D8.1. – Project handbook, Risk management and Quality Assurance plan

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Statement of Originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

Disclaimer

Executive summary

D8.1, project handbook, aims at providing project partners with an overview of project's management procedures, including the applicable legal documents, the management structure and the roles of each participant in the project workflow, the reporting obligations / procedures, payments schedule, targeted contractual outcomes, risk and quality management procedures and communication practices. Where necessary, reference is made to clauses of the project's Grant and Consortium Agreement.[1]

[1] For document consistency reasons, certain clauses from the two Agreements have been also included in D8.1.

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List of Abbreviations

Abbreviation	Explanation
GA	Grant Agreement
CA	Consortium Agreement
EU	European Union.

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1. General Project Information

More than 50% of the newly diagnosed breast cancer patients are elderly and particularly susceptible to cardiotoxicity of cancer treatment due to age-related factors and prevalence of multiple co-morbidities. The cumulative effect of risk factors in the elderly patient resembles a "snowball effect", where baseline age and cancer-related changes are exacerbated by direct therapy-induced cardiotoxicity, resulting to a multi-morbid state and mortality. Frailty and high risk of cardiotoxicity in this group may lead to inappropriate interventions and undertreatment, resulting in poorer outcomes, deterioration of QoL and increased healthcare costs. Considering, that older cancer patients are underrepresented in trials, new interdisciplinary and patient-oriented studies able to provide clinical guidelines and best practices for delivering quality care are needed. CARDIOCARE will contribute to scale up a better management for the multimorbid elderly breast cancer patients. Innovative eHealth applications, coupled with sensors and wearables, will permit a consistent evaluation of the intrinsic capacity and by combining clinical and biological features, will provide a holistic approach to the management of cancer and his co-morbidities in the elderly population. This will allow the development of quality indicators for effective care pathways and allow a more informed approach to breast cancer patients with multimorbidity, training and education of caregivers and stakeholders to boost effectively elderly breast cancer patients along disease trajectory and cardiotoxicity. eHealth applications will increase the involvement and participation of the patients in their care process and self-management improving adherence to their individualized care plan, and a better psychological adaptation to their disease. Overall, the implementation of a comprehensive model for effective risk stratification will positively impact on QoL, adverse events, hospitalizations, and healthcare.

1.1 Grant Agreement

CARDIOCARE Grant Agreement (GA) is the document within which the rules regarding project implementation are defined. CARDIOCARE GA is based upon Model Grant Agreement H2020 General MGA — Multi – V5.0 and has been signed by the Funding Authority (European Commission) and the Coordinator. All consortium members (Parties) have provided their accession to this GA by electronically signing the relevant accession forms.

1.2 Consortium Agreement

CARDIOCARE Consortium Agreement (CA) is an internal agreement between all Parties within which the Parties wish to specify or supplement binding commitments among themselves in addition to the provisions of the specific GA. CARDIOCARE CA is based upon DESCA model. The final version is drafted following negotiations between all Parties which will provide their accession by officially signing the proposed agreement.

CA agreement has been drafted in a way that no conflicts between its provisions and the corresponding included in the GA occur. In the unlikely event that such a conflict occurs, GA provisions always precede the ones included in CA.

1.3 Amendments

According to GA Article 55.1, GA may be amended, unless the amendment entails changes to the GA which would call into question the decision awarding the grant or breach the principle of equal

treatment of applicants. GA amendment procedure is described in GA Article 55.2 which foresees that the party requesting an amendment must submit a request for amendment signed in the electronic exchange system. The coordinator submits and receives requests for amendment on behalf of the beneficiaries. If a change of coordinator is requested without its agreement, the submission must be done by another beneficiary (acting on behalf of the other beneficiaries). The request for amendment must include:

- the reasons why;
- the appropriate supporting documents;
- for a change of coordinator without its agreement: the opinion of the coordinator (or proof that this opinion has been requested in writing).

The Commission may request additional information.

In particular, amendments on the estimated budget breakdown indicated in GA Annex 2 may be adjusted — without an amendment by transfers of amounts between beneficiaries, budget categories and/or forms of costs set out in Annex 2, if the action is implemented as described in GA Annex 1. However, the beneficiaries may not add costs relating to subcontracts not provided for in GA Annex 1, unless such additional subcontracts are approved by an amendment or in accordance with GA Article 13.

Such amendment requests shall be submitted to the coordinator who will review the request and provide an approval following communication with EC services.

2 Management structure

CARDIOCARE management structure has been agreed between the Parties in order to allow an efficient project management both in the administrative as well as the technical level. It includes several bodies and individual roles, amongst which the Project Board and the Coordinator are the governing ones. In this section, details on the managerial structure and relevant procedures are provided.

2.1 Roles

The Project Board (PB)

The PB that will be the highest-level authority of the project having the overall responsibility of technical, financial and administrative management of the project. The PB consists of one representative from each partner (Partners Project Managers) and is chaired by the Project Coordinator. The PB is responsible to monitor and evaluate the progress of the project and take all decisions by voting procedures (see section 2.2). Moreover, the project's management structure foresees five manager positions (Financial, Scientific, Technical, Dissemination and Exploitation) and one Advisory Board. Actual workflow will be managed by Work Package (WP) and Task leaders.

The Project Coordinator (PC)

The PC, **Prof. Dimitrios Fotiadis (UOI)**, will be the chair of the PB and the single contact link with the European Commission as the authorized representative of the project Consortium. The main effort of the PC is to navigate between the conflicting demands of time, resources and activities, where he has to constantly weigh these demands against each other and trade off one against the other. The PC's main responsibilities are to:

- manage and coordinate the project's participants as well as the parties interested in the project,
- take the full control of the project and taking various actions when needed (i.e. overseeing finances, reallocating time and resources, amending the Description of the Action (DoA), ensuring that the CA is discussed and signed, manage assigned resources according to the distinct objectives of the project),
- clarify the activities that need to be undertaken by each member of the consortium according to the objectives and purpose of the project and plan and execute the various project processes,
- provide a reference point in order to resolve any conflicts that may appear among the partners,
- provide feedback to the PB and to all partners and cooperate closely with all Project Managers.

Technical Manager (TM)

The TM, **Prof. Kostas Marias (FORTH)**, will manage the technical resources and efforts in cooperation with the PC in order to ensure that project milestones are met. Furthermore, TM will oversee the overall consistency of the technical objectives and the relevant WP plans, supervise the WP Leaders during the preparation of the technical deliverables and report on the technical progress of the project. Finally, the TM reports status information and issues that may arise to the

PC concerning system development activities. **Mrs Georgia Karanasiou** (UOI) will work together with the TM, acting as Technical Coordinator of the project, on behalf of UOI.

The Clinical Study Manager (CSM)

The CSM, **Prof. Gabriella Pravettoni (IEO)**, will monitor and support the clinical studies of the project, including the approval of the submitted clinical protocols, the patient recruitment, the conduction of the study and coordinate the actions among the participating clinical centers.

The Quality Control (QCM) and Risk Manager (RM)

The QCM and RM **Dr. Federica Rizzi (IMS)**, will be responsible for measuring and tracking the quality of processes and documents during the duration of the project. The private, public and confidential documents that will be produced as deliverables or guides will be monitored by the QCM and the corresponding review team. Quality on procedures is also a crucial factor that provides efficient measures and minimizes risks and unforeseen costs during delays.

The Partners Project Managers (PM)

The PMs will be the representatives of all partners and their main responsibility will be to supervise the corresponding partners' effort and activities. Also, PMs have to monitor the efficiency of the results, possible delays and if are in line with the assigned resources. PMs will inform constantly the PC about the progress and the achievements of the partners during the project activities.

The Scientific Manager (SM)

The SM, **Prof. Curigliano Giuseppe (IEO)**, is responsible for the smooth implementation of the project's scientific objectives. The SM will coordinate the relevant activities including the proof of concept study in strong cooperation with the PC and PB.

The Scientific and Technological Committee (STC)

The role of the STC is to coordinate and assist WP leaders on Scientific and Technological issues related to the implementation of the project's activities. The STC will: (a) undertake initiatives to propose technical solutions and fine-tune technical and scientific orientations whenever necessary, (b) control the technical work carried out in the related tasks and propose technical modifications and reallocation of resources as required to achieve the objectives of the project, (c) report about potential deviations from the project work.

The Work Package Leader (WPL)

The WPL is responsible to perform the actual project work, monitor and manage the activities within the respective WP and match the expected project results with the strategic and research directions of the project. Moreover, they are also responsible to guarantee the highest quality of the deliverables that have been assigned to them assisted by the Task Leaders (TL). More specifically, the WPL is responsible to design and implement the WP (action) plan, supervise and coordinate the tasks and activities of the WP team and monitor the actual progress against the WP plan. The WPL will report the WP status and performance (with respect to schedule, cost, quality and risk) to the TM, SM and PC and manage the assigned financial and human resources.

Each TL will directly report to the related WPL and assist him in the coordination of task's activities.

The Task Leaders (TL)

The TL is responsible to perform the actual work within the respective Task of the WP. Each TL will directly report to the related WPL and assist him in the coordination of task's activities.

The Project Coordination Steering Committee (PCSC)

The PCSC is composed by the PC, the Technical Manager, the Scientific Manager, the Clinical Study Manager. Additional project team members may be invited, when relevant.

The Project Management Office (PMO) of the Research Committee of UOI

The PMO will assist the PC for the operational day-to-day activities, ensure the Consortium's compliance with EU regulations and their contractual and legal requirements, as well as the correct implementation of the Project Management Plan. The PMO will monitor the Consortium Agreement, and generate corrective actions, if needed (in conjunction with the GA). PMO will ensure effective project administration across all partners, collect financial data and other relevant statements from all participants, oversee time management issues (timetables, deliverables, milestones) and provide organizational and management support for joint or common initiatives such as meetings, workshops, conferences, GA meetings, risks identification and management in the GA context, by addressing any existing conflict. **Dr. Evangelos Fotiou** will act as the Administrative coordinator, on behalf of UOI.

The Gender & Equal Opportunity Manager (GEOM)

The GEOM, **Dr. Costanza Conti (IMS),** will be responsible for the consistent monitoring of all ethical, legal and labour law issues that may arise during the implementation of the project. The GEOM will work in close cooperation with PC and PCSC in order to ensure that the activities planned in the Project are in accordance with the corresponding established legal frameworks.

The Ethical Advisory Board (EAB)

The EAB will monitor and review all issues with respect to observation of ethical principles in humans and make recommendations. EAB will be formed by one member of each clinical partner, one from ESC (Dr. Christopher Plummer) and one member from ICOS (Dr. Daniel Lenihan) and EUROPA DONNA (Dr. Antonella Moreo) as external members. The EAB will be led by the GEOM. More details in D6.1.

The Regulatory Advisory Board (RAB)

The role of the RAB will monitor and review all issues related to regulatory aspects. RAB will be formed by the PC, SM, TM, CSM, GEOM, and a member from ESC (Dr. Riccardo Asteggiano), and EUROPA DONNA (Dr. Antonella Moreo), as external members.

The Exploitation Manager (EM)

The EM, **Dr. Anca Bucur (PHILIPS),** will organize and schedule the exploitation strategy and business plan of the CARDIOCARE project to ensure the project's impact among potential users and that the results are fully mainstreamed, multiplied and sustained. The EM will undertake the

main exploitation activities of the project and conduct a detailed market analysis. She will chair the innovation committee and support the partners in setting up the project's health co-production ecosystem, while in cooperation with the PC will handle IPR related issues.

The Dissemination Manager (DM)

The DM, **Prof. Manolis Tsiknakis (HMU),** will organize and schedule the communication and dissemination activities of the project in order to ensure the public awareness for the project and strengthen the wide dissemination of the main outcomes. Each partner will be responsible to disseminate the results of the project individually, but the DM will be responsible to ensure that the necessary actions will be undertaken. The DM will maintain the communication and dissemination plan, where all the tools and activities will be defined and monitored, respectively.

The Dissemination & Exploitation Board

This board will comprise the DM and the EM and representatives from the participating SMEs as commercial partners in order to provide their expertise during the project implementation. The board will be responsible for the maximisation of the project's impact in terms of produced services. The Board will draw the innovation priorities according to the established dissemination, communication and exploitation plan and consult the DM and the EM on the directions that the consortium must focus, in order to accomplish its strategic objective of creating a sustainable business model.

The Scientific Advisory Board

The role of the SAB is to assist WP leaders on Scientific and Technological issues related to the implementation of the project's activities. The SAB will: fine-tune technical and scientific orientations whenever necessary, oversee the technical work carried out in the related tasks and propose technical modifications and reallocation of resources as required to achieve the objectives of the project, report about potential deviations from the project work. SAB members include the : PC, SM, TM, CSM and members from the ICOS (Dr. Susan Dent) and EUROPA DONNA (Dr. Teresa Lopez Fernandez).

2.2 Project meetings and Decision process

Any Partner which is a member of a Consortium Body:

- should be present or represented at any meeting;
- may appoint a substitute or a proxy to attend and vote at any meeting;
- and shall participate in a cooperative manner in the meetings.

PB and PCSC shall assemble **at least** twice a year and quarterly, respectively. Technical meetings per WP shall be organized regularly, to ensure that technical progress is monitored properly, on a monthly basis.

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

or represented. Each Member of a Consortium Body present or represented in the meeting shall have one vote. Decisions shall be taken by a majority of two-thirds (2/3) of the votes cast.

2.3 Meeting Minutes

In the event of a project meeting between the Members of a Consortium Body (i.e. PB, PCSC, SAB, etc.), the chairperson of a Consortium Body shall produce written minutes of each meeting which shall be the formal record of all decisions taken. He/she shall send the draft minutes to all Members within 10 calendar days of the meeting. The minutes shall be considered as accepted if, within 15 calendar days from sending, no Member has sent an objection in writing to the chairperson with respect to the accuracy of the draft of the minutes. The chairperson shall send the accepted minutes to all the Members of the Consortium Body and to the Coordinator, who shall safeguard them. If requested the Coordinator shall provide authenticated duplicates to Parties.

3. Reporting

Project reporting includes an internal procedure of project technical and financial monitoring performed once every 6 months (Internal Progress Reports) and the 4 Formal reports (3 Periodic and 1 Final) through which the coordinator must submit to the Commission the technical and financial reports of the preceding reporting period (or the whole project in the case of Final report). These reports include requests for payment and must be drawn up using the forms and templates provided in the electronic exchange system. In addition, the consortium is obliged to provide information on project progress throughout its implementation via the grant management system under the "continuous reporting" functionality.

3.1 Reporting calendar

Table 1 presents the time-plan of the internal, periodic and final reports along with the corresponding reporting periods.

Table 1: CARDIOCARE reporting periods.

Type	Reporting period	Due date
Internal	M1 – M6	M8
Internal	M7 – M12	M14
Periodic	M1 – M18	M20
Internal	M18 – M24	M26
Internal	M25 – M30	M32
Periodic	M19 – M36	M38
Internal	M36 – M42	M44
Periodic	M37 – M48	M50
Final	M1 – M48	M50

3.2 Internal Progress Reports

Internal Progress reports will be consolidated on a 6-months basis, with the exception of Months 18, 36 and 48 when a Periodic report occurs. The reports will allow the coordinator to efficiently monitor the project technical and financial implementation and apply the appropriate measures for the benefit of all project participants.

3.3 Periodic Reports

The coordinator must submit a periodic report within 60 days following the end of each reporting period. The periodic report must include the following:

a) a **"periodic technical report"** containing:

(i) an explanation of the work carried out by the beneficiaries;

(ii) an overview of the progress towards the objectives of the action, including milestones and deliverables identified in GA Annex 1. This report must include explanations justifying the differences between work expected to be carried out in accordance with GA Annex 1 and that actually carried out. The report must detail the exploitation and dissemination of the results and — if required in GA Annex 1 — an updated "plan for the exploitation and dissemination of the result". The report must indicate the communication activities;

(iii) a summary for publication by the Commission;

(iv) the answers to the "questionnaire", covering issues related to the action implementation and the economic and societal impact, notably in the context of the Horizon 2020 key performance indicators and the Horizon 2020 monitoring requirements;

b) a **'periodic financial report'** containing:

(i) an "individual financial statement" (see GA Annex 4) from each beneficiary, for the reporting period concerned. The individual financial statement must detail the eligible costs (actual costs, unit costs and flat-rate costs; see GA Article 6) for each budget category (see GA Annex 2). The beneficiaries must declare all eligible costs, even if — for actual costs, unit costs and flat-rate costs — they exceed the amounts indicated in the estimated budget (see GA Annex 2). Amounts which are not declared in the individual financial statement will not be taken into account by the Commission. If an individual financial statement is not submitted for a reporting period, it may be included in the periodic financial report for the next reporting period. The individual financial statements of the last reporting period must also detail the receipts of the action (see GA Article 5.3.3).

(ii) Each beneficiary must certify that:

- the information provided is full, reliable and true;
- the costs declared are eligible (see GA Article 6);
- the costs can be substantiated by adequate records and supporting documentation (see GA Article 18) that will be produced upon request (see GA Article 17) or in the context of checks, reviews, audits and investigations (see GA Article 22), and
- for the last reporting period: that all the receipts have been declared (see GA Article 5.3.3);

(iii) an explanation of the use of resources and the information on subcontracting (see GA Article 13) and in-kind contributions provided by third parties (see GA Articles 11 and 12) from each beneficiary, for the reporting period concerned;

(iv) a 'periodic summary financial statement', created automatically by the electronic exchange system, consolidating the individual financial statements for the reporting period concerned and including — except for the last reporting period — the request for interim payment.

3.4 Final Report

In addition to the periodic report for the last reporting period, the coordinator must submit the final report within 60 days following the end of the last reporting period.

The final report must include the following:

a) a **"final technical report"** with a summary for publication containing:

(i) an overview of the results and their exploitation and dissemination;

(ii) the conclusions on the action, and

(iii) the socio-economic impact of the action;

b) a **"final financial report"** containing:

(i) a “final summary financial statement”, created automatically by the electronic exchange system, consolidating the individual financial statements for all reporting periods and including the request for payment of the balance and

(ii) a “certificate on the financial statements” (drawn up in accordance with GA Annex 5) for each beneficiary , if it requests a total contribution of EUR 325,000 or more, as reimbursement of actual costs and unit costs calculated on the basis of its usual cost accounting practices (see GA Article 5.2 and GA Article 6.2, Point A).

3.5 Keeping records

The beneficiaries must — for a period of five years after the payment of the balance — keep records and other supporting documentation in order to prove the proper implementation of the action and the costs they declare as eligible. They must make them available upon request or in the context of checks, reviews, audits or investigations.

If there are on-going checks, reviews, audits, investigations, litigation or other pursuits of claims under the Agreement, the beneficiaries must keep the records and other supporting documentation until the end of these procedures.

The beneficiaries must keep the original documents. Digital and digitalised documents are considered originals if they are authorised by the applicable national law. The Commission may accept non-original documents if it considers that they offer a comparable level of assurance.

The beneficiaries must keep the records and documentation supporting the costs declared, in particular the following:

a) for actual costs: adequate records and other supporting documentation to prove the costs declared, such as contracts, subcontracts, invoices and accounting records. In addition, the beneficiaries' usual cost accounting practices and internal control procedures must enable direct reconciliation between the amounts declared, the amounts recorded in their accounts and the amounts stated in the supporting documentation;

b) for unit costs: adequate records and other supporting documentation to prove the number of units declared. Beneficiaries do not need to identify the actual eligible costs covered or to keep or provide supporting documentation (such as accounting statements) to prove the amount per unit. In addition, for direct personnel costs declared as unit costs calculated in accordance with the beneficiary's usual cost accounting practices, the beneficiaries must keep adequate records and documentation to prove that the cost accounting practices used comply with the conditions set out in Article 6.2, Point A. The beneficiaries may submit to the Commission, for approval, a certificate (drawn up in accordance with Annex 6) stating that their usual cost accounting practices comply with these conditions (“certificate on the methodology”). If the certificate is approved, costs declared in line with this methodology will not be challenged subsequently, unless the beneficiaries have concealed information for the purpose of the approval.

c) for flat-rate costs: adequate records and other supporting documentation to prove the eligibility of the costs to which the flat-rate is applied. The beneficiaries do not need to identify the costs covered or provide supporting documentation (such as accounting statements) to prove the amount declared at a flat-rate.

In addition, for personnel costs (declared as actual costs or on the basis of unit costs), the beneficiaries must keep time records for the number of hours declared. The time records must be in writing and approved by the persons working on the action and their supervisors, at least monthly. In the absence of reliable time records of the hours worked on the action, the Commission may accept alternative evidence supporting the number of hours declared, if it considers that it offers an adequate level of assurance.

As an exception, for persons working exclusively on the action, there is no need to keep time records, if the beneficiary signs a declaration confirming that the persons concerned have worked exclusively on the action.

3.6 Continuous reporting

The Commission requires the continuous maintenance of information regarding the project's progress through the Grant Management System. Table 2 presents the required fields, the responsible partners and the corresponding required content.

Table 2: Continuous reporting schema.

Tab title	Content	Responsible partner
Summary for publication	A publishable summary of the project, readable by non-scientific/ technical audience, without confidential information.	UOI/FORTH
Deliverables	A list of contractual deliverables and their status.	UOI
Milestones	A list of contractual milestones and their status.	UOI
Critical Risks	A list of identified risks, materialization status and mitigation measures.	IMS
Publication	A list of suggested and project publications.	HMU
Dissemination	Quantitative information of dissemination activities.	HMU
Patents (IPR)	A list of registered patents (if any).	PHILIPS
Innovation	Quantitative information of innovation activities, market perspectives and RDI companies participating in the project.	PHILIPS
SME impact	Information on turnover of the company and number of employees (only for SME participants)	UOI
Open Data	Open Datasets suggested by OpenAIRE and project Datasets.	UOI
Gender	Gender of researchers and other workforce involved in the project.	IMS
ABS	EU Access and Benefit Sharing Regulation (NAGOYA Protocol).	UOI

4. Payments

Payments to Parties are the exclusive tasks of the Coordinator.

In particular, the Coordinator shall:

- notify the Party concerned promptly of the date and composition of the amount transferred to its bank account, giving the relevant references
- perform diligently its tasks in the proper administration of any funds and in maintaining financial accounts
- undertake to keep the Funding Authority's financial contribution to the Project separated from its normal business accounts, its own assets and property, except if the Coordinator is a Public Body or is not entitled to do so due to statutory legislation.

With reference to Articles 21.2 and 21.3.2 of the Grant Agreement, no Party shall before the end of the Project receive more than its allocated share of the maximum grant amount from which the amounts retained by the Funding Authority for the Guarantee Fund and for the final payment have been deducted.

The payment schedule, which contains the transfer of pre-financing and interim payments to Parties, will be handled according to the following:

- Funding of costs included in the Consortium Plan will be paid to Parties after receipt from the Funding Authority in separate instalments as agreed below (**Table *3***):

Table 3: Payments installments plan.

48.33 % of maximum grant amount	On receipt of Advance Payment
Up to 36.67% of maximum grant amount	On receipt of Interim Payments following the closure of the first two reporting periods. Payments are subject to the approval of the periodic reports.
Payment of the balance	On receipt of Final Payment following the approval of the Final report and the payment of the balance according to Article 21.4 of the Grant Agreement.

- Funding for costs accepted by the Funding Authority will be paid to the Party concerned.
- The Coordinator is entitled to withhold any payments due to a Party identified by a responsible Consortium Body to be in breach of its obligations under this Consortium Agreement or the Grant Agreement or to a Beneficiary which has not yet signed this Consortium Agreement.

The Coordinator is entitled to recover any payments already paid to a Defaulting Party. The Coordinator is equally entitled to withhold payments to a Party when this is suggested by or agreed with the Funding Authority.

5. Project implementation

The workplan of CARDIOCARE is composed of 8 work-packages. WP1 will define KPIs from available retrospective data and develop eHealth applications for effective monitoring and delivery of the interventions. WP2 will provide omics analyses of biological samples for novel biomarkers of cardiotoxicity. WP3 focuses on the development of the risk stratification model to improve early diagnosis and management of cardiotoxicity and improve QoL. WP4 describes the performance of the multicenter prospective clinical study that will test the efficacy of behavioral and psychological interventions on preserving intrinsic capacity and QoL and countering the cardiotoxic effects of cancer treatment. The prospective study will also provide a panel of validated KPIs for the better management of the elderly multimorbid breast cancer patient at risk for cardiac toxicity. WP5 will develop the CARDIOCARE platform for the provision of eHealth care services, efficient data management and data protection, and high performance computing. WP6 addresses the regulatory, ethical and cost-effectiveness aspects of the CARDIOCARE model while WP7 and WP8 deal with the dissemination, exploitation and project management.

5.1 Deliverables

Table 4 presents the project deliverables, related WP, type, dissemination level and delivery date.

Table 4: Deliverables list

Deliverable Number	Deliverable Title	WP number	Lead beneficiary	Type	Dissemination level	Due Date (in months)
D1.1	First study subject approvals package forthe retrospective study	WP1	2 - IEO	Report	Public	6
D1.2	A first set of quality KPIs for the evaluationof Health status, intrinsic capacity and QoL to be recorded and further validated in the prospective study	WP1	2 - IEO	Report	Confidential, only for membersof the consortium (including the Commission Services)	10
D1.3	Development of the Psychological Outcomes MinimumDataset	WP1	2 - IEO	Report	Confidential, only for membersof the consortium (including the Commission Services)	10
D1.4	Development of the ePsycHeart application	WP1	1 - UOI	Report	Confidential, only for membersof the consortium (including the Commission Services)	12

D1.5	Definition of psychological and behavioral intervention	WP1	2 - IEO	Report	Confidential, only for membersof the consortium (including the Commission Services)	10
D1.6	Development of the eHealthHeartapplication	WP1	4 - FORTH	Other	Confidential, only for membersof the consortium (including the Commission Services)	12
D1.7	Smart recommendations for integrated interventionsand eHealth	WP1	2 - IEO	Report	Confidential, only for membersof the consortium (including the Commission Services)	20
D1.8	Report on status of posting results for theretrospective study	WP1	2 - IEO	Report	Confidential, only for membersof the consortium (including the Commission Services)	36
D2.1	Experimental Design and relevant protocols of omics study. "Detecting miRNA and gut microbiomechanges induced bycancer treatment"	WP2	8 - STREMBLE	Report	Confidential, only for members of the consortium (including the Commission Services)	9
D2.2	Report on -omics analysis with novel setsof omics biomarkers associated with cardiotoxicity, intrinsic capacity and QoL	WP2	8 - STREMBLE	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D2.3	Literature review andreport on the use of biotics as potential treatment strategy	WP2	8 - STREMBLE	Report	Public	48

D3.1	Non-Imaging risk stratification models	WP3	1 - UOI	Report	Confidential, only for membersof the consortium (including the Commission Services)	36
D3.2	Risk stratificationmodels based on imaging data and selected variables	WP3	4 - FORTH	Report	Confidential, only for membersof the consortium (including the Commission Services)	36
D3.3	Integrated CARDIOCARE risk stratification model	WP3	4 - FORTH	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D3.4	AI models based on wearable sensor datafor predicting healthstatus and QoL	WP3	12 - HMU	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D3.5	Validated KPIs for better management of the elderly multimorbidbreast cancer patient	WP3	4 - FORTH	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D3.6	Performance monitoring, logging andretraining of AI models	WP3	4 - FORTH	Report	Public	48
D3.7	Explainable, interpretable, andtrustworthy AI framework	WP3	4 - FORTH	Report	Public	48
D4.1	First study subject approvals package forthe prospective study	WP4	2 - IEO	Report	Public	13
D4.2	Midterm recruitmentreport	WP4	2 - IEO	Report	Public	21

D4.3	Report on status of posting results in thestudy registry	WP4	5 - I.M.S	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D5.1	Data Management Plan	WP5	1 -UOI	ORDP Open Research Data Pilot	Confidential, only for membersof the consortium (including the Commission Services)	6
D5.2	Electronic Case ReportForms (eCRFs)	WP5	6 - PHILIPS	Report	Confidential, only for membersof the consortium (including the Commission Services)	12
D5.3	Initial version of the CARDIOCARE big data and HPC platform	WP5	4 - FORTH	Report	Confidential, only for membersof the consortium (including the Commission Services)	12
D5.4	Final version of the CARDIOCARE big data and HPC platform	WP5	4 - FORTH	Report	Confidential, only for membersof the consortium (including the Commission Services)	36
D5.5	Report on the CARDIOCARE Common Information Model and on the Data Transformation Pipeline	WP5	6 - PHILIPS	Report	Confidential, only for membersof the consortium (including the Commission Services)	24
D5.6	The CARDIOCARE services for cohortselection and study execution	WP5	6 - PHILIPS	Report	Confidential, only for membersof the consortium (including the Commission Services)	36

D5.7	Report summarizingthe work on the FAIRification of the CARDIOCARE datasets	WP5	4 - FORTH	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D6.1	Implementation ofethical standards and guidelines of H2020 and GDPR implementation plan	WP6	1 - UOI	Report	Public	6
D6.2	First ESC organised workshop in Brussels to define the regulatory strategy and roadmap towards the evaluation of the new CARDIOCARE model	WP6	11 - ESC	Other	Confidential, only for membersof the consortium (including the Commission Services)	36
D6.3	Regulatory aspects andcost-effectiveness of the CARDIOCARE model for assessing best practices and healthcare pathways	WP6	5 - I.M.S	Report	Public	48
D6.4	Final ESC organized workshop in Brussels to present the new CARDIOCARE modelat EU policy makers, medical and patient associations	WP6	11 - ESC	Other	Confidential, only for membersof the consortium (including the Commission Services)	48
D6.5	Ethical Advisory Boardreport v1	WP6	1 - UOI	Report	Confidential, only for membersof the consortium (including the Commission Services)	18
D6.6	Ethical Advisory Boardreport v2	WP6	1 - UOI	Report	Confidential, only for membersof the consortium (including the Commission Services)	36

D6.7	Ethical Advisory Boardreport v3	WP6	1 - UOI	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D6.8	Regulatory AdvisoryBoard report v1	WP6	5 - I.M.S	Report	Confidential, only for membersof the consortium (including the Commission Services)	18
D6.9	Regulatory AdvisoryBoard report v2	WP6	5 - I.M.S	Report	Confidential, only for membersof the consortium (including the Commission Services)	36
D6.10	Regulatory AdvisoryBoard report v3	WP6	5 - I.M.S	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D7.1	Project presentationmaterial	WP7	12 - HMU	Other	Public	6
D7.2	Dissemination and communication activities v1	WP7	12 - HMU	Report	Public	18
D7.3	Exploitation and innovation plan v1	WP7	6 - PHILIPS	Report	Confidential, only for membersof the consortium (including the Commission Services)	18
D7.4	Dissemination and communication activities v2	WP7	12 - HMU	Report	Public	30
D7.5	Dissemination and communication activities v3	WP7	12 - HMU	Report	Public	48

D7.6	Exploitation and innovation plan v2	WP7	6 - PHILIPS	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D8.1	Project handbook, Risk management and Quality Assurance plan	WP8	1 - UOI	Report	Public	6
D8.2	Gender and Equal Opportunities	WP8	5 - I.M.S	Report	Confidential, only for members of the consortium (including the Commission Services)	48
D8.3	Scientific AdvisoryBoard report v1	WP8	1 - UOI	Report	Confidential, only for membersof the consortium (including the Commission Services)	18
D8.4	Scientific AdvisoryBoard report v2	WP8	1 - UOI	Report	Confidential, only for membersof the consortium (including the Commission Services)	36
D8.5	Scientific AdvisoryBoard report v3	WP8	1 - UOI	Report	Confidential, only for membersof the consortium (including the Commission Services)	48
D9.1	HCT - Requirement No.4	WP9	1 - UOI	Ethics	Confidential, only for membersof the consortium (including the Commission Services)	13
D9.2	GEN - RequirementNo. 7	WP9	1 - UOI	Ethics	Confidential, only for membersof the consortium (including the Commission Services)	12

5.2 Milestones

Table **5** presents the project milestones, related WP, due date and means of verification.

Table 5: Milestones list.

Milestone number	Milestone title	WP number	Lead beneficiary	Due Date (in months)	Means of verification
MS1	Retrospective study ethics approval	WP1	2 - IEO	6	Signed approval of the study by competent Ethics Committee
MS2	First set of KPIs to be recorded and validatedin the prospective clinical study	WP1	2 - IEO	10	A list of variables/tools defined by clinical experts using scoring methods or possessing high predictive ability in retrospective analysis
MS3	Delivery of the eHealth mobile applications to the prospective study	WP1	4 - FORTH	12	Use by the patients of the prospective study for monitoring and delivery of interventions
MS4	Experimental Designfor Omics Studies finalized	WP2	8 - STREMBLE	9	Sharing of the omics experimental design protocol with the clinical partners to assist the collection and shipping of biologicalsamples.
MS5	Novel sets of omics biomarkers associated with cardiotoxicity, intrinsic capacity and QoL	WP2	1 - UOI	48	A list of SNPs, miRNAs and gut microorganisms statistically associate with cardiotoxicity, intrinsic capacity and QoL phenotypesand used as input to the risk prediction models
MS6	Non-Imaging and Image-based risk stratification models	WP3	1 - UOI	36	Timely delivery of models with 80% accuracy in predicting health outcomes and QoL.
MS7	Development of the integrative CARDIOCARE risk	WP3	4 - FORTH	48	Timely delivery of the integrated model presenting 80% accuracy in predicting health outcomes and QoL.

	stratification model				
MS8	Ethics approval obtained by competentethics committees for the prospective study	WP4	2 - IEO	13	Signed approval of the study by competent Ethics Committees
MS9	Successful enrollmentof 750 patients at the end of the recruitmentperiod	WP4	2 - IEO	24	Accrual of 75O elderly breast cancer patients successfully included in the eCRF
MS10	Clinical evidencefor the efficacy of integrated behavioraland psychological interventions to counteract cardiotoxic effects and promote QoL in elderly breastcancer patients	WP4	2 - IEO	48	Final report of the prospective study with statistically significant associations linking interventions with improved cardiotoxicity, intrinsic capacity and QoLprofiles.
MS11	CARDIOCARE Data Management Plan	WP5	1 - UOI	6	Timely delivery of the Data Management Plan to the EC made publicly available.
MS12	CARDIOCARE Data Management and HPC platform, Initial version	WP5	4 - FORTH	12	A first functional version of the platform supporting wearable sensors and eHealthapplications for the delivery of patient-oriented care to thepatients of the prospective study.
MS13	CARDIOCARE Data Management and HPC platform, final version	WP5	4 - FORTH	36	Timely production of the deliverable presenting to the clinicians a final fully functional version of the platform providing high performance computing alongwith data protection and security services.
MS14	Device of the GDPR implementation plan	WP6	1 - UOI	6	Timely delivery of the GDPR implementation plan to the

					partners made publicly available.
MS15	A first workshop organised by ESC defining the regulatory strategy androadmap towards the evaluation of the new CARDIOCARE model	WP6	11 - ESC	36	Minutes of the meeting, press release, videos, and report on the defined steps andregulatory roadmap.
MS16	Presentation of the new cost-effective CARDIOCARE modeland risk stratification concept in a regulatoryexperts final workshop with EU policy makers,medical and patient associations	WP6	11 - ESC	48	Minutes of the meeting, press release, photographs, location, videos, positive evaluation of regulatory experts and patients association. Final report of the study presenting Increasein Quality Adjusted Life Years (QALYs) and Negative Incremental cost-effectiveness ratio (ICER) of the model compared to the current clinical practice, by 20%.
MS17	Project's website, project's flyer and project's accounts in social media	WP7	12 - HMU	6	Timely creation of the website, flyer social media accounts of the project.
MS18	Kick off meeting	WP8	1 - UOI	2	Minutes of the kick off Meeting, Agenda of the meeting signed by all the partner representatives, Relative information announced in the CARDIOCARE website (photographs, location, outcome).

6. Risk management

Risk management involves the identification of potential problems and elimination or reduction of the damage of those risks. Failure to adequately manage risks will threaten the success of the project. Risk management is under the responsibility of the Risk Manager (IMS), the Project Coordination Steering Committee (PCSC) and Work Package (WP) Leaders. Risk management in CARDIOCARE will take place in three levels:

- Strategic: focuses on the relation between the partners
- Tactical: focuses on the contribution of the WPs to the project's objectives
- Operational: focuses on the actions within the WPs.

The initial identified risk factors that may apply to these three levels are: (i) complexity: activities may be too complex to realize, (ii) capacity: one/more partners may not be able to keep their commitments, (iii) reliability: inappropriate project methods/strategies for the intended outcomes, (iv) validity: findings may not reflect the real needs and priorities of the stakeholders, (v) sustainability: outcomes may not result in a sustainable outcome. During CARDIOCARE **preparation phase**, the following potential risks have been mainly identified, and corresponding contingency plans were suggested (Table 6).

Table 6: CARDIOCARE risks and proposed mitigation measures.

WP	Risk	Proposed risk-mitigation measures	Level
WP1	Patients face difficulties in reporting the QoL outcomes in the provided questionnaires and apps. Likelihood: Low	The department in IEO focusing on QoLevaluation has long term expertise in preparing and utilizing QoL questionnaires from patients before and after cancer treatment. Still, in case the risk emerges, for the objective evaluation of QoL, specific measurements from the wearable devices, along with selected input from the questionnaires will be utilized.	
WP2	Difficulties in the identification of biomarkers and psychomarker profiles linked to cardiotoxicity phenotypes and psychological states. Likelihood: Low. The study on cardiotoxicity association with the gut microbiome through Metagenomics provided limited correlation and causality. Likelihood: Medium.	In case the risk emerges, other types of biomarkers, including radiomic ones and well established tests, clinical examinations and questionnaires will be used. In addition, in case that the identified biomarkers do not provide the necessary results, additional input will be provided from the mechanistic and integrative modelling of cardiomyocyte cardiotoxicity. Recent studies have revealed preliminary findings of correlation of gut microbiome with cardiotoxicity. In case the risk emerges, the consortium will extend this specific WP in order to acquire additional samples	

		for providing increased statistical significance in the computational analyses	
WP3	The amount of data for the development of the risk prediction models is not enough to provide statistically significant results in terms of early diagnosis and management of cardiotoxicity and QoL. Likelihood: Low.	In case the risk emerges, the consortium will provide additional data through virtual population, combining models from existing projects and data.	
WP4	Ethical approval delays and difficulties in patient recruitment delay the acquisition of the necessary patients' data. Likelihood: Medium.	In case the risk emerges, the recruitment period will be extended. This will slightly affect the rest WPs, since retrospective data will be already available for the technical developments.	
WP5	The amount of data for the development of the AI risk prediction models is not enough to provide statistically significant results in terms of early diagnosis and management of cardiotoxicity and QoL. Likelihood: Low	In case the risk emerges, the consortium will provide additional data through virtual population, combining models from existing projects and data.	
WP6	Difficulties in data harmonization because of the heterogeneity of the multidimensional from diverse data sources. Likelihood: Medium	Focus on specific variables of the cohorts and perform a targeted harmonization of those variables. Inclusion of reduced number (well characterized in terms of target analysis variables) of retrospective patients.	
WP7	Patient recruitment in some clinical sites is not achieved according to the plan. Likelihood: Medium	The clinical study has been designed based on the capacity of each clinical center and realistic numbers have been considered for patient recruitment for each clinical site. Six clinical centers have been enrolled in CARDIOCARE to ensure that if one (or more) clinical centers will face problems in patient recruitment, the other clinical centers will be able to guarantee the total target number of 750 patients.	

WP8	Low level of cooperation / interaction among partners. Legal controversies. Likelihood: Low	(i) use of further interactive communication and/or liaise with additional persons in the institution, (ii) effort to decrease the flow of unnecessary information, (iii) involvement of the WP Leaders, (iv) application of mitigation measures contained in the CA, (v) usage of individual background technology and knowledge will be included in the CA and through a comprehensive IPR agreement.	
WP9	Difficulties in approaching the regulatory bodies. Likelihood: Low	The consortium has included Task 6.2 'Analysis of regulatory aspects' to address the regulatory requirements related to the CARDIOCARE solution. IMS, ESC, EUROPA DONNA and ICOS will play a key role in approaching the regulatory bodies.	

 : low, medium, high risk

During the **project implementation** phase, risk management is performed under the following procedure:
IMS as Risk Manager is responsible to maintain a Risk Registry which will facilitate the adequate risk management during the project as well as Risks reporting during both internal and periodic reports. The Risk Registry includes the risks included in the DoA (foreseen risks) and those added later (unforeseen risks). The Risk Registry is updated regularly throughout the project (every 6 months). It will be overviewed by all partners during the plenary and technical meetings. The Risk Registry of the project is maintained in CBMLBox platform and contains the following information for each identified risk:

- Risk ID
- Description
- Relevant WP
- Risk owner (responsible partner)
- State of Play (materialized yes/no)
- Probability (Low/Medium/High)
- Impact (Low/Medium/High)
- Mitigation and Contingency plan

In the case of a risk which is both probable (or already materialized) and of high potential impact, PC will work tightly with any involved partners in order to:

- Define mitigation plans (preventive actions) to prevent the risk from materializing and/or reduce its impact
- Define contingency plans (corrective actions), to be implemented in the event that the risk eventually materializes.

7. Quality assessment and Performance Monitoring

All partners of the CARDIOCARE project have already considered actions and measures to ensure the quality control of methods, tools and processes during the lifecycle of the project. In particular: (i) the cloud data services will be implemented to a secure and GDPR compliant system by providing strong security and privacy safeguards, (ii) the data types that will be collected will be reviewed from experts to ensure the higher level of consistency, (iii) guidelines will be provided to the real settings of application through the solution testing, (iv) monitoring visits will be performed to the pilot sites for the evaluation of the CARDIOCARE solution, (v) missing values from the training artificial intelligent data models will be minimized if not eliminated, (vi) GDPR rules for anonymization and pseudonymization will be implemented, (vii) data transfers between sensor devices and the CARDIOCARE platform will be encrypted, (viii) security and privacy issues will be foreseen from the design phase of the project, (ix) all cloud-based data storage systems will ensure data integrity and data safety, (x) a deliverables preparation time-plan will ensure the effective preparation and high quality of CARDIOCARE deliverables.

Regarding (x), all deliverables (except those in WP8 and WP9) follow the implementation time plan described below.

- Peer Review of all submitted deliverables by (at least) two reviewers (-4 wk)
- Discussion of major comments among reviewers and authors (-3 wk)
- Implementation of minor comments in the drafts (1 wk)
- Completion of “Internal Peer Review Report” by reviewers

Internal reviewers (at least two) must engage in the review process. Internal reviewers’ list is maintained by IMS. Reviewers must not engage in the deliverable incorporation phase, unless this is practically impossible. They must ensure that the deliverable content is consistent with the provided Executive Summary, the objectives of the deliverable, and that it is scientifically sound. Moreover, they should also perform proof-reading and grammar checks. Finally, they must provide a brief review report with their assessment on the deliverable.

Deliverable template is available in the CBMLBox (see section 8).

8. Communication practices

Internal Communication

Collaborative tool

CBMLBox is a NextCloud installation at FORTH's private cloud infrastructure located at its premises in Heraklion, Greece. CBMLBox is a Document Management System (DMS), alternative to Dropbox, Google Suite, Office 365. It is Self hosted, 100% open source and it can be Distributed / Federated

Regarding remote meetings, the Coordinator maintains a virtual meeting room in WebEx (medlab.webex.com), which offers a variety of remote collaboration utilities. WebEx will be used primarily in plenary and review meetings. In other meetings, other web meeting utilities (i.e. Zoom) can also be used.

Mailing list

CARDIOCARE dedicated mailing lists are maintained by FORTH. UOI has coordinated the initial lists population and will forward any future partners requests to FORTH.

External Communication[2]

Project website

CARDIOCARE official website (https://cardiocare-project.eu) is maintained throughout the project duration offering a variety of information including the project's scope, objectives, outcomes and results.

Project logo

Figure 1 presents the project's logo.

Figure 1: CARDIOCARE logo

Presentation template

CARDIOCARE presentation template can be found on CBMLBox.

Acknowledgments

[2] See D7.1 for details.

All partners must follow the Commission's suggestion on EU funding acknowledgment in all project related activities. These are:

(a) display the EU emblem (Figure 2) and

(b) include the following disclaimers:

"This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 945175".

"This article/poster/website reflects only the author's view and the Commission is not responsible for any use that may be made of the information it contains."

When displayed together with another logo, the EU emblem must have appropriate prominence. For the purposes of their obligations under this Article, the beneficiaries may use the EU emblem without first obtaining approval from the Commission.

Figure 2: The EU emblem

Conclusions

D8.1 provides the fundamental elements of CARDIOCARE project management plan. Its scope is to provide project partners with a convenient reference document covering the basic project management operations. Throughout the project, the Project Coordinator remains at partners' disposal for further clarifications and assistance with the day-to-day project management. In any case, the project's Grant Agreement is the legal binding document with which all partners must comply.