Personalised Medicine by using an Advanced Point-of-Care Tool for Stratified Treatment in High Risk Cardiovascular Patients (Grant Agreement No 101095432)

D1.1 Project Quality and Risk Management Plan

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Index:

1 Executive Summary

The deliverable provides an overview of quality procedures, methods, and tools adopted by the PoCCardio project.

The quality procedures in this document are presented on a contextual background with more narratives and more focus on practical implementation than the rules and procedures set forth in the Grant Agreement and the Consortium Agreement, which tends to have a more legal viewpoint.

The document is thus a practical management guide for members of the PoCCardio consortium. However, it shall be stressed that in cases of conflicts and omissions, the text in the Grant Agreement and the Consortium Agreement takes precedence in that order.

1.1 Consortium Bodies

The PoCCardio project will apply an interdisciplinary research and development methodology involving technology developers and medical professionals in synergistic symbiosis. The chosen technical and clinical approach is reflected in the Work Package structure. The project will be implemented through activities in ten dedicated Work Packages (WP), which is described in Section 2.

The management structure and supporting procedures have been designed specifically with the strategic and operational management requirements of an industrial and highly multidisciplinary research project in mind.

The organisational management structure of the consortium comprises five Consortium Bodies i.e. the General Assembly (the ultimate decision-making body of the Consortium), the Coordinator (the legal entity acting as the intermediary between the Parties and the Granting Authority), the Executive Steering Committee (managing the execution of the Project), a Scientific Advisory Board, and an Ethics Board (handling all privacy, ethical, legal, and gender aspects).

The General Assembly will be the executive authority for the overall management and running of the project, the resolution of any major problems that may arise and will decide on the use of the common knowledge resulting from the project. It will comprise one executive member from each partner. It will be chaired by the Coordinator. Procedures for organisation, meetings, tasks and decisions, and voting rules have been defined.

The Executive Steering Committee consists of designated area managers and of work package leaders. The Executive Steering Committee shall undertake the day-to-day management tasks. Procedures for organisation, meetings, tasks have been defined

The tasks of the Coordinator have been defined and a Project Manager is appointed to assist the Coordinator with administrative and financial data.

The Scientific Advisory Board will consist of six experts in relevant areas of PoCCardio. The Scientific Advisory Board will be appointed by the General Assembly and chaired by the Project Manager.

Finally, the Ethics Board will be appointed by the General Assembly. It will be the direct point of contact for the European Commission in cases of ethical issues.

1.2 Procedures

Standard procedures for management, communication, meetings, document production and reporting have been defined. All work in the project will be carried out in accordance with the project DoA and the procedures outlined in this document.

The project plan covers the complete project duration. Each Work Package Leader is responsible for preparing and managing a detailed Work Package plan.

To continuously measure the project's progress in terms of achievements and impact, a set of milestones have been defined. Milestones are control points where decisions are needed with respect to moving on to the next stage of the project.

The project duration of 60 months has been divided into 4 periods in the Grant Agreement. The periodic reports must be submitted to the Granting Authority no later than 60 days after end of reporting period. Procedures for collecting information and submitting the periodic reports have been defined.

Email communication is the preferred method of internal project communication and a project mailing list has been established.

A web-based project extranet has been established to support collaborative working. It contains workspaces for partners to share documents. Other online resources are also available.

Further, procedures for external communication via the project website and social media sites have been defined.

The Ethics Management procedures are set out to allow project partners to share concerns, issues, progress, status of ethical nature across the project and provide efficient and transparent methods of documenting and reporting internally and externally. A set of agreed ethics principles and guidelines will be formulated and published in D1.4 Statement of Ethics (M8). All the trials will implement the project's Ethics Monitoring Framework which includes data privacy framework, AI trustworthiness and GDPR compliance in the respective trials. The tasks will monitor the projects compliance with the Ethics Monitoring Framework during the trial period. Finally, an Ethics Board with two external experts will be created to secure that the appropriate action is taken if any ethical problems are reported by project partners and other participants.

A set of Data Management Procedures will be implemented in the project as a key to achieve good data management and ethically acceptable study conduct. The Data Management is not to be confused with the clinical data management processes that are undertaken in WP9. A Data Management Plan (DMP) will be created to set out the project's approach to data management. The DMP will describe the data management life cycle for the data to be collected, processed and/or generated. It will also set out how data/research outputs are made findable, accessible, interoperable, and reusable (FAIR) to the furthest extent possible considering data privacy restrictions.

Innovation and IPR management procedures aims to ensure that relevant project knowledge (technical, process or user experience) is screened, patent- or trade-secret protected when desirable and are made available. The main paths of innovation are foreseen in two areas: clinical innovation and technological innovation.

For both areas, the overall process for Innovation Management is defined with the aim to identify all the potential innovative elements of the exploitable products. The process will be based on identifying, collecting, describing, and working towards turning creative ideas into innovative value propositions of the PoCCardio solution for the targeted markets. Innovation Forms will be created by the Innovation Manager and will be used as to present innovation status to the Executive Steering Committee and the General Assembly.

The project has defined clear procedures for the management of all risks and issues that are identified at the beginning of the project or arise over its course

All project participants will be responsible for raising any material or perceived risk as part of the normal reporting process and to register all such risks and issues in the project's online risk log. The online risk log will be established in the form of a joint workspace on the project website. It will be updated in the deliverable D1.2 Online Risk Log and Mitigation Actions due in M3

1.2.1 Document handling

Documents under the scope of the Quality Plan (internal and external deliverables plus project working documents) are subject to specific quality procedures regarding the layout and typographic features of the document when viewed or printed. Two templates have been created for mandatory use with all deliverables and power point presentations used with project related content.

All deliverables shall adhere to a detailed set of quality parameters. The deliverable template contains detailed instructions for use. Those instructions relate to content, format, and the document itself and is described in details.

All deliverables must be delivered to the Grant Authority by the Project Manager on or before the due date. The Project Manager will formally submit the deliverable to the Commission. To secure a safe submission process, a certain procedure is outlined and must be followed.

2 Introduction

2.1 Purpose, Context, and Scope

The D1.1 Project Quality and Risk Management Plan is a practical management guide for members of the PoCCardio consortium. It sets out the procedures for Management Decision making, Quality Assurance activities in the project with additional focus on risk management and mitigation planning.

The quality procedures in this document are presented on a contextual background with more narratives and more focus on practical implementation than the rules and procedures set forth in the Grant Agreement and the Consortium Agreement, which tends to have a more legal viewpoint.

The D1.1 Project Quality and Risk Management Plan is closely connected to two other management deliverables: D1.2 Online Risk Log and Mitigation Actions and D1.3 Plan for Managing Knowledge and Intellectual Property. The procedures for IPR management are mainly related to the work in WP10 and contains references to D10.1 Mid-term IPR and exploitation report and the D10.3 Final IPR and exploitation planning report. The procedures for dissemination and exploitation have links to D10.6 Communication and Dissemination Strategies and Plan as well as D10.4 Business and financial plan.

2.2 Content and Structure

The document is structured as follows:

Section 1 provides an executive summary and Section 2 an introduction to the Project Quality and Risk Management Plan.

Section 3 provides a brief overview of the project, its purpose and results, and a list of consortium partners. It also sets out the workplan in which its clinical and technical approach is presented and how the work is structured to bring together the diverse research work in a timely fashion.

In Section 4, the hierarchal project organisation and procedures are presented in a structured, operational manner. The section provides operating procedures for the General Assembly, the Coordinator, the Executive Steering Committee, as well as roles and responsibilities of the Project Manager. Further, it addresses the managerial tasks for the Work Package leaders and task members. Finally, it outlines the functions of the Scientific Advisory Board and the Ethics Board.

Further general management procedures are dealt with in Section 5. It includes procedures for project planning, progress control and milestone management, administrative and financial procedures, and periodic management reports, as well as general communication and online platforms for project co-working. Section 5 also deals with general project management procedures including progress control, periodic reporting, communication, and data management. Finally, Ethics and Data Management procedures are described here.

Section 6 describes the quality procedures to be followed when creating deliverables and the submission of these to the Grant Authority. The Section also lists all the deliverables planned for the duration of the project.

Innovation procedures and IPR management are described in Section 7 and covers both the already defined clinical and technical innovation paths, as well as the method for identifying and assessing other innovations during the project.

Section 8 describes Risk management procedures and the use of an online risk log.

Finally, Section 9 deals with standard procedures for implementing dissemination, communication and exploitation strategies and procedures.

3 Project Approach and Plan

3.1 Purpose

Myocardial infarction (MI) remains a major cause of morbidity and mortality in Europe and the United States. Despite available tools for risk stratification and the availability of a variety of drugs and treatment approaches to lower cardiovascular (CV) risk, the incidence of recurrent CV events remains high in subjects with previous MI. The PoCCardio project partners are proposing a set of CV biomarkers that have repeatedly emerged as predictors of CV event risk, either alone, or even more convincingly in various combinations.

The PoCCardio project thus aims to promote personalised treatment of cardiovascular diseases (CVD) by identification of 'extremely high risk' subjects using biomarkers and to explore the potential of multifactorial intensified risk factor treatment in lowering CV risk and recurrent events. The project will develop an innovative Lab-on-Chip (LoC) test and a compact read-out device that allows rapid and low-cost point-of-care (PoC) measurements of both proteomic biomarkers and genetic risk variants, and 2) validate accuracy, sensitivity, specificity, and feasibility of the PoC device.

The PoCCardio test brings together biomarker measurement and profiling of genetic variations, and thus will be used to enhance risk stratification and to provide the affected individuals with personalised care. It also limits the amount of both expensive reagents and blood samples needed for the tests, and thus reduces both cost and patient's pain and discomfort.

A PoC device, developed within the H2020 PoCOsteo project, will be further developed and tailored to provide a self-contained and portable method of analysing blood samples from patients at the treating sites. Disposable microfluidic cartridges will enable contamination-free sample collection via a user-friendly blood collection method (e.g., capillary) as well as in-device sample preparation overcoming the need for trained personnel and multi-step tests.

The clinical validation of the qualified biomarkers and the PoC tool itself, will be performed in a prospective, randomised multinational trial, including only existing and approved pharmaceuticals. The trial will provide the scientific foundation to support regulatory authorities regarding approval of companion diagnostics, and recommendations for the prescription of drugs, respectively.

The PoCCardio Consortium consists of seven organisations from seven different countries, representing a balanced partnership of clinical, industrial, academic, technology, and business specialists.

3.2 Partners

The PoCCardio Consortium consists of the following Partners:

Beneficiary Number	Beneficiary name	Beneficiary short name	Country
1 (Coordinator)	Medical University of Graz	MUG	Austria
2	Universiteit Gent	UGent	Belgium
3	Universitat Rovira i Virgili	URV	Spain
4	Fraunhofer Gesellschaft zur Förderung der angewandten Forschung E.V.Forschung E.V.	Fraunhofer	Germany
5	Tehran University of Medical Sciences	TUMS	Iran
6	In-Jet ApS	IN-JET	Denmark
7 (Ass. partner)	Labman Automation Ltd	LABMAN	UK

3.3 Technical and Clinical Approach

In order to develop and clinically validate the concept of PoCCardio, the project will follow a clear and well-proven research methodology along the following 5 step roadmap: 1) Development and test of selected biomarkers via a proteomics LoC technology, 2) development of the genomics LoC technology, 3) Integration of the sensing platform into a microsystem cartridge and laboratory validation of the cartridge using a to be developed PoC tool, 4) clinical validation in a multi-centre, multinational clinical study, and 5) development of an AI-based automated biomarker data analysis tool to establish personalised risk prediction and support therapy selection. The methodology is completed with the creation of a shortlist of suitable candidates for licensing the PoCCardio tool with the aim to initiate negotiations with interested parties.

3.4 Project Work Package Structure and Work Plan

The PoCCardio project will apply an interdisciplinary research and development methodology involving technology developers and medical professionals in synergistic symbiosis. The chosen technical and clinical approach is reflected in the Work Package structure. The project will be implemented through activities in ten dedicated Work Packages (WP) structured as depicted in Figure 1.

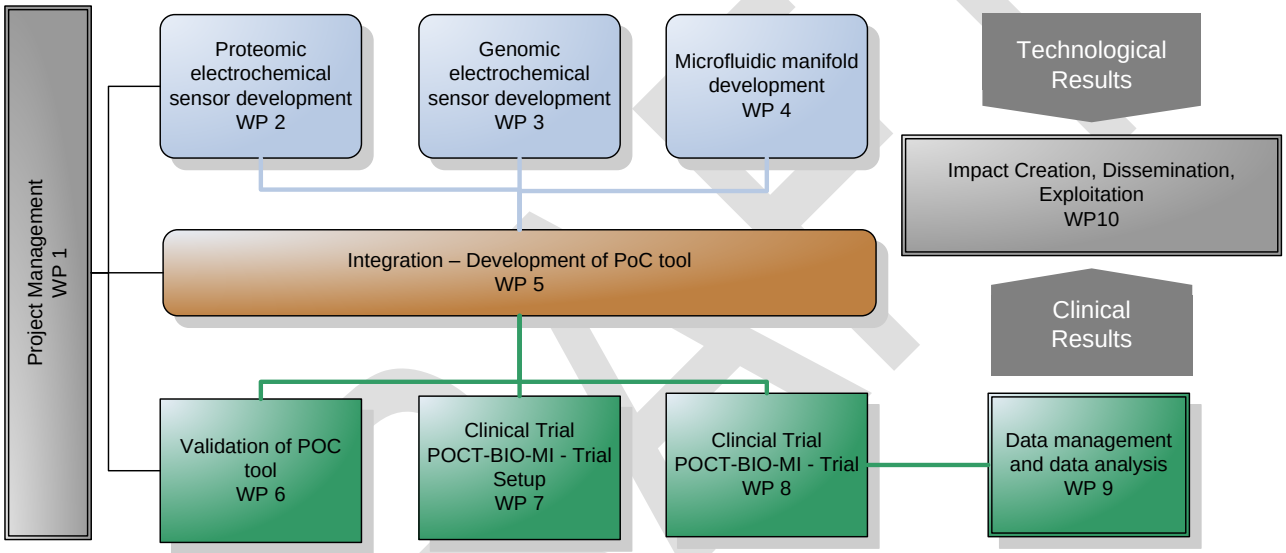


Figure 1 PoCCardio Work Package structure

The technical development of the proteomic and genomic sensors together with the microfluidic manifold will be developed in the technology oriented WP2 – WP4. The results of these WPs will be integrated in WP5 into a clinical grade PoC device for the trials.

The validation of the PoC tool will first be performed in WP6. Once validated, the PoC devices will be deployed in the large-scale, multi-centre, RCT named POCT-BIO-MI in WP7 and WP8. A data management and coordinated AI-based data analysis of the clinical data generated by POCT-BIO-MI trial and retrospective sample analysis will finally be performed in WP9.

Both the clinical results and the technological results will be comprehensively disseminated in WP10 along the planned communication and dissemination strategy. Also, a detailed exploitation planning, including IPR management, will also be performed in WP9.

The overall project management will be performed in WP1.

3.5 List of Work Packages

Table 1 List of Work Packages with lead and duration

WP No.	Work Package Title	Lead Participant Short Name	Start month	End month
1	Project Management	MUG	1	60
2	Proteomic electrochemical sensor development	UGent	1	30
3	Genomic electrochemical sensor development	URV	1	30
4	Microfluidic manifold development	IMM	1	30
5	Integration – Development of PoC tool	Labman	1	32
6	Validation of POC tool	TUMS	1	36
7	Clinical Trial POCT-BIO-MI - Trial Setup	MUG	8	24
8	Execution of the POCT-BIO-MI Trial	MUG	20	60
9	Data management and data analysis	MUG	12	60
10	Impact Creation, Dissemination, Exploitation	UGent	1	60

3.6 Project Plan

The overall project time schedule and timing of the 10 Work Packages and their tasks is shown in the Gantt chart. A great degree of overlap has been achieved in the different tasks to create an efficient workflow with minimal slack. The project plan may be revised during the project subject to approval by the General Assembly and/or the EC Project Officer.

#	Task	STR	END	DUR
	WP 1 Project Management			
1,1	Project initiation	1	2	2
1,2	Overall project management	1	60	60
1,3	Executive Management Committee	1	60	60
	WP 2 Proteomic electrochemical sensor development			
2,1	Evaluation of existing aptamers and identification of SELEX strategies	1	6	6
2,2	Selection, characterization and optimisation of aptamers selected	1	18	18
2,3	Development of Monoclonal Antibody selective against known	6	12	7
2,4	Assay development using selected aptamers	6	18	13
2,5	Evaluation of optimum method for using finger prick blood samples	6	18	13
2,6	Design of the Electrochemical platform	1	18	18
2,7	Analytical evaluation and validation of PoCCardio-BM using real samples	18	30	13
	WP 3 Genomic electrochemical sensor development			
3,1	Design and solution-phase testing of forward and reverse primers	1	6	6
3,2	Evaluation of optimum method for cell lysis from finger prick blood sample	1	6	6
3,3	Optimisation of primer elongation conditions	3	12	10
3,4	Demonstration of multiplexed solid-phase primer elongation	12	18	7
3,5	Demonstration of multiplexed solid-phase primer elongation	18	30	13
	WP 4 Microfluidic manifold development			
4,1	Testing of lyophilised reagents	12	18	7
4,2	Microfluidics integration for proteomic sensor	1	6	6
4,3	Microfluidics integration for genomic sensor	1	6	6
4,4	Development of a prototype cartridge	6	24	19
4,5	Small-series production of cartridges for clinical validation	12	30	19
	WP 5 Integration – Development of PoC tool			
5,1	Specification of PoC tool taking into account changes required from	1	3	3
5,2	Development of test rigs to evaluate any new technologies and/or	2	6	5
5,3	Development of Engineering prototype for testing microfluidic concepts	5	13	9
5,4	Development of Laboratory prototypes for testing of devices and assays in	11	22	12
5,5	Upgrade/low volume production of Laboratory prototypes for clinical use	21	30	10
5,6	Pre-clinical testing of devices	24	28	5
	WP 6 Validation of POC tool			
6,1	Finalise Protocols and Obtain Approvals	1	18	18
6,2	Validation of the proteomic tool	18	24	7
6,3	Validation of the genomic tool	18	24	7
6,4	Patient Recruitment	10	24	15
6,5	Results and lessons learned for multi-centre trial	18	36	19
	WP 7 Clinical Trial POCT-BIO-MI - Trial Setup			
7,1	Selection and Coordination of Study Centers	8	14	7
7,2	Protocol development and Obtaining Approvals	6	18	13
7,3	Planning of Statistical Analyses	10	20	11
7,4	Site recruitment and Monitoring Plans	15	22	8
7,5	Organisational Integration	14	24	11
7,6	Implementation of Data Safety Monitoring Board (DSMB)	16	20	5
	WP 8 Execution of the POCT-BIO-MI Trial			
8,1	Finalise Timeline and Milestones for the Trial	20	28	9
8,2	Overall Clinical Trial Management	20	60	41
8,3	Staff instructions and training at study center and support	24	32	9
8,4	Recruitment and Study Intervention	20	60	41
8,5	Clinical Trial Monitoring	24	60	37
8,6	Clinical Evaluation and Technical Validation	56	60	5
	WP 9 Data management and data analysis			
9,1	Clinical Data Management plan	11	15	5
9,2	Implementation and maintenance of a database for shared results	16	60	45
9,3	Develop AI tool for risk prediction and therapy response in MI-patients	45	60	16
9,4	Cross-validation configurations	36	54	19
9,5	Model selection and cross-validation comparison	6	54	49
	WP 10 Impact Creation, Dissemination, Exploitation			
10,1	Communication and Dissemination strategies and plans	1	60	60
10,2	Dissemination coordination	1	60	60
10,3	Bottom-up Market study in EU, US and Canad	1	24	24
10,4	Exploitation planning	1	60	60
10,5	Business and Financial plan	24	48	25
10,6	Licence preparations	48	60	13
10,7	Implementation of training and workshops	48	60	13

Figure 2 Project GANTT chart

4 Project Organisation and Procedures

The management structure and supporting procedures have been designed specifically with the strategic and operational management requirements of an industrial and highly multidisciplinary research project in mind. The project management structure is shown in Figure 3.

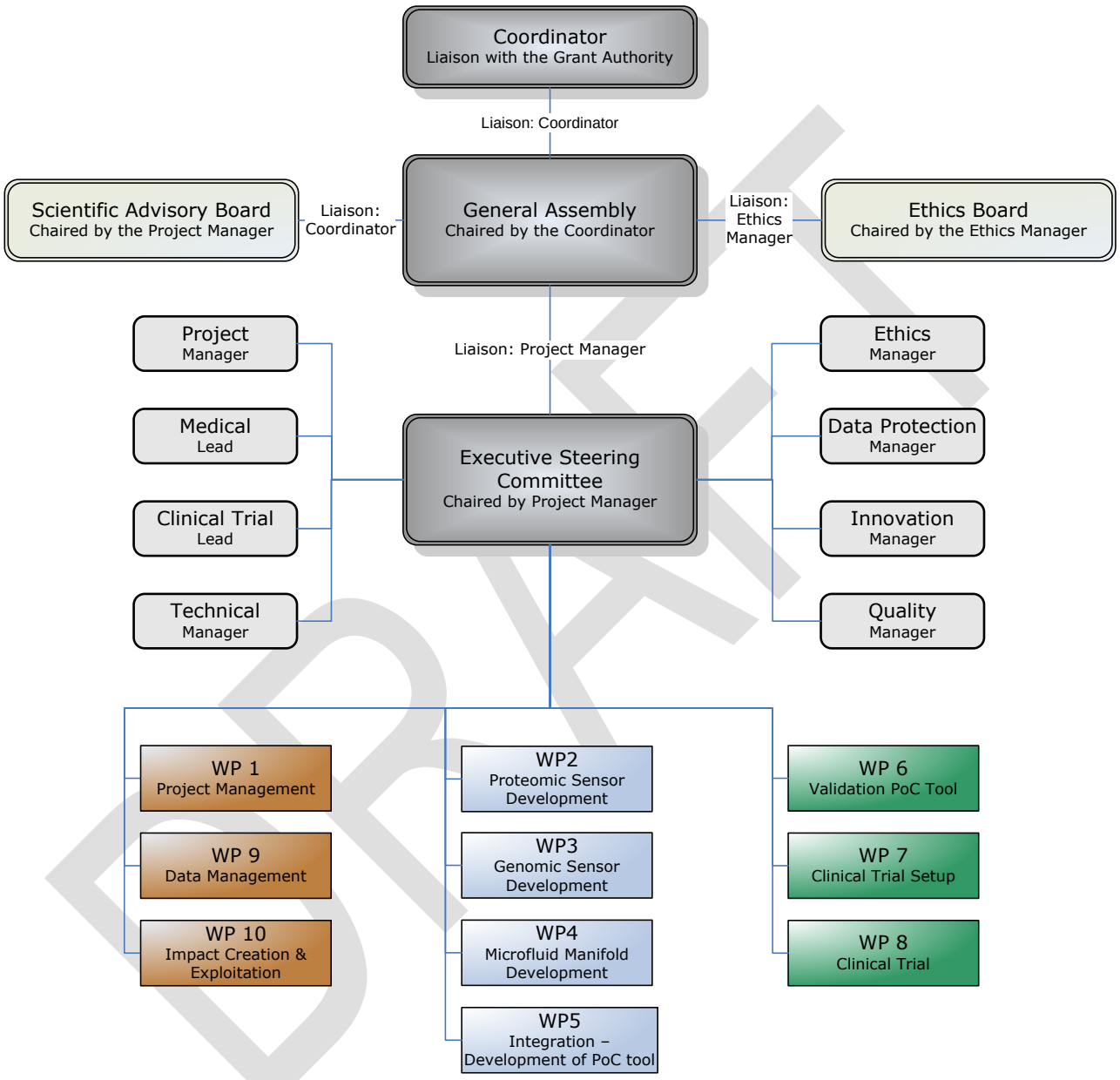


Figure 3: PoCCardio Management Structure

The organisational management structure of the consortium comprises the following five Consortium Bodies (grey boxes with double boarders):

1. The “General Assembly” is the ultimate decision-making body of the Consortium
2. The “Coordinator” is the legal entity acting as the intermediary between the Parties and the Granting Authority. The “Coordinator” shall appoint a physical person who, in addition to his/her responsibilities as a party, performs the tasks assigned to the Coordinator as described in this document, the Grant Agreement, and the Consortium Agreement.

3. The “Executive Steering Committee” is the Consortium Body for managing the execution of the Project, which shall report to and be accountable to the General Assembly.
4. The “Scientific Advisory Board” is the Consortium Body for providing specific input from industry partners in the field of metabolic disease.
5. The “Ethics Board” is the Consortium Body for handling all privacy, ethical, legal, and gender aspects of the project.

The project roles will be maintained for the duration of the project and their effectiveness reviewed by the General Assembly on an on-going basis. Any changes to the established roles deemed necessary or changes in the Consortium participants will be appropriately reflected in the management organisation of the project. Leaving participants will be replaced with other participants assigned by the General Assembly.

4.1 Operational Procedures for the General Assembly

The General Assembly is the ultimate decision-making body of the consortium. Any Party which is appointed to take part in the General Assembly shall designate one representative.

4.1.1 Organisation

The General Assembly will be the executive authority for the overall management and running of the project, the resolution of any major problems that may arise and will decide on the use of the common knowledge resulting from the project. It will comprise one executive member from each partner. It will be chaired by the Coordinator.

The General Assembly will also be the highest executive authority for scientific and technical management of the project and resolution of any major scientific and technical issues that need cross-project resolutions. This will ensure that technical solutions developed in the project support the projects vision and the scientific and technological objectives in all aspects and in all involved areas of research and will approve major architectural solutions and technological components of the PoCCardio solution, that has a direct impact on the projects vision and the exploitability of the results.

Detailed operational procedures for the General Assembly are set forth in the Consortium Agreement, which has been approved and signed by all partners. The main functions of the General Assembly are included in this chapter for completeness. In case of divergence or conflicts, the provisions of the Grant Agreement and the Consortium Agreement shall prevail.

Each General Assembly Member shall be deemed to be duly authorised to deliberate, negotiate, and decide on all matters that are presented to the General Assembly. The Coordinator shall chair all meetings of the General Assembly, unless decided otherwise in a meeting of the General Assembly.

Any item requiring a decision by the General Assembly must be identified as such on the agenda. Any Member of the General Assembly may add an item to the original agenda by written notice to all the other General Assembly Members up to 14 calendar days preceding an ordinary meeting and 7 calendar days preceding an ordinary meeting. During a meeting the Members of the General Assembly present or represented can unanimously agree to add a new item to the original agenda.

4.1.2 Meetings

The chairperson shall convene ordinary meetings of the General Assembly at least twice a year. An extraordinary meeting can be requested at any time by the Executive Steering Committee or by 1/3 of the Members of the General Assembly. Meetings of the General Assembly may be held by tele- or videoconference, with hybrid participation, or using other telecommunication means as decided by the Coordinator.

The chairperson of the General Assembly shall give written notice of a meeting to each party no later than 45 calendar days preceding an ordinary meeting and 15 calendar days preceding an extraordinary meeting. The chairperson of the General Assembly shall prepare and send each party an agenda no later than 21 calendar days preceding an ordinary meeting and 10 calendar days preceding an extraordinary meeting.

In connection with a physical meeting of the General Assembly, the Coordinator may call a general meeting with the participation of all team members from the PoCCardio project. Such meeting can deal with various

aspects of the project, requires no formal procedures, and based on an agenda decided by the Coordinator and Project Manager.

4.1.3 Tasks and decisions

The General Assembly shall be free to act on its own initiative to formulate proposals and take decisions in accordance with the procedures set out in the Consortium Agreement. The following topics may, inter alia, be presented and debated by the General Assembly:

- Oversee the overall project activities and the adherence to provisions of the Grant Agreement, the Consortium Agreement, and other legal agreements established in the project.
- Oversee the financial performance of the project and its adherence to time schedules and budgets
- Oversee the project risk management activities and the appropriateness of the proposed mitigation plans in relation to the medical research performed in the project.
- Oversee the project risk management activities and the appropriateness of the proposed mitigation plans in relation to the technical development work performed in the project.
- Oversee the project risk management activities and the appropriateness of the proposed, mitigation plans in relation to the clinical studies.
- Sign-off on the achievement of milestones.
- Sign-off on the Statement of Ethics
- Review and accept the Clinical Innovation and Technical Innovation Indicators
- Debate potential areas suitable for patent protection, assess their exploitability, and recommend proper courses of action to the consortium partners including financial aspects and protection of intellectual property rights.
- Approve the final “Results Ownership List”.
- Evolution of the consortium, breach, defaulting party status and litigation.
- Approve appointments for members of the Executive Steering Committee.
- Make appointments for members to the Scientific Advisory Board and the Ethics Board upon recommendation from the Executive Steering Committee.

According to the Consortium Agreement, the following decisions shall further be taken by the General Assembly:

- Content, finances, and intellectual property rights
    - Proposals for changes to Annexes 1 and 2 of the Grant Agreement to be agreed by the Granting Authority
    - Changes to the Consortium Plan
    - Modifications or withdrawal of Background in Attachment 1 (Background Included)
    - Additions to Attachment 3 (List of Third Parties for simplified transfer according to Section 8.3.2)
- Evolution of the consortium
    - Entry of a new Party to the Project and approval of the settlement on the conditions of the accession of such a new Party
    - Withdrawal of a Party from the Project and the approval of the settlement on the conditions of the withdrawal
    - Proposal to the Granting Authority for a change of the Coordinator
    - Proposal to the Granting Authority for suspension of all or part of the Project
    - Proposal to the Granting Authority for termination of the Project and the Consortium Agreement
- Breach, defaulting party status and litigation
    - Identification of a breach by a Party of its obligations under this Consortium Agreement or the Grant Agreement

- Declaration of a Party to be a Defaulting Party
- Remedies to be performed by a Defaulting Party
- Termination of a Defaulting Party's participation in the consortium and measures relating thereto
- Steps to be taken for litigation purposes and the coverage of litigation costs in case of joint claims of the parties of the consortium against a Party (Section 4.2, Section 7.1.4)

For the avoidance of doubt, any change to the Consortium Agreement (including the Parties' rights and/or obligations hereunder, additions of further Background under specific restrictions and/or conditions or changes to existing ones) any budget-related change to the Grant Agreement shall only be legally binding between the Beneficiaries if agreed in writing and executed by the duly authorized representatives of each Beneficiary.

Members of the General Assembly, who are not authorised to address some or all of the matters listed above without receiving advice from their institution, shall ensure that they consult with their institution's legal department or with other relevant departments prior to participating in any vote, upon receiving the meeting agenda.

In addition, all proposals made by the Executive Steering Committee shall also be considered and decided upon by the General Assembly.

Any decision may also be taken without a meeting provided that the Coordinator circulates a written (including via email) suggestion for the decision to all members of the General Assembly. The deadline for responses shall be at least 10 calendar days after receipt by a party and the decision is agreed in writing (including via email) by a majority of the parties. The Coordinator shall inform all the Parties of the outcome of the vote.

The Project Manager, or a designated substitute, shall produce minutes of each meeting which shall be the formal record of all decisions taken and send a draft of such minutes to all Members within 10 calendar days of the meeting. The minutes shall be considered as accepted if, within 15 calendar days from receipt, no member has sent an objection by written notice to the chairperson with respect to the accuracy of the draft of the minutes.

4.1.4 Voting

The General Assembly cannot deliberate and decide validly in meetings unless two-thirds (2/3) of its members are present or represented (quorum). If the quorum is not reached, the chairperson of the General Assembly shall convene another ordinary meeting within 15 calendar days. If in this meeting the quorum is again not reached, the chairperson shall convene an extraordinary meeting which shall be entitled to decide even if less than the quorum of Members is present or represented.

Each Member of the General Assembly present or represented in the meeting shall have one vote. A Party which the General Assembly has declared to be a Defaulting Party may not vote. The Associated Partners are excluded from voting on and vetoing the following decisions of the General Assembly and therefore are not counted towards any respective quorum:

- Distribution of EU contribution among the project's Beneficiaries
- Proposals for changes to the budget (Annex 2 of the Grant Agreement) to be agreed by the Granting Authority
- Decisions related to handling excess payments (Section 7.1.4 of the Consortium Agreement)

Decisions shall be taken with a majority of two-thirds (2/3) of the votes cast.

A party which can show that its own work, time for performance, costs, liabilities, intellectual property rights or other legitimate interests would be severely affected by a decision of the General Assembly may exercise a veto with respect to the corresponding decision or relevant part of the decision. When a decision has been taken without a formal meeting of the General Assembly, a party may veto such decision within 15 calendar days after written notice by the chairperson of the outcome of the vote.

A Party may neither veto decisions relating to its identification to be in breach of its obligations nor to its identification as a Defaulting Party. The Defaulting Party may not veto decisions relating to its participation and termination in the consortium or the consequences of them. A Party requesting to leave the consortium may not veto decisions relating thereto.

4.2 Operational Procedures for the Executive Steering Committee

4.2.1 Organisation

The Executive Steering Committee shall consist of the appointed area managers handling day-to-day management tasks and of all the Work Package managers.

Their titles and roles of the area managers are assigned as shown in Table 2.

Table 2 Identified Management Roles

Role	Organisation	Qualifications
Project Manager	MUG	The Project Manager will be responsible for coordinating the project and its reporting activities. The Project Manager will chair the Executive Steering Committee and assist the Coordinator in the General Assembly meetings.
Medical Lead	MUG	The Medical Lead has the responsibility to lead the project's medical and clinical activities, will continuously assess the risks of delays in the clinical studies, and design appropriate mitigation plans. The Medical Lead will also represent the project in medical communities internationally.
Technical Manager	UGENT	The Technical Manager is responsible for coordination of the technical Work Packages and the transfer of knowledge between them to ensure a smooth and trouble-free integration of components.
Clinical Trial Lead	MUG	The Clinical Trial Lead will coordinate the initiation and time planning of the clinical trials and ensure that timelines are coordinated with the technical progression, that the milestones are met in both time and scope.
Data Protection Officer	MUG	The Data Protection Officer (DPO) is to ensure that the project processes personal data of any data subject in compliance with applicable data protection rules.
Ethics Manager	N-JET	The Ethics Manager will ensure that ethics and gender aspects as well as security and privacy aspects is properly considered in the project and will chair the Ethics Board.
Innovation Manager	IN-JET	The Innovation Manager will ensure that the project is enhancing the innovation potential from the research work performed.
Quality Manager	IN-JET	The Quality Manager is responsible for the management of all quality processes related to reports and internal/external documents, as well as presentation of the project to external parties.

Their titles and roles of the Work Package leaders are assigned as shown in Table 3 Work Package Leaders.

Each Executive Steering Committee Member shall be deemed to be duly authorised to deliberate, negotiate, and decide on all matters being put in front of them.

In case of overlap of a person being both area manager and Work Package leader, such person is assumed to be able to cover both roles without any conflict of interest. If this is not the case, the Project Manager will assume one of those roles.

4.2.2 Meetings

The Project Manager shall chair all meetings of the Executive Steering Committee unless decided otherwise by the General Assembly. The Project Manager may delegate the chair to the Quality Manager periodically.

Meetings of the Executive Steering Committee shall preferably be held by tele- or videoconference, hybrid, or other telecommunication means.

The chairperson shall convene meetings of the Executive Steering Committee at regular interval and at least once a month. An extraordinary meeting can be requested at any time by any member of the Executive Steering Committee.

The chairperson shall arrange for a videoconference platform meeting with a fixed access link for each meeting for a period of at least 6 months at any given time.

The chairperson shall give written notice of the proposed agenda on an online platform to each member no later than 7 calendar days prior to the meeting. Any member the Executive Steering Committee may add an item to the online agenda up to 3 calendar days prior to the meeting. During a meeting the Member the Executive Steering Committee present can unanimously agree to add a new item to the original agenda.

Participation in the meetings is not mandatory, unless demanded so by the Project Manager. Members may decide to participate or not depending on the agenda provided. If the agenda contains subject with direct implication for a specific area manager or a specific Work Package leader, their presence at the meeting is normally requested and any hindrance should be arranged with the Project Manager prior to the meeting.

4.2.3 Tasks and decisions

The Executive Steering Committee shall supervise and support the implementation of the project work plan with respect to:

- Coordinate the timely execution and preparation of deliverables to assure the attainment of objectives;
- Monitoring of Work Package status measured against deliverable and milestone planning, control of deliverable timeliness and quality to ensure timely and accurate work plan follow-up, early identification of possible technical, medical, and organizational problems;
- Deciding upon any exchange of tasks and related budgets between the parties in a Work Package when such exchange has no impact beyond the scope of the Work Package and its budget.
- Coordination at Consortium level of the dissemination and exploitation activities with a strong support from the Dissemination Manager.
- Coordinate project reporting;
- Organise meetings and ensuring that all scientific and technical issues and risks are identified and managed and that decisions are properly recorded.
- Making proposals to the General Assembly for the admission of new parties to the Grant Agreement and to the Consortium Agreement for such new parties to participate in the project;
- Alerting the General Assembly in case of delay in the performance of a Work Package or in case of breach of responsibilities of any Party and prepare a proposal of remedies to the General Assembly.
- Analysing and documenting a presumed breach of responsibilities of a Party under the Work Package and preparing a proposal of remedies to the General Assembly.

The Project Manager, or one of two designated substitutes, shall produce action points minutes of each meeting and send such minutes to all members within 5 calendar days of the meeting.

4.2.4 Voting

There are no specific voting procedures for the Executive Steering Committee and all decisions are expected to be taken in unity between the involved members from the area managers and Work Package leaders.

In case of a minority discord to a specific decision, such decision may be escalated to the General Assembly for discussion at the first upcoming meeting. The case will be presented in writing by the Coordinator and the Project Manager with a clear discussion of the relevant foundations for the case, the arguments presented by the individual members of the ESC, and the disagreement experienced. The Coordinator is responsible for bringing the decision from the General Assembly back to the ESC and for its proper implementation.

4.3 The Coordinator

The “Coordinator” is a physical person appointed by the legal “Coordinator” who performs the tasks assigned to the legal Coordinator as described in the Grant Agreement, and the Consortium Agreement.

The tasks of the Coordinator are:

- Act as the intermediary for all communications between the beneficiaries and the Granting Authority.
- Ensuring cooperation among partners, including anticipation, and managing potential conflicts.
- Chair the General Assembly meetings
- Chair the Scientific Advisory Board and its liaison with the General Assembly
- Monitoring compliance by the Parties with their obligations under the Consortium Agreement and the Grant Agreement.
- Reviewing to verify consistency of reports, deliverables (including financial statements and related certifications) and specific requested documents.
- Providing, upon request, the parties with official copies or originals of documents that are in the sole possession of the Coordinator when such copies or originals are necessary for the Parties to present claims.
- Managing the special relationship to the Associated Partner including, but not limited to, providing a copy of the Grant Agreement and its Annexes and other relevant documents from the project.
- Keeping the address list of members of the consortium and other contact persons updated and available.

4.4 The Project Manager

The Project Manager is appointed by the Coordinator and will assist the Coordinator with the timely delivery of accurate administrative and financial data. In particular, the Project Manager will be responsible for:

- Coordination and organisation of management bodies.
- Definition and implementation of the management structure and procedures to be adopted throughout the project and the maintenance of detailed project plans.
- Prepare meetings and the agenda and propose decisions.
- Keeping the documentation of changes made in the GA, which are not reported to the Granting Authority, updated in a Table of Changes
- Overseeing that project Deliverables and Milestones are properly assessed and signed off.
- Administering the financial contribution of the Granting Authority and fulfilling the financial tasks described in the Consortium Agreement and the Grant Agreement by working closely together with the coordinator’s financial and research department.
- Editing and submission of the Periodic Reports to the Granting Authority and Coordinating the collection of cost statements and audit certificates.
- Transmitting deliverables, documents and other information connected with the project to the Granting Authority in due time and in high quality.

4.5 Work Package Management

The work plan (in the DoA) has established clear objectives for each Work Package, and interfaces to other Work Packages have been made as simple as possible to create transparency and promote responsibility among Work Package team members. Each Work Package has been assigned a Work Package Leader (party) who is responsible for the following tasks:

- Communicating any plans, deliverables, documents, and information connected with Work Package between its Members and, if relevant, to the Project Manager and the Coordinator.
- Submitting the Work Package report to the Project Manager for review and inclusion in the Periodic Report and proposing an update of the work plan, if necessary.

- Coordinating on a day-to-day basis the progress of the technical and administrative work under the Work Package;
- Following up decisions made by Consortium Bodies insofar as they affect the Work Package;
- Advising the Project Manager and the Coordinator of any discrepancy with the work plan, including any delay in delivery.

The Work Package Leader is further responsible for escalating any issue to the Executive Steering Committee that cannot be satisfactorily dealt with at the Work Package level.

The Work Package Leaders are identified in Table 3.

Table 3 Work Package Leaders

#	Work Package	WP Leader
1	Project Management	MUG
2	Proteomic electrochemical sensor development	UGent
3	Genomic electrochemical sensor development	URV
4	Microfluidic manifold development	Fraunhofer
5	Integration – Development of PoC tool	Labman
6	Validation of POC tool	TUMS
7	Clinical Trial POCT-BIO-MI - Trial Setup	MUG
8	Execution of the POCT-BIO-MI Trial	MUG
9	Data management and data analysis	MUG
10	Impact Creation, Dissemination, Exploitation	UGent

4.6 The Scientific Advisory Board

The Scientific Advisory Board will consist of six experts in relevant areas of PoCCardio. The Scientific Advisory Board will be appointed by the General Assembly and chaired by the Project Manager.

The Scientific Advisory Board will not make decisions on behalf of the project but shall assist and facilitate the decisions to made by the General Assembly. Its members shall be allowed to participate in General Assembly meetings upon invitation, but have no voting rights.

The Scientific Advisory Board shall be consulted for specific input from external experts in relevant scientific areas such as metabolic disease, microfluid laboratory systems, Point of Care instrumentations. The Scientific Advisory Board shall give input from both a medical scientific and an industrial perspective to help the General Assembly perform the best strategic decisions.

The chairperson will ensure that a non-disclosure agreement is executed between all Parties and each member of the Scientific Advisory Board. Its terms shall be not less stringent than those stipulated in the Consortium Agreement, and it shall be concluded no later than 30 days after their nomination or before any confidential information will be exchanged/disclosed, whichever date is earlier.

The Scientific Advisory Board is foreseen to hold three meetings during the course of the project; some will be physical and some will be remote. The Project Manager shall record minutes from each meeting of the Scientific Advisory Board and submit these to the General Assembly-.

4.7 The Ethics Board

An Ethics Board will be appointed by the General Assembly and chaired by the Ethics Manager. Its purpose is to handle the various privacy, ethical, and legal aspects emerging in the project in a professional and generally acceptable way. The Ethics Board will, in this respect, be the direct point of contact for the European Commission in cases of ethical issues.

The Ethics Board will establish clear ethical guidelines and monitor that the project trials are executed in an ethically sound manner according to its guidelines. The project will ensure that the end-users participating in the trials are made aware of and understand the implications of and the conditions for participating in trials.

The Ethics Board will secure that the appropriate action is taken if project partners and other participants report any ethical problems or violations of the ethical guidelines.

5 General Management Procedures

This section describes standard procedures for management, communication, meetings, document production and reporting. All work in the project will be carried out in accordance with the project DoA and the procedures outlined in this document.

5.1 Planning

The project will be executed according to an established and proven project management approach based on this quality and risk management plan and a detailed project plan to be regularly updated.

The project plan covers the complete project duration and will be refined and agreed with the European Commission as necessary. It contains a detailed work plan setting out the duration and interdependencies of Work Packages and tasks defined for the period, and the anticipated resources and timeframe required to complete each task.

Each Work Package Leader is responsible for preparing and managing a detailed Work Package plan and maintaining a risk log using a common template. The plan is to be submitted to the Project Manager for consolidation with other Work Package plans.

5.2 Progress Control and Milestones

To continuously measure the project's progress in terms of achievements and impact, a set of milestones have been defined.

Milestones are control points where decisions are needed with respect to moving on to the next stage of the project. For example, a milestone may occur when a major technical result has been achieved, if its successful attainment is a required for the next phase of work. Milestones are consecutively numbered according to WPs.

To monitor major project results and allow the project management to assess the progress of work in interdependent Work Packages and for the project as-a-whole, the milestones have been defined in terms of both means of verification and success criteria for go/no-go decisions. Whereas the former item has been defined in the DoA, the go/no-go decisions have been added as shown in Table 4 below.

The *Milestone Name* provides an indication of the nature and significance of the milestone. More information can be found in the relevant task description in the indicated WP.

The *Lead* is the beneficiary responsible for leading the team towards the achievement of the Milestone. The Lead is also responsible for presenting the Milestone achievement verification to the consortium

The *Means of Verification* points to the method for how the Milestone achievement shall be verified. The short text is detailed in the relevant task description in the indicated WP. The deliverable, which provides the argumentation and background information for the achievement, is indicated.

The *Success Criteria* provides provisions for how the milestone result shall be transferred into a go/no-go decision and which consortium body (Executive Steering Committee (ESC) or General Assembly (GA) as described in section 4 Project Organisation) should be responsible for making the go/no-go decision. In case of a no-go decision, the consortium body, the Lead, and the Project Manager, shall provide a mitigation plan for how to re-evaluate the milestone and possible impact on the overall project plan and results.

The Project Manager oversees that project's Milestones are properly assessed and signed off at the point foreseen in the work plan and will include deviations from the project plans in the Periodic Reports to the Granting Authority, together with an impact assessment and, if needed, a mitigation plan.

Table 4 List of Milestones arranged in order of due date

Milestone Number	Milestone Name	WP	Lead	Means of Verification	Succes Criteria	Due Date
3	Method for rapid and cost-effective cell lysis from finger prick blood sample	WP3	URV	Assessed by comparing the results using PCR (D3.2)	Lysis efficiency of the two approaches approved by GA	M06
5	Provision of a pre-production PoCCardio-BM cartridge	WP4	Fraunhofer	Prototype cartridges delivered and tested against existing state-of-the-art (D4.4)	Prototype cartridges test results approved by GA	M15
6	Provision of a pre-production PoCCardio-GM cartridge	WP4	Fraunhofer	Prototype cartridges delivered and Prototype cartridges tested against existing state-of-the-art (D4.4)	Prototype cartridges test results approved by GA	M15
1	Aptamers selected, characterised, and optimised against identified targets	WP2	UGent	Assessed using SPR, BLI, MST, CD (D2.2)	Decision on best anticoagulant and sample type approved by GA	M18
10	Operational Setup for the Multicentre Trial available	WP7	MUG	Regulatory approval for POCT-BIO-MI trial is available (D8.2)	Regulatory approval obtained and Ethics Monitoring Framework approved by Ethics Board	M24
11	First patients' first visit in the POCT-BIO-MI trial	WP8	MUG	First patient enrolled in the POCT-BIO-MI trial (D8.3)	First patient successfully enrolled	M24
7	Provision of two prototypes devices for laboratory-based testing	WP5	LABMAN	Prototype devices delivered and tested with preproduction cartridges (D5.4)	Prototype devices approved by clinical trials leaders	M25
2	Analytical evaluation and validation of PoCCardio-BM	WP2	UGent	Platform tested against existing state-of-the-art (D2.4)	Performance of the platform along with its reproducibility and stability over time approved by GA	M30
4	Analytical evaluation and validation of PoCCardio-GM	WP3	URV	Platform tested against existing state-of-the-art (D3.4)	Evaluation results approved by GA	M30
8	Provision of clinical specification device for pre-clinical testing in up to three clinical centres	WP5	LABMAN	Clinical specification devices tested onsite with pre-clinical cartridges (D5.5)	Clinical devices approved by three clinical centres	M30
9	Final result of PoCCardio-BM/GM Tool validation	WP6	TUMS	Based on Assured Guidelines (D6.3)	Results reviewed by technical partners and approved by GA	M30
13	Model selection completed	WP9	MUG	Initial predictions available (D9.4 and D9.5)	Models approved by GA	M40
12	Top-level results for the POCT-BIO-MI trial available	WP8	MUG	Results for the primary outcome available (D8.5 and D8.6)	Reports approved by GA	M58

5.3 Administrative and Financial Management

The administrative and financial management will be carried out by the Project Manager with a team of administrative and financial experts from the Coordinator's research and financial departments. The Project Manager is responsible for the day-to-day administration and the financial management of the project, including ensuring the proper completion and consolidation of management reports and cost claims.

5.4 Periodic Reporting Procedures

The project duration of 60 months has been divided into 4 periods in the Grant Agreement as follows:

Table 5 Project periodic reporting

RP#	From	To	Type
1	1	18	Periodic report
2	19	36	Periodic report
3	37	54	Periodic report
4	55	60	Periodic report

The periodic reports include a technical and financial part. They must be submitted to the Granting Authority no later than 60 days after end of reporting period.

The technical part includes an overview of the action implementation. It must be prepared using the template available in the Portal Periodic Reporting tool.

The financial part of the periodic report includes:

- the financial statements (individual and consolidated; for all beneficiaries/affiliated entities);
- the explanation on the use of resources (or detailed cost reporting table, if required);
- the certificates on the financial statements (CFS) (if required).

Project reviews will be carried out at the end of each period. Arrangements for these reviews will be managed by the Project Manager.

The following process will be used to generate the periodic reports:

1. Each Partner will complete a Periodic Activity Report to cover their activity over the reporting period and forward it to the Project Manager by the 15th day of the last month of the reporting
    - The report should describe the main achievements and decisions and on what background they were made. Less successful activities should also be mentioned and explained. Bullet point lists will not be accepted
    - If project, task or Work Package meetings have taken place in the period, this should be reported, mentioning the major result(s) of that meeting.
2. The Work Package Leaders will aggregate the information from the Work Package partners into the Periodic Report Template for their Work Package and forward it to the Project Manager
3. The Project Manager will aggregate this information into a consolidated report and deliver it to the Commission by the end of the month following the period under review.

Each partner must complete a financial statement at the end of each periodic report together with an explanation of the use of the resources. Partners are also required to present a Certificate on Financial Statement (CFS) if the cumulative claim of community financial contribution for the period is more than EUR 430,000.

5.5 Communication Procedures

The Consortium consists of a geographically spread group of partners. Hence, email communication is the preferred method of internal project communication. However, a certain amount of communication skills and discipline is required to deliver a smooth communication experience.

A few sound principles will guide email communication in the project:

- Make sure that the subject of the mail is short, clear, and properly reflecting its content. Most email users receive a mountain of emails and the subject allows recipients to properly organise, prioritize and reply to them.
- Think twice before using “reply all”. In a large recipients’ group, the volume of mails will increase exponentially with the constant use of “reply all”.
- Use the mailing list(s) to send to an updated and relevant group of recipients within the project. Maintaining private “threads” of recipients can lead to some project members not receiving important information.
- Address single recipients in all cases where person-to-person(s) communication of more personal or specific purposes. Sending irrelevant mails to all recipients may lower the attention level.
- Use only email accounts belonging to your organisational domain. Email servers such as gmail.com, hotmail.com and others are not GDPR compliant. Further, if the content is confidential and important for Intellectual Property Rights protection, these email servers may be determined to be “public domain”.

To support these principles, a project mailing list has been established. Sending an email to the mailing list will multiply the mail to all the members registered on the mailing list. The following mailing list(s) have been established:

For the entire project team: poccardio-general@in-jet.dk

Specialised lists may be created in the future for specific subjects aimed at subsets of project members, e.g. technical developments, specialised medical subjects, trial organisation details.

The mailing list is managed by the *ezmlm* program provided by partner IN-JET. The mail server is hosted in Denmark and is fully GDPR compliant. It uses the most updated verification and security tools required.

It is possible to use special commands to interact with the *ezmlm* program. Simply send an email without any subject or content to the following addresses:

For a full list of commands: poccardio-general-help@in-jet.dk
To contact the administrator: poccardio-general-owner@in-jet.dk
To subscribed a new user: poccardio-general-subscribe@in-jet.dk
To unsubscribe yourself as user: poccardio-general-unsubscribe@in-jet.dk

The user will receive a confirmation request to make sure that the subscription address is valid. Once this is verified, the user is subscribed/unsubscribed.

5.6 Online Resources

A web-based project extranet has been established to support collaborative working. It contains workspaces for partners to share documents. The extranet, together with the project website, will be the focal point for project management and coordination activities.

The following online resources are available to support PoCCardio partners:

- The PoCCardio mug-box (https://box.medunigraz.at/s/5KDTfMpKZxRaoWe) provides a central repository for project documents accessible for all partners during the project lifetime.
- The Project website (https://www.poccardio-project.eu) website is used to disseminate the project vision and results to a wider audience and in particular defined target groups.
  The website will also be used for online risk management and to coordinate dissemination activities such as events, articles, and presentation papers given by consortium members.

- The In-JeT JIRA repository from Atlassian (https://jira.in-jet.dk) will be used to manage Innovation Forms (see section 7.2 General Innovation Management) and the procedure for managing Data Management Plans (see section 5.7)
- CISCO Webex for video conferences
- LinkedIn and X (formerly Twitter) accounts have been established targeting the professional community. The LinkedIn page can be found at: https://www.linkedin.com/company/poccardio-project and the X (formerly Twitter) account can be found at: https://twitter.com/PoCCardio.
- The project plans to launch a YouTube channel and will also consider Facebook at a later stage, to further target the broader public community and to enforce visibility and collaboration.

5.7 Ethics Management Procedures

The Ethics Management procedures (subtask 1.3.2) will ensure that the project is complying with applicable ethical & legal requirements and that security and privacy aspects are considered in a uniform way across the WPs and the clinical studies.

The procedures will allow project partners to share concerns, issues, progress, status of ethical nature across the project and provide efficient and transparent methods of documenting and reporting internally and externally.

An Ethics Manager has been appointed with the responsibility to establish, implement, and manage the ethical procedures during the project's lifetime.

5.7.1 Statement of Ethics

A set of agreed ethics principles and guidelines will be formulated and published in D1.4 Statement of Ethics (M8). It will include a set of ethics principles agreed by all consortium members and must be signed off at by the General Assembly. It will also establish, inter alia, the Ethics Monitoring Framework containing:

a) A set of internal rules and procedures that will guide the creation and monitoring of ethical compliance against the ethics guidelines, report on implementation outcomes in the pilots and trials, collect reports on unexpected events, and formulate recommendations on how to improve the observance of applicable ethical principles.

b) A framework for assessing compliance with the Ethics Guidelines for Trustworthy AI (EC 2019) which will include the use of the Assessment List for Trustworthy Artificial Intelligence (ALTAI).

c) Identify Data Protection Officers (DPOs).

d) Establish an PoCCardio Ethics Board and define its Terms of Reference.

5.7.2 Compliance Monitoring

With the aim to build experience and knowledge of ethical excellence in the project, several compliance monitoring actions are embedded in all the clinical trial Work Packages: In WP6, it is task 6.6 Implementation of Ethics Monitoring Framework, in WP7 it is task 7.7 Implementation of Ethics Monitoring Framework and in WP8 it is task 8.6 Ethics Compliance Monitoring.

All the trials will implement the project's Ethics Monitoring Framework which includes data privacy framework, AI trustworthiness and GDPR compliance in the respective trials. The task will monitor the projects compliance with the Ethics Monitoring Framework during the trial period.

The tasks will also assist in the coordination of applicable national and international ethics requirements. The work will be undertaken in full coordination with the partners' DPOs and the trial's Principal Investigator.

WP1 will submit D1.8 Preliminary Ethics Monitoring Report in M18 which focuses on the preparation stage of the clinical trials, particularly the validation protocol in T6.1. Subsequently, Each task in WP6-WP8 will report its findings in the deliverables D8.7 – D8.10 Annual Ethics Compliance Report (M24/36/42/60). The reports will contain as a minimum:

- Reporting against the Ethics Monitoring Framework
- Status on ethical and legal requirements
- Documenting the ethical issues that have been raised (if any)

5.7.3 Ethics Board

An Ethics Board will be created to secure that the appropriate action is taken if any ethical problems are reported by project partners and other participants. The purpose of the board is to monitor compliance with the project's own ethical principles and guidelines. Its Terms of Reference will be developed in subtask 1.3.2.

The Ethics Board will consist of the following ten individuals:

- 2 external ethics experts
- Representatives (ethics expert) from the clinical trial sites countries
- The Coordinator
- The Project Manager
- The Ethics Manager

The Ethics Board will conduct annual meetings to be held either physically or online. For physical meetings, the project will reimburse travel and accommodation external experts according to a reimbursement scheme established in the Term of Reference.

The Ethics Board is the single point of contact with the Granting Authority in matters of ethics.

5.8 Data Management Procedures

A set of Data Management Procedures will be implemented in the project as a key to achieve good data management and ethically acceptable study conduct. The Data Management is not to be confused with the clinical data management processes that are undertaken in WP9.

The Data Management Procedures will cover the following areas:

- Data Protection and Privacy (GDPR)
- Data Lifecycle Management
    - Findable – Accessible – Interoperable – Reusable (FAIR)
- Data Controllers
    - Trial partners responsible for clinical studies
    - Data Processing Agreements with individual Data Processors

5.8.1 Data Management Plan

A Data Management Plan (DMP) will be created to set out the project's approach to data management. It will be based on the Horizon Europe template and will stipulate information for all beneficiaries on the handling of research data during and after the end of the project. The DMP will describe the data management life cycle for the data to be collected, processed and/or generated by PoCCardio. The DMP will set out how data/research outputs are made findable, accessible, interoperable, and reusable (FAIR) to the furthest extent possible considering data privacy restrictions.

The disclosure of pseudonymised patient data held by the clinical sites is subject to authorisation from the local data clearing house in keeping with the local regulations reflected in the DMP. The data clearing house ensures that personal data (including pseudonymised data) meet relevant legal data protection standards, as well as the contractual and internal requirements, prior to authorising the disclosure of these data to consortium members. The DMP will include a description of methodology and standards to be followed, and which data sets will be made accessible for verification and re-use after project closure. The DMP thus needs to be approved by the local ethics committees to support the project specific data handling and storage.

The data will be deposited in repositories that guarantees data integrity on bit level. No continuous data curation policy to guarantee full long-term digital preservation of datasets is planned. A JIRA online tool will be used to manage the workflow for each of the identified datasets that are identified in the project for FAIR data management.

An initial DMP will be released in D1.5 Data Management Plan (M3). It is a living document that will be continuously updated as the project progresses. Formally the progress will be documented in D1.6 Midterm Data Management Plan (M18) and the final version in D1.7 Final Data Management Plan (M60).

5.8.2 Data Protection Officers and Data Processing Agreements

The DMP will contain data processing requirements to be included in all Data Processor Agreements between the involved beneficiaries.

All beneficiaries have a data protection committee and at each clinical site, one individual will be assigned to be the responsible Data Protection Officer (DPO) for that trial site. The DPO relies on in-house support to comply with the data protection requirements related to the disclosure to third parties of data for which the beneficiaries are responsible under the General Data Protection Regulation (GDPR).

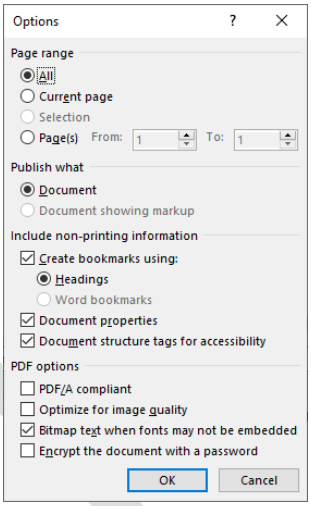
To assure compliance with data privacy regulations across all the clinical studies, the project will appoint a coordinating project Data Protection Officers (DPO) from the Coordinator's organisation (MUG). The Coordinating DPO will oversee the implementation of the DMP. The coordinating DPO will liaise with the DPO from each of the trial organisations responsible for the clinical studies.

To comply with the requirements of the GDPR framework, each project partner that processes personal data on behalf of the trial partner or any other partner in the project, will have to establish and agree to a Data Processing Agreement (DPA).

6 Documents, Deliverables and Reports

6.1 Document Format

Documents under the scope of this Quality Plan (internal and external deliverables plus project working documents) are subject to specific quality procedures regarding the layout and typographic features of the document when viewed or printed.



Deliverables and reports should be distributed in one of the following formats:

- Word Document (docx)
- Portable Document Format (PDF)

The PDF format is advised for final, non-editable versions and doc/docx for intermediate versions. Non-editable documentation to be distributed externally to the Consortium or elsewhere is to be distributed in Portable Document Format (PDF). When saving a document in PDF format, it is advisable to click the Options button and the check: Create bookmarks using Headings. In this way, the PDF document will have a navigation pane in the left side of the screen as is known from Word.

Two templates have been created for mandatory use with all deliverables and power point presentations used with project related content:

Deliverable template: (PoCCardio_Deliverable_Template.dotx)
A sample document exemplifying the layout and typographical features of the cover page, executive summary page, header, footer and heading levels to be employed in a MS Word template file (.dotx file) is available on the mug-box. The document template may be updated or revised from time to time and it is the responsibility of each partner to always use the latest published template.

Presentation template: (PoCCardio_Presentation_Template.potx)
Presentation slides should conform to a prescribed layout and typographical features. Sample slides are available as a PowerPoint template file (.potx file) on the mug-box. The presentation template may be updated or revised from time to time, and it is the responsibility of each partner to always use the latest published template.

6.2 Quality Assurance

All deliverables shall adhere to the following quality parameters:

- The scope of the work must be covered
- Premises for the work must be stated as well as any limitations are stated
- The results must be described and documented in sufficient detail
- Uncertainties in the results must reported, or at least indicated
- Interpretations and conclusions should be clearly and unambiguously identified and included figures, illustrations and tables should be properly referenced
- Text should be written in clear and understandable language
- Documents should be well structured and contain references to relevant supporting documents
- Partners contributing to the content should be clearly identified

Those preparing deliverables should discuss the contents with all contributors and other participants involved with the task, and take account of their comments. Circulation of a draft for comment is recommended, where feasible.

Further, all documents should generally be:

- Written in English for use among partners. Documents for public dissemination at partner level can be written in the native language
- Include sufficient identification in line with the DoA and standard template to ensure that there cannot be any confusion on what they are
- Include versioning and a sufficient Document History to unambiguously identify their status and state of completion or change
- Use the PoCCardio acronym and logo, contract number, date, unique document identified, as indicated in the deliverable template.
- Use the EU flag to reference the Granting Authority – not the EU Commission logo.

6.3 Project Deliverables

Deliverables comprise the direct, measurable outcome of the projects and are keenly monitored by the Granting Authority. Hence, deliverables must adhere to the highest quality criteria and must present a uniform impression across the entire project. Moreover, on time submission of deliverables to the Granting Authority is of the utmost importance; the date of submission is recorded and cannot be changed!

The list of deliverables is defined in the Description of Action (DoA) and are entered into the Participant Portal. The current list is also presented here in Table 6.

Table 6 List of Deliverables

Deliv. No.	Deliverable Title	WP	Lead participant	Type *)	Dissem-ination Level **)	Due Date
D1.1	Project Quality and Risk Management Plan	WP1	IN-JET	R	PU	M2
D1.2	Online Risk Log and Mitigation Actions	WP1	IN-JET	OTHER	SEN	M3
D1.3	Plan for Managing Knowledge and Intellectual Property	WP1	UGent	R	SEN	M9
D1.4	Statement of Ethics	WP1	IN-JET	R	SEN	M8
D1.5	Data management Plan (DMP)	WP1	MUG	DMP	PU	M3
D1.6	Midterm Data Management Plan	WP1	IN-JET	DMP	PU	M36
D1.7	Final Data Management Plan	WP1	IN-JET	DMP	PU	M60
D1.8	Preliminary Ethics Compliance Report	WP1	IN-JET	R	PU	M18
D2.1	Identification of SELEX strategies for each identified target	WP2	URV	R	SEN	M1
D2.2	Selection of aptamers against the selected targets	WP2	URV	R	SEN	M15
D2.3	Demonstration of multiplexed detection of target biomarkers	WP2	UGent	R	SEN	M18
D2.4	Analytical evaluation and validation of PoCCardio-BM using real samples	WP2	UGent	R	PU	M30
D3.1	Solution-phase demonstration of SNO detection via primer elongation	WP3	URV	R	SEN	M6
D3.2	Optimum method for cell lysis from finger prick blood samples	WP3	URV	R	SEN	M6
D3.3	Demonstration of multiplexed detection solid-phase primer elongation of the polymorphisms	WP3	URV	R	SEN	M18

D3.4	Analytical evaluation and validation of PoCCardio-GM using real samples	WP3	URV	R	PU	M30
D4.1	Lyophilisation of assay reagents	WP4	UGent	R	SEN	M24
D4.2	Proteomic electrode arrays assembled in microfluidic manifold	WP4	IMM	R	SEN	M6
D4.3	Genomic electrode arrays assembled in microfluidic manifold	WP4	IMM	R	PU	M6
D4.4	First prototype cartridges ready for genomic/proteomic testing	WP4	IMM	R	PU	M12
D4.5	First batch of manufactured cartridges ready for validation	WP4	IMM	R	PU	M30
D5.1	Technical specification document (circulated to and agreed by stakeholder partners)	WP5	Labman	R	SEN	M3
D5.2	Report on evaluation of any new technologies, techniques, or consumables	WP5	Labman	R	SEN	M8
D5.3	Engineering prototype for proving microfluidic concepts	WP5	Labman	DEM	SEN	M16
D5.4	Laboratory prototype devices (x2) delivered to university partners	WP5	Labman	DEM	PU	M25
D5.5	Clinical prototype devices (x10) built, and factory tested	WP5	Labman	DEM	PU	M32
D5.6	Pre-clinical test report	WP5	Labman	R	SEN	M30
D6.1	First Study Subject Approvals Package (Clinical Pilot Trial)	WP6	TUMS	R	SEN	M18
D6.2	Midterm Recruitment Report (Clinical Pilot Trial)	WP6	TUMS	R	SEN	M20
D6.3	Report on PoCCardio-BM/GM Tool validation and status of posting results	WP6	TUMS	R	SEN	M36
D7.1	First study subject approvals package (Clinical Multicentre Trial)	WP7	MUG	R	SEN	M24
D7.2	Statistical Analysis and Data Management Plan of Multicentre Trial	WP7	MUG	R	SEN	M24
D7.3	Recruitment and Monitoring Plans	WP7	MUG	R	SEN	M22
D7.4	Setup of a Data Safety Monitoring Board	WP7	MUG	R	PU	M20
D8.1	Registration of the trial (EU clinical trials registry)	WP8	MUG	R	PU	M20
D8.2	Final study protocol version approved by regulators and ethics committees	WP8	MUG	R	SEN	M20
D8.3	First patient first visit	WP8	MUG	R	SEN	M24
D8.4	Midterm Recruitment Report (Clinical Study A)	WP8	MUG	R	SEN	M30
D8.5	Report after half of the follow-up period	WP8	MUG	R	SEN	M46
D8.6	Report on Status of Posting Results	WP8	MUG	R	SEN	M58
D8.7	Annual Ethics Compliance Report 1	WP8	IN-JET	R	SEN	M24
D8.8	Annual Ethics Compliance Report 2	WP8	IN-JET	R	SEN	M36
D8.9	Annual Ethics Compliance Report 3	WP8	IN-JET	R	SEN	M48
D8.10	Annual Ethics Compliance Report 4	WP8	IN-JET	R	SEN	M60
D9.1	Clinical data management plan available	WP9	MUG	R	SEN	M15

D9.2	Data quality assessment on and First Cross validation on initial cohort performed	WP9	MUG	R	SEN	M30
D9.3	Models for risk prediction developed and first cross validation performed	WP9	MUG	R	SEN	M40
D9.4	Metrics and model selection of risk prediction for the testing phase data established	WP9	MUG	R	SEN	M48
D9.5	Robustness using different metrics for established models assessed	WP9	MUG	R	SEN	M54
D9.6	Advanced Model selection and metrics for risk and therapy response prediction determined	WP9	MUG	DEM	SEN	M60
D10.1	Mid-term IPR and exploitation report	10	IN-JET	R	SEN	M30
D10.2	Bottom-up market study in EU, US and Canada	10	UGent	R	SEN	M24
D10.3	Final IPR and exploitation planning report	10	IN-JET	R	SEN	M60
D10.4	Business and financial plan	10	UGent	R	SEN	M48
D10.5	Licence term sheet, mapping of potential licensees, progressed or finalised licence negotiations	10	UGent	R	SEN	M60
D10.6	Communication and Dissemination Strategies and Plan	10	IN-JET	R	PU	M3
D10.7	Project Website	10	IN-JET	DEC	PU	M1

*) Deliverable Type: R = Report, DEM = Demonstrator, DEC = Websites, Press, etc., OTHER = Other

**) Dissemination Level: SEN = Sensitive, only for members of the Consortium (including the Commission Services), PU = Public

6.3.1 Deliverable template

The deliverable template contains detailed instructions for use. Those instructions relate to content, format, and the document itself.

6.3.1.1 Document automation

Document identify information is used in different parts of the document (front page, headers, footers). To have a uniform appearance, a set of document properties are used to hold this information rather than typing it in many different places.

Moreover, the mandatory deliverable information (type, dissemination levels, partners, etc.) are inserted using dropdown menus rather than typing. Again, this is to have a uniform appearance using the correct terms.

Tables of contents and list of figures and tables are automatic inserted. However, this requires the strict use of Word Styles (Heading1…, Figure and Table) to work correctly.

6.3.1.2 Document Control Page

After the mandatory front page, a document control page is inserted. The control page contains all relevant document references (file names, document type, WP, etc.), a list of contributors to the content, as well as the result of the internal review page. The Document Control Page information is shown in Appendix 1.

6.3.1.3 Document sections

The deliverable contains several mandatory pages that cannot be omitted:

- The Executive summary provides a short introduction to the content of the deliverable. The reader should be able to read the summary on its own to understand the main content and conclusions.
- The Introduction explains the purpose, context, and scope of the deliverable (important to show any connections with other deliverables) and the content and structure of the deliverable.

- The Conclusion is a conclusion on what the deliverable has presented. It can be a conclusion on specific work performed, a conclusion on a decision or recommendation that has been made, or similar round-off text. This section is NOT required for deliverables, if no conclusion is to be made.
- List of Figures and Tables is automatically filled in from the Styles used.
- References are always entered as end notes and will automatically be placed in this section.

6.3.2 Document owner and internal review procedures

The Document Owner is defined in the DoA and listed in Table 6 List of Deliverables. The Document Owner is responsible for starting the work on the deliverable in due time for a successful submission according to its due date.

1. The Document Owner starts the process with a preliminary Table of Contents (ToC) and circulates it to the partners that are expected to contribute content to the deliverable.
2. The deliverable will then be produces in an interactive process managed and edited by the Document Owner until the deliverable has reached a sufficient quality level.
3. The final step in the procedure is to ask for two, independent project members to review the deliverable. Ideally, internal reviewers should not have been contributors to the deliverable they review, and must be selected for their knowledge of the subject matter. Reviewers' comments must be documented and copied to the Document Owner. The Document Owner must then respond by accepting or rejecting changes.

The review comments and response are noted in the Document Control Page. All reviews should be completed within 1 week of the due date.

6.3.3 Version control

The mug-box does not provide means for collective creating and editing documents. Hence, a manual version control system must be in place to track the progress of a document under edit..

1. The version number is attached to the document filename as "vx.x" such as in: *D1.1 Project Quality Control Plan V0.5.docx*.
2. The numbering system is x.y where x is a major version and y is a minor revision. For deliverables only x=0 or x=1 is uses, since version v1.0 is the version to be submitted (if the deliverable needs and unlikely revision after the initial submission, the version number is increased accordingly). The ToC is thus version v0.1 and the submitted version is v1.0.
3. Only the Document Owner can change the version number. When a version is sent out for comments or contributions, the contributor appends an identification to the end of the document file name such as *D1.1 Project Quality Control Plan V0.5_in-jet.docx.* The only requirement is that the identification uniquely identifies the contributor.
4. When the Document Owner has edited all comments and contributions into the document, a clean version is issued with the next version number (e.g., v0.6) and the procedure repeats itself.

6.3.4 Deliverable submission procedures

All deliverables must be delivered to the Grant Authority by the Project Manager on or before the due date. To secure a safe submission process, the following procedure must be followed.

1. One week before the due date, at the latest, the responsible Document Owner must upload a final version of the deliverable to the mug-box in the assigned folder (under each Work Package) in both docx and pdf format. The "Document Status" check boxes on the Control Page must be checked.
2. All project members are notified that the deliverable is ready for submission together with a link to the folder in the mug-box
3. The Project Manager will formally submit the deliverable to the Commission as follows:
    a. Upload the final version to a proper section of the Participant Portal
    b. Place the pfd version in the folder "Submitted deliverables" in the mug-box
4. The Project Manager finally informs all partners that the deliverable has been submitted

7 Innovation and IPR Management Procedures

The Innovation and IPR management procedures aims to ensure that relevant project knowledge (technical, process or user experience) is screened, patent- or trade-secret protected when desirable and are made available by the generator of such knowledge and appropriately transferred to those who need this knowledge. A proper IPR management procedure is essential to the subsequent exploitation preparation phase and thus to maximise the impact of the project.

The project already has outlined major innovations in the form of clinical methods, tools, and procedures for risk categorisation of CVD patients using innovative PoC instruments. However, the general innovation procedures laid out in this chapter aim at also identifying other elements of innovations, which can be exploited alone, outside or in addition to, the main PoCCardio devices. Moreover, the components of the PoCCardio device may themselves representant innovations that might be exploited in other contexts. The full innovation process will be laid out in greater details in D1.3 Plan for Managing Knowledge and Intellectual Property (M9).

7.1 Expected Innovation paths

The main paths of innovation are foreseen in two areas: clinical innovation and technological innovation.

7.1.1 Clinical innovation

Personalised medicine as a concept relies on disease-specific biomarkers for the adjustment of treatments to individual patients. This approach to therapy has been pioneered in oncology with the advent of targeted drugs, which required the presence of actionable molecular targets. Accordingly, for an increasing number of anti-cancer therapies relevant companion diagnostics (CDx) are required for patient selection. Translating this concept to CVD holds great potential to improve clinical management, but also poses significant challenges as many therapeutics have a confirmed and potent effect on LDL-C. However, preventing hard CV events requires a larger number of patients to be treated over a longer period.

By using a score of biomarkers representative of inflammation, coronary atherosclerosis, neurohormonal activation and cardiomyocyte injury, prediction of CV events as well as heart failure endpoints could be significantly improved. Learning from existing studies, we have decided to use a panel of 10 biomarkers (including safety parameters for renal function) for identification of individuals at “extremely high-risk”.

Further, an improved risk model for CVD will also be developed to appropriately support treatment decision making, as traditional clinical risk factors for CVD fail to accurately characterise risk in a population experiencing initial events.

Methodologies and procedures

The PoCCardio approach results in new, innovative, validated clinical concepts and rigorous data analysis of longitudinal data, which further hold great potential to advance companion diagnostics in CVD with new innovative biomarkers. The methodology in this path contains three elements:

- Complete a clinical validation study POCT-Cardio-Val
- Carry out a full clinical RCT study POCT-BIO-MI with 1,836 patients
- Perform additional data and biomarker analysis

The starting point is the development of an innovative risk stratification model, translating it into a companion solution through integrating proteomics and genomics with a functional PoC microfluidic device. By using a score of biomarkers representative of inflammation, coronary atherosclerosis, neurohormonal activation and cardiomyocyte injury, prediction of CV events as well as heart failure endpoints could be significantly improved.

Sensitivity, specificity, turnaround time and robustness of the PoC-device in assessing the targeted biomarkers (proteomic and genomic) will be assessed in the general population in an initial validation trial POCT-Cardio-Val.

The clinical validation of the qualified biomarkers and the PoC tool will finally be performed in a prospective, randomised multinational trial, POCT-BIO-MI, including only existing and approved pharmaceuticals. The trial will provide the scientific foundation to support regulatory authorities regarding approval of companion diagnostics, and recommendations for the prescription of drugs, respectively.

The PoCCardio data will constitute a rich resource for complex computational analysis to explore correlations between primary and secondary outcome parameters to identify parameters with predictive power for outcome

and therapy selection. A comprehensive AI-supported analysis will facilitate further stratification of MI patients and monitoring of treatment effects of cardioprotective drugs.

Indicators and criteria

For the detailed descriptions in D1.3 Plan for Managing Knowledge and Intellectual Property, a set of indicators and criteria for measuring the clinical impact innovation level will be established. The indicators will also be used for the exploitation strategy and business planning work. The following initial indicators with quality criteria have been identified:

Table 7 Initial KPIs for clinical innovation

Clinical Innovation Indicator	KPI	Quality Criterion
Identify MI patients with an “extremely high risk” via blood-based biomarkers and genetic markers and examine the value of these markers as a companion diagnostic to treat MI patients		Achieve KPI end of trials
Pave the way for the use of more complex, multi-variate companion diagnostic tests, both for stratification and therapy guidance, driving significant progress towards personalised care.		Achieve KPIs end of project
Improved impact on CV morbidity and mortality compared to traditional hospital-based interventions		Achieve KPIs 3 years after project

The progress in achieving the quality level shall be governed by the Quality Manager supported by the Medical Lead and Clinical Trial Lead and reviewed annually by the General Assembly.

7.1.2 Technological innovation

To overcome the important gaps in the clinical armamentarium of CVD management and identification of high-risk individuals who would best benefit from an intensified intervention and a low-cost accessible monitoring solution for the affected individuals, various technologies including molecular medicine, nanobiotechnology, microfluidics and biochemistry should come together. The PoC tool will be broadly based on technology developed during previous EU-financed projects (MIRACLE, PoCOsteo, ELEVATE) but will be adapted to suit a set of newly developed microfluidic sensors.

In this innovation path, the project will develop a PoCCardio test for biomarker detection and genomic detection consisting of two cartridges (one for a genomic test and one for a proteomic test) and a single read-out device. The cartridge consists of three main components

- Proteomic electrochemical sensor (to be developed in WP2) (For the proteomic test)
- Genomic electrochemical sensor (to be developed in WP3) (For the genomic test)
- Microfluidic manifold (to be developed in WP4) (present in both cartridges)

The main innovation in the PoCCardio device (compared to the PoCOsteo device) lies in its innovative focus on measuring CV disease-specific biomarkers for enhanced risk stratification at the point-of-care with a single affordable desktop device, and to provide the affected individuals with personalised care.

Methodologies and procedures

A proteomic electrochemical sensor will be developed. Following the selection and optimisation of the aptamers, sandwich assays will be developed and the optimum assays will be implemented on the electrochemical platform. An evaluation of the optimum method for using finger prick blood samples will be performed.

A genomic electrochemical sensor will be developed. The sensor will perform multiplexed simultaneous detection of single nucleotide polymorphisms (SNPs) in genomic DNA extracted from a finger prick blood sample followed by an evaluation of the optimum method for cell lysis from such samples. After optimisation and demonstration using extracted genomic DNA, the generic platform will be evaluated and validated using >300 real samples collected using extracted genomic DNA.

A Microfluidic manifold is used for sampling and sample preparation technologies for handling and preparing finger prick blood. After initial testing of lyophilised reagents for the proteomic sensor, the introduction procedure for blood into the microfluidic manifold will be optimised regarding simplicity and usability for easy

handling. For the genomic sensor, the integration and storage of the DNA amplification reagents on-chip represents an additional challenge.

Finally, both microfluidic manifold designs will be merged to integrate either proteomics or genomics sensors into an otherwise identical cartridge layout.

Indicators and criteria

For the detailed descriptions in D1.3 Plan for Managing Knowledge and Intellectual Property, a set of indicators and criteria for measuring the technical innovation level will be established. KPIs will be established at a later date and approved by the ESC. The following initial indicators with quality criteria have been identified:

Table 8 Initial KPIs for technological innovation

Technical Innovation Indicator	KPI	Quality Criterion
The PoC device will be capable of measuring a panel of 10 biomarkers		Achieve KPI before trials
Limit the number of time consuming sample preparation steps		Achieve KPI before trials
Improved error rate for PoC devices		Achieve KPI at the end of trials
Boost the European PoC IVD ecosystem with new IP and interoperability between industrial providers of key systems and components		Achieve KPIs 3 years after project
…		

The progress in achieving the quality level shall be governed by the Quality Manager supported by the Technical Manager and reviewed annually by the General Assembly.

7.2 General Innovation Management

The overall aim of Innovation Management is to identify all the potential innovative elements of the exploitable products. The process will be based on identifying, collecting, describing, and working towards turning creative ideas into innovative value propositions of the PoCCardio solution for the targeted markets.

The general innovation management procedures aim towards identifying, collecting, and describing other innovations, or other elements of innovations, which can be exploited alone, outside or in addition to, the main PoCCardio devices.

The General Innovation Management method calls for the continuously capture of new knowledge generated in the project as well as discovery of new needs from the market. This procedure will be implemented around “Innovation Forms” containing a description, a list of functionalities enabled by the innovation, a classification, and links to implementation workflow. Innovation Forms will be created by the Innovation Manager with help from a relevant technical team and agreed with the Technical Manager and Clinical Lead. The forms will be used as to present innovation status to the Executive Steering Committee and the General Assembly.

The forms are accessible online for project members to view and update. Only the Innovation Manager can create innovations forms.

The Innovation Manager will lead the Innovation and IPR Management process and the Executive Steering Committee will oversee the implementation of the plan.

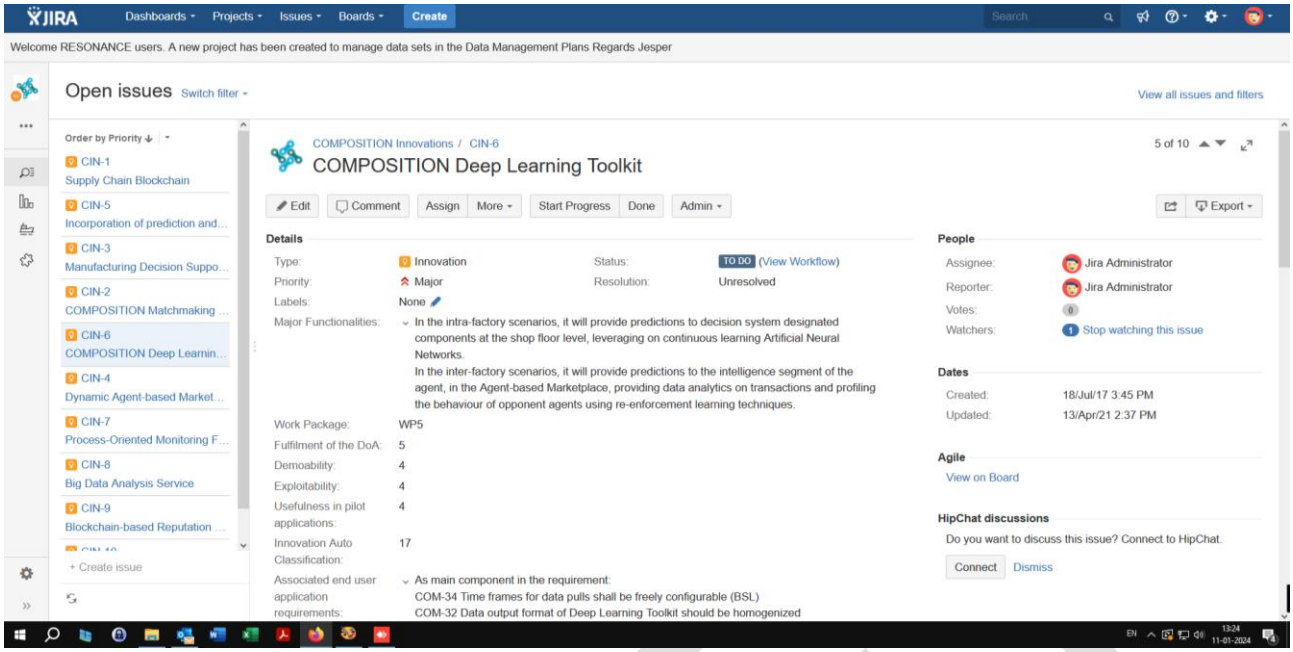


Figure 4 Innovation Form online management screen (example © the COMPOSITION project)

7.3 IPR Management

The result of the Innovation Management procedures described above will be subjected to IP assessment and the potential rights management. The IPR Management procedures thus aim to identify potential exploitable products and the associated IP ownership and agreeing on distribution of ownership. Subtask 1.2.3 in WP1 will ensure that IPRs are properly handled, and patents can be filed if possible.

The full framework for IPR management will be developed and reported in D1.4 Plan for Managing Knowledge and Intellectual Property (M9). The PoCCardio consortium will follow the recommendations for EU research projects, and IPR management will be handled according to Grant Agreement Article 16 and its Annex 5, and the Consortium Agreement section 8.1 Ownership of Results.

Further, the identification of IP to be used for exploitation will be analysed in WP10 and identification of protected IPR results will be published in D10.1 Mid-term IPR and exploitation report (M30) and D10.3 Final IPR and exploitation planning report (M60).

The work on identification of Intellectual Property (IP) starts in the first year, when the components of the PoCCardio platform are known in detail. Each exploitable outcome/IP will be identified and recorded as soon as possible (e.g. when filing for a patent application), but at the latest at the end of the project. The partners will agree on the IP ownership of each component and a “Results Ownership List” will be created, as set out in the Consortium Agreement. The list will take the form of a template to be filled out listing the owner of each of the results being identified as the Key Exploitable Results.

The main internal tool for identifying Intellectual Property and establishing the ownership to the rights is a simple Excel spreadsheet, the IPR Registry, provided by In-JeT. The sheet provides a short description of all potential IP identified by project partners or from other project material. Each IP is registered with short name, short description, and reference to a more detailed description. Relations to project objectives and expected progression of Technology Readiness Level can be included. Further in the process, the Background needed and the Access to Foreground needed for exploitation of the IP will be reviewed and wherever necessary, proposals for updates will be made. On this background, all project partners are requested to register their claim to IPR based on their contributions to said IP. The Innovation Manager manages the registered claims on foreground and issues a first version of all IPR and their potential ownership. In case of a patent, the inventors and applicants will have to be determined when the application is filed.

Finally. the IPR ownership is bilaterally discussed in the cases of IPR with potential joint ownership. When agreement subject and size of ownership is achieved, the Innovation Manager presents the result to the General Assembly for approval. Further, the final “Results Ownership List” will be presented to the General Assembly for approval.

8 Risk Management Procedures

The project has defined clear procedures for the management of all risks and issues that are identified at the beginning of the project or arise over its course. This Quality and Risk Management Plan defines policies for identifying threats and for implementing corrective or mitigating actions.

8.1 Risk Identification

All project participants, and in particular the project managers and WP leaders, will be responsible for raising any material or perceived risk as part of the normal reporting process and to register all such risks and issues in the project's online risk log. The status and mitigation of each identified risk will be reviewed regularly by the Executive Steering Committee, and formally at each General Assembly meeting.

8.2 Online Risk Log

The Online Risk Login will comprise 12 elements:

1. A unique Risk ID
2. Reference to the involved Work Package
3. Risk description
4. Risk Probability
5. Risk Impact
6. Remedial action(s)
7. Name of person responsible for reviewing the risk
8. Status (which can be 'Open', 'Addressed' or 'Closed')
9. Risk priority
10. Name of person responsible for checking that the risk has been handled or reviewed
11. Check date for #10) (which can be an individual date, or, typically, approx. 1 week prior to the next online or physical meeting)
12. Comments (which may be used to elaborate on the status and to describe the next steps to be taken, if relevant).

The online risk log will be established in the form of a joint workspace on the project website. It will be updated in the deliverable D1.2 Online Risk Log and Mitigation Actions due in M3 and presented with a full description of the Online Risk Log.

8.3 Identified Risks and Mitigation Plans

Fourteen initial risks were identified prior to project start, as listed in Table 9. These risks will form the core of the Online Risk Log when created.

Table 9 Critical Implementation Risks and Mitigation Actions

Risk No.	Description of Risk	WP	Proposed Risk Mitigation Measures
R1	Failure of aptamers to achieve required selectivity (Low, Med)	2	The fallback would be the use of commercial or custom-produced monoclonal antibodies. The selectivity of the aptamers will be established before the end of Year 1 to allow for implementation of this fallback. However, SELEX involves a counter SELEX in the selection process, so the risk of a lack of selectivity is very low.
R2	Failure of aptamers to achieve required detection limits (Low, Med)	2	For most of the biomarkers the required detection limits are easily achievable. The challenging targets are hs-TnT and hs-CRP, and the proposal already has a built-in fallback by beginning the process of producing custom monoclonal antibodies from the beginning of the project. URV has observed that the use of hybrid antibody-aptamer sandwich assays improves detection limits as compared to either aptamer-aptamer or antibody-antibody combinations.

R3	Failure to correctly identify SNPs (Low, Med)	3	The concept of isothermal solid-phase primer elongation for the identification of SNPs has already been demonstrated for single SNPs and this risk is very low. In the case that problems with multiplexed detection are problematic, assay parameters can be adjusted to increase stringency to facilitate correct SNP detection.
R4	Lack of stability of lyophilised reagents / functionalised electrodes (Low, Med)	2, 3, 4	The partners involved have extensive expertise in achieving stability of reagents and electrodes using in-house solutions, and this risk is thus low. As a fallback, there are many commercial stabilising agents that can be tested to improve long-term stability.
R5	Difficulty in executing electrode spotting (Low, Med)	2, 3, 4	Partners have electrode spotting capabilities available in-house and have worked on electrode spotting manually and with these commercial spotters in many projects. The risk is low, and in the case that none of the in-house spotters, is either to test other commercially available spotters, or for LABMAN to develop a tailor-made spotting instrument.
R6	Cartridge initial fabrication investment is too expensive (Med, Med)	4	Study different fabrication strategies
R7	Fluids cannot be precisely controlled in the cartridge/tool (Med, Med)	4, 5	Use of integrated camera or passive fluid elements to detect/control fluid positioning
R8	Representative cartridges not provided prior to laboratory validation and/or not in sufficient quantities to validate device operation (Med, Med)	5	The production will be in batches based on the number of tests to be done in the clinical setting to address this issue.
R9	The device cannot be sent to Iran for the validation studies (Med, Med)	6	Considering the PoCOsteo experience, efforts will be made in advance to complete all the necessary paperwork. In case any issues persist, another validation site, from a non-European ethnicity, will be selected for this task.
R10	Challenges with handling of PoC device (Med, Med)	6, 8	Using novel devices can be challenging for clinical sites, hence we will prepare print and video-training material for the PoC device and will facilitate the required training of the site staff. In case of any technical or medical issues arising for the participating sites, the trial management and a medical hotline will be available.
R11	Trial sites will commit to too few study participants (Med, Med)	7	Given the time available for thorough site selection process and the number of potential sites available in Austria, Germany, Belgium, and Poland, we might need to increase the number of participating sites from 30 to 35. This will have limited financial implications, as the study will be paid per patient fee basis. The monitoring plan will be adjusted accordingly.

R12	Slow trial recruitment (Med, Med)	8	We have therefore factored in 6 months of site selection procedure to identify and include only those sites with a high number of people suffering from acute MI and those having the infrastructure to perform clinical trials. Moreover, while this is going to be an academic trial, we have asked for a reasonable budget for site reimbursement, which will also help to meet the recruitment targets.
R13	Number of available PoC devices is less than projected (Med, Med)	8	As the biomarkers required for the clinical trial can also be measured in the routine lab, the trial will move ahead as projected.
R14	Patient data insufficient for training set or underperformance of prediction model (Med, Med)	9	In case of problems with the prediction model in depth analysis of potential causes will yield pointers towards possible approaches to remedy the underperformance by redesign and retraining of the algorithm. If this fails to resolve the problem alternative data sources from retrospective data sets will be explored to expand the available data sets.

New risks arising during the project must be analysed with respect to appropriate preventive and remedial actions.

The risk must first be described and all its potential impacts must be assessed. The Quality Manager will obtain proposals from the clinical and technical experts for appropriated prevention and remedial actions. Both actions shall be evaluated by the Executive Steering Committee and the overall effect of the risk prevention and/or mitigation will be evaluated. After acceptance, the affected WP leaders will assess the need for changes in requirements or in development work and implement such actions in the project plan.

9 Dissemination, Communication, and Exploitation

9.1 Dissemination and Communication

The overall objective of dissemination is to maximise the transfer of knowledge to the outside world and thus optimizing the market uptake of the innovations and knowledge delivered by the project. The PoCCardio dissemination strategy and procedures are described and set out in the DoA and elaborated in D10.6 Communication and Dissemination Strategies and Plan (M3).

9.1.1 Dissemination strategy

The leader of task 10.2 is responsible for coordinating the dissemination of the knowledge coming out of the project. Each partner is responsible for carrying out their own dissemination activities, such as journal and conference contributions, and for reporting these activities for coordination and alignment with the established KPIs.

The goal of the dissemination and communication strategy is to ensure awareness of project knowledge and results in the full range of stakeholders who have a primary interest in PoC tools for CVD patients at high-risk. The strategy is to progressively increase dissemination and communication activities as results are obtained, moving from initially assuring wide awareness of the PoCCardio project to creating favourable conditions for wider replication of the results towards the end of the project and finally to support efforts to identify and prioritise candidates for licensing. The dissemination strategy is thus closely linked to the project's IP, exploitation, and licensing strategy. Based on this strategy, a draft dissemination and communication plan has been developed.

The comprehensive dissemination and communication plan implements the project's stated strategy towards maximising impact and replication potential, also paving the way for the Consortium's exploitation and licensing plans.

9.1.2 Dissemination procedures

Dissemination activities, including, but not restricted to publications and presentations, shall be governed by the procedure of Annex 5, Article 17 of the Grant Agreement and og section 8.4 of the CA which contains the following provisions:

- Prior notice of any planned publication shall be given to the other Parties at least 45 calendar days before the publication. Any objection to the planned publication shall be made in accordance with the Grant Agreement by written notice to the Coordinator and to the Party or Parties proposing the dissemination within 30 calendar days after receipt of the notice. If no objection is made within the time limit stated above, the publication is permitted.
- A partner shall not publish foreground or background information of another Party, even if such foreground or background is amalgamated with the partner's own foreground, without the other partner's prior written approval.

All partners shall cooperate to allow the timely submission, examination, publication and defence of any dissertation or thesis for a degree which includes their foreground or background subject to the confidentiality and publication provisions agreed in this Consortium Agreement.

9.1.3 Dissemination coordination

The coordination of all dissemination is performed by task 10.2 Dissemination Coordination. The purpose of standard procedures for coordination of dissemination is the ensure a uniform, professional dissemination of project results and outcomes based in the following principles:

- Create knowledge of our common goals and plans as they are presented in D10.6
- Enforce a joint commitment to the principles and goals outlined in the strategy and plan
- Ensure that all partners are active in dissemination to maximise overall impact
- Facilitate that communication/dissemination/exploitation thoughts are built into everything done as part of PoCCardio work

- Engage the partners own communication channels for project

A successful coordination requires that partners share the good stories with other project and partners. The coordinator registers and coordinates the partners' joint activities. To this end, a website plugin will be created on the project website https://www.poccardio-project.eu. Partners are required to login here and list their planned events, publications, press releases, news articles etc.

Obligations and restrictions on dissemination activities are set out in Grant Agreement (Articles 16 & 17 + Annex 5) and Consortium Agreement (Section 8.4). The key aspects are:

- It is important to acknowledge all authors and contributors who have been involved in the work
- Procedures for Open Access to scientific publications should be followed according to the Open Access portal to be used
- Acknowledgement of EU funding is mandatory as set out in Article 17.1 and 17.2 in the Grant Agreement and should be translated into local languages where appropriate:

"Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or HADEA (EU Health and Digital Executive Agency). Neither the European Union nor the granting authority can be held responsible for them."

- Moreover, all acknowledgements must display the European flag (emblem). Apart from the emblem, no other visual identity or logo may be used to highlight the EU support.

Procedures are further detailed in D10.6 Communication and Dissemination Strategies and Plan.

9.1.4 Indicators and criteria

A set of indicators and criteria for the dissemination quality level have been established to measure and assess the progress of the dissemination activities in terms of visibility and knowledge creation.

The definition and description of the quality indicators and the corresponding criteria are further motivated and addressed in deliverables throughout the project phases, D10.6 Communication and Dissemination Strategies and Plan. The following quality indicators have been identified:

Table 10 KPIs for dissemination

Key performance Indicators: Visibility	Success criteria	Key performance Indicators: Knowledge	Success criteria
Number of sessions on website	>60.000	Number of medical conference presentations	25
Number of downloads from the website/journals	>500	Number of biotec ICT conference presentations	16
Number of press releases issued	4	Number of workshops/events organised	2
Number of newsletters issued	6	Number of readers reached with publications:	1,500
Number of social media posts	300	Number of citations of publications	5,000
Number of impressions with social media	100.000	Number of medical journal publications	48
Number of contacts in networks	4	Number of biotec ICT journal publications	48

The progress in achieving the quality criteria shall be governed by the Quality Manager supported by the WP10 Leader and reviewed annually by the Executive Steering Committee. Further, a section on the result of dissemination activities shall be included in the Periodic Management Reports.

9.2 Exploitation

The overall objective of exploitation planning is to prepare for an optimal market uptake of the innovations and knowledge delivered by the PoC device and a subsequent sustainable commercial success. The PoCCardio exploitation strategy and procedures are described and set out in the DoA and elaborated in D10.1 Mid-term IPR and exploitation report (M39) and D10.3 Final IPR and exploitation planning report (M60).

The overall exploitation preparation will be carried out in task 10.3 and will follow a roadmap including the following activities:

1) Define targets and routes to relevant market segments for the PoCCardio device
2) Positioning the PoCCardio device and associated exploitable assets on the market and perform relevant business analyses
3) Prepare final exploitation and business and financial plans which detail the utilisation of results for all partners
4) Prepare for regulatory approvement
5) Identify suitable candidates to licence the IP

With the established plans for exploitation, task 10.6 will identify a shortlist of suitable candidates to licence the IP, to prepare a term sheet with all consortium partners and to initiate and finalise negotiations with interested third parties. The suitable licence candidates will be identified in deliverable D10.5 Licence term sheet, mapping of potential licensees, progressed or finalised licence negotiations (M60).

9.2.1 Exploitation strategy

PoCCardio is part of a concerted strategy to bring PoC devices for biomarker assessment to health care provision, which has been developed throughout several EU funded projects. Central to the strategy is the generation of clinical evidence of the highest standard, as is provided by a randomised clinical trial.

Potential exploitable products and their associated IP ownership will be identified and classified as part of the innovation management activities in WP1 task 1.2. However, the target identification and market planning will be made in WP10.

The targets and routes to relevant market segments will be selected based on a bottom-up market study undertaken in task 10.4 and documented in deliverable D10.2 Bottom-up market study in EU, US and Canada.

The positioning will be performed as part of the business and financial planning undertaken in task 10.5. The aim is to ensuring optimal market impact towards both market needs and competitive situation.

A “SWOT” analysis will firstly identify the opportunities in each market segment and map the PoCCardio solution to the opportunities, while at the same time considering the PoCCardio weaknesses towards the competing solutions. Threats in the market segments will be identified and mapped to the strength and weaknesses of the PoCCardio solution.

Based on the bottom-up market study a benchmarking methodology will be used to analyse the position of the PoCCardio solution (or with applications developed using the PoCCardio test) vis-à-vis the existing healthcare solutions on the one hand, and the identified market needs and requirements on the other hand. Markets will be segmented and prioritized for relevance and maturity for exploitation.

From the SWOT analysis, a set of Unique Selling Points will be defined with clear and marketing-oriented arguments for the PoCCardio approach; also highlighting its added business value. The information will be mapped into a General Electric – McKinsey Market Attractiveness Matrix as show in Based on the bottom-up market study a benchmarking methodology will be used to analyse the position of the PoCCardio solution (or with applications developed using the PoCCardio test) vis-à-vis the existing healthcare solutions on the one hand, and the identified market needs and requirements on the other hand. Markets will be segmented and prioritized for relevance and maturity for exploitation.

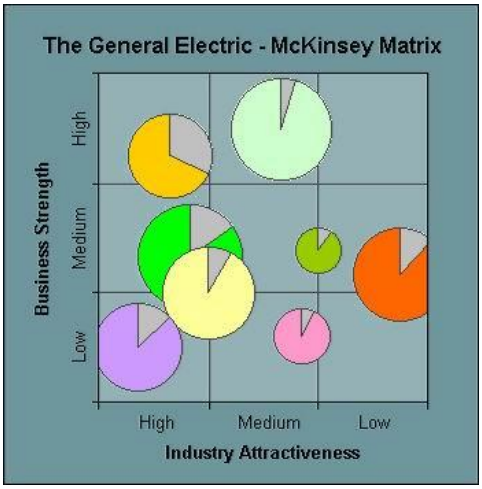


Figure 5: Market attractiveness matrix

Figure 5. The results will form the basis for the subsequent exploitation strategies and will ensure stronger user engagement and better product positioning in the global market. The analysis will also help to identify the most like IP license partners, thus leading to maximum market impact.

The market analysis and benchmarking will be described in the D10.4 Business and financial plan (M48).

9.2.2 Business and financial planning process

The project further focuses on analysing the business system and its stakeholders, modelling potential ecosystems, and developing sustainable business cases for important actors. This work is undertaken in WP10.

The first step is to 1) obtain a clear understanding of the added value that a PoC in-office diagnostic device can bring and what our main strengths are as well as the main hurdles for market introduction. This will give important input to assess the overall economic viability of the technology and the optimal market introduction- and marketing approach and will allow us to identify the best medtech company to license the PoCCardio technology to.

Two specialised consultancy companies will be hired as subcontractors: One for North America and one for Europe. The consultancy firms will be chosen following a public procurement method as required according to the best-value-for-money principle. Regular consultation with medical experts will be required to interpret the results, and to draft a clear picture of the healthcare situation in Austria This will include providing a list of different stakeholder groups, then facilitating interviews between these groups and the business plan team, and finally helping synthesise and draw conclusions.

Based on the market study, the subsequent step will be to identify the actors and the value that is created for each actor when deploying the PoCCardio device in clinical practice. Based on this, sustainable business models to support deployment of PoCCardio devices in the EU and the US will be developed and validated as realistic business cases for the selected application domains. Moreover, the work will finish with a quantification of the Serviceable Available Market (SAM) in the first five years after bringing the technology to market.

The full results business and financial plan will be described in D10.4 Business and financial plan (M48).

9.2.3 Roadmap to regulatory approval

PoCCardio is part of a concerted strategy to bring PoC devices for biomarker assessment to health care provision, which has been developed throughout several EU funded projects. The partners have been conducting their R&D from the start in consultation with experts on the new IVDR, including TüV Süd and Medidee Services. Central to the strategy is the generation of clinical evidence of the highest standard, as is provided by a randomised clinical trial. The consortium will update its development process in the light of regulations currently under development and will continue to obtain professional input from experts engaged in regulatory approval. Once these inputs are available, PoCCardio will engage a European notified body to take all measures to secure a smooth application for regulatory approval initially in Europe and subsequently in the US.

9.2.4 Indicators and criteria

A set of indicators and criteria for the market impact quality level have been established to measure and assess the progress of the market innovations impact. They will be elaborated in the D10.1 Mid-term IPR and exploitation report and D10.3 Final IPR and exploitation planning report.

Relevant economic indicators for market impact can be increased cost efficiency and an overall positive cost-benefit analysis for the PoCCardio solutions; both of which will open new market opportunities in the existing healthcare markets. Further, a large number of relevant use cases makes the PoCCardio platform easier to communicate to the market and will thus allow for a larger group of stakeholders to take interest.

Obviously, the number of relevant business models defined is important. Different business models will allow a larger variety of business and user stakeholders to be interested in the features of the PoCCardio platform, because it has a clear business potential.

Eventually, the number of market segments identified and prioritised as well as the quantified, competitive position of the PoCCardio solution against competing solutions (the market attractiveness matrix) indicates the marketability of the project's outcome and thus the overall market impact.

The following initial KPIs have been identified:

Table 11 Initial KPIs for market innovation

Market Innovation	KPI	Quality Criterion

European citizens will benefit from targeted and faster research resulting in improved CVD prevention and therapy monitoring for better patient outcomes. This will moreover significantly lower the overall health care expenses of the therapy.		
PoCCardio will put a spotlight for the diagnostics industry and the regulatory authorities on the value of a new companion diagnostic test and that of existing prescription medication for intensified treatment guided by this companion test, stimulating uptake in guidelines and steps towards market approval for companion diagnostics.		
Leveraging extensive background technology IP, PoCCardio will deliver a mass manufacturable, robust, and low-cost PoC solution, bringing the companion diagnostic test to the specialists' and physicians' office, thereby creating the necessary boundary conditions for a broad uptake of the test by the medical community.		

10 List of figures and tables

10.1 Figures

10.2 Tables

11 Appendix 1 – Document Control Page

Document control page

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