advisory boards, and the *working groups* (WGs).** The latter have the purpose of ensuring **appropriate levels of collaboration among *work packages* (WPs) and partners towards the achievement of specific overarching goals of the project**. The following WGs have been established, while others (e.g., WP10) will be created as soon as specific interaction between partners is required:

- *WP1/3/5/6 - Data management & ethics (DME-WG)*
- *WP7 - Virtual cohorts (VC-WG)*
- *WP8/9- Modelling & Simulation (MS-WG)*
- *WP3 - System requirements (SR-WG)*
- *WP4 - Regulatory issues and SOPs (RI-WG), and internal WGs for each task/deliverable*
- *WP2 - Communication, dissemination and exploitation (CDE-WG)*
- *WP1 - Coordination and management (PM-WG).*

The interaction within WGs and WPs are the most frequent, with regular monthly or fortnightly e-meetings. The work of the WGs is particularly important at the very beginning of the project, whereas the overall approach and strategy for the implementation of key outcomes of the project is thoroughly discussed amongst partners to ensure clarity, alignment, and coordination.

Besides, *project general (e)meetings* are held every 6 months (M6, M12, M18, M24, M30, M36) and *advisory board meetings* are held within general meetings, **at yearly schedule (M12, M24, M36)** and can be rounded up on other occasions when needed.

To keep a high-level monitoring of the activities, the project agreed on a **quarterly reporting activity (*internal quarterly progress reports*, IQPRs)**, for having a common understanding of the activities undertaken by WGs and WPs, reciprocal expectations of the WPs, forthcoming major deliverables, and risks.

Risk assessment

Risk identification is conducted using the 'risk charting approach', which focuses on resources, threats, modifying factors and adverse consequences. The assessment uses a classic risk assessment matrix (probability vs consequences) and will be revised and updated throughout the project implementation. Risk management will follow the classic *tolerate, treat, terminate, transfer* (4T) model and treatments that require actions will generate new milestones in the work plan.

As far as the risk management process is adopted, SIMCor adopted a risk management approach aimed at continuously monitoring the risks that may potentially affect project outcomes and to allow a prompt reaction by the relevant project bodies, devising appropriate mitigation strategies and alternative plans.

The risk management process consists of three phases:

- **Risk identification.** All project partners are concerned with risk detection. When a risk is detected, it is reported to the *Project Coordinator* (PC) and *Project Manager* (PM). This activity is performed by each WP Leader and reported within the quarterly report.
- **Risk estimation.** Once a specific risk is identified, it is assessed and discussed with the relevant partners of the consortium. Risk assessment will focus on two aspects: *risk likelihood* and *risk impact*.
- **Risk mitigation and follow-up.** Once the risk is identified, a specific partner is appointed for its management, monitoring, and reporting, while all the concerned partners are involved in conceiving appropriate mitigation strategies.

An overview of risks and relevant mitigation strategies will be provided in the periodic reports to the EC, while the risk assessment methodology is summarised in the figure below.

Figure 1: Risk management approach adopted in SIMCor.

Each person contributing to the project will be allowed to report, anonymously if appropriate (e.g., in cases where retaliation is feared), any risks that are not listed in the plan. A preliminary assessment of potential risks carried out by members of the consortium, is documented in *Table 1* below, together with envisaged mitigation steps.

Description of risk	WPs	Proposed risk-mitigation measures
Cloud insufficient or uneconomical to run workflows over virtual patient population (Med)	3	Resources requirements monitored by SC. Local institutional resources used to provide additional HPC computational infrastructure.
Conflict between infrastructure constraints and model requirements (Low)	3	Early and comprehensive planning to avoid such conflicts. Alternative infrastructure technologies present within the team existing capabilities.
Web interface inadequate (Low)	3	Technology assessment against specification conducted prior to final selection. Development of task-specific plugins.
Data storage limits reached (Low)	3	Data requirements already estimated. Altered balance between cloud and HPC ensuring limits are not overcome.
Inadequate retrospective data to inform seed patient population (Low)	5,6	Initial assessment indicates consortium resources are adequate. Clinical partners will engage with collaborating institutions to extend sources, if needed, following appropriate ethical approval.
Lesion segmentation methods produce output of insufficient quality for simulation tasks (Med)	5,6	Project is developing novel but already impressive image improvement technology. Alternative parameterised approaches are possible.
Workflow for device effect simulation is too labour intensive to adopt them in a reasonable time scale (Low)	5,6	Expertise of consortium members in 1D/0D/3D modelling for these applications allows the modelling approach to be adapted to provide results within a feasible timescale. Access to extreme computing facilities is available via TUE.
Insufficient data available within the project to inform modelling of vessel biological response (Med)	7,8,9	Retrospective and prospective data sources have been carefully assessed to ensure adequacy. TUG is able to draw on significant resources from previous analysis of the arterial wall to inform the development of SIMCor simulations.
Workflow for in-silico clinical trial is too computationally intensive to run over the full VPP (Med)	7,8,9	Work in other projects has established satisfactory levels of performance improvement. Additional approaches to achieving efficiency are under consideration.
Insufficient data is available to inform estimates of model input uncertainty (Med)	7,8,9	Data sources have been assessed and considered adequate, taking into account several both retrospective and prospective studies data sources, and will be further supplemented with review of the literature.
Proliferation methodology proves more complex than planned (Low)	7,8,9	Initial considerations have identified multiple possible approaches. Replacement of approach is possible, with some reallocated resources.
Virtual physiology requirements place higher than expected demands on infrastructure (Low)	3,7, 8,9	Early tests will determine the level of required complexity. Further alternatives will be available and will be appropriately selected if needed.
Ethical approval takes longer than planned (Low)	4,7, 8,9	Each clinical centre has already prepared similar protocols, so content and local processes are familiar. Preparation of protocols and submission to ethical committees will actually begin on award of funding, before the planned start date, indicatively by November 2020.

Insufficient patient recruitment data (Med)	5	Protocol study design has been tailored to carry out the envisaged activities with existing data sources maximise enrolment and minimise dropouts. If needed, additional patient data will be gathered from clinical routine data from participating clinical centres (2021-2013) or clinical trial studies retrieved from the ECRIN-MDR registry. Recruitment will be a routine PB-level agenda item. There is the potential to alter the balance of recruitment between the centres.
Insufficient compliance with follow-up (Low)	7,8,9	Follow-up procedures can be subject to dropouts. The SIMCor design has already reduced the requirement for full follow-up data. This will also be a factor in deciding whether to alter the recruitment balance between centres.
In-silico clinical trial complexity requires more effort than anticipated (Low)	7,8,9	Realistic estimates have already been obtained from modellers. Early indications will be available, in time for resource reallocation.
In-silico clinical trial computations require more time than expected (Low)	7,8,9	The technical team now has experience of *reduced order modelling* (ROM) capabilities and has provided actual performance data. Access to extreme computing facilities is available via TUE.
Lower than expected interest from device manufacturers (Low)	2	Manufacturers are already seeking low-risk solutions to accelerate time to market. Preparation of targeted case studies to demonstrate utility and cost-effectiveness.
Failure to engage adequately with regulatory bodies (Low)	4,2	Consortium partners have strong links with regulatory bodies, including FDA, EMA and ISO committees. Representatives of FDA and TUV SUD have been included in the RAB. Liaison with regulatory authorities will start early in the project and feedback will be regularly gathered and incorporated in relevant deliverables (D2.5, D2.6).
Limited availability of some real-world data (Med)	10	Evaluate available items and make estimates for missing items from literature and interviews.
Uncertainty of WP7 results (Med)	10	Calculate sensitivity analyses, use break-even analysis.

Table 1: Potential risks, probability, WPs involved, and envisaged mitigation measures as identified by consortium partner at preliminary level.

Deliverables and reporting

One essential element of the SIMCor quality assurance process addresses the production of *deliverables* (D) and *project reports* (PR) and the relevant quality control mechanisms. Reporting documents are drafted by responsible partners (D) or WP Leaders (PR). After that, they pass through a review and refinement process which involves the PC and PM, WP Leaders and, for deliverables, other internal review partners, qualified for assessing a specific deliverable.

Internal deliverable review process

The internal review process for each deliverable involves the *responsible partner* (i.e., partner indicated as responsible for the deliverable in the DoA), an *internal review partner* (i.e., a subject-matter expert indicated by the PM and PC, possibly within partners of the same WP), the WP Leader, the PM and PC, who has administrative responsibility to submit all deliverables to the EC portal by the deadline indicated in the DoA. The process is organised as follows.

- **DRAFT 1 (within 4 weeks *ahead deadline*, AD):** the deliverable is drafted by the **responsible partner** and reviewed by its PI and the rest of the partner's team.
- **DRAFT 2 (within 3 weeks AD)**: The partner appointed as **internal reviewer** provides a content-wise proof-reading of the document, under the supervision of the PM. This phase also includes an interaction with the document author, who is responsible for taking into account the comments provided by the reviewer and producing an updated version. This activity follows an iterative approach which is concluded when all remarks made by the internal reviewer in the subsequent reviews performed are fully considered. The internal review partner is indicated by the PM and PC, possibly among the other WP partners, according to the topic and relevant expertise needed.
- **DRAFT 3 (within 2 weeks AD)**: if the responsible partner is different from the WP Leader, another round of review is done by the WP Leader, to assess content quality and verify consistency with the WP objectives and work plan.
- **PREFINAL and FINAL VERSION:** the last phase of the process involves the PM and the PC, who will both review the document and assess its coherence and alignment with the project intended outcomes and relevant approach, and make a final proofreading for typos, layout and formatting.
- **SUBMISSION:** The PDF of the final version, signed by the PC, is submitted by the PC on the EC portal. After submission to the EC, the final documents (i.e., Word and signed PDF files) are uploaded on the project Google Drive (*SIMCor > 3_Deliverables*) and kept for reference.

This process is fully documented in the *'Version log'* section included in each deliverable and summarised in *Figure 2* below. *Table 2* below summarises all deliverables due from M6 onwards for each WP, with relevant internal review partners.

Document style guide

- A standard deliverable template (*SIMCor_Deliverabletemplate*) is provided on the project Google Drive (*SIMCor > 3_Deliverables* and *SIMCor > Templates*), to be used as reference for the initial drafting of the deliverable. This template is adopted by all partners and ensures consistency of the deliverable format and structure across work packages.
- Further indications for layout and formatting (i.e., naming convention, document styles) are included in the *'Reporting guidelines'* section of *D1.3 - Project handbook (LYN, M4)*.

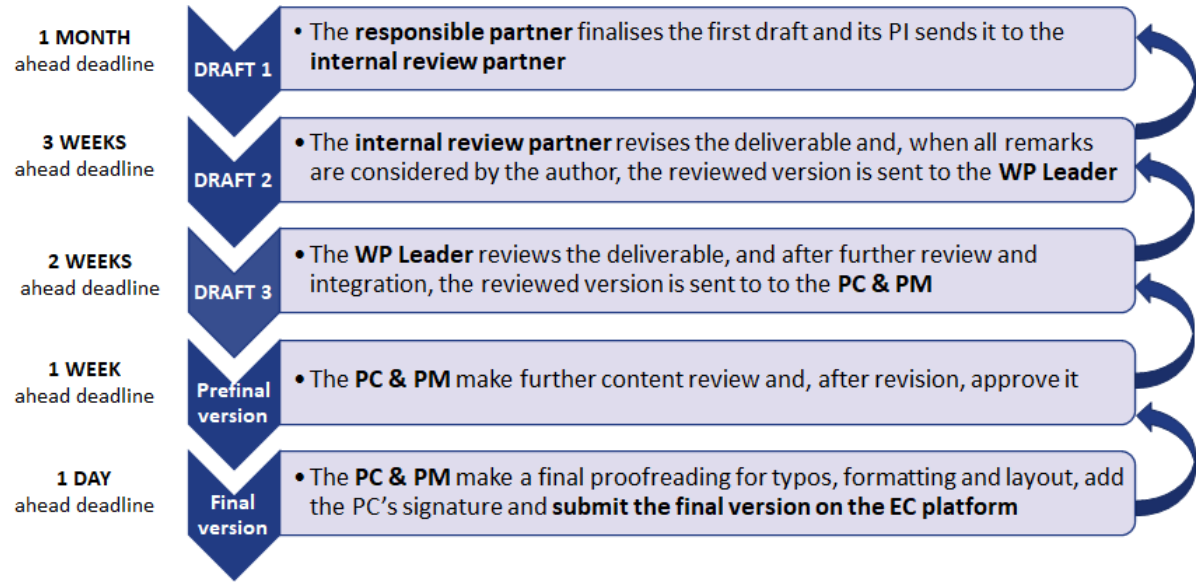

Figure 2: SIMCor internal deliverable review process.

N	Name	WP	Responsible partner	Internal review partner	Due month	Due date
D1.1	Research strategy plan	WP1	CHA	TUE, ALL	M6	30/06/2021
D1.4	Self-assessment plan	WP1	LYN	ALL	M6	30/06/2021
D1.5	Quality assurance guidelines	WP1	LYN	ALL	M8	31/08/2021
D1.9	Ethical and legal compliance final assessment	WP1	LYN	UCL	M9	30/09/2021
D2.5	Regulatory feedback report (1)	WP2	VPH	ALL	M19	31/07/2022
D2.6	Regulatory feedback report (2)	WP2	VPH	ALL	M31	31/07/2023
D2.3	Communication channels and materials	WP2	LYN	ALL	M36	31/12/2023
D2.4	Dissemination events	WP2	LYN	ALL	M36	31/12/2023
D2.7	IPR and exploitation plan	WP2	LYN	ALL	M36	31/12/2023
D3.1	System requirements	WP3	UTBV	ALL	M6	30/06/2021
D3.2	Data management plan	WP3	LYN	ALL	M6	30/06/2021
D3.3	Data repository	WP3	UTBV	ALL	M18	30/06/2022
D3.4	Cloud and HPC facilities	WP3	UTBV	ALL	M24	31/12/2022
D3.5	Web-based interface	WP3	UTBV	ALL	M36	31/12/2023
D4.2	SOPs for data processing for in-silico models	WP4	CHA	UCL	M12	31/12/2021
D4.4	Guidelines for documentation	WP4	IIB	BIO	M12	31/12/2021
D4.1	SOPs for data acquisition for in-silico models	WP4	UCL	CHA	M18	30/06/2022
D4.5	SOPs for in-silico analysis of TAVI	WP4	IIB	PHI	M24	31/12/2022
D4.3	SOPs for virtual cohorts generation and validation	WP4	TUE	UCL	M36	31/12/2023
D4.6	SOPs for validation of in-silico models	WP4	BIO	IIB	M36	31/12/2023
D5.7	Ethical committees approval process reports and documents	WP5	UCL	CHA	M6	30/06/2021
D5.3	Review and report of retrospective data quality	WP5	UCL	CHA	M16	30/04/2022
D5.4	Completion and report of animal study	WP5	CHA	BIO	M18	30/06/2022
D5.5	Report on retrospective clinical data collection	WP5	CHA	UCL	M18	30/06/2022

D5.6	Completion of synthetic data creation process	WP5	UCL	TUE	M18	30/06/2022
D6.2	Database for anatomy and function based on preclinical and clinical data	WP6	CHA	UCL	M12	31/12/2021
D6.3	Uncertainty quantification for input data	WP6	CHA	TUE	M21	30/09/2022
D6.4	Specification and quantification of subject-specific data-based boundary conditions	WP6	CHA	TUE	M24	31/12/2022
D6.5	Specification and quantification of synthetic boundary conditions	WP6	CHA	TUE	M30	30/06/2023
D7.1	Definition of model output	WP7	TUE	BIO	M6	30/06/2021
D7.2	First version of the simulation models	WP7	TUE	PHI, BIO	M9	30/09/2021
D7.3	First version of the definition of the input space	WP7	TUE	UCL	M12	31/12/2021
D7.4	Sensitivity and uncertainty quantification toolbox	WP7	TUE	UTBV	M15	31/03/2022
D7.5	Uncertainty quantification and re-definition of input space	WP7	TUE	IIB	M18	30/06/2022
D7.6	Proof of principle of the complete virtual patient generator	WP7	TUE	TUG	M24	31/12/2022
D7.7	Virtual cohort generation for in-silico trials	WP7	TUE	VPH	M36	31/12/2023
D7.8	Validated virtual cohorts for in-silico trials	WP7	TUE	ECRIN	M36	31/12/2023
D8.1	PAPS model	WP8	BIO	IIB	M12	31/12/2021
D8.2	TAVI model	WP8	IIB	BIO	M12	31/12/2021
D8.3	Constitutive vessel model	WP8	TUG	BIO	M16	30/04/2022
D8.8	IGA model	WP8	TUE	TUG	M28	30/04/2022
D8.4	Validated constitutive models of the vessel wall	WP8	TUG	BIO	M20	31/08/2022
D8.5	Fast device deployment model	WP8	CHA	PHI	M24	31/12/2022
D8.6	Report on 3D finite element simulation	WP8	PHI	TUG	M24	31/12/2022
D8.7	Reduced order model	WP8	PHI	IIB	M30	30/06/2023
D9.1	Constitutive vessel model	WP9	TUG	BIO	M18	30/06/2022
D9.2	Device specific models	WP9	IIB	BIO	M24	31/12/2022
D9.3	Low-fidelity validation results	WP9	BIO	TUG	M24	31/12/2022
D9.4	Effect simulations of devices report	WP9	BIO	IIB	M30	30/06/2023
D9.5	High-fidelity devices validation report	WP9	BIO	IIB	M36	31/12/2023
D9.6	Devices approval experience report	WP9	BIO	VPH	M36	31/12/2023
D10.1	In-silico trial impact assessment framework	WP10	ECRIN	VPH	M12	31/12/2021
D10.3	Conceptual framework report	WP10	IHS	VPH	M20	31/08/2022
D10.2	Impact analysis on clinical and preclinical trials	WP10	ECRIN	UCL	M36	31/12/2023
D10.4	Industry and market impact report	WP10	IHS	PHI, BIO	M36	31/12/2023
D10.5	Socio-economic impact report	WP10	IHS	VPH	M36	31/12/2023

Table 2: SIMCor deliverables (M6-M36) with WP, responsible partner, internal review partner, due month, due date.

Periodic report preparation and review process

The preparation and internal review process for periodic reports involves the WP Leader, Task Leaders, the PM and PC, who has administrative responsibility to submit the report to the EC portal within 60 days after the end of the reporting period. The process is organised as follows.

- **WP DRAFTS (within 6 weeks ahead deadline):** WP Leaders, with the support of the Task leaders, prepare the WP reports following the PR template and send them to the PM and PC.
- **WP REVIEW (within 3 weeks AD)**: the PM and PC review the provided WP drafts and provide feedback, asking for clarifications, revisions and integrations where necessary. The feedback cycle goes on until the necessary quality of reporting is achieved.
- **REPORT FINALISATION (within 2 weeks AD):** the PM and PC finalises the overall report.
- **SUBMISSION:** The PC submits the final report on the EC portal. The final document is uploaded on the project Google Drive (*SIMCor > 3_Deliverables*) and kept for reference.

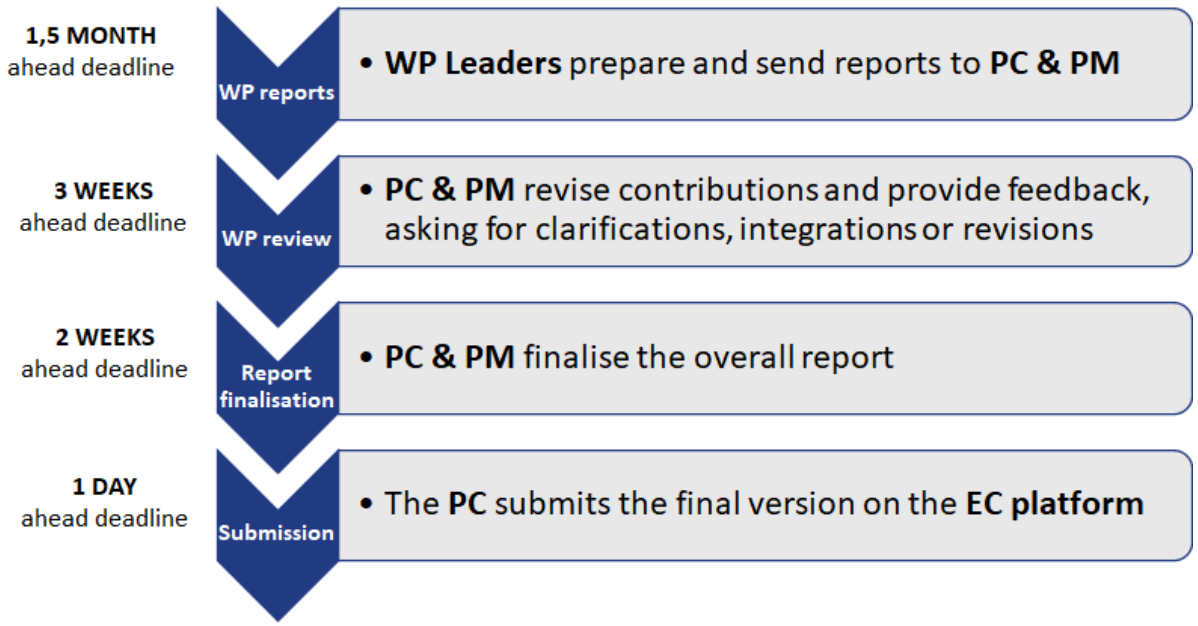

Figure 3: SIMCor periodic report preparation and review process.

Software implementation

The consortium will also make sure that high-level best practices for software implementation are adopted and documented in relevant deliverables and reports. In particular, partners will be required to offer, at the release of working software, a set of basic information about the model, including:

1. **Key features**
2. **Input/output parameters and formats**
3. **Expected performances**
4. **Usage requirements (i.e., computational capacity, storage space required, etc.)**
5. **Integration/interaction with external modules**
6. **Guidance for usage**
7. **Bugs reporting**
8. **Report on the conditions and outcomes of any testing activity performed on the tool.**

Such a set of information is intended to avoid misunderstanding among partners, offering a clear description of capabilities and features of the produced software, setting the expectations and clarifying the requirements for usage.