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ENDOTARGET PROJECT HANDBOOK

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ENDOTARGET

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EXECUTIVE SUMMARY

The aim of this Project Handbook is to provide a reference point and a resource for all members of the ENTOTARGET team, providing them with the necessary information to execute their roles and responsibilities effectively.

The purpose is to ensure that all members have a shared understanding of the project's goals, requirements and expectations. This manual helps to create a standardized approach to project management, reducing the risk of errors and miscommunications.

Key aspects such as project scope, objectives, timeline, budget, deliveries, agreements, project management structure, project governance, responsibilities, communication and dissemination practices, internal review process of the deliverables, periodic and final reporting, finances and payments, and our day-to-day work practices, are included in this handbook as a single working document.

The Grant Agreement, Consortium Agreement, and their Annexes, develop in depth what is included here , and this handbook will never replace or prevail over them.

This handbook is one of the first deliverables of ENDOTARGET, and it will be revised and adapted as needed as the procedures change during the course of the project.

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LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
AE	Affiliated entities
AI	Artificial intelligence
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BEN	Beneficiary
CA	Consortium Agreement
CI	Chronic inflammation
COO	Coordinator
DC	Dissemination and Communication
DSMB	Data and Safety Monotoring Board
EB	Ethics Board
EBRIS	Fondazione Ebris
EC	European Commission
ECV	Extracellular vesicles
ELISA	Enzyme linked immunosorbent assay
EOSC	European Open Science Cloud
EstBB	Estonian Biobank cohort
ETH Zürich	Eidgenoessische Technische Hochschule Zuerich
EU	European Union
FIDIS	Fundación Instituto de Investigación Sanitaria de Santiago de Compostela
FinnGen	Finnish Biobank
FINRISK	Finnish Biobank
FMT	Fecal microbiota transplantation
GA	Grant Agreement

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GDPR	General Data Protection Regulation
GWAS	Genome-wide association study
HaDEA	European Health and Digital Executive Agency
HBS	Helsinki Businessmen cohort
HC	Healthy control
HUS	Helsingin ja Uudenmaan Sairaanhoitopiirin Kuntayhtymä
ICD	International classification of diseases
I-FABP	Intestinal fatty acid-binding protein
iMM	Instituto de Medicina Molecular Joao Lobo Antunes
LPS	Lipopolysaccharides
MASES	Maastricht ankylosing spondylitis entheses score
ME	Metabolic endotoxemia
MIM	Mutual Insurance Mecanism
ML	Machine learning
MVIB	Multimodal variational information bottleneck
NEC	NEC Labotatories Europe GMBH
NEC ITALIA	NEC Italia SPA
NFBC	Northern Finland birth cohort
OA	Osteoarthritis
OMV	Outer membrane vesicles
PbD	Privacy by design
PC	Project Coordinator
PoC	Proof of concept
PRS	Polygenic risk score
RA	Rheumatoid arthritis
RDPT	Rheumatic disease prediction tool
RDs	Rheumatic diseases
SE	Systemic endotoxemia
SERGAS	Servizo Galego de Saúde

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SEZ	Steinbeis 2I GMBH
SIB	SIB Swiss Institute of Bioinformatics
SpA	Spondylarthritis
TLR	Toll like receptors
TU WIEN	Technische Universitaet Wien
UH	Helsingin Yliopisto
UNICAM	Universita Degli Studi Della Campania Luigi Vanvitelli
UTARTU	Tartu Ülikool
VAT	Value Added Tax
WP	Work Package
WPL	Work Package Leader

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1. INTRODUCTION

The Project Manual is the basis for day-to-day project management throughout the ENDOTARGET project life cycle, and it is an important reference point for all the project members and their stakeholders.

This handbook is one of the first deliverables of the project, and it will be revised and adapted as needed as procedures change during the course of the project.

The signed documents Grant Agreement, Consortium Agreement, and their Annexes, will always prevail over this handbook.

This manual does not include guidelines on Communication, Dissemination and Exploitation; Data management; Data protection; Ethics issues and Risk management, as these have their own plans and deliverables.

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2. ENDOTARGET PROJECT

2.1 PROJECT SUMMARY

Rheumatic diseases (RDs) affect more than 40% of Europe's population and cause significant disability, pain, reduced lifespan and a very high economic burden.

In this project, we will explore the role of chronic systemic inflammation caused by intestinal microbiota derived immunologically active compounds, as a driver in the transition from health to disease, with a special focus on three RDs; osteoarthritis (OA), rheumatoid arthritis (RA), and spondylarthritis (SpA).

We aim to explore the relationship between gut microbiota, intestinal permeability, and endotoxemia.

We aim to understand their role as drivers of disease onset and disease activity in RA, SpA and OA, as well as targets of preventive and therapeutic approaches.

We will study the events leading from health to disease onset by

i) taking advantage of geographically diverse large cohorts of people with available blood and faeces samples,

ii) search for novel risk biomarkers for RA, SpA, and OA by using high-throughput OMICS-based analyses

iii) conducting targeted clinical studies,

iv) performing in vitro mechanistic studies to explore the gut-joint axis using tissue explant cultures and organ-on-chip models

v) conducting interventional proof of concept studies of diet, faecal transplantation and a gut permeability decreasing drug in RA and SpA patients,

vi) exploring in vitro new potential drugs or nutraceuticals to cope with endotoxemia effects on target tissues.

By combining all these results, machine learning and AI-informed rheumatic disease prediction tool will be developed for clinicians to help them identify patients with increased risk of developing the target diseases.

It will thus assist in the choice of personalized blueprint intervention to reduce the risk of these diseases and disease activity in RA and SpA and to slow down the progression of OA.

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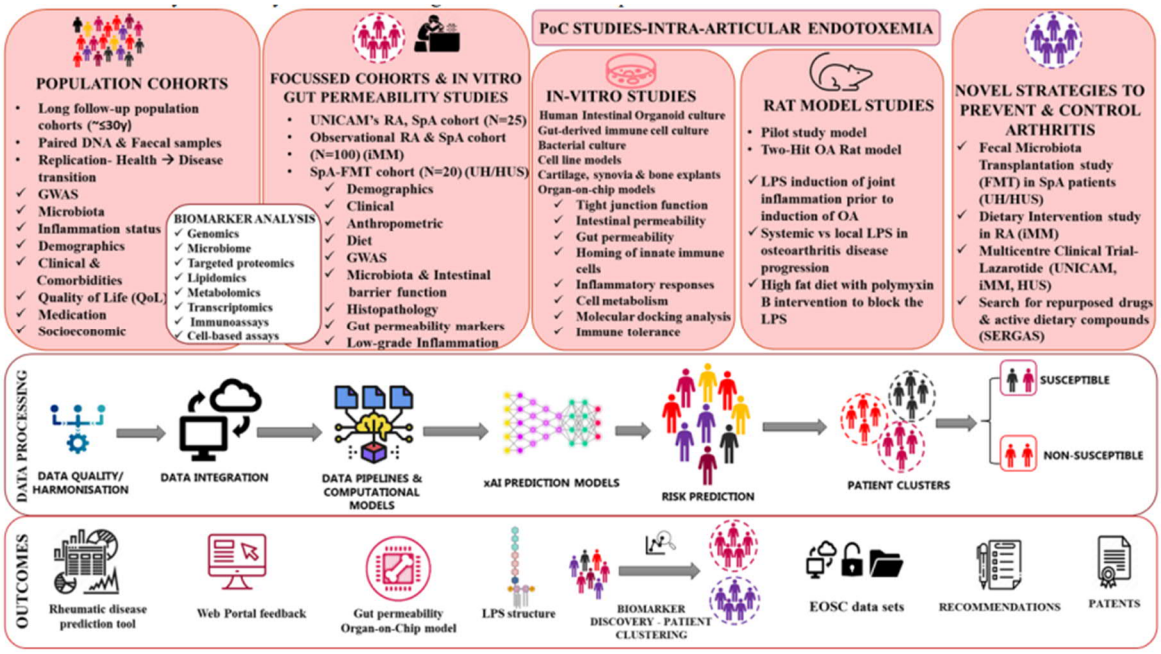

Figure 1 Project Scope and Outcomes

2.2 PARTICIPANTS

The ENDOTARGET project´s participants are listed in the Grant Agreement and in the Consortium agreement.

ENDOTARGET has 10 beneficiaries, two affiliated entities, and two associated partners.

The ENDOTARGET beneficiaries are:

1. HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRIN KUNTAYHTYMÄ (HUS), PIC 999483830 as Coordinator
2. TARTU ULIKOOL (UTARTU), PIC 999895013
3. UNIVERSITA DEGLI STUDI DELLA CAMPANIA LUIGI VANVITELLI (UNICAM), PIC 999848356
4. INSTITUTO DE MEDICINA MOLECULAR JOAO LOBO ANTUNES (iMM), PIC 999813339
5. SERVIZO GALEGO DE SAUDE (SERGAS), PIC 974720409
6. HELSINGIN YLIOPISTO (UH), PIC 999994535
7. TECHNISCHE UNIVERSITAET WIEN (TU WIEN), PIC 999979888
8. NEC LABORATORIES EUROPE GMBH (NEC), PIC 910561893
9. STEINBEIS 2I GMBH (SEZ), PIC 916274126
10. FONDAZIONE EBRIS (EBRIS), PIC 935386230

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The affiliated entities which are linked to two ENDOTARGET beneficiaries are:

- FUNDACION INSTITUTO DE INVESTIGACION SANITARIA DE SANTIAGO DE COMPOSTELA (FIDIS), PIC 986488255, linked to SERVIZO GALEGO DE SAUDE (SERGAS)
- NEC ITALIA SPA (NEC ITALIA), PIC 888842526, linked to NEC LABORATORIES EUROPE GMBH (NEC)

The ENDOTARGET associated partners are:

- SIB SWISS INSTITUTE OF BIOINFORMATICS (SIB), PIC 999629815
- EIDGENOESSISCHE TECHNISCHE HOCHSCHULE ZUERICH (ETH Zürich), PIC 999979015

Table 1. Endotarget Participants

Number	Role	Short name	Legal name	Country
1	COO	HUS	HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRIN KUNTAYHTYMÄ	FI
2	BEN	UTARTU	TARTU ÜLIKOOL	EE
3	BEN	UNICAM	UNIVERSITA DEGLI STUDI DELLA CAMPANIA LUIGI VANVITELLI	IT
4	BEN	iMM	INSTITUTO DE MEDICINA MOLECULAR JOAO LOBO ANTUNES	PT
5	BEN	SERGAS	SERVIZO GALEGO DE SAUDE	ES
5.1	AE	FIDIS	FUNDACION INSTITUTO DE INVESTIGACION SANITARIA DE SANTIAGO DE COMPOSTELA	ES
6	BEN	UH	HELSINGIN YLIOPISTO	FI
7	BEN	TU WIEN	TECHNISCHE UNIVERSITAET WIEN	AT
8	BEN	NEC	NEC LABORATORIES EUROPE GMBH	DE
8.1	AE	NEC ITALIA	NEC ITALIA SPA	IT
9	BEN	SEZ	STEINBEIS 2I GMBH	DE
10	BEN	EBRIS	FONDAZIONE EBRIS	IT
11	AP	SIB	SIB SWISS INSTITUTE OF BIOINFORMATICS	CH
12	AP	ETH Zürich	EIDGENOESSISCHE TECHNISCHE HOCHSCHULE ZUERICH	CH

2.3 DURATION AND BUDGET

ENDOTARGET project has a duration of 48 months. The starting fixed date is January 1, 2023, and it will continue until the end date of December 31, 2026.

The total EU contribution matches 100% of the total eligible costs, which are 6.997.820 euros.

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The budget detailed by beneficiary and the EU contribution is detailed at the Grant Agreement.

2.4 CONTRACTUAL DOCUMENTS

Contract documents and their annexes are always available online at the ENDOTARGET Team in Microsoft Teams.

2.4.1 Grant Agreement

The Grant Agreement sets out the rights and obligations and terms and conditions applicable to the grant awarded for the implementation of the action set out in the Chapter 2 (Action) of the GA.

The beneficiaries, as signatories of the Agreement, are fully responsible towards the granting authority for implementing it and for complying with all its obligations.

They must implement the Agreement to their best abilities, in good faith and in accordance with all the obligations and terms and conditions it sets out.

They must have the appropriate resources to implement the action and implement the action under their own responsibility and in accordance with Article 11 of the GA. If they rely on affiliated entities or other participants, they retain sole responsibility towards the granting authority and the other beneficiaries.

They are jointly responsible for the *technical* implementation of the action. If one of the beneficiaries fails to implement their part of the action, the other beneficiaries must ensure that this part isimplemented by someone else (without being entitled to an increase of the maximum grant amount and subject to an amendment; see Article 39).

The beneficiaries (and their action) must remain eligible under the EU programme funding the grant for the entire duration of the action. Costs and contributions will be eligible only as long as the beneficiary and the action are eligible.

2.4.2 Consortium Agreement

The purpose of the signed Consortium Agreement is to specify with respect to the Project the relationship among the Parties, in particular concerning the organisation of the work between the Parties, the management of the Project and the rights and obligations of the Parties concerning inter alia liability, Access Rights and dispute resolution.

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The general principles are:

- Each Party undertakes to take part in the efficient implementation of the Project, and to cooperate, perform and fulfil, promptly and on time, all of its obligations under the Grant Agreement and this Consortium Agreement as may be reasonably required from it and in a manner of good faith as prescribed by Belgian law.
- Each Party undertakes to notify promptly the Granting Authority and the other Parties, in accordance with the governance structure of the Project, of any significant information, fact, problem or delay likely to affect the Project.
- Each Party shall promptly provide all information reasonably required by a Consortium Body or by the Coordinator to carry out its tasks and shall responsibly manage the access of its employees to the EU Funding & Tenders Portal.
- Each Party shall take reasonable measures to ensure the accuracy of any information or materials it supplies to the other Parties.

2.5 ETHICS

The Art 14 GA, says that "the action must be carried out in line with the highest ethical standards and the applicable EU, international and national law on ethical principles."

ENDOTARGET project will consider ethics across the project and all WPs.

The consortium will adopt the EC's Ethics Guidelines and appoint a ethics board and coordinate their work by passing on feedback to relevant WPs.

The Ethic Board and Independent External Ethic advisor will have their own reports at M18, M36 and M48, which correspond to the EC Ethics requierements deliverables D9.2, D9.3 and D9.4.

2.5.1 Ethical Board

The Art 6.5 of the CA says: The Consortium will have an Ethics Board (EB). The EB will consist of one representative of each Party participating in clinical trials (at the time of entering this Consortium Agreement: HUS, UTARTU, SERGAS, UH, UNICAM, iMM).

The EB is a consultative body established to review and assess the research activities carried out under Project to ensure compliance with ethical principles. In addition, there will be an external ethics advisor.

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At the GA is mention that "This project has formed its internal ethics committee to perform the respective clinical trials as coordinated action. The Project will also have an external ethics advisor by M1 who will be taking care of EU data protection and largescale processing of genetic data.

Other members of committee include the PI's of WP4 participants such as, Prof. Alessio Fasano, Prof. Kari Eklund, Prof. Reetta Saatokari, Prof. Patricia Costa Reis, Prof. Ciccia Francesco, Prof. Rodolfo Gomez Vaamonde."

2.5.2 Independent Ethics Advisor

The Independent Ethics Advisor must be consulted on matters concerning identifiability; lawful basis for each of the personal data processing activities in the project, including a lawful basis for secondary use of personal data; lawful basis for personal data processing in clinical trials in line with EDPB Opinion 03/2019; data minimization; open science plans, and AI development and deployment.

The external ethics advisor was appointed by M1 at the Deliverable 9.1.

The Coordinator will ensure that a non-disclosure commitment is executed by the external ethics advisor. 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.

2.6 DATA PROTECTION

At the Art 4.5 CA stablishes the specific responsibilities regarding data protection:

1. Personal Data shall be Processed by the Parties for the purposes of the Project only where it is necessary for implementing, performing, managing and monitoring the Grant Agreement and/or the Consortium Agreement and that such Processing shall take place in accordance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and any relevant national data protection law applicable to said Party ("Data Protection Legislation").
2. Processing of Personal Data for the purposes of the Project shall be compliant with Data Protection Legislation and shall be subject to prior approval by the competent ethics committee or other body, where required by the applicable legislation and/or internal rules of each Party.

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3. All Parties are required to keep appropriate documentary evidence of data generation and handling.
4. Before any processing of personal data takes place, in particular but not limited to transfer or disclosure of Personal Data between the Parties or joint Processing by the Parties(joint Controllership), or Processing on behalf of a Party (Processor and Controller relationship), an appropriate data protection agreement according to GDPR shall be concluded by the Parties involved that will set out the purpose of such Personal Data Processing and define the roles and responsibilities of the Parties involved in accordance with the Data Protection Legislation requirements.
   If the envisaged processing is to be considered as joint control according to the GDPR and one Party requires a valid consent as a legal basis for his processing, the Party who has the direct contact with the data subjects needs to collect and provide such valid consent t even if it is not necessary for the data processing of the providing Party.
5. Upon completion of the Project, Personal Data shall be handled in accordance with the data protection agreement referred to in Section 4.5.4 Further retention and processing of such data shall be subject to the requirements of the Data Protection Legislation as well as subject to the terms of the agreement referred to in Section 4.5.4.

At ENDOTARGET GA is stipulated that a framework for data security and privacy will be constructed through interactions with hospital security specialists and ethics committees.

The code key of the subjects is in the hands of the clinicians and the researcher sees pseudonymous (coded) data. To prevent pseudonymous research data from being accessed by unauthorized persons, the research data will be stored as computer files bearing a secret code, which is not accessible to anyone except the investigators in charge of the work.

The name of the subject and the sample code are not reconciled at any stage of the study. Information enabling pseudonymisation is stored for a limited duration, as requested by local regulatory requirements.

We will ensure that all personal data is processed to not unduly prejudice the rights and freedoms of the data subjects. Each clinical partner will secure necessary approvals for their work from their local ethical committees.

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Figure 2: GDPR

Work package 6 includes, among others, D6.1 Data Management Plan (M6), D6.2 Data security architecture and interim compliance update (M24), D6.5 Data Management Plan Update (M48).

2.6.1 Data and Safety Monotoring Board

At the GA Annex 1, part B, establishes a Data and Safety Monotory Board to ensure access to regulatory expertise necessary to get advice on, and management of, regulatory affairs activities in all concerned jurisdictions.

Description of composition, role and responsibilities of the Data and Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) will be an independent group of experts that will monitor each of the proposed studies.

The members of the DSMB will be chosen to represent each country involved in the proposed trials to take into account potential differences in rules, regulations, and jurisdiction of the countries involved.

Members of the DSMB will serve in an individual capacity and provide their expertise and recommendations.

During the trial, the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trials. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants.

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The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.

Items reviewed by the DSMB include:

1. Interim/cumulative data for evidence of study-related adverse events;

2. Interim/cumulative data for evidence of efficacy according to the pre-established statistical guidelines, if appropriate;

3. Data quality, completeness, and timeliness;

4. Performance of individual centers;

5. Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;

6. Adherence to the protocol;

7. Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,

8. Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

DSMB members must maintain strict confidentiality concerning all privileged study results provided to them. The DSMB should review data only by masked study group (such as X vs. Y rather than experimental vs. control) unless or until the DSMB determines that the group identifiers are necessary for decision making. Whenever masked data are presented to the DSMB, the key to the group coding must be available for immediate unmasking.

Membership of the DSMB

The membership of the DSMB should reflect the disciplines and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety.

A total of 5 DSMB members with the following expertise: Expert(s) in rheumatic disorders and their complications; One biostatistician; and, Two investigators with expertise in current clinical trials conduct and methodology and Ethics.

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3. PROJECT STRUCTURE

3.1 PROJECT METHODOLOGY

Identification of drivers of CI that determines the transition from health to pre-symptomatic and early stages of RDs is a big challenge.

Overcoming this challenge requires a consortium that brings together academia, hospitals, and industry.

We will address this challenge by exploring SE in population level together with microbiome data and genome-wide association (GWAS) studies.

We will develop robust and validated tools and analytical methods to translate the obtained data from system-wide technologies into mechanistic insights and PoC studies. We will also develop a customised organ-on-chip model to mimic and replicate the in-vivo disease environment that would be validated during the project.

We will employ robust methods and model systems to study the ability of different LPS to activate TLR4-signaling.

To this extent, a software tool (RDPT) will be developed for predicting risk of developing RDs and for patient stratification.

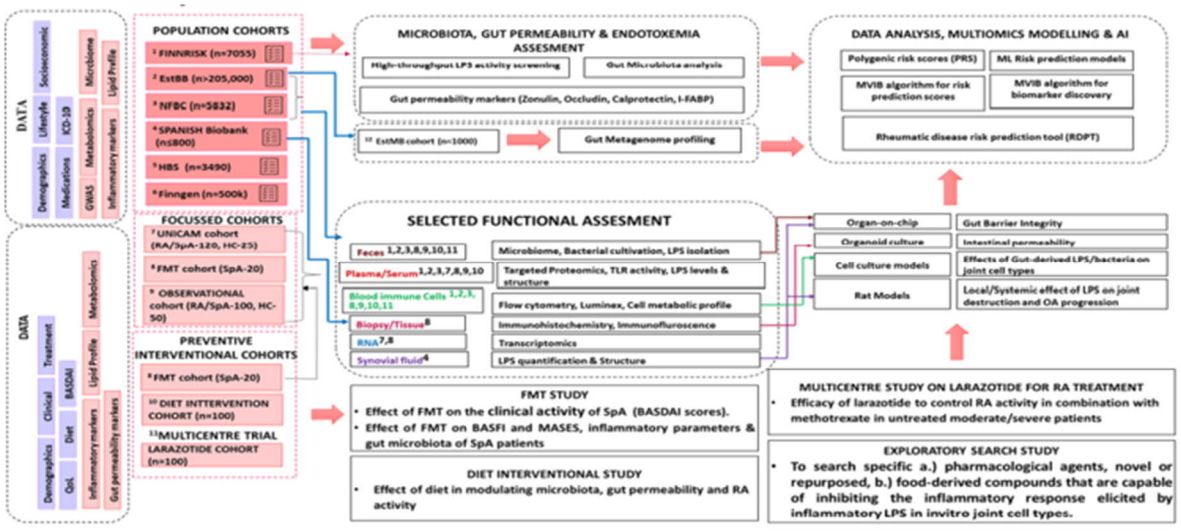

Figure 3. Project methodology

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3.2 STRUCTURE OF THE WORK PLAN. WORK PACKAGES AND TASKS.

ENDOTARGET project has 9 work packages:

- WP1 & WP2 will collect and analyse data and verify the link between SE and RDs in population cohorts.
- WP3 will utilize LPS isolated from microbial cultures and study their effects in in vitro cell and animal models. Derived parameters, biomarkers, and pathways will be validated through WP5 by utilising ML and AI analysis.
- WP4 will study new dietary and drug interventions like Larazotide in modulating the microbiota, intestinal permeability and RDs disease activity.
- WP5 will integrate biomarker signatures and risk scores using multimodal AI to predict disease outcome and cluster/stratify patients based on risk: RDPT-Rheumatic Disease Prediction Tool.
- WP6 will carefully handle the ethical considerations for personal, clinical and AI data. All clinical partners will make an inventory of current clinical practises across Member States, to translate WP1-5 results into suitable candidate for RD prevention and management guidelines.
- WP7 and WP8 are responsible for dissemination & exploitation and management of the project respectively. WP7 is well interconnected to relevant initiatives and stakeholder groups which will be actively engaged in the project to ensure an end-user-oriented approach.
- W9 Ethics requirements.

The following table 3.1 shows the 9 WPs and their corresponding tasks. Details can be found in the GA, Annex 1.

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Table 2.: Work Package List

WP No	Work Package name	WP Lead Beneficiary	Effort: Person/ Months	Start Month	End Month
1	**Population cohort analysis to explore biomarkers & lifestyle factors influencing health to disease transition** Task 1.1 Measurement of parameters of low-grade inflammation & ME. Task 1.2 Measurement of parameters of intestinal permeability. Task 1.3 Targeted proteomic analysis of serum and synovial fluid samples of OA, RA and SpA patients. Task 1.4 Microbiota associated with SE. Task 1.5 Detection of genomic, metabolomic and lifestyle predictive risk factors for SE in healthy and in OA, RA, andSpA patients.	1- HUS	139	1	48
2	**Focused cohorts and in vitro studies addressing gut permeability and SE** Task 2.1 Investigate the influence of SE on circulating and gut-derived immune cells in SpA, RA and healthy controls (HCs). Task 2.2 Investigate the relationship between SE in SpA, RA and HC with the subclinical intestinal inflammation. Task 2.3 Characterization of LPS types and their biological effects on intestinal cells and permeability. Task 2.4 Ability of bacteria and their structures, including LPS-carrying outer membrane vesicles (OMV) and extracellular vesicles (ECV) to induce tolerance or inflammatory responses in epithelial cells. Task 2.5 In vitro proinflammatory capacity of complex bacterial communities, such as fecal microbiota, and possibilities to attenuate it by modulating the composition. Task 2.6 Study of LPS, OMVs and ECV's impact on gut barrier permeability and functionality using organ-on-chip technology. Task 2.7 Characterization of intestinal microbiota dysbiosis in SpA and its correlation with epithelial gene expression and markers of systemic inflammation. Task 2.8 Gut permeability study in RA, SpA, and healthy controls.	3- UNICAM	121	1	48
3	**PoC Studies-Systemic and local mechanism driving intra-articular SE & joint destruction** Task 3.1 Quantification and structural characterization of LPS in serum and synovial fluid of RA and OA patients. Task 3.2 Molecular docking analysis.	5- SERGAS	141	1	48

	Task 3.3 Inflammatory effect of different LPS or bacteria-derived elements on joint tissues - in vitro models. Task 3.4 Effect of LPS or bacteria-derived elements on metabolism of different joint celltypes. Task 3.5 Ability of specific LPS, proinflammatory cytokines or factors to induce tolerance or amplification of inflammatory response. Task 3.6 Effect of different LPS types on promoting autoimmunity. Task 3.7 LPS impact on the onset and progression of joint destruction and its effect on effusion into synovial joint using organ-on-chip technology. Task 3.8 Animal model showing role of LPS on OA progression Task 3.9 Animal model comparison of systemic and local LPS on OA progression				
4	**Novel Strategies to prevent and control arthritis by interfering with the gut-joint axis** Task 4.1 Search for drugs and food-derived compounds to block the innate immune responses elicited by LPS. Task 4.2 Effect of FMT on SpA activity and correlation of SpA activity with microbiota characteristics. Task 4.3 Diet intervention study in RA patients. Task 4.4 Multicentre clinical trial on the efficacy of larazotide in combination with methotrexate in patients with untreated RA.	4- iMM	176	1	48
5	**Data management, multiomics modelling and AI** Task 5.1 Data extraction, standardization and harmonisation. Task 5.2 Quality control of data available in population cohorts. Task 5.3 Multilevel data integration and biomarker discovery. Task 5.4 Risk prediction scores using genomic, metabolomic, life style and other predictive risk factors for ME, OA, RA, and SpA. Task 5.5 Web-portal based feedback on the risk of SE, OA, RA, and SpA for all study participants. Task 5.6 AI multimodal data integration for novel biomarkers extraction and risk prediction. Task 5.7 Interpretable AI models to predict novel intervention strategies. Task 5.8 Development of RDPT-Rheumatic disease prediction tool.	11- SIB	127	1	48

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6	**Ethics, Regulation & GDPR** Task 6.1 Ensuring data privacy. Task 6.2 Secure data sharing. Task 6.3 Delivering an ethical project. Task 6.4 Monitoring and Assessing regulatory compliance. Task 6.5 Data & innovation management.	10- EBRIS	70	1	48
7	**Dissemination, Exploitation and Communication** Task 7.1 Dissemination. Task 7.2 Communication. Task 7.3 Stakeholder engagement. Task 7.4 Exploitation support.	9- SEZ	60	1	48
8	**Project Management** Task 8.1 Co-ordination. Task 8.2 Day-to-day management.	1- HUS	86.5	1	48
9	**Ethics requirements**	1- HUS		1	48

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3.3 PROJECT GANTT CHART

ENDOTARGET Grantt Chart helps us to visually how the project will unfold and it defines the sequence of tasks that require completion.

ENDOTARGET grant chart consists of a list of tasks and bars depicting each task's progress, where the length is proportional to the time necessary for a task's completion. The project tasks are represented on the vertical axis.

Our chart visually shows the project schechule, the tasks and their own timelines/deadlines, and also the relationship between the work packages and how they will be developed in the time.

		Year 1												Year 2												Year 3												Year 4											
WP	Work package	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
WP1	**Population cohort analysis to explore biomarkers & lifestyle factors influencing health to disease transition**																																																
T1.1	Low-grade inflammation & endotoxemia measures																																															
T1.2	Intestinal permeability measures																																															
T1.3	Targetted proteomic analysis																																															
T1.4	Microbiota associated with endotoxemia																																															
T1.5	Predictive risk factors for endotoxemia																																															
WP2	**Focused cohorts and in vitro studies addressing gut permeability and SE**																																															
T2.1	Endotoxemia on circulating gut-derived immune cells																																															
T2.2	Endotoxemia & subclinical intestinal inflammation																																															
T2.3	LPS characterisation & its effects on intestinal permeability																																															
T2.4	Ability of LPS-OMV to induce immune tolerance																																															
T2.5	Invitro modulation of bacterial communities																																															
T2.6	Organ-on-chip gut barrier permeability model																																															
T2.7	Intestinal microbiota dysbiosis in SpA																																															
T2.8	Permeability clinical study in RA & SpA																																															
WP3	**PoC Studies- Systemic and local mechanism driving intra-articular "endotoxemia" and joint destruction**																																															
T3.1	Quantification and structural characterization of LPS																																															
T3.2	Molecular docking analysis																																															
T3.3	Effects of different LPS or bacteria-derived elements on joint tissues (in-vitro)																																															
T3.4	Effects of different LPS or bacteria-derived elements on cell metabolism																																															
T3.5	Ability of LPS to induce immune tolerance or amplification																																															
T3.6	Effect of different LPS types on promoting autoimmunity																																															
T3.7	Organ-in-chip-Synovial joint establishment																																															
T3.8	Animal model comparison of systemic and local LPS on OA progression																																															
T3.9	Animal model showing role of LPS on OA progression																																															
WP4	**Novel Strategies to prevent and control arthritis by interfering with the gut-joint axis**																																															
T4.1	Search for drugs and food-derived compounds to block innate immune response																																															
T4.2	SpA-FMT study																																															
T4.3	Diet intervention study in RA																																															
T4.4	Multicentre study: LARA trial																																															
WP5	**Data management, multiomics modelling and AI**																																															
T5.1	Data extraction, standardization and harmonisation																																															
T5.2	QC of data																																															
T5.3	Multilevel data integration and biomarker discovery																																															
T5.4	PRS for predictive risk factors for endotoxemia, OA, RA, and SpA																																															
T5.5	Web-portal based feedback																																															
T5.6	Multimodal AI for novel biomarkers extraction & risk prediction																																															
T5.7	Interpretable AI models to predict novel intervention strategies																																															
T5.8	Development of RDPT-Rheumatic disease prediction tool																																															
WP6	**Ethics, Regulation & GDPR**																																															
T6.1	Ensuring data privacy																																															
T6.2	Secure data sharing																																															
T6.3	Delivering an ethical project																																															
T6.4	Monitoring and Assessing regulatory compliance																																															
T6.5	Data and innovation management																																															
WP7	**Dissemination & Exploitation**																																															
T7.1	Dissemination																																															
T7.2	Communication																																															
T7.3	Stakeholder engagement																																															
T7.4	Exploitation support																																															
WP8	**Project Management**																																															
T8.1	Coordination																																															
T8.2	Day-to-day management																																															

Table 3. Gantt Chart

3.4 DELIVERABLE LIST *(TABLE 4. DELIVERABLE LIST)*

Public —fully open (⚠ automatically posted online)
Sensitive — limited under the conditions of the Grant Agreement
EU classified —RESTREINT-UE/EU-RESTRICTED, CONFIDENTIEL-UE/EU-CONFIDENTIAL, SECRET-UE/EU-SECRET under Decision 2015/444

Deliverable No	Deliverable Name	WP No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D1.1	Association of gut permeability with SE.	WP1	1 - HUS	R — Document, report	SEN - Sensitive	12
D1.2	List of up-regulated and down-regulated proteins in each pathology or condition studied.	WP1	5 - SERGAS	R — Document, report	SEN - Sensitive	24
D1.3	Report on ME and OA/RA risk	WP1	11 - SIB	R — Document, report	PU - Public	18
D1.4	Identification of factors predisopsing to SE,OA, RA, SpA.	WP1	2 - UTARTU	R — Document, report	SEN - Sensitive	36
D2.1	Report on the link between intestinalinflammation and SE in RA and SpA patients	WP2	3 - UNICAM	R — Document, report	PU - Public	36
D2.2	First report on the effects of various LPS types on intestinal epithelium in vitro	WP2	6 - UH	R — Document, report	PU - Public	30
D2.3	Effects of cells, OMVs and ECVs of different gut bacteria on enterocytes	WP2	6 - UH	R — Document, report	SEN - Sensitive	36
D2.4	In vitro pro/anti-inflammatory potential of microbial consortia with different compositions	WP2	6 - UH	R — Document, report	SEN - Sensitive	48
D2.5	Report on effect of LPS, OMVs and ECVson on-chip based gut barrier integrity	WP2	7 - TU WIEN	R — Document, report	PU - Public	36

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Deliverable No	Deliverable Name	WP No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D2.6	Report on gut permeability in RA and SpA	WP2	4 - iMM	R — Document, report	PU - Public	36
D2.7	Second report on the effects of various LPS types on intestinal epithelium in vitro	WP2	6 - UH	R — Document, report	PU - Public	42
D3.1	Values of free energy to predict the potentialbinding affinity of a given LPS, drug and compound to a target receptor.	WP3	5 - SERGAS	R — Document, report	PU - Public	28
D3.2	Expression changes of genes related to the inflammatory response, anabolism/ catabolism of joint tissues	WP3	5 - SERGAS	R — Document, report	SEN - Sensitive	46
D3.3	Report on mitigating effects of LPS andcyclic mechanical loading on onset and progression of RA using on-chip 3D synovium cultures	WP3	7 - TU WIEN	R — Document, report	SEN - Sensitive	48
D3.4	Demonstrate impact of local and systemic LPS effect on joint destruction in in vivo OAanimal	WP3	12 - ETH Zürich	R — Document, report	PU - Public	36
D3.5	Establishment of causality of LPS in OA progression in vivo OA animal model study	WP3	12 - ETH Zürich	R — Document, report	PU - Public	42
D4.1	List of drugs or functional foods that are ableto decrease the responses of different cell types to pro-inflammatory LPS.	WP4	5 - SERGAS	R — Document, report	SEN - Sensitive	46

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Deliverable No	Deliverable Name	WP No	Lead Beneficiary	Type	Dissemination Level	Due Date(month)
D4.2	Efficacy of microbiota modulation by FMT in the treatment of SpA	WP4	6 - UH	R — Document, report	PU - Public	48
D4.3	Report on the results of a diet intervention in RA patients	WP4	4 - iMM	R — Document, report	SEN - Sensitive	36
D4.4	Report on the efficacy of larazotide in combination with methotrexate to treat RA patients	WP4	4 - iMM	R — Document, report	SEN - Sensitive	48
D4.5	Clinical study: Initiation package	WP4	10 - EBRIS	R — Document, report	SEN - Sensitive	6
D4.6	Clinical study: Mid-term recruitment report	WP4	4 - iMM	R — Document, report	SEN - Sensitive	24
D4.7	Clinical study: Report of posting results	WP4	4 - iMM	R — Document, report	SEN - Sensitive	42
D5.1	Report on harmonisation and standardization of population clinical cohorts and QC of data for analysis and processing	WP5	11 - SIB	R — Document, report	SEN - Sensitive	24
D5.2	New candidate biomarkers for risk prediction of health to disease transition in RA, OA	WP5	2 - UTARTU	R — Document, report	SEN - Sensitive	36
D5.3	AI-based risk prediction model & Interpretability module in RDPT	WP5	8 - NEC	OTHER	PU - Public	42
D5.4	Report on results of feedback and feasibility	WP5	2 - UTARTU	R — Document, report	SEN - Sensitive	48

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Deliverable No	Deliverable Name	WP No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
	of risk prediction tools for prevention and early detection of RA, OA and SpA.					
D5.5	Rheumatic disease risk prediction tool (RDPT)	WP5	11 - SIB	OTHER	SEN - Sensitive	48
D6.1	Data Management Plan	WP6	10 - EBRIS	DMP — Data Management Plan	PU - Public	6
D6.2	Data security architecture and interimcompliance update	WP6	10 - EBRIS	DEC —Websites, patent filings, videos, etc	PU - Public	24
D6.3	Report on ethics	WP6	10 - EBRIS	R — Document, report	PU - Public	36
D6.4	Summary of regulatory compliance	WP6	10 - EBRIS	R — Document, report	PU - Public	48
D6.5	Data Management Plan Update	WP6	10 - EBRIS	DMP — Data Management Plan	PU - Public	48
D6.6	Report on data and innovation management	WP6	1 - HUS	R — Document, report	SEN - Sensitive	40
D7.1	First version of dissemination and communication plan	WP7	9 - SEZ	R — Document, report	PU - Public	6
D7.2	Project website	WP7	9 - SEZ	DEC —Websites, patent filings, videos, etc	PU - Public	4
D7.3	EU innovation ecosystem on CI & health-to-disease transition	WP7	9 - SEZ	R — Document, report	PU - Public	24

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Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D7.4	First exploitation plan and exploitation road map	WP7	9 - SEZ	R — Document, report	SEN - Sensitive	6
D7.5	Second version of dissemination andcommunication plan	WP7	9 - SEZ	R — Document, report	PU - Public	24
D7.6	Third version of dissemination andcommunication plan	WP7	9 - SEZ	R — Document, report	PU - Public	48
D7.7	Second exploitation plan and exploitation road map	WP7	9 - SEZ	R — Document, report	SEN - Sensitive	48
D8.1	Project handbook	WP8	1 - HUS	R — Document, report	PU - Public	3
D8.2	Risk Management plan	WP8	1 - HUS	R — Document, report	PU - Public	12
D9.1	OEI - Requirement No. 1	WP9	1 - HUS	ETHICS	SEN - Sensitive	1
D9.2	OEI - Requirement No. 2	WP9	1 - HUS	ETHICS	SEN - Sensitive	18
D9.3	OEI - Requirement No. 3	WP9	1 - HUS	ETHICS	SEN - Sensitive	36
D9.4	OEI - Requirement No. 4	WP9	1 - HUS	ETHICS	SEN - Sensitive	48

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3.5 MILESTONES *(TABLE 5. MILESTONES)*

Milestone No	Milestone Name	WP No	Lead Beneficiary	Means of Verification	Due Date (month)
1	Clinical cohort studies' protocols tested andready for implementation	WP1	1-HUS	D4.5 & D6.1	6
2	Data from 2-3 key cohorts available for harmonisation and standardization	WP1, WP5	-	D6.1	10
3	Identification of patients with SE and novel biomarkers in OA, RA and SpA patients (WP1 & WP5)	WP1, WP5	1-HUS	D1.1	12
4	Adopt the EC's Ethics Guidelines and appointethics boards	WP6	10-EBRIS	D6.3	12
5	Bacterial origin of LPS is identified	WP1, WP2	1-HUS	D1.1 & D2.2	18
6	Identification of candidate pathogenic LPS types in RA and OA	WP3	5-SERGAS	D3.1, D3.3, D3.5	18
7	Identified metabolic signatures associated to SE in SpA and RA	WP2	3-UNICAM	D2.1	24
8	Mapping of stakeholders in CI and health-to-disease transition	WP7	9-SEZ	D7.3	24
9	Conclusion of the recruitment and intervention phases of the clinical trial on the efficacy of diet in RA	WP4	4-iMM	D4.3	30
10	List of the key molecular mediatiors in the gut contributing to SE	WP2	3-UNICAM	D2.1, D2.3, D2.6	36
11	Identification of novel molecular therapeutic	WP2	3-UNICAM	D2.1 & D4.1	36

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Milestone No	Milestone Name	WP No	Lead Beneficiary	Means of Verification	Due Date (month)
	targets to preserve intestinal barrier and counteract SE in arthritis				
12	Rapid prototyping of organ-on-a-chip systems accomplished	WP3	5-SERGAS	D3.3	36
13	Risk models available for development of prediction tool software	WP5	-	D5.3	36
14	Completion of recruitment and intervention phase of multicentre clinical trial on the effectof larazotide in RA	WP4	4-iMM	D4.4	42
15	Roadmap for exploitation of project results	WP7	9-SEZ	D7.4	42
16	Consensus submitted for recommendations of RDPT	WP1	1-HUS	D5.4, D5.5, D1.3, D1.4	48
17	Summary of data and RDPT report	WP5	-	D5.5 & D8.3	48

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4. PROJECT MANAGEMENT

4.1 MANAGEMENT STRUCTURE: ROLES AND RESPONSABILITY

4.1.1 Organisational structure

ENDOTARGET organisational structure is as follows:

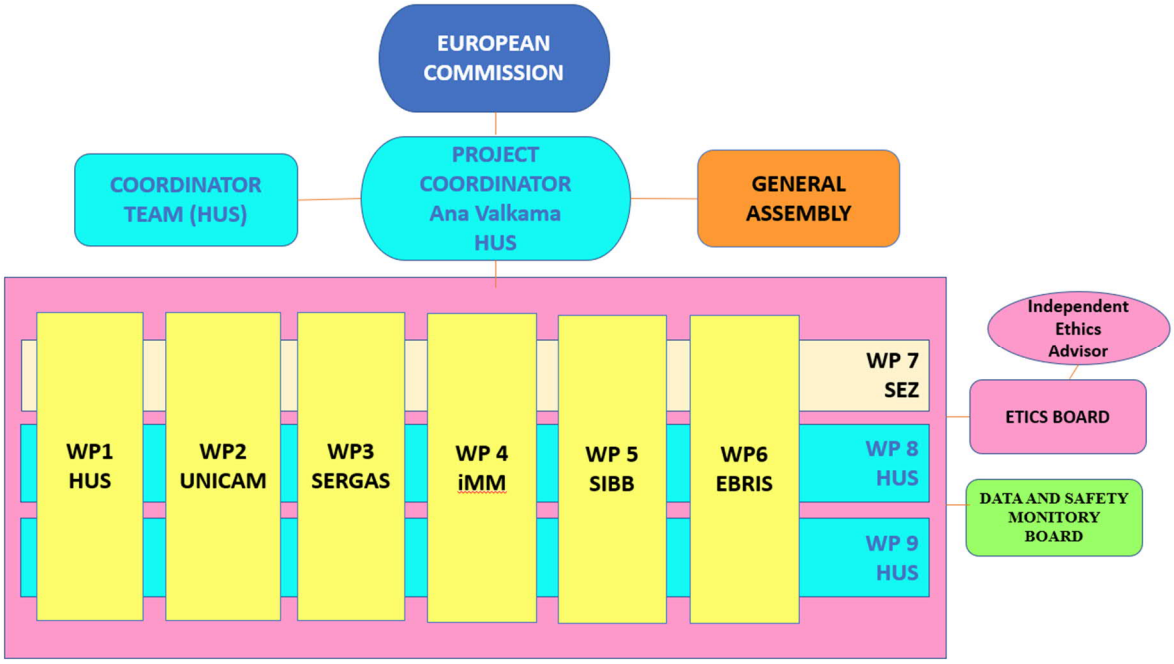

Figure 4. Organisational structure

The Art. 6 at the CA says that the organisational structure of the consortium shall comprise the following Consortium Bodies:

- The **General Assembly** is the decision-making body of the consortium. The General Assembly shall consist of one representative of each Party (hereinafter referred to as "Member").
- The **Coordinator** is the legal entity acting as the intermediary between the Parties and the Granting Authority. The Coordinator shall, in addition to its responsibilities as a Party, perform the tasks assigned to it as described in the Grant Agreement and this Consortium Agreement.
- The **Ethics Board** is a consultative body to review and assess the research activities carried out under Project to ensure compliance with ethical principles.

4.1.2 Management structure

Management body	Responsible person
Project Leader	Kari Eklund (HUS)
Project Coordinator	Ana Valkama (HUS)
General Assembly	One representative of each Party
HUS Coordinator Team	Kari Eklund (HUS) Ana Valkama (HUS) Gonçalo Barreto (HUS) Katariina Nurmi (HUS) Jukka Parantainen (HUS)
Work Package Leaders	WP1: Kari Eklund (HUS) WP2: Francesco Ciccia (UNICAM) WP3: Rodolfo Gomez Bahamonde (SERGAS) WP4: Patrícia Costa Reis (iMM) WP5: Mark Ibberson / Vassilios Ioannidis (SIB) WP6: Alessio Fasano (EBRIS) WP7: Lena Schleicher (SEZ) WP8: Ana Valkama (HUS) WP9: Kari Eklund (HUS)

Table 6. Management structure

ENDOTARGET Project Leader is the Prof. Kari Eklund from HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRIN KUNTAYHTYMÄ (HUS).

The Project Coordinator appointed by HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRIN KUNTAYHTYMÄ (HUS) is Ana Valkama.

The General Assembly consists of one representative of each Party and is the decision-making body of the Consortium.

HUS Coordinator Team is a multidisciplinary team for discussing the project process and controlling the risks during the 4 years.

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Work Package Leaders are the responsible of each WP and they manage the work, the eficience of team and the tasks done into the their WP to ensure the progress of the work package with respect the overall work plan.

4.1.3 General Assembly

The **General Assembly is the decision-making body** of the consortium and is is enshrined in the CA art 6.

The General Assembly consists of one representative of each Party (hereinafter referred to as "Member").

Each Member shall be deemed to be duly authorised to deliberate, negotiate and decide on all matters listed in Section 6.3.7 of this Consortium Agreement.

The Coordinator shall chair all meetings of the General Assembly, unless decided otherwise by the General Assembly.

The Parties agree to abide by all decisions of the General Assembly.

As resume, the CA says:

Representation in meetings:

Any Member: - 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.

Preparation and organisation of meetings:

- Convening meetings:

The chairperson shall convene ordinary meetings of the General Assembly at least once every six months and shall also convene extraordinary meetings at any time upon written request of any Member.

- Notice of a meeting

The chairperson shall give written notice of a meeting to each Member as soon as possible and no later than 14 calendar days preceding an ordinary meeting and 7 calendar days preceding an extraordinary meeting.

- Sending the agenda:

The chairperson shall prepare and send each Member an agenda no later than 14 calendar days preceding the meeting, or 7 calendar days before an extraordinary meeting.

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- Adding agenda items:

Any agenda item requiring a decision by the Members must be identified as such on the agenda.

Any Member may add an item to the original agenda by written notice to all of the other Members no later than 7 calendar days preceding the meeting and 2 days preceding an extraordinary meeting.

- During a meeting of the General Assembly the Members present or represented can unanimously agree to add a new item to the original agenda.
- Meetings of the General Assembly may also be held by tele- or videoconference or other telecommunication means.

DECISION MAKING AT THE GENERAL ASSEMBLY

Decisions without a meeting:

Any decision may also be taken without a meeting if
a) the Coordinator circulates to all Members of the General Assembly a suggested decision with a deadline for responses of at least 10 calendar days after receipt by a Party and

b) the decision is agreed by 51 % of all Parties.

The Coordinator shall inform all the Members of the outcome of the vote.

A veto according to Section 6.3.5 may be submitted up to 15 calendar days after receipt of this information.

The decision will be binding after the Coordinator sends a notification to all Members. The Coordinator will keep records of the votes and make them available to the Parties on request.

Voting rules and quorum

- The General Assembly shall not deliberate and decide validly in meetings unless two-thirds (2/3) of its Members are present or represented (quorum).
- Decisions shall be taken by a majority of two-thirds (2/3) of the votes cast.

Decisions of the General Assembly

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 herein.

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The following decisions shall be taken by the General Assembly:

- Content, finances and intellectual property rights
- Evolution of the consortium
- Breach, defaulting party status and litigation

4.1.4 HUS as the Coordinator. Coordinator Team and Project Coordinator

HUS, as the Coordinator, will manage the project between the Consortium and the European Commission. (CA, art. 6.4)

ENDOTARGET Project Leader is Prof. Kari Eklund from HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRIN KUNTAYHTYMÄ (HUS).

The Coordinator (HUS) is the legal entity acting as the intermediary between the Partners and the European Commission.

HUS shall chair all meetings of the General Assembly, unless decided otherwise by the General Assembly.

The financial contribution of the European Commission to the Project shall be distributed by HUS.

Payments to Beneficiaries are the exclusive task of HUS.

HUS shall not be entitled to act or to make legally binging declarations on behalf of any other Party or of the Consortium.

Any change of persons or contact details shall be immediately communicated to HUS by written notice.

Figure 5. HUS as the coordinator

Manage the project between the Consortium and the European Commission means:

- Managing that the action/project is implemented properly, including the technical coordination;
- Acting as the intermediary for all communications between the beneficiaries and the EC;

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- Requesting and reviewing any documents or information required by EC and verifying their completeness and correctness before passing them on to EC;
- Submitting the deliverables and reports;
- Ensuring that all payments are made to the other beneficiaries without unjustified delay;
- Informing the EC of the amounts paid to each beneficiary, when required under the Grant Agreement or requested by the EC.
- HUS is also responsible that all legal arrangements within the project consortium and between individual partners are in place.
- The partners are responsible for sending their deliverables in time to the coordinator, deliver financial reports to the EC and to attend consortium meetings and decision making.

And also, as the Coordinator, HUS will manage the project inside the Consortium. That means that HUS will take care of the day-to-day management, that include for example:

• Ensuring compliance with project planning and appropriate quality of activities.

• Effective coordination, communication, reporting inside the consortium.

• Risk management, i.e., preparing risk management plan (with regular updates) and managing the risks under the whole project duration.

• Organizing consortium meetings (General Assembly and technical committee meetings) as well as other meetings if found necessary.

• Preparation and incorporation of periodic reports for Coordinator to check, accept and submit.

Coordinator Team and Project Coordinator

For an efficient developing of the coordination tasks during the project cycle, HUS as the coordinator has a Project Coordinator and a Coordinator Team.

The Project Coordinator appointed by HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRIN KUNTAYHTYMÄ (HUS) is Ana Valkama. The Project Coordinator is the responsible of managing the project from the beginning to the end.

ENDOTARGET project involves 14 partners with multidisciplinary members and teams. Scientific lab investigations, clinic trials, artificial intelligence methods, ethics, data

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architect and security, and so on, and all of them, working together, will generate for sure incredible synergies and results.

Due to this multidisciplinary aspect of ENDOTARGET, the Project Coordinator propossed the creation of a multidisciplinary Coordinator Team for discussing the project process and controlling the risks during the 4 years.

The HUS Coordinator Team is ready working and it is a multidisciplinary team which consists in a clinical expert (Kari Eklund), a scientific expert (Gonçalo Barreto), and a coordinator manager (Ana Valkama). Also Katariina Nurmi and Jukka Parantainen will participate at the meetings when their schedules allow it.

The team will meet every 2 weeks and their duties will be evaluate the project real progress in all its disciplines. They will analyse and solve possible conflicts between disciplines, observe and analize problems or bottlenecks that may occur in one and/or several areas and how those could affect to other wp progress, among other tasks as review deliverables, participate in other meetings when are required, and so on.

Partners can also request (or be requested by the coordinator) to attend this meeting if they need support, need to agree on an exceptional occurrence, among other reasons.

Extraordinary meetings may be convened.

4.1.5 ENDOTARGET Parners

GA Art. 6 says: Each beneficiary must:

(i) keep information stored in the Portal Participant Register up to date (see Article 19)

(ii) inform the granting authority (and the other beneficiaries) immediately of any events or circumstances likely to affect significantly or delay the implementation of the action (see Article 19)

(iii) submit to the coordinator in good time:

- the prefinancing guarantees (if required; see Article 23)

- the financial statements and certificates on the financial statements (CFS) (if required; see Articles 21 and 24.2 and Data Sheet, Point 4.3)

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- the contribution to the deliverables and technical reports (see Article 21)

- any other documents or information required by the granting authority under the Agreement

(iv) submit via the Portal data and information related to the participation of their affiliated entities.

Also, the CA says:

Each Party undertakes to take part in the efficient implementation of the Project, and to cooperate, perform and fulfil, promptly and on time, all of its obligations under the Grant Agreement and this Consortium Agreement as may be reasonably required from it and in a manner of good faith as prescribed by Belgian law.

The partners are responsible for sending their deliverables in time to the coordinator, deliver financial reports to the EC and to attend consortium meetings and decision making.

4.1.6 WP Leaders

Each Work Package has a Leader, who is going to manage the team and the tasks into the WP to ensure the progress of the work package with respect the overall work plan.

Work Project Leaders are:

WP	WP Leader	Email contact
1	Kari Eklund (HUS)	kari.eklund@hus.fi
2	Francesco Ciccia (UNICAM)	francesco.ciccia@unicampania.it
3	Rodolfo Gomez Bahamonde (SERGAS)	Rodolfo.Gomez.Bahamonde@idisantiago.es
4	Patrícia Costa Reis (iMM)	pcr.patricia@gmail.com
5	Mark Ibberson (SIB) Vassilios Ioannidis (SIB)	Mark.Ibberson@sib.swiss Vassilios.Ioannidis@sib.swiss
6	Alessio Fasano (EBRIS)	afasano@mgh.harvard.edu
7	Lena Schleicher (SEZ)	lena.schleicher@steinbeis-europa.de
8	Ana Valkama (HUS)	ana.valkama@hus.fi
9	Kari Eklund (HUS)	kari.eklund@hus.fi

Table 7. WPL list

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The WP Leader will lead and coordinate its own Work Package and responds to the Project Coordinator.

The WP Leader is responsible:

- To coordinate the activities in the work package and its tasks.
- The performance and progress of the WP with regard to the planned milestones.
- Reporting the WP progress at project meetings and when it is required by the coordinator.
- Monitoring the time, budget and the quality control.
- The transfer of information to the coordinator or other WPL.
- Informing the project coordinator of any potential problem, bottleneck or desviation to the work plan.
- Notify of changes in the work team's personnel as well as changes in contact information.
- Work together with the Task Team to organize the Team, control de eficicience of the work, determine the adecuate number of Task meetings, and so on.
- WP Leaders will manage their own Teams section at the ENDOTARGET team at Microsoft Teams:
    - WP Internal documents
    - WP meetings
    - WP deliverables
    - WP status (open to others WP leades): Excel file for the task status: TO DO, IN PROGRESS, IN REVIEW, DONE.
    - Others.

4.1.7 ENDOTARGET Meetings

GENERAL MEETINGS:

- Annual Project meeting. General Assembly.
- Biannual Consortium meetings.
- Biannual WP meeting.
- Ethics Board meetings. These meetings will be convene in coincidence with the General Assembly or/and the Biannual Consortium meetings.

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OTHER MEETINGS: Organization and management meetings

- COORDINATOR TEAM MEETING: Coordinator team meetings will be proposed every 2 weeks, on Wednesday. Partners can also request (or be requested by the coordinator) to attend this meeting if they need support, need to agree on an exceptional occurrence, among other reasons.

- TUESDAYS, PM MEETINGS: Tuesdays will be the meeting day with the Projec Coordinator. Any partner or participant who needs a meeting with the Project Coordinator, can request to meet with her virtualy on Tuesdays. These meetings and sessions, in addition to labor and organizational issues, include coaching, problem solving, management needs, conflict resolution, as well as other issues that all project participants may need.
  To convene one of these meetings, a simple request email to the project coordinator will be enough.

- WPs MEETINGS: Except for WP 7, 8 and 9, and the meetings mentioned in the General meetings (biannual WP meeting), the WP leaders will coordinate and hold internal WP meetings to ensure the wp progresses and the Tasks are organized.
  - WP Leaders will convene a remote monthly meeting with the PIs/Managers/Directors involved in their WP to define the work strategies and monitor the WP progress. (Minimum 12 per year)
  - WP Leaders will convene every three months a remote scientific meeting for the WP team, in order to share with them (and receive feedback) about the WP progress. (Minimum 4 per year)
  - Task meetings: In each WP, the Task leaders will organize their tasks and also determine the necessary task meetings. The meeting´s periodicity depends on the task´s development.
  - In case it is needed, any PI/Manager/Director may request their WP Leader to call an extraordinary meeting.
  - The Project Coordinator has the right to request and participate in the WP meetings and the Task meetings, especially whenever a request is made by one of the participants.

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4.2 DOCUMENT MANAGEMENT

All partners are already connected by Microsoft Teams as the main IT tool. Of course emails and remote calls will also be produced during our daily work.

ENDOTARGET Team channel has several Sections and it is a efficient tool to share documentation, information, knowledge and being in contact with all the team.

The ENDOTARGET Team sections will minimum have a chat for discussions and a files folder.

The Sections and channels can change as is needed.

Currently, at M3, the ENDOTARGET TEAM contains:

- General
- Communication Material (logo, material, templates, FAQs, …)
- Communication, Dissemination and Exploitation WP7
- Contact List: General list, WP leaders list, WP member list.
- Documents: Contractual documents, containing for example the Consortium Agreement and the Grant Agreement and its annexes.
- Finances
- Guidelines: Access to the generic guidelines provided by the EC for H2020 projects
- HUS Project Coordinator team: private.
- Meetings and events.
- Project Management WP8
- Private channels for each WP:
    - WP1 HUS,
    - WP2 UNICAM,
    - WP3 SERGAS,
    - WP4iMM,
    - WP5 SIB,
    - WP6 EBRIS,
    - WP9 HUS.

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4.3 INFORMATION MANAGEMENT AND FLOW INFORMATION CHART

The establishment and maintenance of an efficient and clear management information system during the whole project is one of the keys for project success.

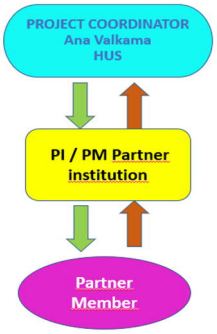
It is important because will improve our decision-making (having accurate and timely information, means make better decissions about operations, strategies and investments), increase our efficiency (streamline workflows and improve operational efficiency, reducing costs and improving productivity), enhance our collaboration (helps to break down silos and improve communication) and provide a better risk management (helps to identify and mitigate risks, compilance issues, or operational challentes).

ENDOTARGET General information and documentation will be shared on the Microsoft Team Endotarget channel, and all the WP have their own private channel.

Other types of information's communication (for example deliverables or other particular issues, ..) will flow as follows:

Related to Work Packages: Work package participants report to WP Leaders, and WP Leader reports to the project Coordinator, and vice versa.

Figure 6. WP Information flow chart



Related with other types of issue, the Partner Member reports to his/her PI /PM, and the PI/PM of the partner institution reports to the Project Coordinator, and vice versa.

All participants can contact the Project Coordinator if needed.

Figure 7: Other information flow chart

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4.4 DISSEMINATION AND COMMUNICATION PRACTICES

Dissemination and communication (DC) activities are crucial for the success of the ENDOTARGET project. These activities aim (i) to raise awareness, (ii) to ensure project visibility, (iii) to engage with key stakeholders, (iv) to maximize the project's impact and (v) to influence decision makers. Thus, the activities result in the publication of ENDOTARGET results/progress or in promoting/informing stakeholders about the project (publication of scientific papers, press releases, blog entries and social media posts; participation in academic conferences and external fairs & workshops; hosting of roundtables & workshops, exchanges with policy makers and webinars; collaborative activities with other projects; etc.).

DC activities are integrated into WP7 "Dissemination, Exploitation and Communication" of the ENDOTARGET project. SEZ as WP leader is responsible for the development of the DC strategy, methodologies and activities. Nevertheless, these activities are strongly related to all work packages, as they promote the project activities, results and developments and set the grounds for their further exploitation and market deployment. Thus, the input and involvement of all consortium partners, especially in the implementation and reporting of the activities, are crucial.

Therefore, SEZ set up a DC team, which consists of at least one person of each consortium partner and they meet. The DC team acts as the main contact point between SEZ and the other consortium members and is thus a tool for communication and conveying information to execute the actions. The DC Team meet monthly, every first Monday, in a virtual meeting to discuss ongoing, planned and reported DC activities. Furthermore, these meetings are an opportunity for the consortium partners to discuss DC practice and ask SEZ and HUS for advice.

For external communication SEZ will provide a tool kit of different materials for the partners. Next to the ENDOTARGET logo and visual identity, several templates (reporting template, scientific poster template, presentation template) will be designed for a uniform presentation of ENDOTARGET and to ensure a high recognition value. Furthermore, several promotion materials will be created (infographic, flyer, non-scientific poster) for the partners activities. The partners are responsible to use these materials for their DC activities.

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When a DC activity was implemented, the responsible partner must report this activity directly after implementation. In order to monitor and ensure DC activity implementation and to simplify the reporting to the European Commission, an easy monitoring process has been put in place: SEZ regularly checks the progress through a general DC reporting template and a dedicated publications template. The templates are available on the project's online repository (MS TEAMS). SEZ will send a monthly reminder (via E-mail) to be sure that the whole consortium is accordingly reporting all their DC activities and actions.

In general, the ENDOTARGET MS TEAMS (coordinated by HUS) is an important tool for the consortium partners to share data, knowledge and advice. For the DC activities, the two channels "Communication Material" and "Communication, Dissemination & Exploitation WP7" are important. The first channel includes DC materials for especially external communication: DC templates, DC promotion materials, ENDOTARGET logo files, EU finding logo files, partner logo files and information about disclaimer and funding acknowledgments. Furthermore, a document was created with FAQs from the consortium partners. This file aims to answer these FAQs in an easy and quick applicable manner. The second channel includes working documents, reporting material and project results: deliverables (working documents), reporting files (for general DC activities and publications), publications, blog entries, press releases, information about WP7 meetings (agenda, presentation, minutes) and a file for the planning of DC activities.
In the first six month of the ENDOTARGET project a dedicated DC strategy will be developed by SEZ together with the DC Team, which will be published in the deliverable D7.1. This strategy will be regularly updated according to the project development and demands.

4.5 DELIVERABLES: REVIEW AND SUBMISSION

All the deliverables must be finalized and submitted respecting the deadlines defined at the GA, Annex 1, Part A.

The lead beneficiaries in charge of the deliverables, are responsible for the technical quality of the deliverable and its content.

In order to ensure a procedure that ensures the quality and robustness of the ENDOTARGET deliverables, the following review procedure is established:

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4.5.1 Deliverable review

The deliverable must be sent to the Project Coordinator 14 calendar days before the deadline.

Once received, it will be proposed for examination by the Project Coordinator and the Coordinator Team, with 7 days for its review.

The Project Coordinator has the final say concerning the deliverable.

CASE A: If the document is approved for delivery, the PC will contact the partner responsible to notify the acceptance, and the deliverable will be delivered to the EC within 3 days.

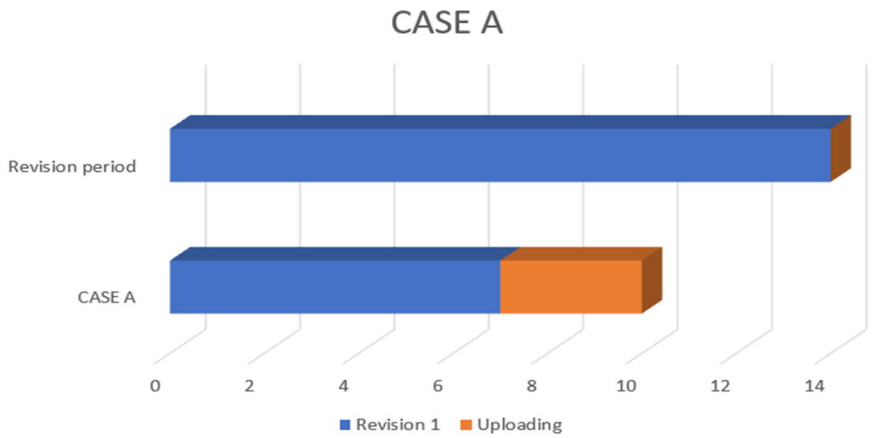

Figure 8. Deliverable review CASE A

CASE B:

In case the deliverable is not accepted and needs to be corrected and/or does not meet the stipulated quality, format, and requirement standards, it will be returned to the partner responsible, who will have a period of 4 days to correct it based on the comments / suggestions given from the reviewers. The new corrected version must be sent to the Project Coordinator within the mentioned 4-day period.

In the second review, which will last for 2 days, the deliverable will be reviewed again, and it will be verified if the improvements/corrections suggested have been made.

The Project Coordinator has the final say concerning the deliverable.

If this second version is accepted, the deliverable will be immediately delivered to the EC.

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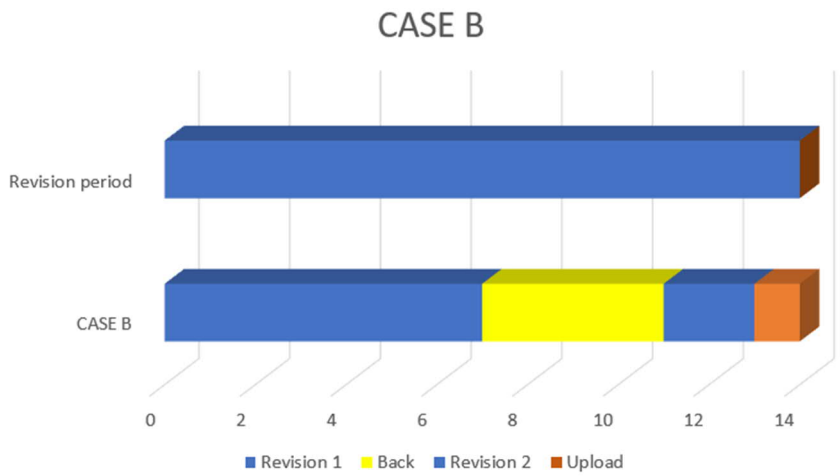

Figure 9. Deliverable review CASE B

4.5.2 Deliverable delay

Figure 10. Deliverable delay

In case of delay of a deliverable, the WP leader should be notified as soon as possible. If the cause of the delay cannot be resolved by the WP leader, the Project Coordinator should be contacted immediately to discuss the case.

In certain cases, it is possible to consider acceptable delays of 1-2 months, following a notification via Communication Center from the Coordinator to the EC Project Officer where the reason behind that delay must be provided. For bigger delays, the coordinator needs to reach out the Project Officer to discuss through a meeting (case by case) the scenario at "project implementation" level.

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5. PROJECT REPORTING

Each partner is responsible for delivering required reporting materials after reporting periods. The Coordinator must submit a periodic report **within 60 days** following the end of each reporting period. The Coordinator will provide a deadline, reporting forms and guidance before a reporting period ends. This deadline is max. **40 days after the period end** to allow time for review and modifications as needed.

The reports are to be done in English. Project Periodic Reports (3) are scheduled as:
• RP1: from month 1 to month 18 (01/2023 – 06/2024)
• RP2: from month 19 to month 36 (07/2024 – 12/2025)
• RP3: from month 37 to month 48 (01/2026 – 12/2026)

5.1 PERIODIC REPORTING AND FINAL REPORTING

The **periodic report** must include a periodic technical report and a periodic financial report.

The Technical Report is itself also divided in two parts, Parts A and B:

- Part A: contains the structured tables with project information (retrieved from the Grant Management System).

- Part B (the narrative part): mirrors the application form and requires the participants to report on differences (delays, work not implemented, new subcontracts, budget overruns etc.) It must be uploaded as PDF document.

The Financial Report contains an individual financial statement from everyone for the reporting period. It also contains an explanation of the use of resources and a periodic financial statement.

The technical report Part A and the financial report is generated automatically on the basis of the data in the Grant Management System; Part B needs to be prepared outside the tools (using the template downloaded from the system) and then uploaded as PDF (together with Annexes, if any).

All participants should contribute to the parts, but it is the Coordinator who will have to submit them as a single report.

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The final report is due within 60 days of the last reporting period. **The final technical report** is a summary containing:

- Overview of the results, exploitation and dissemination
- Conclusions
- Socio-economic impact

The final financial report is:

- Final summary financial statement generated automatically from the periodic reports
- Certificate on the financial statements (CFS) drawn up in accordance with CFS template provided by EC for all partners that requests EU contribution to costs ≥ EUR 430 000.00. Template available at EC website under Reference Documents

Financial training for partners by the Coordinator will be organized. The presentation slides are recorded in ENDOTARGET Teams financial folder.

5.2 FINANCIAL REPORTING (EC REPORTING)

This section covers only EC financial reporting. For national funding reporting guidelines, please contact your National Coordinator or national funding authority.

Personnel costs

Time worked for the action must be supported by declarations signed monthly by the person working and their supervisor. Declaration template is available at EC website under Reference Documents. Time recording can alternatively be some other reliable time recording system, in which the time records are also signed monthly.

For the personnel cost calculation you will need to run for each person the number of days worked for the project during the reporting period. This will then be multiplied by the daily rate for each person. The daily rates are calculated based on the **actual personnel cost during the months within the reporting period**, including salary, social security contributions, taxes and other costs and payments linked to the remuneration, if they arise from national law or the employment contract (or equivalent appointing act) (please contact your financial department, they should have the details) which is divided by **maximum declarable day equivalents.**

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Other goods, works and services:

Date of invoice	WP	Reference number of accounting document	Date of payment	Supplier	Item description	Detailed cost item explanation/ category	Invoiced amount in national currency (excl. VAT)	Exchange rate	Invoiced amount in €

It is important to record the WP numbers, and the number of the invoice in your accounting system. In case of audit the auditors need to be able to trace the receipts in your accounting back to the actions being done in the project, and the reason why the purchase was necessary.

Travel and subsistence:

For all travel, please keep track of the following:

- Name(s) of person(s) traveling
- WP
- Reference number of accounting document
- Date in accounting documents
- Date of first day of travel
- Purpose of the travel (refer to list of project meetings)
- Location (from/to)
- Cost type (e.g. taxi, hotel, tickets, daily allowances)
- Amount in national currency including VAT
- Amount in national currency excluding VAT
- Exchange rate
- Eligible cost in €, excl. VAT

Also remember to store all meeting agendas and meeting minutes, to be able to prove that the travel was necessary for the project.

Equipment

Similar records as for purchases should be kept also for all Equipment cost items.

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Note that you can declare depreciations made in your accounting for any equipment purchased or needed in the project. This depreciation must be multiplied with the percentage of usage of this equipment in the project.

The project duration has also to be accounted for. This means that you can claim only the full amount of depreciation if the equipment is used solely in this project and is not used in other projects. The percentage of usage must be given in the explanation of the equipment cost item, e.g. "50 % usage in the project". The costs of renting or leasing equipment are also eligible if they do not exceed the depreciation costs of similar equipment and do not include any financing fees.

Subcontracting

Similar records as for purchases should be kept also for all Subcontracting cost items. Note that you will usually need to ask for offers or do a tendering process for all subcontracts to prove that they are best value for money. For smaller sums, it is enough to ask for tenders from three suppliers by email and keep the records of those.

VATs

Rule of thumb: VATs are not eligible costs and cannot be claimed. VATs are eligible only in the case that they cannot be deducted even theoretically (e.g. VAT from an Asian country).

Indirect costs

Indirect costs are claimed on a flat-rate (25 %) basis on top of eligible direct costs, except volunteers' costs, subcontracting costs, financial support to third parties and exempted specific cost categories, if any.

5.2.1 Filling in financial reporting forms

Financial reporting forms

Once you have accrued all the costs by the category they fall under, they can be reported. The financial reporting will be done in the EC Funding & Tenders portal.

All costs except Indirect costs are filled in as € totals in the Financial statement home screen pictures below:

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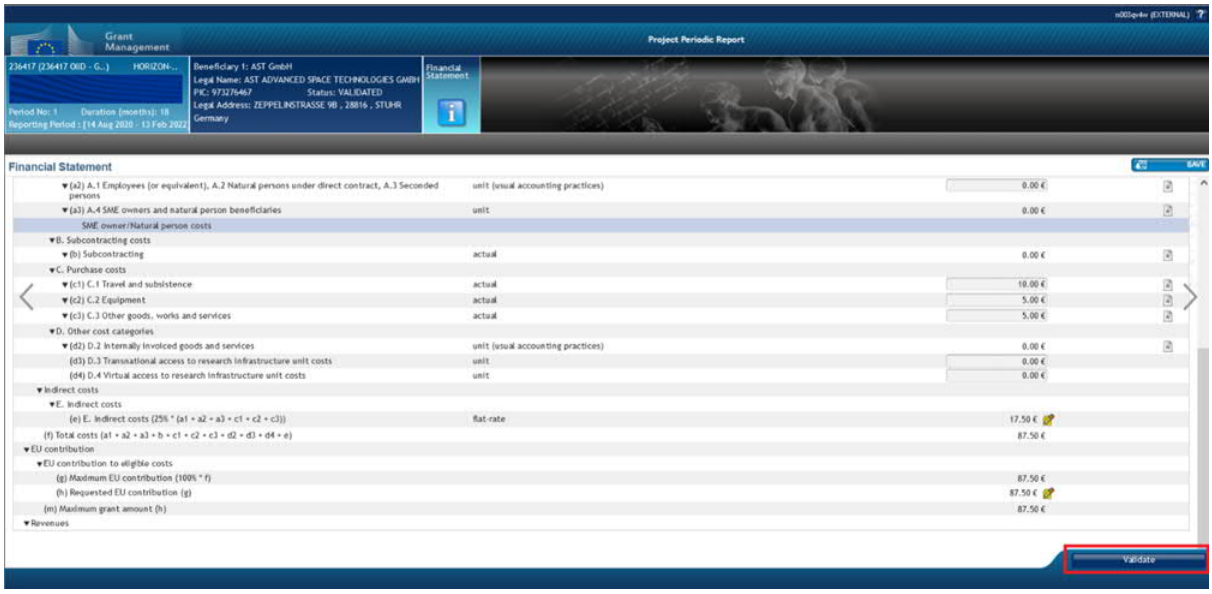

Figure 11. Financial reporting picture 1

Clicking "Actions" takes you to a screen where you need to fill in **more detail for each cost item**, e.g. person months per WP for personnel costs:

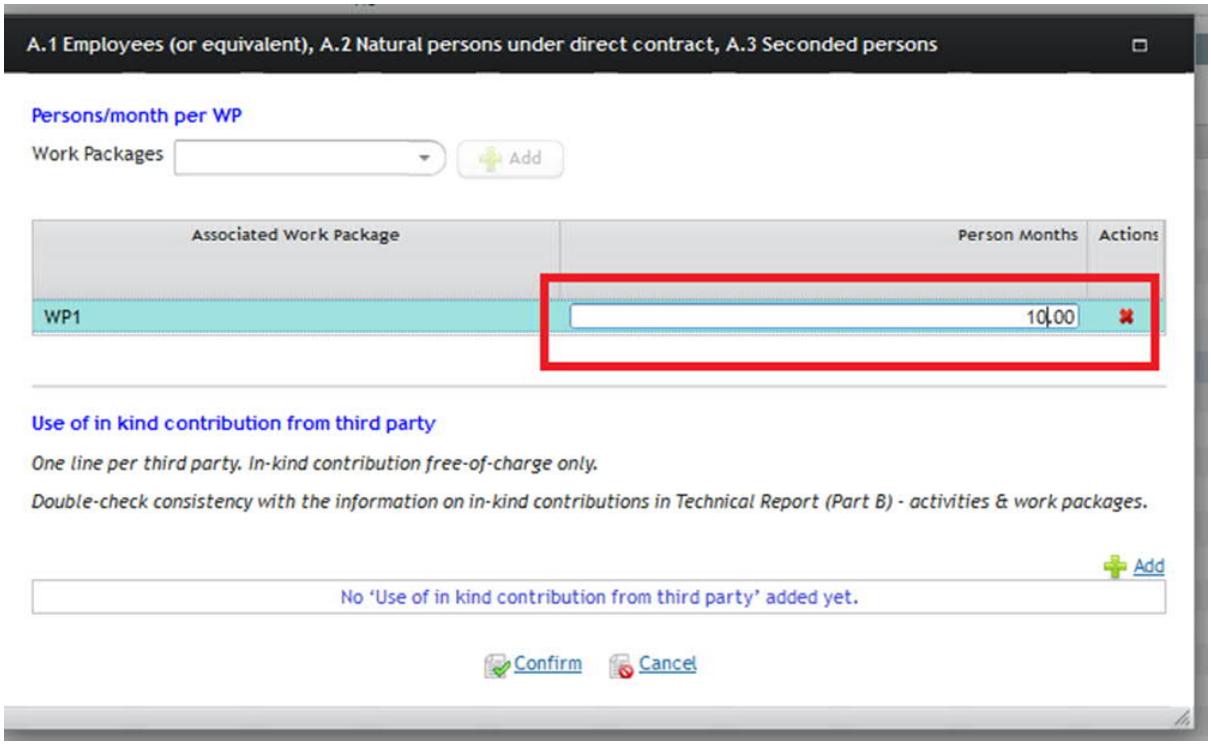

Figure 12. Financial reporting picture 2

If your **purchase costs are higher than 15 % of the claimed personnel costs**, you need to provide explanations of the largest items until the you reach the threshold given by the system them. Best practice is to use the same descriptions that you have in Annex I so that the costs are comparable and divide them by WP:

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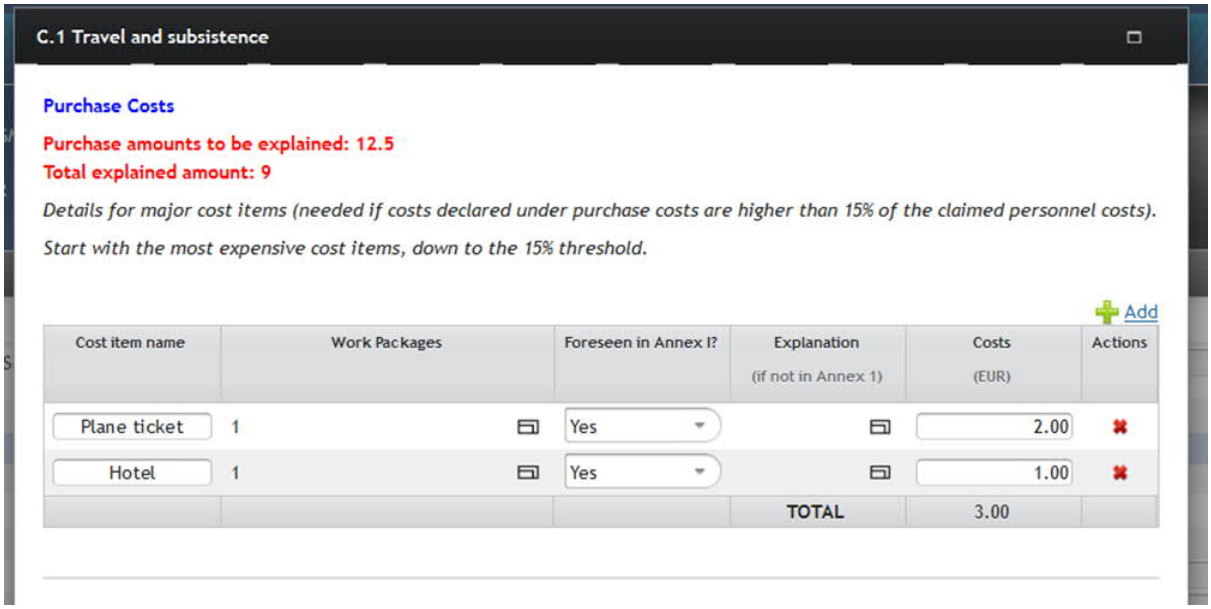

Figure 13. Financial reporting picture 3

To report **subcontracting** click the Actions button and a screen will open. You do not need to explain best value for money here but keep records of how best value was ensured when the subcontractor was chosen:

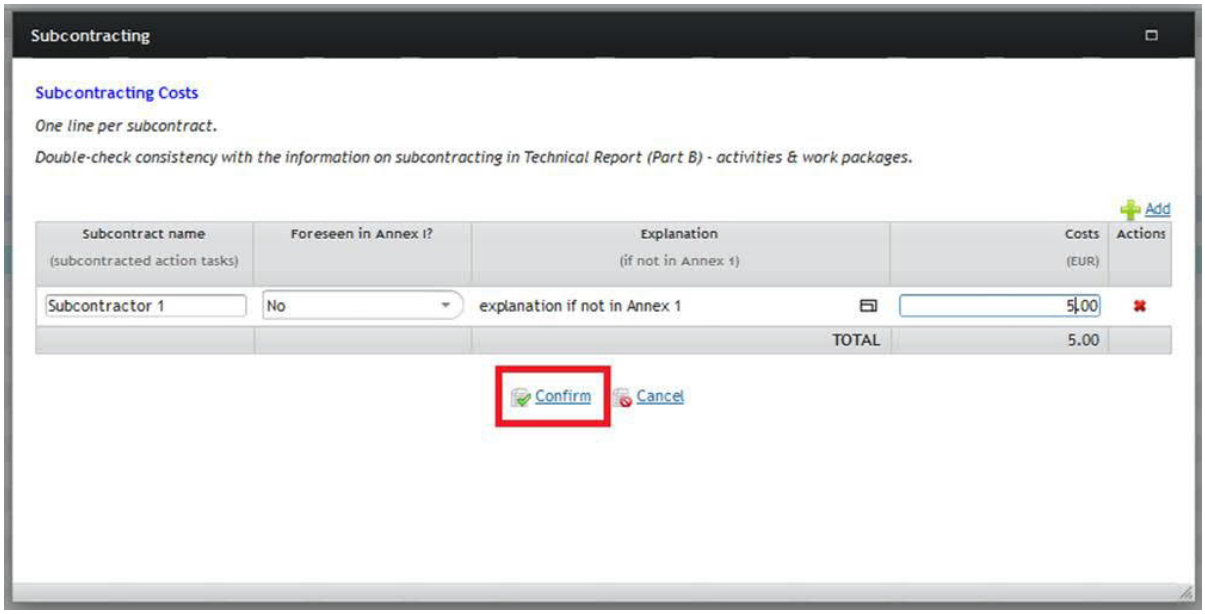

Figure 14. Financial reporting picture 4

Budget transfers

Budget may be adjusted without amendment between cost categories within partners own budget. Amendment is not required, but the reallocation of resources needs to be explained in the periodic reports. If the change is caused by change in actions tasks it requires an amendment. Adding subcontracting requires an

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amendment. In HADEA (European Health and Digital Executive Agency) projects budget transfers between partners are not allowed without amendment.

The Coordinator and the Project Coordination Office must be informed of all changes to the budget and PMs.

5.3 PAYMENTS FROM EC

PRE-FINANCING

Pre-financing is paid to the Coordinator by the HADEA and distributed to the beneficiaries by the Coordinator. An amount corresponding to 5% of the maximum grant amount is retained by the HADEA/HEU from the pre-financing payment and transferred into to the Mutual Insurance Mechanism (MIM). Pre-financing is property of EU until the final payment and must be paid back unless enough eligible costs entitling to grant are declared.

INTERIM PAYMENTS

Interim payments reimburse the eligible costs incurred for the implementation of the action during the corresponding reporting periods. The EC will pay to the coordinator the amount due as interim payment within 90 days from receiving the periodic report. Payment is subject to the approval of the periodic report.
The amount due as interim payment is calculated by the EC in the following steps:
Step 1 – Calculation of the total accepted EU contribution
Step 2 – Limit to 90% interim payment ceiling

FINAL PAYMENT

The final payment will be made after the approval of final reports. The final payment consists of the difference between the total EU contribution and the amounts already paid, but min. 10% of the total EU contribution.
Final payment may take the form of recovery if the total amount of earlier payments is greater than the final grant amount. If this happens, the MIM is depleted first.

CASH FLOW

In the beginning of the project, the pre-financing will mean that partners will be cash-flow positive for a while. After that, the cash-flow situation will be negative for a while, and finally corrected at the final payments.

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6. CRITICAL RISKS & RISK MANAGEMENT STRATEGY

In the Grant Agreement preparation stage, the main risk areas were identified and mitigation measures proposed to avoid or at least mitigate the impact of such risks on the successful completion of the project.

The WP8 Project Management has a Risk Management plan deliverable at M12. This plan will include the processes, tools and procedures that will be used to manage and control those events within the Endotarget project that could have a negative impact. It will expose the proposed risk management approach of the project for managing and controlling all project risks. Deliverable will be updated throughout the project.

By the moment, the following Table 6 lists the possible risks identified at the GA preparation and their management strategy:

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Table 8. Critical risks & Risk management Strategy

Critical risks & risk management strategy			
Risk No	**Description**	**WP No(s)**	**Proposed Mitigation Measures**
1	Re-emergence of COVID-19 and risk of; i.) non-attainment of target number of patient samples in cohort studies (WP2) ii.) Difficulty to fulfil the clinical interventional study design (WP4), iii.) Challenges to participate in in-person F2F dissemination activities (WP7)	WP4, WP2, WP7	i. WP2 will continue to perform analysis on previously collected samples. Diet Intervention Study in RA (WP4) will transform the in-person activities to remote ones, including virtual culinary workshops, weekly online nutrition appointments and home- delivery of food baskets with recipes. The multicentre trial on larazotide in RA will provide the drug and the placebo at home (WP4). ii. iii. All "in presence events" will be switched to an online-only format (WP7)
2	Methodologic Risk: Not recruiting the target number of patients for the clinical trial (Diet intervention study & Multicentre study on the efficacy of larazotide in RA) (WP4)	WP4	iMM has vast experience in conducting translation studies and clinical trials and it follows a large group of RA patients. We will analyse recruitment rate monthly. If there is under- enrolment, we will plan strategically in order to recruit 4 RA patients/month in 2 years for thediet intervention study and 33 patients/centre for 2 years for the multicentre trial on larazotidein RA. HUS and UNICAM also have a track record of recruiting patients for interventional studies. If required, recruitment can be expanded to other local hospitals with rheumatologyunits and national patients' organizations.
3	Technology risk: Poor correlation between the high-throughput technologies and other diagnostic platforms used in the clinics.	WP2, WP3	Lab testing shows good correlation in biomarker performance between standard ELISA, lipidprofiling and microbiome analysis. However, data obtained can be used immediately for development of clinically useful tests.
4	Technology risk: Unknown whether new biomarker profiles will be discovered as the disease heterogeneity cannot be predicted - there is a risk of not finding clinically stratifying biomarkers.	WP1, WP5	Integration of data with genomic, lipidomic and microbiome data will lessen the risks of not providing clinically useful biomarkers. Consortium has experience in profiling many diseases with excellent results.

Critical risks & risk management strategy			
Risk No	**Description**	**WP No(s)**	**Proposed Mitigation Measures**
5	Statistical risk: Lack of power to identify risk factors that drive health to disease transition	WP1, WP5	Our power calculations indicate that we should be successful. As the major aim is not to identify single risk factors for these outcomes this is not a major problem. We will use a relaxed significance level, aiming to a considerable enrichment of true risk factors for eachmeasure being aware that some of the identified risk factors may be false positive.
6	Methodology risk: Large variability of identified LPS origin from mass-spectroscopy and microbiome data (WP2, WP3)	WP2, WP3	Search for commonalities in LPS structures and use a common structures LPS for functionalstudies
7	Methodology risk: No clear profile of candidate cytokines/proteins to be involved in trained immunity or tolerance is identified through proteomic analysis (WP3)	WP3	Select candidate cytokines/proteins based on previous literature
8	Technological risk: Technology risk: Unauthorized data access	WP5, WP6	All precautions to survive from automated attacks are used, most importantly performingdata security upgrades regularly, and regularly following system log files. The software has active safety features like enforcement of strong passwords, and account locking after multiple authentication failures
9	Legal: Getting access to sufficient data to ensurerobust and unbiased AI models (WP6)	WP6	Sufficient and legal measures will be put in place to show that data is handled appropriately. Clinical partners will provide a contact person to help facilitate access to data.
10	Ethical risk: Potential resistance to use AI-based predictions in clinical practice making it hard to assess effectiveness (WP6)	WP6	All AI models will be created in accordance with the EU Ethics Guidelines for Trustworthy AI. The project partners will ensure use of the RDPT in their own institutions.

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7. PROJECT REVIEWS

Table 9. Project Reviews

Project Reviews			
Review No	**Timing** (month)	**Location**	**Comments**
RV1	20	TBC	Linked to first reporting period. Subjected to final approval by the Project Officer.
RV2	38	TBC	Linked to second reporting period. Subjected to final approval by the Project Officer.

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