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EUROPEAN HEALTH AND DIGITAL EXECUTIVE AGENCY (HADEA)

HADEA.A – Health and Food
A.3 – Health research

GRANT AGREEMENT

Project 101095672 — PRAESIIDIUM

PREAMBLE

This **Agreement** ('the Agreement') is **between** the following parties:

on the one part,

the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and

on the other part,

1. 'the coordinator':

SPINDOX LABS SRL (SPXL), PIC 903350816, established in VIA ALLA CASCATA 56/C, TRENTO 38123, Italy,

and the following other beneficiaries, if they sign their 'accession form' (see Annex 3 and Article 40):

2. **CONSIGLIO NAZIONALE DELLE RICERCHE (CNR)**, PIC 999979500, established in PIAZZALE ALDO MORO 7, ROMA 00185, Italy,

3. **ELEKTRONIKAS UN DATORZINATNU INSTITUTS (EDI)**, PIC 997829883, established in DZERBENES IELA 14, RIGA 1006, Latvia,

4. **EURONET CONSULTING (EURO)**, PIC 907542089, established in 43 RUE SAINT CHRISTOPHE, BRUSSELS 1000, Belgium,

5. **SCUOLA DI ROBOTICA (SdR)**, PIC 951668747, established in STUDIO MARTINETTO, VIA FIESCHI 20/9, GENOVA 16149, Italy,

6. **CHECKHEALTH SWEDEN AB (CHK)**, PIC 900926010, established in SVARDVAGEN 3 A, DANDERYD 182 33, Sweden,

7. **FONDAZIONE ITALIANA FEGATO ONLUS (FIF)**, PIC 997492808, established in AREA SCIENCE PARK, BLDG Q, SS14, KM 163.5, TRIESTE 34149, Italy,

8. **MEDIZINISCHE UNIVERSITAT GRAZ (MUG)**, PIC 999836231, established in AUENBRUGGERPLATZ 2, GRAZ 8036, Austria,

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9. **HK3 LAB S.R.L. (HKL)**, PIC 895500121, established in VIA PARTELI 19, ROVERETO 38068, Italy,

10. **LATVIJAS UNIVERSITATE (UNIL)**, PIC 999871830, established in RAINIS BOULEVARD 19, RIGA 1586, Latvia,

Unless otherwise specified, references to 'beneficiary' or 'beneficiaries' include the coordinator and affiliated entities (if any).

If only one beneficiary signs the grant agreement ('mono-beneficiary grant'), all provisions referring to the 'coordinator' or the 'beneficiaries' will be considered — mutatis mutandis — as referring to the beneficiary.

The parties referred to above have agreed to enter into the Agreement.

By signing the Agreement and the accession forms, the beneficiaries accept the grant and agree to implement the action under their own responsibility and in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

The Agreement is composed of:

Preamble

Terms and Conditions (including Data Sheet)

Annex 1	Description of the action[1]
Annex 2	Estimated budget for the action
Annex 2a	Additional information on unit costs and contributions (if applicable)
Annex 3	Accession forms (if applicable)[2]
Annex 3a	Declaration on joint and several liability of affiliated entities (if applicable)[3]
Annex 4	Model for the financial statements
Annex 5	Specific rules (if applicable)

[1] Template published on Portal Reference Documents.
[2] Template published on Portal Reference Documents.
[3] Template published on Portal Reference Documents.

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TERMS AND CONDITIONS

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DATA SHEET

1. General data

Project summary:

Project summary
The incidence of undiagnosed diabetes accounts for 36% European adults, while 541M adults worldwide have Impaired Glucose Tolerance (IGT), an important risk factor for further T2D development. Both IGT and/or Impaired Fasting Glucose (IFG) are intermediate glucose mishandling (i.e. intermediate conditions in the healthy-T2D transition) and are manifestations of the so-called prediabetes condition. Prediabetes itself is not an extensively studied condition compared to the overt T2D, but it is also a condition that can be reversed without the prescription usage to not proceed into T2D. The aim of our project is to develop a prototype tool for the real-time prediction of the prediabetic risk based on a series of patient-specific mathematical models (firstly developed during the FP7 MISSION-T2D project) that simulate metabolism, pancreas hormone production, microbiome metabolites, inflammatory process and immune system response. The prediction algorithm will be based on a "physics-informed machine learning" approach. A rich dataset of real-life data will be combined with a mathematical model to overcome the limits of a "black-box" ML approach, while reducing the computational time for simulating the solutions of a heavy mathematical models and improving its prediction performances.We will collect the necessary training data (e.g., diet questionnaire, physical activity, blood metabolites and microbiome) from already existing clinical studies (used as retrospective trials) which are representative of the real-life scenarios of a prediabetes/diabetes risk insurgence in adulthood (20-80y): family history, Metabolic Syndrome, Liver disease and obesity. A newly dedicated multicentric pilot prospective observational study will be also performed, during which we will also equip the participants with wearable sensors (e.g. glucose monitoring, bioimpedance, heart rate, accelerometer).

Keywords:

- Disease prevention

Project number: 101095672

Project name: PHYSICS INFORMED MACHINE LEARNING-BASED PREDICTION AND REVERSION OF IMPAIRED FASTING GLUCOSE MANAGEMENT

Project acronym: PRAESIIDIUM

Call: HORIZON-HLTH-2022-STAYHLTH-02

Topic: HORIZON-HLTH-2022-STAYHLTH-02-01

Type of action: HORIZON Research and Innovation Actions

Granting authority: European Health and Digital Executive Agency

Grant managed through EU Funding & Tenders Portal: Yes (eGrants)

Project starting date: fixed date: 1 January 2023

Project end date: 31 December 2025

Project duration: 36 months

Consortium agreement: Yes

2. Participants

List of participants:

N°	Role	Short name	Legal name	Ctry	PIC	Total eligible costs (BEN and AE)	Max grant amount
1	COO	SPXL	SPINDOX LABS SRL	IT	903350816	930 625.00	930 625.00
2	BEN	CNR	CONSIGLIO NAZIONALE DELLE RICERCHE	IT	999979500	802 750.00	802 750.00
3	BEN	EDI	ELEKTRONIKAS UN DATORZINATNU INSTITUTS	LV	997829883	571 250.00	571 250.00
4	BEN	EURO	EURONET CONSULTING	BE	907542089	420 000.00	420 000.00

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N°	Role	Short name	Legal name	Ctry	PIC	Total eligible costs (BEN and AE)	Max grant amount
5	BEN	SdR	SCUOLA DI ROBOTICA	IT	951668747	102 000.00	102 000.00
6	BEN	CHK	CHECKHEALTH SWEDEN AB	SE	900926010	589 875.00	589 875.00
7	BEN	FIF	FONDAZIONE ITALIANA FEGATO ONLUS	IT	997492808	642 841.25	642 841.00
8	BEN	MUG	MEDIZINISCHE UNIVERSITAT GRAZ	AT	999836231	576 286.25	576 286.00
9	BEN	HKL	HK3 LAB S.R.L.	IT	895500121	507 500.00	507 500.00
10	BEN	UNIL	LATVIJAS UNIVERSITATE	LV	999871830	665 613.75	665 613.00
11	AP	SUPSI	SCUOLA UNIVERSITARIA PROFESSIONALE DELLA SVIZZERA ITALIANA	CH	999587620	0.00	0.00
Total						5 808 741.25	5 808 740.00

Coordinator:

– SPINDOX LABS SRL (SPXL)

3. Grant

Maximum grant amount, total estimated eligible costs and contributions and funding rate:

Total eligible costs (BEN and AE)	Funding rate (%)	Maximum grant amount (Annex 2)	Maximum grant amount (award decision)
5 808 741.25	100	5 808 740.00	5 808 740.00

Grant form: Budget-based

Grant mode: Action grant

Budget categories/activity types:

- A. Personnel costs
  - A.1 Employees, A.2 Natural persons under direct contract, A.3 Seconded persons
  - A.4 SME owners and natural person beneficiaries
- B. Subcontracting costs
- C. Purchase costs
  - C.1 Travel and subsistence
  - C.2 Equipment
  - C.3 Other goods, works and services
- D. Other cost categories
  - D.2 Internally invoiced goods and services
- E. Indirect costs

Cost eligibility options:

- In-kind contributions eligible costs
- Parental leave
- Project-based supplementary payments
- Average personnel costs (unit cost according to usual cost accounting practices)

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- Limitation for subcontracting

- Travel and subsistence:
  - Travel: Actual costs
  - Accommodation: Actual costs
  - Subsistence: Actual costs

- Equipment: depreciation only

- Indirect cost flat-rate: 25% of the eligible direct costs (categories A-D, except volunteers costs, subcontracting costs, financial support to third parties and exempted specific cost categories, if any)

- VAT: Yes

- Other ineligible costs

Budget flexibility: Yes (no flexibility cap)

4. Reporting, payments and recoveries

4.1 Continuous reporting (art 21)

Deliverables: see Funding & Tenders Portal Continuous Reporting tool

4.2 Periodic reporting and payments

Reporting and payment schedule (art 21, 22):

Reporting					Payments	
Reporting periods			Type	Deadline	Type	Deadline (time to pay)
RP No	Month from	Month to				
					Initial prefinancing	30 days from entry into force/10 days before starting date – whichever is the latest
1	1	18	Periodic report	60 days after end of reporting period	Interim payment	90 days from receiving periodic report
2	19	36	Periodic report	60 days after end of reporting period	Final payment	90 days from receiving periodic report

Prefinancing payments and guarantees:

Prefinancing payment	
Type	Amount
Prefinancing 1 (initial)	4 646 992.00

Reporting and payment modalities (art 21, 22):

Mutual Insurance Mechanism (MIM): Yes

MIM contribution: 5% of the maximum grant amount (290 437.00), retained from the initial prefinancing

Restrictions on distribution of initial prefinancing: The prefinancing may be distributed only if the minimum number of

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beneficiaries set out in the call condititions (if any) have acceded to the Agreement and only to beneficiaries that have acceded.

Interim payment ceiling (if any): 90% of the maximum grant amount

Exception for revenues: Yes

No-profit rule: Yes

Late payment interest: ECB + 3.5%

Bank account for payments:

IT50T0503401636000000009879

Conversion into euros: Double conversion

Reporting language: Language of the Agreement

4.3 Certificates (art 24):

Certificates on the financial statements (CFS):

Conditions:

Schedule: only at final payment, if threshold is reached

Standard threshold (beneficiary-level):

- financial statement: requested EU contribution to costs ≥ EUR 430 000.00

Special threshold for beneficiaries with a systems and process audit(see Article 24): financial statement: requested EU contribution to costs ≥ EUR 725 000.00

4.4 Recoveries (art 22)

First-line liability for recoveries:

Beneficiary termination: Beneficiary concerned

Final payment: Each beneficiary for their own debt

After final payment: Beneficiary concerned

Joint and several liability for enforced recoveries (in case of non-payment):

Individual financial responsibility: Each beneficiary is liable only for its own debts (and those of its affiliated entities, if any)

5. Consequences of non-compliance, applicable law & dispute settlement forum

Suspension and termination:

Additional suspension grounds (art 31)

Additional termination grounds (art 32)

Applicable law (art 43):

Standard applicable law regime: EU law + law of Belgium

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Dispute settlement forum (art 43):

Standard dispute settlement forum:

EU beneficiaries: EU General Court + EU Court of Justice (on appeal)

Non-EU beneficiaries: Courts of Brussels, Belgium (unless an international agreement provides for the enforceability of EU court judgements)

6. Other

Specific rules (Annex 5): Yes

Standard time-limits after project end:

Confidentiality (for X years after final payment): 5

Record-keeping (for X years after final payment): 5 (or 3 for grants of not more than EUR 60 000)

Reviews (up to X years after final payment): 2

Audits (up to X years after final payment): 2

Extension of findings from other grants to this grant (no later than X years after final payment): 2

Impact evaluation (up to X years after final payment): 5 (or 3 for grants of not more than EUR 60 000)

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CHAPTER 1 GENERAL

ARTICLE 1 — SUBJECT OF THE AGREEMENT

This 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 Chapter 2.

ARTICLE 2 — DEFINITIONS

For the purpose of this Agreement, the following definitions apply:

Actions — The project which is being funded in the context of this Agreement.

Grant — The grant awarded in the context of this Agreement.

EU grants — Grants awarded by EU institutions, bodies, offices or agencies (including EU executive agencies, EU regulatory agencies, EDA, joint undertakings, etc.).

Participants — Entities participating in the action as beneficiaries, affiliated entities, associated partners, third parties giving in-kind contributions, subcontractors or recipients of financial support to third parties.

Beneficiaries (BEN) — The signatories of this Agreement (either directly or through an accession form).

Affiliated entities (AE) — Entities affiliated to a beneficiary within the meaning of Article 187 of EU Financial Regulation 2018/1046[4] which participate in the action with similar rights and obligations as the beneficiaries (obligation to implement action tasks and right to charge costs and claim contributions).

Associated partners (AP) — Entities which participate in the action, but without the right to charge costs or claim contributions.

Purchases — Contracts for goods, works or services needed to carry out the action (e.g. equipment, consumables and supplies) but which are not part of the action tasks (see Annex 1).

Subcontracting — Contracts for goods, works or services that are part of the action tasks (see Annex 1).

In-kind contributions — In-kind contributions within the meaning of Article 2(36) of EU Financial

[4] For the definition, see Article 187 Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council of 18 July 2018 on the financial rules applicable to the general budget of the Union, amending Regulations (EU) No 1296/2013, (EU) No 1301/2013, (EU) No 1303/2013, (EU) No 1304/2013, (EU) No 1309/2013, (EU) No 1316/2013, (EU) No 223/2014, (EU) No 283/2014, and Decision No 541/2014/EU and repealing Regulation (EU, Euratom) No 966/2012 ('EU Financial Regulation') (OJ L 193, 30.7.2018, p. 1): "**affiliated entities** [are]:
(a) entities that form a sole beneficiary [(i.e. where an entity is formed of several entities that satisfy the criteria for being awarded a grant, including where the entity is specifically established for the purpose of implementing an action to be financed by a grant)];
(b) entities that satisfy the eligibility criteria and that do not fall within one of the situations referred to in Article 136(1) and 141(1) and that have a link with the beneficiary, in particular a legal or capital link, which is neither limited to the action nor established for the sole purpose of its implementation".

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Regulation 2018/1046, i.e. non-financial resources made available free of charge by third parties.

Fraud — Fraud within the meaning of Article 3 of EU Directive 2017/1371[5] and Article 1 of the Convention on the protection of the European Communities' financial interests, drawn up by the Council Act of 26 July 1995[6], as well as any other wrongful or criminal deception intended to result in financial or personal gain.

Irregularities — Any type of breach (regulatory or contractual) which could impact the EU financial interests, including irregularities within the meaning of Article 1(2) of EU Regulation 2988/95[7].

Grave professional misconduct — Any type of unacceptable or improper behaviour in exercising one's profession, especially by employees, including grave professional misconduct within the meaning of Article 136(1)(c) of EU Financial Regulation 2018/1046.

Applicable EU, international and national law — Any legal acts or other (binding or non-binding) rules and guidance in the area concerned.

Portal — EU Funding & Tenders Portal; electronic portal and exchange system managed by the European Commission and used by itself and other EU institutions, bodies, offices or agencies for the management of their funding programmes (grants, procurements, prizes, etc.).

CHAPTER 2 ACTION

ARTICLE 3 — ACTION

The grant is awarded for the action **101095672 — PRAESIIDIUM** ('action'), as described in Annex 1.

ARTICLE 4 — DURATION AND STARTING DATE

The duration and the starting date of the action are set out in the Data Sheet (see Point 1).

CHAPTER 3 GRANT

ARTICLE 5 — GRANT

5.1 Form of grant

[5] Directive (EU) 2017/1371 of the European Parliament and of the Council of 5 July 2017 on the fight against fraud to the Union's financial interests by means of criminal law (OJ L 198, 28.7.2017, p. 29).
[6] OJ C 316, 27.11.1995, p. 48.
[7] Council Regulation (EC, Euratom) No 2988/95 of 18 December 1995 on the protection of the European Communities financial interests (OJ L 312, 23.12.1995, p. 1).

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The grant is an action grant[8] which takes the form of a budget-based mixed actual cost grant (i.e. a grant based on actual costs incurred, but which may also include other forms of funding, such as unit costs or contributions, flat-rate costs or contributions, lump sum costs or contributions or financing not linked to costs).

5.2 Maximum grant amount

The maximum grant amount is set out in the Data Sheet (see Point 3) and in the estimated budget (Annex 2).

5.3 Funding rate

The funding rate for costs is 100% of the action's eligible costs.

Contributions are not subject to any funding rate.

5.4 Estimated budget, budget categories and forms of funding

The estimated budget for the action is set out in Annex 2.

It contains the estimated eligible costs and contributions for the action, broken down by participant and budget category.

Annex 2 also shows the types of costs and contributions (forms of funding)[9] to be used for each budget category.

If unit costs or contributions are used, the details on the calculation will be explained in Annex 2a.

5.5 Budget flexibility

The budget breakdown may be adjusted — without an amendment (see Article 39) — by transfers (between participants and budget categories), as long as this does not imply any substantive or important change to the description of the action in Annex 1.

However:

- changes to the budget category for volunteers (if used) always require an amendment
- changes to budget categories with lump sums costs or contributions (if used; including financing not linked to costs) always require an amendment
- changes to budget categories with higher funding rates or budget ceilings (if used) always require an amendment
- addition of amounts for subcontracts not provided for in Annex 1 either require an amendment or simplified approval in accordance with Article 6.2

[8] For the definition, see Article 180(2)(a) EU Financial Regulation 2018/1046: '**action grant**' means an EU grant to finance "an action intended to help achieve a Union policy objective".

[9] See Article 125 EU Financial Regulation 2018/1046.

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- other changes require an amendment or simplified approval, if specifically provided for in Article 6.2

- flexibility caps: not applicable.

ARTICLE 6 — ELIGIBLE AND INELIGIBLE COSTS AND CONTRIBUTIONS

In order to be eligible, costs and contributions must meet the **eligibility** conditions set out in this Article.

6.1 General eligibility conditions

The **general eligibility conditions** are the following:

(a) for actual costs:

(i) they must be actually incurred by the beneficiary

(ii) they must be incurred in the period set out in Article 4 (with the exception of costs relating to the submission of the final periodic report, which may be incurred afterwards; see Article 21)

(iii) they must be declared under one of the budget categories set out in Article 6.2 and Annex 2

(iv) they must be incurred in connection with the action as described in Annex 1 and necessary for its implementation

(v) they must be identifiable and verifiable, in particular recorded in the beneficiary's accounts in accordance with the accounting standards applicable in the country where the beneficiary is established and with the beneficiary's usual cost accounting practices

(vi) they must comply with the applicable national law on taxes, labour and social security and

(vii) they must be reasonable, justified and must comply with the principle of sound financial management, in particular regarding economy and efficiency

(b) for unit costs or contributions (if any):

(i) they must be declared under one of the budget categories set out in Article 6.2 and Annex 2

(ii) the units must:

- be actually used or produced by the beneficiary in the period set out in Article 4 (with the exception of units relating to the submission of the final periodic report, which may be used or produced afterwards; see Article 21)

- be necessary for the implementation of the action and

(iii) the number of units must be identifiable and verifiable, in particular supported by records and documentation (see Article 20)

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(c) for flat-rate costs or contributions (if any):

(i) they must be declared under one of the budget categories set out in Article 6.2 and Annex 2

(ii) the costs or contributions to which the flat-rate is applied must:

- be eligible
- relate to the period set out in Article 4 (with the exception of costs or contributions relating to the submission of the final periodic report, which may be incurred afterwards; see Article 21)

(d) for lump sum costs or contributions (if any):

(i) they must be declared under one of the budget categories set out in Article 6.2 and Annex 2

(ii) the work must be properly implemented by the beneficiary in accordance with Annex 1

(iii) the deliverables/outputs must be achieved in the period set out in Article 4 (with the exception of deliverables/outputs relating to the submission of the final periodic report, which may be achieved afterwards; see Article 21)

(e) for unit, flat-rate or lump sum costs or contributions according to usual cost accounting practices (if any):

(i) they must fulfil the general eligibility conditions for the type of cost concerned

(ii) the cost accounting practices must be applied in a consistent manner, based on objective criteria, regardless of the source of funding

(f) for financing not linked to costs (if any): the results must be achieved or the conditions must be fulfilled as described in Annex 1.

In addition, for direct cost categories (e.g. personnel, travel & subsistence, subcontracting and other direct costs) only costs that are directly linked to the action implementation and can therefore be attributed to it directly are eligible. They must not include any indirect costs (i.e. costs that are only indirectly linked to the action, e.g. via cost drivers).

In-kind contributions provided by third parties free of charge may be declared as eligible direct costs by the beneficiaries which use them (under the same conditions as if they were their own, provided that they concern only direct costs and that the third parties and their in-kind contributions are set out in Annex 1 (or approved ex post in the periodic report, if their use does not entail changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants; 'simplified approval procedure').

6.2 Specific eligibility conditions for each budget category

For each budget category, the **specific eligibility conditions** are as follows:

Direct costs

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A. Personnel costs

A.1 Costs for employees (or equivalent) are eligible as personnel costs if they fulfil the general eligibility conditions and are related to personnel working for the beneficiary under an employment contract (or equivalent appointing act) and assigned to the action.

They must be limited to salaries (including net payments during parental leave), social security contributions, taxes and other costs linked to the remuneration, if they arise from national law or the employment contract (or equivalent appointing act) and be calculated on the basis of the costs actually incurred, in accordance with the following method:

{daily rate for the person

multiplied by

number of day-equivalents worked on the action (rounded up or down to the nearest half-day)}.

The daily rate must be calculated as:

{annual personnel costs for the person

divided by

215}.

The number of day-equivalents declared for a person must be identifiable and verifiable (see Article 20).

The actual time spent on parental leave by a person assigned to the action may be deducted from the 215 days indicated in the above formula.

The total number of day-equivalents declared in EU grants, for a person for a year, cannot be higher than 215, minus time spent on parental leave (if any).

For personnel which receives supplementary payments for work in projects (project-based remuneration), the personnel costs must be calculated at a rate which:

- corresponds to the actual remuneration costs paid by the beneficiary for the time worked by the person in the action over the reporting period
- does not exceed the remuneration costs paid by the beneficiary for work in similar projects funded by national schemes (‘national projects reference’)
- is defined based on objective criteria allowing to determine the amount to which the person is entitled

and

- reflects the usual practice of the beneficiary to pay consistently bonuses or supplementary payments for work in projects funded by national schemes.

The national projects reference is the remuneration defined in national law, collective labour agreement or written internal rules of the beneficiary applicable to work in projects funded by national schemes.

If there is no such national law, collective labour agreement or written internal rules or if the project-

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based remuneration is not based on objective criteria, the national project reference will be the average remuneration of the person in the last full calendar year covered by the reporting period, excluding remuneration paid for work in EU actions.

If the beneficiary uses average personnel costs (unit cost according to usual cost accounting practices), the personnel costs must fulfil the general eligibility conditions for such unit costs and the daily rate must be calculated:

- using the actual personnel costs recorded in the beneficiary's accounts and excluding any costs which are ineligible or already included in other budget categories; the actual personnel costs may be adjusted on the basis of budgeted or estimated elements, if they are relevant for calculating the personnel costs, reasonable and correspond to objective and verifiable information

and

- according to usual cost accounting practices which are applied in a consistent manner, based on objective criteria, regardless of the source of funding.

A.2 and **A.3 Costs for natural persons working under a direct contract** other than an employment contract and costs for **seconded persons by a third party against payment** are also eligible as personnel costs, if they are assigned to the action, fulfil the general eligibility conditions and:

(a) work under conditions similar to those of an employee (in particular regarding the way the work is organised, the tasks that are performed and the premises where they are performed) and

(b) the result of the work belongs to the beneficiary (unless agreed otherwise).

They must be calculated on the basis of a rate which corresponds to the costs actually incurred for the direct contract or secondment and must not be significantly different from those for personnel performing similar tasks under an employment contract with the beneficiary.

A.4 The work of **SME owners** for the action (i.e. owners of beneficiaries that are small and medium-sized enterprises[10] not receiving a salary) or **natural person beneficiaries** (i.e. beneficiaries that are natural persons not receiving a salary) may be declared as personnel costs, if they fulfil the general eligibility conditions and are calculated as unit costs in accordance with the method set out in Annex 2a.

B. Subcontracting costs

Subcontracting costs for the action (including related duties, taxes and charges, such as non-deductible or non-refundable value added tax (VAT)) are eligible, if they are calculated on the basis

[10] For the definition, see Commission Recommendation 2003/361/EC: micro, small or medium-sized enterprise (SME) are enterprises

- engaged in an economic activity, irrespective of their legal form (including, in particular, self- employed persons and family businesses engaged in craft or other activities, and partnerships or associations regularly engaged in an economic activity) and

- employing fewer than 250 persons (expressed in 'annual working units' as defined in Article 5 of the Recommendation) and which have an annual turnover not exceeding EUR 50 million, and/or an annual balance sheet total not exceeding EUR 43 million.

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of the costs actually incurred, fulfil the general eligibility conditions and are awarded using the beneficiary's usual purchasing practices — provided these ensure subcontracts with best value for money (or if appropriate the lowest price) and that there is no conflict of interests (see Article 12).

Beneficiaries that are 'contracting authorities/entities' within the meaning of the EU Directives on public procurement must also comply with the applicable national law on public procurement.

Subcontracting may cover only a limited part of the action.

The tasks to be subcontracted and the estimated cost for each subcontract must be set out in Annex 1 and the total estimated costs of subcontracting per beneficiary must be set out in Annex 2 (or may be approved ex post in the periodic report, if the use of subcontracting does not entail changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants; 'simplified approval procedure').

C. Purchase costs

Purchase costs for the action (including related duties, taxes and charges, such as non-deductible or non-refundable value added tax (VAT)) are eligible if they fulfil the general eligibility conditions and are bought using the beneficiary's usual purchasing practices — provided these ensure purchases with best value for money (or if appropriate the lowest price) and that there is no conflict of interests (see Article 12).

Beneficiaries that are 'contracting authorities/entities' within the meaning of the EU Directives on public procurement must also comply with the applicable national law on public procurement.

C.1 Travel and subsistence

Purchases for **travel, accommodation** and **subsistence** must be calculated as follows:

- travel: on the basis of the costs actually incurred and in line with the beneficiary's usual practices on travel
- accommodation: on the basis of the costs actually incurred and in line with the beneficiary's usual practices on travel
- subsistence: on the basis of the costs actually incurred and in line with the beneficiary's usual practices on travel .

C.2 Equipment

Purchases of **equipment, infrastructure or other assets** used for the action must be declared as depreciation costs, calculated on the basis of the costs actually incurred and written off in accordance with international accounting standards and the beneficiary's usual accounting practices.

Only the portion of the costs that corresponds to the rate of actual use for the action during the action duration can be taken into account.

Costs for **renting or leasing** equipment, infrastructure or other assets are also eligible, if they do not exceed the depreciation costs of similar equipment, infrastructure or assets and do not include any financing fees.

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C.3 Other goods, works and services

Purchases of **other goods, works and services** must be calculated on the basis of the costs actually incurred.

Such goods, works and services include, for instance, consumables and supplies, promotion, dissemination, protection of results, translations, publications, certificates and financial guarantees, if required under the Agreement.

D. Other cost categories

D.2 Internally invoiced goods and services

Costs for internally invoiced goods and services directly used for the action may be declared as unit cost according to usual cost accounting practices, if and as declared eligible in the call conditions, if they fulfil the general eligibility conditions for such unit costs and the amount per unit is calculated:

- using the actual costs for the good or service recorded in the beneficiary's accounts, attributed either by direct measurement or on the basis of cost drivers, and excluding any cost which are ineligible or already included in other budget categories; the actual costs may be adjusted on the basis of budgeted or estimated elements, if they are relevant for calculating the costs, reasonable and correspond to objective and verifiable information

and

- according to usual cost accounting practices which are applied in a consistent manner, based on objective criteria, regardless of the source of funding.

'Internally invoiced goods and services' means goods or services which are provided within the beneficiary's organisation directly for the action and which the beneficiary values on the basis of its usual cost accounting practices.

This cost will not be taken into account for the indirect cost flat-rate.

Indirect costs

E. Indirect costs

Indirect costs will be reimbursed at the flat-rate of 25% of the eligible direct costs (categories A-D, except volunteers costs, subcontracting costs, financial support to third parties and exempted specific cost categories, if any).

Contributions

Not applicable

6.3 Ineligible costs and contributions

The following costs or contributions are **ineligible**:

(a) costs or contributions that do not comply with the conditions set out above (Article 6.1 and 6.2), in particular:

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(i) costs related to return on capital and dividends paid by a beneficiary

(ii) debt and debt service charges

(iii) provisions for future losses or debts

(iv) interest owed

(v) currency exchange losses

(vi) bank costs charged by the beneficiary's bank for transfers from the granting authority

(vii) excessive or reckless expenditure

(viii) deductible or refundable VAT (including VAT paid by public bodies acting as public authority)

(ix) costs incurred or contributions for activities implemented during grant agreement suspension (see Article 31)

(x) in-kind contributions by third parties: not applicable

(b) costs or contributions declared under other EU grants (or grants awarded by an EU Member State, non-EU country or other body implementing the EU budget), except for the following cases:

(i) Synergy actions: not applicable

(ii) if the action grant is combined with an operating grant[11] running during the same period and the beneficiary can demonstrate that the operating grant does not cover any (direct or indirect) costs of the action grant

(c) costs or contributions for staff of a national (or regional/local) administration, for activities that are part of the administration's normal activities (i.e. not undertaken only because of the grant)

(d) costs or contributions (especially travel and subsistence) for staff or representatives of EU institutions, bodies or agencies

(e) other :

(i) country restrictions for eligible costs: not applicable

(ii) costs or contributions declared specifically ineligible in the call conditions.

6.4 Consequences of non-compliance

If a beneficiary declares costs or contributions that are ineligible, they will be rejected (see Article 27).

This may also lead to other measures described in Chapter 5.

[11] For the definition, see Article 180(2)(b) of EU Financial Regulation 2018/1046: '**operating grant**' means an EU grant to finance "the functioning of a body which has an objective forming part of and supporting an EU policy".

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CHAPTER 4 GRANT IMPLEMENTATION

SECTION 1 CONSORTIUM: BENEFICIARIES, AFFILIATED ENTITIES AND OTHER PARTICIPANTS

ARTICLE 7 — BENEFICIARIES

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. If they rely on affiliated entities or other participants (see Articles 8 and 9), 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 is implemented by someone else (without being entitled to an increase of the maximum grant amount and subject to an amendment; see Article 39). The *financial* responsibility of each beneficiary in case of recoveries is governed by Article 22.

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.

The **internal roles and responsibilities** of the beneficiaries are divided as follows:

(a) 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)
- 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.

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(b) The coordinator must:

(i) monitor that the action is implemented properly (see Article 11)

(ii) act as the intermediary for all communications between the consortium and the granting authority, unless the Agreement or granting authority specifies otherwise, and in particular:

- submit the prefinancing guarantees to the granting authority (if any)
- request and review any documents or information required and verify their quality and completeness before passing them on to the granting authority
- submit the deliverables and reports to the granting authority
- inform the granting authority about the payments made to the other beneficiaries (report on the distribution of payments; if required, see Articles 22 and 32)

(iii) distribute the payments received from the granting authority to the other beneficiaries without unjustified delay (see Article 22).

The coordinator may not delegate or subcontract the above-mentioned tasks to any other beneficiary or third party (including affiliated entities).

However, coordinators which are public bodies may delegate the tasks set out in Point (b)(ii) last indent and (iii) above to entities with 'authorisation to administer' which they have created or which are controlled by or affiliated to them. In this case, the coordinator retains sole responsibility for the payments and for compliance with the obligations under the Agreement.

Moreover, coordinators which are 'sole beneficiaries'[12] (or similar, such as European research infrastructure consortia (ERICs)) may delegate the tasks set out in Point (b)(i) to (iii) above to one of their members. The coordinator retains sole responsibility for compliance with the obligations under the Agreement.

The beneficiaries must have **internal arrangements** regarding their operation and co-ordination, to ensure that the action is implemented properly.

If required by the granting authority (see Data Sheet, Point 1), these arrangements must be set out in a written **consortium agreement** between the beneficiaries, covering for instance:

- the internal organisation of the consortium
- the management of access to the Portal
- different distribution keys for the payments and financial responsibilities in case of recoveries (if any)
- additional rules on rights and obligations related to background and results (see Article 16)

[12] For the definition, see Article 187(2) EU Financial Regulation 2018/1046: "Where several entities satisfy the criteria for being awarded a grant and together form one entity, that entity may be treated as the **sole beneficiary**, including where it is specifically established for the purpose of implementing the action financed by the grant."

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- settlement of internal disputes
- liability, indemnification and confidentiality arrangements between the beneficiaries.

The internal arrangements must not contain any provision contrary to this Agreement.

ARTICLE 8 — AFFILIATED ENTITIES

Not applicable

ARTICLE 9 — OTHER PARTICIPANTS INVOLVED IN THE ACTION

9.1 Associated partners

The following entities which cooperate with a beneficiary will participate in the action as 'associated partners':

- **SCUOLA UNIVERSITARIA PROFESSIONALE DELLA SVIZZERA ITALIANA (SUPSI)**, PIC 999587620

Associated partners must implement the action tasks attributed to them in Annex 1 in accordance with Article 11. They may not charge costs or contributions to the action and the costs for their tasks are not eligible.

The tasks must be set out in Annex 1.

The beneficiaries must ensure that their contractual obligations under Articles 11 (proper implementation), 12 (conflict of interests), 13 (confidentiality and security), 14 (ethics), 17.2 (visibility), 18 (specific rules for carrying out action), 19 (information) and 20 (record-keeping) also apply to the associated partners.

The beneficiaries must ensure that the bodies mentioned in Article 25 (e.g. granting authority, OLAF, Court of Auditors (ECA), etc.) can exercise their rights also towards the associated partners.

9.2 Third parties giving in-kind contributions to the action

Other third parties may give in-kind contributions to the action (i.e. personnel, equipment, other goods, works and services, etc. which are free-of-charge) if necessary for the implementation.

Third parties giving in-kind contributions do not implement any action tasks. They may not charge costs or contributions to the action, but the costs for the in-kind contributions are eligible and may be charged by the beneficiaries which use them, under the conditions set out in Article 6. The costs will be included in Annex 2 as part of the beneficiaries' costs.

The third parties and their in-kind contributions should be set out in Annex 1.

The beneficiaries must ensure that the bodies mentioned in Article 25 (e.g. granting authority, OLAF, Court of Auditors (ECA), etc.) can exercise their rights also towards the third parties giving in-kind contributions.

9.3 Subcontractors

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Subcontractors may participate in the action, if necessary for the implementation.

Subcontractors must implement their action tasks in accordance with Article 11. The costs for the subcontracted tasks (invoiced price from the subcontractor) are eligible and may be charged by the beneficiaries, under the conditions set out in Article 6. The costs will be included in Annex 2 as part of the beneficiaries' costs.

The beneficiaries must ensure that their contractual obligations under Articles 11 (proper implementation), 12 (conflict of interest), 13 (confidentiality and security), 14 (ethics), 17.2 (visibility), 18 (specific rules for carrying out action), 19 (information) and 20 (record-keeping) also apply to the subcontractors.

The beneficiaries must ensure that the bodies mentioned in Article 25 (e.g. granting authority, OLAF, Court of Auditors (ECA), etc.) can exercise their rights also towards the subcontractors.

9.4 Recipients of financial support to third parties

If the action includes providing financial support to third parties (e.g. grants, prizes or similar forms of support), the beneficiaries must ensure that their contractual obligations under Articles 12 (conflict of interest), 13 (confidentiality and security), 14 (ethics), 17.2 (visibility), 18 (specific rules for carrying out action), 19 (information) and 20 (record-keeping)also apply to the third parties receiving the support (recipients).

The beneficiaries must also ensure that the bodies mentioned in Article 25 (e.g. granting authority, OLAF, Court of Auditors (ECA), etc.) can exercise their rights also towards the recipients.

ARTICLE 10 — PARTICIPANTS WITH SPECIAL STATUS

10.1 Non-EU participants

Participants which are established in a non-EU country (if any) undertake to comply with their obligations under the Agreement and:

- to respect general principles (including fundamental rights, values and ethical principles, environmental and labour standards, rules on classified information, intellectual property rights, visibility of funding and protection of personal data)

- for the submission of certificates under Article 24: to use qualified external auditors which are independent and comply with comparable standards as those set out in EU Directive 2006/43/EC[13]

- for the controls under Article 25: to allow for checks, reviews, audits and investigations (including on-the-spot checks, visits and inspections) by the bodies mentioned in that Article (e.g. granting authority, OLAF, Court of Auditors (ECA), etc.).

Special rules on dispute settlement apply (see Data Sheet, Point 5).

10.2 Participants which are international organisations

[13] Directive 2006/43/EC of the European Parliament and of the Council of 17 May 2006 on statutory audits of annual accounts and consolidated accounts or similar national regulations (OJ L 157, 9.6.2006, p. 87).

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Participants which are international organisations (IOs; if any) undertake to comply with their obligations under the Agreement and:

- to respect general principles (including fundamental rights, values and ethical principles, environmental and labour standards, rules on classified information, intellectual property rights, visibility of funding and protection of personal data)

- for the submission of certificates under Article 24: to use either independent public officers or external auditors which comply with comparable standards as those set out in EU Directive 2006/43/EC

- for the controls under Article 25: to allow for the checks, reviews, audits and investigations by the bodies mentioned in that Article, taking into account the specific agreements concluded by them and the EU (if any).

For such participants, nothing in the Agreement will be interpreted as a waiver of their privileges or immunities, as accorded by their constituent documents or international law.

Special rules on applicable law and dispute settlement apply (see Article 43 and Data Sheet, Point 5).

10.3 Pillar-assessed participants

Pillar-assessed participants (if any) may rely on their own systems, rules and procedures, in so far as they have been positively assessed and do not call into question the decision awarding the grant or breach the principle of equal treatment of applicants or beneficiaries.

'Pillar-assessment' means a review by the European Commission on the systems, rules and procedures which participants use for managing EU grants (in particular internal control system, accounting system, external audits, financing of third parties, rules on recovery and exclusion, information on recipients and protection of personal data; see Article 154 EU Financial Regulation 2018/1046).

Participants with a positive pillar assessment may rely on their own systems, rules and procedures, in particular for:

- record-keeping (Article 20): may be done in accordance with internal standards, rules and procedures

- currency conversion for financial statements (Article 21): may be done in accordance with usual accounting practices

- guarantees (Article 23): for public law bodies, prefinancing guarantees are not needed

- certificates (Article 24):

    - certificates on the financial statements (CFS): may be provided by their regular internal or external auditors and in accordance with their internal financial regulations and procedures

    - certificates on usual accounting practices (CoMUC): are not needed if those practices are covered by an ex-ante assessment

and use the following specific rules, for:

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- recoveries (Article 22): in case of financial support to third parties, there will be no recovery if the participant has done everything possible to retrieve the undue amounts from the third party receiving the support (including legal proceedings) and non-recovery is not due to an error or negligence on its part

- checks, reviews, audits and investigations by the EU (Article 25): will be conducted taking into account the rules and procedures specifically agreed between them and the framework agreement (if any)

- impact evaluation (Article 26): will be conducted in accordance with the participant's internal rules and procedures and the framework agreement (if any)

- grant agreement suspension (Article 31): certain costs incurred during grant suspension are eligible (notably, minimum costs necessary for a possible resumption of the action and costs relating to contracts which were entered into before the pre-information letter was received and which could not reasonably be suspended, reallocated or terminated on legal grounds)

- grant agreement termination (Article 32): the final grant amount and final payment will be calculated taking into account also costs relating to contracts due for execution only after termination takes effect, if the contract was entered into before the pre-information letter was received and could not reasonably be terminated on legal grounds

- liability for damages (Article 33.2): the granting authority must be compensated for damage it sustains as a result of the implementation of the action or because the action was not implemented in full compliance with the Agreement only if the damage is due to an infringement of the participant's internal rules and procedures or due to a violation of third parties' rights by the participant or one of its employees or individual for whom the employees are responsible.

Participants whose pillar assessment covers procurement and granting procedures may also do purchases, subcontracting and financial support to third parties (Article 6.2) in accordance with their internal rules and procedures for purchases, subcontracting and financial support.

Participants whose pillar assessment covers data protection rules may rely on their internal standards, rules and procedures for data protection (Article 15).

The participants may however not rely on provisions which would breach the principle of equal treatment of applicants or beneficiaries or call into question the decision awarding the grant, such as in particular:

- eligibility (Article 6)

- consortium roles and set-up (Articles 7-9)

- security and ethics (Articles 13, 14)

- IPR (including background and results, access rights and rights of use), communication, dissemination and visibility (Articles 16 and 17)

- information obligation (Article 19)

- payment, reporting and amendments (Articles 21, 22 and 39)

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- rejections, reductions, suspensions and terminations (Articles 27, 28, 29-32)

If the pillar assessment was subject to remedial measures, reliance on the internal systems, rules and procedures is subject to compliance with those remedial measures.

Participants whose assessment has not yet been updated to cover (the new rules on) data protection may rely on their internal systems, rules and procedures, provided that they ensure that personal data is:

- processed lawfully, fairly and in a transparent manner in relation to the data subject
- collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes
- adequate, relevant and limited to what is necessary in relation to the purposes for which they are processed
- accurate and, where necessary, kept up to date
- kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the data is processed and
- processed in a manner that ensures appropriate security of the personal data.

Participants must inform the coordinator without delay of any changes to the systems, rules and procedures that were part of the pillar assessment. The coordinator must immediately inform the granting authority.

Pillar-assessed participants that have also concluded a framework agreement with the EU, may moreover — under the same conditions as those above (i.e. not call into question the decision awarding the grant or breach the principle of equal treatment of applicants or beneficiaries) — rely on the provisions set out in that framework agreement.

SECTION 2 RULES FOR CARRYING OUT THE ACTION

ARTICLE 11 — PROPER IMPLEMENTATION OF THE ACTION

11.1 Obligation to properly implement the action

The beneficiaries must implement the action as described in Annex 1 and in compliance with the provisions of the Agreement, the call conditions and all legal obligations under applicable EU, international and national law.

11.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 28).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 12 — CONFLICT OF INTERESTS

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12.1 Conflict of interests

The beneficiaries must take all measures to prevent any situation where the impartial and objective implementation of the Agreement could be compromised for reasons involving family, emotional life, political or national affinity, economic interest or any other direct or indirect interest (‘conflict of interests’).

They must formally notify the granting authority without delay of any situation constituting or likely to lead to a conflict of interests and immediately take all the necessary steps to rectify this situation.

The granting authority may verify that the measures taken are appropriate and may require additional measures to be taken by a specified deadline.

12.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 28) and the grant or the beneficiary may be terminated (see Article 32).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 13 — CONFIDENTIALITY AND SECURITY

13.1 Sensitive information

The parties must keep confidential any data, documents or other material (in any form) that is identified as sensitive in writing (‘sensitive information’) — during the implementation of the action and for at least until the time-limit set out in the Data Sheet (see Point 6).

If a beneficiary requests, the granting authority may agree to keep such information confidential for a longer period.

Unless otherwise agreed between the parties, they may use sensitive information only to implement the Agreement.

The beneficiaries may disclose sensitive information to their personnel or other participants involved in the action only if they:

(a) need to know it in order to implement the Agreement and

(b) are bound by an obligation of confidentiality.

The granting authority may disclose sensitive information to its staff and to other EU institutions and bodies.

It may moreover disclose sensitive information to third parties, if:

(a) this is necessary to implement the Agreement or safeguard the EU financial interests and

(b) the recipients of the information are bound by an obligation of confidentiality.

The confidentiality obligations no longer apply if:

(a) the disclosing party agrees to release the other party

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(b) the information becomes publicly available, without breaching any confidentiality obligation

(c) the disclosure of the sensitive information is required by EU, international or national law.

Specific confidentiality rules (if any) are set out in Annex 5.

13.2 Classified information

The parties must handle classified information in accordance with the applicable EU, international or national law on classified information (in particular, Decision 2015/444[14] and its implementing rules).

Deliverables which contain classified information must be submitted according to special procedures agreed with the granting authority.

Action tasks involving classified information may be subcontracted only after explicit approval (in writing) from the granting authority.

Classified information may not be disclosed to any third party (including participants involved in the action implementation) without prior explicit written approval from the granting authority.

Specific security rules (if any) are set out in Annex 5.

13.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 28).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 14 — ETHICS AND VALUES

14.1 Ethics

The action must be carried out in line with the highest ethical standards and the applicable EU, international and national law on ethical principles.

Specific ethics rules (if any) are set out in Annex 5.

14.2 Values

The beneficiaries must commit to and ensure the respect of basic EU values (such as respect for human dignity, freedom, democracy, equality, the rule of law and human rights, including the rights of minorities).

Specific rules on values (if any) are set out in Annex 5.

14.3 Consequences of non-compliance

[14] Commission Decision 2015/444/EC, Euratom of 13 March 2015 on the security rules for protecting EU classified information (OJ L 72, 17.3.2015, p. 53).

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If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 28).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 15 — DATA PROTECTION

15.1 Data processing by the granting authority

Any personal data under the Agreement will be processed under the responsibility of the data controller of the granting authority in accordance with and for the purposes set out in the Portal Privacy Statement.

For grants where the granting authority is the European Commission, an EU regulatory or executive agency, joint undertaking or other EU body, the processing will be subject to Regulation 2018/1725[15].

15.2 Data processing by the beneficiaries

The beneficiaries must process personal data under the Agreement in compliance with the applicable EU, international and national law on data protection (in particular, Regulation 2016/679[16]).

They must ensure that personal data is:

- processed lawfully, fairly and in a transparent manner in relation to the data subjects
- collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes
- adequate, relevant and limited to what is necessary in relation to the purposes for which they are processed
- accurate and, where necessary, kept up to date
- kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the data is processed and
- processed in a manner that ensures appropriate security of the data.

The beneficiaries may grant their personnel access to personal data only if it is strictly necessary for implementing, managing and monitoring the Agreement. The beneficiaries must ensure that the personnel is under a confidentiality obligation.

The beneficiaries must inform the persons whose data are transferred to the granting authority and provide them with the Portal Privacy Statement.

[15] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC (OJ L 295, 21.11.2018, p. 39).

[16] 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 repealing Directive 95/46/EC (‘GDPR’) (OJ L 119, 4.5.2016, p. 1).

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15.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 28).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 16 — INTELLECTUAL PROPERTY RIGHTS (IPR) — BACKGROUND AND RESULTS —ACCESS RIGHTS AND RIGHTS OF USE

16.1 Background and access rights to background

The beneficiaries must give each other and the other participants access to the background identified as needed for implementing the action, subject to any specific rules in Annex 5.

'Background' means any data, know-how or information — whatever its form or nature (tangible or intangible), including any rights such as intellectual property rights — that is:

(a) held by the beneficiaries before they acceded to the Agreement and

(b) needed to implement the action or exploit the results.

If background is subject to rights of a third party, the beneficiary concerned must ensure that it is able to comply with its obligations under the Agreement.

16.2 Ownership of results

The granting authority does not obtain ownership of the results produced under the action.

'Results' means any tangible or intangible effect of the action, such as data, know-how or information, whatever its form or nature, whether or not it can be protected, as well as any rights attached to it, including intellectual property rights.

16.3 Rights of use of the granting authority on materials, documents and information received for policy, information, communication, dissemination and publicity purposes

The granting authority has the right to use non-sensitive information relating to the action and materials and documents received from the beneficiaries (notably summaries for publication, deliverables, as well as any other material, such as pictures or audio-visual material, in paper or electronic form) for policy, information, communication, dissemination and publicity purposes — during the action or afterwards.

The right to use the beneficiaries' materials, documents and information is granted in the form of a royalty-free, non-exclusive and irrevocable licence, which includes the following rights:

(a) **use for its own purposes** (in particular, making them available to persons working for the granting authority or any other EU service (including institutions, bodies, offices, agencies, etc.) or EU Member State institution or body; copying or reproducing them in whole or in part, in unlimited numbers; and communication through press information services)

(b) **distribution to the public** (in particular, publication as hard copies and in electronic or digital format, publication on the internet, as a downloadable or non-downloadable file, broadcasting

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by any channel, public display or presentation, communicating through press information services, or inclusion in widely accessible databases or indexes)

(c) **editing or redrafting** (including shortening, summarising, inserting other elements (e.g. meta-data, legends, other graphic, visual, audio or text elements), extracting parts (e.g. audio or video files), dividing into parts, use in a compilation)

(d) **translation**

(e) **storage** in paper, electronic or other form

(f) **archiving**, in line with applicable document-management rules

(g) the right to authorise **third parties** to act on its behalf or sub-license to third parties the modes of use set out in Points (b), (c), (d) and (f), if needed for the information, communication and publicity activity of the granting authority

(h) **processing**, analysing, aggregating the materials, documents and information received and **producing derivative works**.

The rights of use are granted for the whole duration of the industrial or intellectual property rights concerned.

If materials or documents are subject to moral rights or third party rights (including intellectual property rights or rights of natural persons on their image and voice), the beneficiaries must ensure that they comply with their obligations under this Agreement (in particular, by obtaining the necessary licences and authorisations from the rights holders concerned).

Where applicable, the granting authority will insert the following information:

"© – [year] – [name of the copyright owner]. All rights reserved. Licensed to the [name of granting authority] under conditions."

16.4 Specific rules on IPR, results and background

Specific rules regarding intellectual property rights, results and background (if any) are set out in Annex 5.

16.5 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 28).

Such a breach may also lead to other measures described in Chapter 5.

ARTICLE 17 — COMMUNICATION, DISSEMINATION AND VISIBILITY

17.1 Communication — Dissemination — Promoting the action

Unless otherwise agreed with the granting authority, the beneficiaries must promote the action and its results by providing targeted information to multiple audiences (including the media and the public), in accordance with Annex 1 and in a strategic, coherent and effective manner.

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Before engaging in a communication or dissemination activity expected to have a major media impact, the beneficiaries must inform the granting authority.

17.2 Visibility — European flag and funding statement

Unless otherwise agreed with the granting authority, communication activities of the beneficiaries related to the action (including media relations, conferences, seminars, information material, such as brochures, leaflets, posters, presentations, etc., in electronic form, via traditional or social media, etc.), dissemination activities and any infrastructure, equipment, vehicles, supplies or major result funded by the grant must acknowledge EU support and display the European flag (emblem) and funding statement (translated into local languages, where appropriate):









The emblem must remain distinct and separate and cannot be modified by adding other visual marks, brands or text.

Apart from the emblem, no other visual identity or logo may be used to highlight the EU support.

When displayed in association with other logos (e.g. of beneficiaries or sponsors), the emblem must be displayed at least as prominently and visibly as the other logos.

For the purposes of their obligations under this Article, the beneficiaries may use the emblem without first obtaining approval from the granting authority. This does not, however, give them the right to exclusive use. Moreover, they may not appropriate the emblem or any similar trademark or logo, either by registration or by any other means.

17.3 Quality of information — Disclaimer

Any communication or dissemination activity related to the action must use factually accurate information.

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Moreover, it must indicate the following disclaimer (translated into local languages where appropriate):

> "Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or [name of the granting authority]. Neither the European Union nor the granting authority can be held responsible for them."

17.4 Specific communication, dissemination and visibility rules

Specific communication, dissemination and visibility rules (if any) are set out in Annex 5.

17.5 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 28).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 18 — SPECIFIC RULES FOR CARRYING OUT THE ACTION

18.1 Specific rules for carrying out the action

Specific rules for implementing the action (if any) are set out in Annex 5.

18.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 28).

Such a breach may also lead to other measures described in Chapter 5.

SECTION 3 GRANT ADMINISTRATION

ARTICLE 19 — GENERAL INFORMATION OBLIGATIONS

19.1 Information requests

The beneficiaries must provide — during the action or afterwards and in accordance with Article 7 — any information requested in order to verify eligibility of the costs or contributions declared, proper implementation of the action and compliance with the other obligations under the Agreement.

The information provided must be accurate, precise and complete and in the format requested, including electronic format.

19.2 Participant Register data updates

The beneficiaries must keep — at all times, during the action or afterwards — their information stored in the Portal Participant Register up to date, in particular, their name, address, legal representatives, legal form and organisation type.

19.3 Information about events and circumstances which impact the action

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The beneficiaries must immediately inform the granting authority (and the other beneficiaries) of any of the following:

(a) **events** which are likely to affect or delay the implementation of the action or affect the EU's financial interests, in particular:

(i) changes in their legal, financial, technical, organisational or ownership situation (including changes linked to one of the exclusion grounds listed in the declaration of honour signed before grant signature)

(ii) linked action information: not applicable

(b) **circumstances** affecting:

(i) the decision to award the grant or

(ii) compliance with requirements under the Agreement.

19.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 28).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 20 — RECORD-KEEPING

20.1 Keeping records and supporting documents

The beneficiaries must — at least until the time-limit set out in the Data Sheet (see Point 6) — keep records and other supporting documents to prove the proper implementation of the action in line with the accepted standards in the respective field (if any).

In addition, the beneficiaries must — for the same period — keep the following to justify the amounts declared:

(a) for actual costs: adequate records and supporting documents to prove the costs declared (such as contracts, subcontracts, invoices and accounting records); in addition, the beneficiaries' usual accounting 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 documents

(b) for flat-rate costs and contributions (if any): adequate records and supporting documents to prove the eligibility of the costs or contributions to which the flat-rate is applied

(c) for the following simplified costs and contributions: the beneficiaries do not need to keep specific records on the actual costs incurred, but must keep:

(i) for unit costs and contributions (if any): adequate records and supporting documents to prove the number of units declared

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(ii) for lump sum costs and contributions (if any): adequate records and supporting documents to prove proper implementation of the work as described in Annex 1

(iii) for financing not linked to costs (if any): adequate records and supporting documents to prove the achievement of the results or the fulfilment of the conditions as described in Annex 1

(d) for unit, flat-rate and lump sum costs and contributions according to usual cost accounting practices (if any): the beneficiaries must keep any adequate records and supporting documents to prove that their cost accounting practices have been applied in a consistent manner, based on objective criteria, regardless of the source of funding, and that they comply with the eligibility conditions set out in Articles 6.1 and 6.2.

Moreover, the following is needed for specific budget categories:

(e) for personnel costs: time worked for the beneficiary under the action must be supported by declarations signed monthly by the person and their supervisor, unless another reliable time-record system is in place; the granting authority may accept alternative evidence supporting the time worked for the action declared, if it considers that it offers an adequate level of assurance

(f) additional record-keeping rules: not applicable

The records and supporting documents must be made available upon request (see Article 19) or in the context of checks, reviews, audits or investigations (see Article 25).

If there are on-going checks, reviews, audits, investigations, litigation or other pursuits of claims under the Agreement (including the extension of findings; see Article 25), the beneficiaries must keep these 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 granting authority may accept non-original documents if they offer a comparable level of assurance.

20.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, costs or contributions insufficiently substantiated will be ineligible (see Article 6) and will be rejected (see Article 27), and the grant may be reduced (see Article 28).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 21 — REPORTING

21.1 Continuous reporting

The beneficiaries must continuously report on the progress of the action (e.g. **deliverables, milestones, outputs/outcomes, critical risks, indicators,** etc; if any), in the Portal Continuous Reporting tool and in accordance with the timing and conditions it sets out (as agreed with the granting authority).

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Standardised deliverables (e.g. progress reports not linked to payments, reports on cumulative expenditure, special reports, etc; if any) must be submitted using the templates published on the Portal.

21.2 Periodic reporting: Technical reports and financial statements

In addition, the beneficiaries must provide reports to request payments, in accordance with the schedule and modalities set out in the Data Sheet (see Point 4.2):

- for additional prefinancings (if any): an **additional prefinancing report**
- for interim payments (if any) and the final payment: a **periodic report**.

The prefinancing and periodic reports include a technical and financial part.

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

The financial part of the additional prefinancing report includes a statement on the use of the previous prefinancing payment.

The financial part of the periodic report includes:

- the financial statements (individual and consolidated; for all beneficiaries/affiliated entities)
- the explanation on the use of resources (or detailed cost reporting table, if required)
- the certificates on the financial statements (CFS) (if required; see Article 24.2 and Data Sheet, Point 4.3).

The **financial statements** must detail the eligible costs and contributions for each budget category and, for the final payment, also the revenues for the action (see Articles 6 and 22).

All eligible costs and contributions incurred should be declared, even if they exceed the amounts indicated in the estimated budget (see Annex 2). Amounts that are not declared in the individual financial statements will not be taken into account by the granting authority.

By signing the financial statements (directly in the Portal Periodic Reporting tool), the beneficiaries confirm that:

- the information provided is complete, reliable and true
- the costs and contributions declared are eligible (see Article 6)
- the costs and contributions can be substantiated by adequate records and supporting documents (see Article 20) that will be produced upon request (see Article 19) or in the context of checks, reviews, audits and investigations (see Article 25)
- for the final periodic report: all the revenues have been declared (if required; see Article 22).

Beneficiaries will have to submit also the financial statements of their affiliated entities (if any). In case of recoveries (see Article 22), beneficiaries will be held responsible also for the financial statements of their affiliated entities.

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21.3 Currency for financial statements and conversion into euros

The financial statements must be drafted in euro.

Beneficiaries with general accounts established in a currency other than the euro must convert the costs recorded in their accounts into euro, at the average of the daily exchange rates published in the C series of the *Official Journal of the European Union* (ECB website), calculated over the corresponding reporting period.

If no daily euro exchange rate is published in the *Official Journal* for the currency in question, they must be converted at the average of the monthly accounting exchange rates published on the European Commission website (InforEuro), calculated over the corresponding reporting period.

Beneficiaries with general accounts in euro must convert costs incurred in another currency into euro according to their usual accounting practices.

21.4 Reporting language

The reporting must be in the language of the Agreement, unless otherwise agreed with the granting authority (see Data Sheet, Point 4.2).

21.5 Consequences of non-compliance

If a report submitted does not comply with this Article, the granting authority may suspend the payment deadline (see Article 29) and apply other measures described in Chapter 5.

If the coordinator breaches its reporting obligations, the granting authority may terminate the grant or the coordinator's participation (see Article 32) or apply other measures described in Chapter 5.

ARTICLE 22 — PAYMENTS AND RECOVERIES — CALCULATION OF AMOUNTS DUE

22.1 Payments and payment arrangements

Payments will be made in accordance with the schedule and modalities set out in the Data Sheet (see Point 4.2).

They will be made in euro to the bank account indicated by the coordinator (see Data Sheet, Point 4.2) and must be distributed without unjustified delay (restrictions may apply to distribution of the initial prefinancing payment; see Data Sheet, Point 4.2).

Payments to this bank account will discharge the granting authority from its payment obligation.

The cost of payment transfers will be borne as follows:

- the granting authority bears the cost of transfers charged by its bank
- the beneficiary bears the cost of transfers charged by its bank
- the party causing a repetition of a transfer bears all costs of the repeated transfer.

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Payments by the granting authority will be considered to have been carried out on the date when they are debited to its account.

22.2 Recoveries

Recoveries will be made, if — at beneficiary termination, final payment or afterwards — it turns out that the granting authority has paid too much and needs to recover the amounts undue.

Each beneficiary's financial responsibility in case of recovery is in principle limited to their own debt and undue amounts of their affiliated entities.

In case of enforced recoveries (see Article 22.4), affiliated entities will be held liable for repaying debts of their beneficiaries, if required by the granting authority (see Data Sheet, Point 4.4).

22.3 Amounts due

22.3.1 Prefinancing payments

The aim of the prefinancing is to provide the beneficiaries with a float.

It remains the property of the EU until the final payment.

For **initial prefinancings** (if any), the amount due, schedule and modalities are set out in the Data Sheet (see Point 4.2).

For **additional prefinancings** (if any), the amount due, schedule and modalities are also set out in the Data Sheet (see Point 4.2). However, if the statement on the use of the previous prefinancing payment shows that less than 70% was used, the amount set out in the Data Sheet will be reduced by the difference between the 70% threshold and the amount used.

The contribution to the Mutual Insurance Mechanism will be retained from the prefinancing payments (at the rate and in accordance with the modalities set out in the Data Sheet, see Point 4.2) and transferred to the Mechanism.

Prefinancing payments (or parts of them) may be offset (without the beneficiaries' consent) against amounts owed by a beneficiary to the granting authority — up to the amount due to that beneficiary.

For grants where the granting authority is the European Commission or an EU executive agency, offsetting may also be done against amounts owed to other Commission services or executive agencies.

Payments will not be made if the payment deadline or payments are suspended (see Articles 29 and 30).

22.3.2 Amount due at beneficiary termination — Recovery

In case of beneficiary termination, the granting authority will determine the provisional amount due for the beneficiary concerned. Payments (if any) will be made with the next interim or final payment.

The **amount due** will be calculated in the following step:

Step 1 — Calculation of the total accepted EU contribution

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Step 1 — Calculation of the total accepted EU contribution

The granting authority will first calculate the 'accepted EU contribution' for the beneficiary for all reporting periods, by calculating the 'maximum EU contribution to costs' (applying the funding rate to the accepted costs of the beneficiary), taking into account requests for a lower contribution to costs and CFS threshold cappings (if any; see Article 24.5) and adding the contributions (accepted unit, flat-rate or lump sum contributions and financing not linked to costs, if any).

After that, the granting authority will take into account grant reductions (if any). The resulting amount is the 'total accepted EU contribution' for the beneficiary.

The **balance** is then calculated by deducting the payments received (if any; see report on the distribution of payments in Article 32), from the total accepted EU contribution:

{total accepted EU contribution for the beneficiary

minus

{prefinancing and interim payments received (if any)}}.

If the balance is **positive**, the amount will be included in the next interim or final payment to the consortium.

If the balance is **negative**, it will be **recovered** in accordance with the following procedure:

The granting authority will send a **pre-information letter** to the beneficiary concerned:

- formally notifying the intention to recover, the amount due, the amount to be recovered and the reasons why and
- requesting observations within 30 days of receiving notification.

If no observations are submitted (or the granting authority decides to pursue recovery despite the observations it has received), it will confirm the amount to be recovered and ask this amount to be paid to the coordinator (**confirmation letter**).

If payment is not made to the coordinator by the date specified in the confirmation letter, the granting authority may call on the Mutual Insurance Mechanism to intervene, if continuation of the action is guaranteed and the conditions set out in the rules governing the Mechanism are met.

In this case, it will send a **beneficiary recovery letter**, together with a **debit note** with the terms and date for payment.

The debit note for the beneficiary will include the amount calculated for the affiliated entities which also had to end their participation (if any).

If payment is not made by the date specified in the debit note, the granting authority will **enforce recovery** in accordance with Article 22.4.

The amounts will later on also be taken into account for the next interim or final payment.

22.3.3 Interim payments

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Interim payments reimburse the eligible costs and contributions claimed for the implementation of the action during the reporting periods (if any).

Interim payments (if any) will be made in accordance with the schedule and modalities set out the Data Sheet (see Point 4.2).

Payment is subject to the approval of the periodic report. Its approval does not imply recognition of compliance, authenticity, completeness or correctness of its content.

The **interim payment** will be calculated by the granting authority in the following steps:

Step 1 — Calculation of the total accepted EU contribution

Step 2 — Limit to the interim payment ceiling

Step 1 — Calculation of the total accepted EU contribution

The granting authority will calculate the 'accepted EU contribution' for the action for the reporting period, by first calculating the 'maximum EU contribution to costs' (applying the funding rate to the accepted costs of each beneficiary), taking into account requests for a lower contribution to costs, and CFS threshold cappings (if any; see Article 24.5) and adding the contributions (accepted unit, flat-rate or lump sum contributions and financing not linked to costs, if any).

After that, the granting authority will take into account grant reductions from beneficiary termination (if any). The resulting amount is the 'total accepted EU contribution'.

Step 2 — Limit to the interim payment ceiling

The resulting amount is then capped to ensure that the total amount of prefinancing and interim payments (if any) does not exceed the interim payment ceiling set out in the Data Sheet (see Point 4.2).

Interim payments (or parts of them) may be offset (without the beneficiaries' consent) against amounts owed by a beneficiary to the granting authority — up to the amount due to that beneficiary.

For grants where the granting authority is the European Commission or an EU executive agency, offsetting may also be done against amounts owed to other Commission services or executive agencies.

Payments will not be made if the payment deadline or payments are suspended (see Articles 29 and 30).

22.3.4 Final payment — Final grant amount — Revenues and Profit — Recovery

The final payment (payment of the balance) reimburses the remaining part of the eligible costs and contributions claimed for the implementation of the action (if any).

The final payment will be made in accordance with the schedule and modalities set out in the Data Sheet (see Point 4.2).

Payment is subject to the approval of the final periodic report. Its approval does not imply recognition of compliance, authenticity, completeness or correctness of its content.

The **final grant amount for the action** will be calculated in the following steps:

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Step 1 — Calculation of the total accepted EU contribution

Step 2 — Limit to the maximum grant amount

Step 3 — Reduction due to the no-profit rule

Step 1 — Calculation of the total accepted EU contribution

The granting authority will first calculate the 'accepted EU contribution' for the action for all reporting periods, by calculating the 'maximum EU contribution to costs' (applying the funding rate to the total accepted costs of each beneficiary), taking into account requests for a lower contribution to costs, CFS threshold cappings (if any; see Article 24.5) and adding the contributions (accepted unit, flat-rate or lump sum contributions and financing not linked to costs, if any).

After that, the granting authority will take into account grant reductions (if any). The resulting amount is the 'total accepted EU contribution'.

Step 2 — Limit to the maximum grant amount

If the resulting amount is higher than the maximum grant amount set out in Article 5.2, it will be limited to the latter.

Step 3 — Reduction due to the no-profit rule

If the no-profit rule is provided for in the Data Sheet (see Point 4.2), the grant must not produce a profit (i.e. surplus of the amount obtained following Step 2 plus the action's revenues, over the eligible costs and contributions approved by the granting authority).

'Revenue' is all income generated by the action, during its duration (see Article 4), for beneficiaries that are profit legal entities (— with the exception of income generated by the exploitation of results, which are not considered as revenues).

If there is a profit, it will be deducted in proportion to the final rate of reimbursement of the eligible costs approved by the granting authority (as compared to the amount calculated following Steps 1 and 2 minus the contributions).

The **balance** (final payment) is then calculated by deducting the total amount of prefinancing and interim payments already made (if any), from the final grant amount:

{final grant amount

minus

{prefinancing and interim payments made (if any)}}.

If the balance is **positive**, it will be **paid** to the coordinator.

The amount retained for the Mutual Insurance Mechanism (see above) will be released and **paid** to the coordinator (in accordance with the rules governing the Mechanism).

The final payment (or part of it) may be offset (without the beneficiaries' consent) against amounts owed by a beneficiary to the granting authority — up to the amount due to that beneficiary.

For grants where the granting authority is the European Commission or an EU executive agency,

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offsetting may also be done against amounts owed to other Commission services or executive agencies.

Payments will not be made if the payment deadline or payments are suspended (see Articles 29 and 30).

If — despite the release of the Mutual Insurance Mechanism contribution — the balance is **negative**, it will be **recovered** in accordance with the following procedure:

The granting authority will send a **pre-information letter** to the coordinator:

- formally notifying the intention to recover, the final grant amount, the amount to be recovered and the reasons why
- requesting a report on the distribution of payments to the beneficiaries within 30 days of receiving notification and
- requesting observations within 30 days of receiving notification.

If no observations are submitted (or the granting authority decides to pursue recovery despite the observations it has received) and the coordinator has submitted the report on the distribution of payments, it will calculate the **share of the debt per beneficiary**, by:

(a) identifying the beneficiaries for which the amount calculated as follows is negative:

{{{total accepted EU contribution for the beneficiary

divided by

total accepted EU contribution for the action}

multiplied by

final grant amount for the action},

minus

{prefinancing and interim payments received by the beneficiary (if any)}}

and

(b) dividing the debt:

{{amount calculated according to point (a) for the beneficiary concerned

divided by

the sum of the amounts calculated according to point (a) for all the beneficiaries identified according to point (a)}

multiplied by

the amount to be recovered}.

and confirm the amount to be recovered from each beneficiary concerned (**confirmation letter**), together with **debit notes** with the terms and date for payment.

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The debit notes for beneficiaries will include the amounts calculated for their affiliated entities (if any).

If the coordinator has not submitted the report on the distribution of payments, the granting authority will **recover** the full amount from the coordinator (**confirmation letter** and **debit note** with the terms and date for payment).

If payment is not made by the date specified in the debit note, the granting authority will **enforce recovery** in accordance with Article 22.4.

22.3.5 Audit implementation after final payment — Revised final grant amount — Recovery

If — after the final payment (in particular, after checks, reviews, audits or investigations; see Article 25) — the granting authority rejects costs or contributions (see Article 27) or reduces the grant (see Article 28), it will calculate the **revised final grant amount** for the beneficiary concerned.

The **beneficiary revised final grant amount** will be calculated in the following step:

Step 1 — Calculation of the revised total accepted EU contribution

Step 1 — Calculation of the revised total accepted EU contribution

The granting authority will first calculate the 'revised accepted EU contribution' for the beneficiary, by calculating the 'revised accepted costs' and 'revised accepted contributions'.

After that, it will take into account grant reductions (if any). The resulting 'revised total accepted EU contribution' is the beneficiary revised final grant amount.

If the revised final grant amount is lower than the beneficiary's final grant amount (i.e. its share in the final grant amount for the action), it will be **recovered** in accordance with the following procedure:

The **beneficiary final grant amount** (i.e. share in the final grant amount for the action) is calculated as follows:

{{total accepted EU contribution for the beneficiary

divided by

total accepted EU contribution for the action}

multiplied by

final grant amount for the action}.

The granting authority will send a **pre-information letter** to the beneficiary concerned:

- formally notifying the intention to recover, the amount to be recovered and the reasons why and
- requesting observations within 30 days of receiving notification.

If no observations are submitted (or the granting authority decides to pursue recovery despite the observations it has received), it will confirm the amount to be recovered (**confirmation letter**), together with a **debit note** with the terms and the date for payment.

Recoveries against affiliated entities (if any) will be handled through their beneficiaries.

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If payment is not made by the date specified in the debit note, the granting authority will **enforce recovery** in accordance with Article 22.4.

22.4 Enforced recovery

If payment is not made by the date specified in the debit note, the amount due will be recovered:

(a) by offsetting the amount — without the coordinator or beneficiary's consent — against any amounts owed to the coordinator or beneficiary by the granting authority.

In exceptional circumstances, to safeguard the EU financial interests, the amount may be offset before the payment date specified in the debit note.

For grants where the granting authority is the European Commission or an EU executive agency, debts may also be offset against amounts owed by other Commission services or executive agencies.

(b) financial guarantee(s): not applicable

(c) joint and several liability of beneficiaries: not applicable

(d) by holding affiliated entities jointly and severally liable (if any, see Data Sheet, Point 4.4)

(e) by taking legal action (see Article 43) or, provided that the granting authority is the European Commission or an EU executive agency, by adopting an enforceable decision under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 100(2) of EU Financial Regulation 2018/1046.

If the Mutual Insurance Mechanism was called on by the granting authority to intervene, recovery will be continued in the name of the Mutual Insurance Mechanism. If two debit notes were sent, the second one (in the name of the Mutual Insurance Mechanism) will be considered to replace the first one (in the name of the granting authority). Where the MIM intervened, offsetting, enforceable decisions or any other of the above-mentioned forms of enforced recovery may be used mutatis mutandis.

The amount to be recovered will be increased by **late-payment interest** at the rate set out in Article 22.5, from the day following the payment date in the debit note, up to and including the date the full payment is received.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2015/2366[17] applies.

For grants where the granting authority is an EU executive agency, enforced recovery by offsetting or enforceable decision will be done by the services of the European Commission (see also Article 43).

22.5 Consequences of non-compliance

[17] Directive (EU) 2015/2366 of the European Parliament and of the Council of 25 November 2015 on payment services in the internal market, amending Directives 2002/65/EC, 2009/110/EC and 2013/36/EU and Regulation (EU) No 1093/2010, and repealing Directive 2007/64/EC (OJ L 337, 23.12.2015, p. 35).

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22.5.1 If the granting authority does not pay within the payment deadlines (see above), the beneficiaries are entitled to **late-payment interest** at the rate applied by the European Central Bank (ECB) for its main refinancing operations in euros ('reference rate'), plus the rate specified in the Data Sheet (Point 4.2). The reference rate is the rate in force on the first day of the month in which the payment deadline expires, as published in the C series of the *Official Journal of the European Union*.

If the late-payment interest is lower than or equal to EUR 200, it will be paid to the coordinator only on request submitted within two months of receiving the late payment.

Late-payment interest is not due if all beneficiaries are EU Member States (including regional and local government authorities or other public bodies acting on behalf of a Member State for the purpose of this Agreement).

If payments or the payment deadline are suspended (see Articles 29 and 30), payment will not be considered as late.

Late-payment interest covers the period running from the day following the due date for payment (see above), up to and including the date of payment.

Late-payment interest is not considered for the purposes of calculating the final grant amount.

22.5.2 If the coordinator breaches any of its obligations under this Article, the grant may be reduced (see Article 29) and the grant or the coordinator may be terminated (see Article 32).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 23 — GUARANTEES

Not applicable

ARTICLE 24 — CERTIFICATES

24.1 Operational verification report (OVR)

Not applicable

24.2 Certificate on the financial statements (CFS)

If required by the granting authority (see Data Sheet, Point 4.3), the beneficiaries must provide certificates on their financial statements (CFS), in accordance with the schedule, threshold and conditions set out in the Data Sheet.

The coordinator must submit them as part of the periodic report (see Article 21).

The certificates must be drawn up using the template published on the Portal, cover the costs declared on the basis of actual costs and costs according to usual cost accounting practices (if any), and fulfil the following conditions:

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(a) be provided by a qualified approved external auditor which is independent and complies with Directive 2006/43/EC[18] (or for public bodies: by a competent independent public officer)

(b) the verification must be carried out according to the highest professional standards to ensure that the financial statements comply with the provisions under the Agreement and that the costs declared are eligible.

The certificates will not affect the granting authority's right to carry out its own checks, reviews or audits, nor preclude the European Court of Auditors (ECA), the European Public Prosecutor's Office (EPPO) or the European Anti-Fraud Office (OLAF) from using their prerogatives for audits and investigations under the Agreement (see Article 25).

If the costs (or a part of them) were already audited by the granting authority, these costs do not need to be covered by the certificate and will not be counted for calculating the threshold (if any).

24.3 Certificate on the compliance of usual cost accounting practices (CoMUC)

Not applicable

24.4 Systems and process audit (SPA)

Beneficiaries which:

- use unit, flat rate or lump sum costs or contributions according to documented (i.e. formally approved and in writing) usual costs accounting practices (if any) or

- have formalised documentation on the systems and processes for calculating their costs and contributions (i.e. formally approved and in writing), have participated in at least 150 actions under Horizon 2020 or the Euratom Research and Training Programme (2014-2018 or 2019-2020) and participate in at least 3 ongoing actions under Horizon Europe or the Euratom Research and Training Programme (2021-2025 or 2026-2027)

may apply to the granting authority for a systems and process audit (SPA).

This audit will be carried out as follows:

Step 1 – Application by the beneficiary.

Step 2 – If the application is accepted, the granting authority will carry out the systems and process audit, complemented by an audit of transactions (on a sample of the beneficiary's Horizon Europe or the Euratom Research and Training Programme financial statements).

Step 3 – The audit result will take the form of a risk assessment classification for the beneficiary: low, medium or high.

Low-risk beneficiaries will benefit from less (or less in-depth) ex-post audits (see Article 25) and a higher threshold for submitting certificates on the financial statements (CFS; see Articles 21 and 24.2 and Data Sheet, Point 4.3).

[18] Directive 2006/43/EC of the European Parliament and of the Council of 17 May 2006 on statutory audits of annual accounts and consolidated accounts or similar national regulations (OJ L 157, 9.6.2006, p. 87).

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24.5 Consequences of non-compliance

If a beneficiary does not submit a certificate on the financial statements (CFS) or the certificate is rejected, the accepted EU contribution to costs will be capped to reflect the CFS threshold.

If a beneficiary breaches any of its other obligations under this Article, the granting authority may apply the measures described in Chapter 5.

ARTICLE 25 — CHECKS, REVIEWS, AUDITS AND INVESTIGATIONS — EXTENSION OF FINDINGS

25.1 Granting authority checks, reviews and audits

25.1.1 Internal checks

The granting authority may — during the action or afterwards — check the proper implementation of the action and compliance with the obligations under the Agreement, including assessing costs and contributions, deliverables and reports.

25.1.2 Project reviews

The granting authority may carry out reviews on the proper implementation of the action and compliance with the obligations under the Agreement (general project reviews or specific issues reviews).

Such project reviews may be started during the implementation of the action and until the time-limit set out in the Data Sheet (see Point 6). They will be formally notified to the coordinator or beneficiary concerned and will be considered to start on the date of the notification.

If needed, the granting authority may be assisted by independent, outside experts. If it uses outside experts, the coordinator or beneficiary concerned will be informed and have the right to object on grounds of commercial confidentiality or conflict of interest.

The coordinator or beneficiary concerned must cooperate diligently and provide — within the deadline requested — any information and data in addition to deliverables and reports already submitted (including information on the use of resources). The granting authority may request beneficiaries to provide such information to it directly. Sensitive information and documents will be treated in accordance with Article 13.

The coordinator or beneficiary concerned may be requested to participate in meetings, including with the outside experts.

For **on-the-spot visits**, the beneficiary concerned must allow access to sites and premises (including to the outside experts) and must ensure that information requested is readily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the review findings, a **project review report** will be drawn up.

The granting authority will formally notify the project review report to the coordinator or beneficiary concerned, which has 30 days from receiving notification to make observations.

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Project reviews (including project review reports) will be in the language of the Agreement.

25.1.3 Audits

The granting authority may carry out audits on the proper implementation of the action and compliance with the obligations under the Agreement.

Such audits may be started during the implementation of the action and until the time-limit set out in the Data Sheet (see Point 6). They will be formally notified to the beneficiary concerned and will be considered to start on the date of the notification.

The granting authority may use its own audit service, delegate audits to a centralised service or use external audit firms. If it uses an external firm, the beneficiary concerned will be informed and have the right to object on grounds of commercial confidentiality or conflict of interest.

The beneficiary concerned must cooperate diligently and provide — within the deadline requested — any information (including complete accounts, individual salary statements or other personal data) to verify compliance with the Agreement. Sensitive information and documents will be treated in accordance with Article 13.

For **on-the-spot** visits, the beneficiary concerned must allow access to sites and premises (including for the external audit firm) and must ensure that information requested is readily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the audit findings, a **draft audit report** will be drawn up.

The auditors will formally notify the draft audit report to the beneficiary concerned, which has 30 days from receiving notification to make observations (contradictory audit procedure).

The **final audit report** will take into account observations by the beneficiary concerned and will be formally notified to them.

Audits (including audit reports) will be in the language of the Agreement.

25.2 European Commission checks, reviews and audits in grants of other granting authorities

Where the granting authority is not the European Commission, the latter has the same rights of checks, reviews and audits as the granting authority.

25.3 Access to records for assessing simplified forms of funding

The beneficiaries must give the European Commission access to their statutory records for the periodic assessment of simplified forms of funding which are used in EU programmes.

25.4 OLAF, EPPO and ECA audits and investigations

The following bodies may also carry out checks, reviews, audits and investigations — during the action or afterwards:

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- the European Anti-Fraud Office (OLAF) under Regulations No 883/2013[19] and No 2185/96[20]

- the European Public Prosecutor's Office (EPPO) under Regulation 2017/1939

- the European Court of Auditors (ECA) under Article 287 of the Treaty on the Functioning of the EU (TFEU) and Article 257 of EU Financial Regulation 2018/1046.

If requested by these bodies, the beneficiary concerned must provide full, accurate and complete information in the format requested (including complete accounts, individual salary statements or other personal data, including in electronic format) and allow access to sites and premises for on-the-spot visits or inspections — as provided for under these Regulations.

To this end, the beneficiary concerned must keep all relevant information relating to the action, at least until the time-limit set out in the Data Sheet (Point 6) and, in any case, until any ongoing checks, reviews, audits, investigations, litigation or other pursuits of claims have been concluded.

25.5 Consequences of checks, reviews, audits and investigations — Extension of results of reviews, audits or investigations

25.5.1 Consequences of checks, reviews, audits and investigations in this grant

Findings in checks, reviews, audits or investigations carried out in the context of this grant may lead to rejections (see Article 27), grant reduction (see Article 28) or other measures described in Chapter 5.

Rejections or grant reductions after the final payment will lead to a revised final grant amount (see Article 22).

Findings in checks, reviews, audits or investigations during the action implementation may lead to a request for amendment (see Article 39), to change the description of the action set out in Annex 1.

Checks, reviews, audits or investigations that find systemic or recurrent errors, irregularities, fraud or breach of obligations in any EU grant may also lead to consequences in other EU grants awarded under similar conditions ('extension to other grants').

Moreover, findings arising from an OLAF or EPPO investigation may lead to criminal prosecution under national law.

25.5.2 Extension from other grants

Results of checks, reviews, audits or investigations in other grants may be extended to this grant, if:

(a) the beneficiary concerned is found, in other EU grants awarded under similar conditions, to have committed systemic or recurrent errors, irregularities, fraud or breach of obligations that have a material impact on this grant and

[19] Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council of 11 September 2013 concerning investigations conducted by the European Anti-Fraud Office (OLAF) and repealing Regulation (EC) No 1073/1999 of the European Parliament and of the Council and Council Regulation (Euratom) No 1074/1999 (OJ L 248, 18/09/2013, p. 1).

[20] Council Regulation (Euratom, EC) No 2185/1996 of 11 November 1996 concerning on-the-spot checks and inspections carried out by the Commission in order to protect the European Communities' financial interests against fraud and other irregularities (OJ L 292, 15/11/1996, p. 2).

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(b) those findings are formally notified to the beneficiary concerned — together with the list of grants affected by the findings — within the time-limit for audits set out in the Data Sheet (see Point 6).

The granting authority will formally notify the beneficiary concerned of the intention to extend the findings and the list of grants affected.

If the extension concerns **rejections of costs or contributions**: the notification will include:

(a) an invitation to submit observations on the list of grants affected by the findings

(b) the request to submit revised financial statements for all grants affected

(c) the correction rate for extrapolation, established on the basis of the systemic or recurrent errors, to calculate the amounts to be rejected, if the beneficiary concerned:

(i) considers that the submission of revised financial statements is not possible or practicable or

(ii) does not submit revised financial statements.

If the extension concerns **grant reductions**: the notification will include:

(a) an invitation to submit observations on the list of grants affected by the findings and

(b) the **correction rate for extrapolation**, established on the basis of the systemic or recurrent errors and the principle of proportionality.

The beneficiary concerned has **60 days** from receiving notification to submit observations, revised financial statements or to propose a duly substantiated **alternative correction method/rate**.

On the basis of this, the granting authority will analyse the impact and decide on the implementation (i.e. start rejection or grant reduction procedures, either on the basis of the revised financial statements or the announced/alternative method/rate or a mix of those; see Articles 27 and 28).

25.6 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, costs or contributions insufficiently substantiated will be ineligible (see Article 6) and will be rejected (see Article 27), and the grant may be reduced (see Article 28).

Such breaches may also lead to other measures described in Chapter 5.

ARTICLE 26 — IMPACT EVALUATIONS

26.1 Impact evaluation

The granting authority may carry out impact evaluations of the action, measured against the objectives and indicators of the EU programme funding the grant.

Such evaluations may be started during implementation of the action and until the time-limit set out

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in the Data Sheet (see Point 6). They will be formally notified to the coordinator or beneficiaries and will be considered to start on the date of the notification.

If needed, the granting authority may be assisted by independent outside experts.

The coordinator or beneficiaries must provide any information relevant to evaluate the impact of the action, including information in electronic format.

26.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the granting authority may apply the measures described in Chapter 5.

CHAPTER 5 CONSEQUENCES OF NON-COMPLIANCE

SECTION 1 REJECTIONS AND GRANT REDUCTION

ARTICLE 27 — REJECTION OF COSTS AND CONTRIBUTIONS

27.1 Conditions

The granting authority will — at beneficiary termination, interim payment, final payment or afterwards — reject any costs or contributions which are ineligible (see Article 6), in particular following checks, reviews, audits or investigations (see Article 25).

The rejection may also be based on the extension of findings from other grants to this grant (see Article 25).

Ineligible costs or contributions will be rejected.

27.2 Procedure

If the rejection does not lead to a recovery, the granting authority will formally notify the coordinator or beneficiary concerned of the rejection, the amounts and the reasons why. The coordinator or beneficiary concerned may — within 30 days of receiving notification — submit observations if it disagrees with the rejection (payment review procedure).

If the rejection leads to a recovery, the granting authority will follow the contradictory procedure with pre-information letter set out in Article 22.

27.3 Effects

If the granting authority rejects costs or contributions, it will deduct them from the costs or contributions declared and then calculate the amount due (and, if needed, make a recovery; see Article 22).

ARTICLE 28 — GRANT REDUCTION

28.1 Conditions

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The granting authority may — at beneficiary termination, final payment or afterwards — reduce the grant for a beneficiary, if:

(a) the beneficiary (or a person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed:

(i) substantial errors, irregularities or fraud or

(ii) serious breach of obligations under this Agreement or during its award (including improper implementation of the action, non-compliance with the call conditions, submission of false information, failure to provide required information, breach of ethics or security rules (if applicable), etc.), or

(b) the beneficiary (or a person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed — in other EU grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (see Article 25).

The amount of the reduction will be calculated for each beneficiary concerned and proportionate to the seriousness and the duration of the errors, irregularities or fraud or breach of obligations, by applying an individual reduction rate to their accepted EU contribution.

28.2 Procedure

If the grant reduction does not lead to a recovery, the granting authority will formally notify the coordinator or beneficiary concerned of the reduction, the amount to be reduced and the reasons why. The coordinator or beneficiary concerned may — within 30 days of receiving notification — submit observations if it disagrees with the reduction (payment review procedure).

If the grant reduction leads to a recovery, the granting authority will follow the contradictory procedure with pre-information letter set out in Article 22.

28.3 Effects

If the granting authority reduces the grant, it will deduct the reduction and then calculate the amount due (and, if needed, make a recovery; see Article 22).

SECTION 2 SUSPENSION AND TERMINATION

ARTICLE 29 — PAYMENT DEADLINE SUSPENSION

29.1 Conditions

The granting authority may — at any moment — suspend the payment deadline if a payment cannot be processed because:

(a) the required report (see Article 21) has not been submitted or is not complete or additional information is needed

(b) there are doubts about the amount to be paid (e.g. ongoing audit extension procedure, queries

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about eligibility, need for a grant reduction, etc.) and additional checks, reviews, audits or investigations are necessary, or

(c) there are other issues affecting the EU financial interests.

29.2 Procedure

The granting authority will formally notify the coordinator of the suspension and the reasons why.

The suspension will **take effect** the day the notification is sent.

If the conditions for suspending the payment deadline are no longer met, the suspension will be **lifted** — and the remaining time to pay (see Data Sheet, Point 4.2) will resume.

If the suspension exceeds two months, the coordinator may request the granting authority to confirm if the suspension will continue.

If the payment deadline has been suspended due to the non-compliance of the report and the revised report is not submitted (or was submitted but is also rejected), the granting authority may also terminate the grant or the participation of the coordinator (see Article 32).

ARTICLE 30 — PAYMENT SUSPENSION

30.1 Conditions

The granting authority may — at any moment — suspend payments, in whole or in part for one or more beneficiaries, if:

(a) a beneficiary (or a person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed or is suspected of having committed:

(i) substantial errors, irregularities or fraud or

(ii) serious breach of obligations under this Agreement or during its award (including improper implementation of the action, non-compliance with the call conditions, submission of false information, failure to provide required information, breach of ethics or security rules (if applicable), etc.), or

(b) a beneficiary (or a person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed — in other EU grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant.

If payments are suspended for one or more beneficiaries, the granting authority will make partial payment(s) for the part(s) not suspended. If suspension concerns the final payment, the payment (or recovery) of the remaining amount after suspension is lifted will be considered to be the payment that closes the action.

30.2 Procedure

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Before suspending payments, the granting authority will send a **pre-information letter** to the beneficiary concerned:

- formally notifying the intention to suspend payments and the reasons why and
- requesting observations within 30 days of receiving notification.

If the granting authority does not receive observations or decides to pursue the procedure despite the observations it has received, it will confirm the suspension (**confirmation letter**). Otherwise, it will formally notify that the procedure is discontinued.

At the end of the suspension procedure, the granting authority will also inform the coordinator.

The suspension will **take effect** the day after the confirmation notification is sent.

If the conditions for resuming payments are met, the suspension will be **lifted**. The granting authority will formally notify the beneficiary concerned (and the coordinator) and set the suspension end date.

During the suspension, no prefinancing will be paid to the beneficiaries concerned. For interim payments, the periodic reports for all reporting periods except the last one (see Article 21) must not contain any financial statements from the beneficiary concerned (or its affiliated entities). The coordinator must include them in the next periodic report after the suspension is lifted or — if suspension is not lifted before the end of the action — in the last periodic report.

ARTICLE 31 — GRANT AGREEMENT SUSPENSION

31.1 Consortium-requested GA suspension

31.1.1 Conditions and procedure

The beneficiaries may request the suspension of the grant or any part of it, if exceptional circumstances — in particular *force majeure* (see Article 35) — make implementation impossible or excessively difficult.

The coordinator must submit a request for **amendment** (see Article 39), with:

- the reasons why
- the date the suspension takes effect; this date may be before the date of the submission of the amendment request and
- the expected date of resumption.

The suspension will **take effect** on the day specified in the amendment.

Once circumstances allow for implementation to resume, the coordinator must immediately request another **amendment** of the Agreement to set the suspension end date, the resumption date (one day after suspension end date), extend the duration and make other changes necessary to adapt the action to the new situation (see Article 39) — unless the grant has been terminated (see Article 32). The suspension will be **lifted** with effect from the suspension end date set out in the amendment. This date may be before the date of the submission of the amendment request.

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During the suspension, no prefinancing will be paid. Costs incurred or contributions for activities implemented during grant suspension are not eligible (see Article 6.3).

31.2 EU-initiated GA suspension

31.2.1 Conditions

The granting authority may suspend the grant or any part of it, if:

(a) a beneficiary (or a person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed or is suspected of having committed:

(i) substantial errors, irregularities or fraud or

(ii) serious breach of obligations under this Agreement or during its award (including improper implementation of the action, non-compliance with the call conditions, submission of false information, failure to provide required information, breach of ethics or security rules (if applicable), etc.), or

(b) a beneficiary (or a person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed — in other EU grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant

(c) other:

(i) linked action issues: not applicable

(ii) the action has lost its scientific or technological relevance, for EIC Accelerator actions: the action has lost its economic relevance, for challenge-based EIC Pathfinder actions and Horizon Europe Missions: the action has lost its relevance as part of the Portfolio for which it has been initially selected

31.2.2 Procedure

Before suspending the grant, the granting authority will send a **pre-information letter** to the coordinator:

- formally notifying the intention to suspend the grant and the reasons why and
- requesting observations within 30 days of receiving notification.

If the granting authority does not receive observations or decides to pursue the procedure despite the observations it has received, it will confirm the suspension (**confirmation letter**). Otherwise, it will formally notify that the procedure is discontinued.

The suspension will **take effect** the day after the confirmation notification is sent (or on a later date specified in the notification).

Once the conditions for resuming implementation of the action are met, the granting authority will formally notify the coordinator a **lifting of suspension letter**, in which it will set the suspension end date and invite the coordinator to request an amendment of the Agreement to set the resumption

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date (one day after suspension end date), extend the duration and make other changes necessary to adapt the action to the new situation (see Article 39) — unless the grant has been terminated (see Article 32). The suspension will be **lifted** with effect from the suspension end date set out in the lifting of suspension letter. This date may be before the date on which the letter is sent.

During the suspension, no prefinancing will be paid. Costs incurred or contributions for activities implemented during suspension are not eligible (see Article 6.3).

The beneficiaries may not claim damages due to suspension by the granting authority (see Article 33).

Grant suspension does not affect the granting authority's right to terminate the grant or a beneficiary (see Article 32) or reduce the grant (see Article 28).

ARTICLE 32 — GRANT AGREEMENT OR BENEFICIARY TERMINATION

32.1 Consortium-requested GA termination

32.1.1 Conditions and procedure

The beneficiaries may request the termination of the grant.

The coordinator must submit a request for **amendment** (see Article 39), with:

- the reasons why
- the date the consortium ends work on the action ('end of work date') and
- the date the termination takes effect ('termination date'); this date must be after the date of the submission of the amendment request.

The termination will **take effect** on the termination date specified in the amendment.

If no reasons are given or if the granting authority considers the reasons do not justify termination, it may consider the grant terminated improperly.

32.1.2 Effects

The coordinator must — within 60 days from when termination takes effect — submit a **periodic report** (for the open reporting period until termination).

The granting authority will calculate the final grant amount and final payment on the basis of the report submitted and taking into account the costs incurred and contributions for activities implemented before the end of work date (see Article 22). Costs relating to contracts due for execution only after the end of work are not eligible.

If the granting authority does not receive the report within the deadline, only costs and contributions which are included in an approved periodic report will be taken into account (no costs/contributions if no periodic report was ever approved).

Improper termination may lead to a grant reduction (see Article 28).

After termination, the beneficiaries' obligations (in particular Articles 13 (confidentiality and security), 16 (IPR), 17 (communication, dissemination and visibility), 21 (reporting), 25 (checks,

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reviews, audits and investigations), 26 (impact evaluation), 27 (rejections), 28 (grant reduction) and 42 (assignment of claims)) continue to apply.

32.2 Consortium-requested beneficiary termination

32.2.1 Conditions and procedure

The coordinator may request the termination of the participation of one or more beneficiaries, on request of the beneficiary concerned or on behalf of the other beneficiaries.

The coordinator must submit a request for **amendment** (see Article 39), with:

- the reasons why
- the opinion of the beneficiary concerned (or proof that this opinion has been requested in writing)
- the date the beneficiary ends work on the action ('end of work date')
- the date the termination takes effect ('termination date'); this date must be after the date of the submission of the amendment request.

If the termination concerns the coordinator and is done without its agreement, the amendment request must be submitted by another beneficiary (acting on behalf of the consortium).

The termination will **take effect** on the termination date specified in the amendment.

If no information is given or if the granting authority considers that the reasons do not justify termination, it may consider the beneficiary to have been terminated improperly.

32.2.2 Effects

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a **report on the distribution of payments** to the beneficiary concerned

(ii) a **termination report** from the beneficiary concerned, for the open reporting period until termination, containing an overview of the progress of the work, the financial statement, the explanation on the use of resources, and, if applicable, the certificate on the financial statement (CFS; see Articles 21 and 24.2 and Data Sheet, Point 4.3)

(iii) a second **request for amendment** (see Article 39) with other amendments needed (e.g. reallocation of the tasks and the estimated budget of the terminated beneficiary; addition of a new beneficiary to replace the terminated beneficiary; change of coordinator, etc.).

The granting authority will calculate the amount due to the beneficiary on the basis of the report submitted and taking into account the costs incurred and contributions for activities implemented before the end of work date (see Article 22). Costs relating to contracts due for execution only after the end of work are not eligible.

The information in the termination report must also be included in the periodic report for the next reporting period (see Article 21).

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If the granting authority does not receive the termination report within the deadline, only costs and contributions which are included in an approved periodic report will be taken into account (no costs/ contributions if no periodic report was ever approved).

If the granting authority does not receive the report on the distribution of payments within the deadline, it will consider that:

- the coordinator did not distribute any payment to the beneficiary concerned and that
- the beneficiary concerned must not repay any amount to the coordinator.

If the second request for amendment is accepted by the granting authority, the Agreement is **amended** to introduce the necessary changes (see Article 39).

If the second request for amendment is rejected by the granting authority (because it calls into question the decision awarding the grant or breaches the principle of equal treatment of applicants), the grant may be terminated (see Article 32).

Improper termination may lead to a reduction of the grant (see Article 31) or grant termination (see Article 32).

After termination, the concerned beneficiary's obligations (in particular Articles 13 (confidentiality and security), 16 (IPR), 17 (communication, dissemination and visibility), 21 (reporting), 25 (checks, reviews, audits and investigations), 26 (impact evaluation), 27 (rejections), 28 (grant reduction) and 42 (assignment of claims)) continue to apply.

32.3 EU-initiated GA or beneficiary termination

32.3.1 Conditions

The granting authority may terminate the grant or the participation of one or more beneficiaries, if:

(a) one or more beneficiaries do not accede to the Agreement (see Article 40)

(b) a change to the action or the legal, financial, technical, organisational or ownership situation of a beneficiary is likely to substantially affect the implementation of the action or calls into question the decision to award the grant (including changes linked to one of the exclusion grounds listed in the declaration of honour)

(c) following termination of one or more beneficiaries, the necessary changes to the Agreement (and their impact on the action) would call into question the decision awarding the grant or breach the principle of equal treatment of applicants

(d) implementation of the action has become impossible or the changes necessary for its continuation would call into question the decision awarding the grant or breach the principle of equal treatment of applicants

(e) a beneficiary (or person with unlimited liability for its debts) is subject to bankruptcy proceedings or similar (including insolvency, winding-up, administration by a liquidator or court, arrangement with creditors, suspension of business activities, etc.)

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(f) a beneficiary (or person with unlimited liability for its debts) is in breach of social security or tax obligations

(g) a beneficiary (or person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has been found guilty of grave professional misconduct

(h) a beneficiary (or person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed fraud, corruption, or is involved in a criminal organisation, money laundering, terrorism-related crimes (including terrorism financing), child labour or human trafficking

(i) a beneficiary (or person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) was created under a different jurisdiction with the intent to circumvent fiscal, social or other legal obligations in the country of origin (or created another entity with this purpose)

(j) a beneficiary (or person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed:

  (i) substantial errors, irregularities or fraud or

  (ii) serious breach of obligations under this Agreement or during its award (including improper implementation of the action, non-compliance with the call conditions, submission of false information, failure to provide required information, breach of ethics or security rules (if applicable), etc.)

(k) a beneficiary (or person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed — in other EU grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (extension of findings from other grants to this grant; see Article 25)

(l) despite a specific request by the granting authority, a beneficiary does not request — through the coordinator — an amendment to the Agreement to end the participation of one of its affiliated entities or associated partners that is in one of the situations under points (d), (f), (e), (g), (h), (i) or (j) and to reallocate its tasks, or

(m) other:

  (i) linked action issues: not applicable

  (ii) the action has lost its scientific or technological relevance, for EIC Accelerator actions: the action has lost its economic relevance, for challenge-based EIC Pathfinder actions and Horizon Europe Missions: the action has lost its relevance as part of the Portfolio for which it has been initially selected

32.3.2 Procedure

Before terminating the grant or participation of one or more beneficiaries, the granting authority will send **a pre-information letter** to the coordinator or beneficiary concerned:

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- formally notifying the intention to terminate and the reasons why and
- requesting observations within 30 days of receiving notification.

If the granting authority does not receive observations or decides to pursue the procedure despite the observations it has received, it will confirm the termination and the date it will take effect (**confirmation letter**). Otherwise, it will formally notify that the procedure is discontinued.

For beneficiary terminations, the granting authority will — at the end of the procedure — also inform the coordinator.

The termination will **take effect** the day after the confirmation notification is sent (or on a later date specified in the notification; 'termination date').

32.3.3 Effects

(a) for **GA termination**:

The coordinator must — within 60 days from when termination takes effect — submit a **periodic report** (for the last open reporting period until termination).

The granting authority will calculate the final grant amount and final payment on the basis of the report submitted and taking into account the costs incurred and contributions for activities implemented before termination takes effect (see Article 22). Costs relating to contracts due for execution only after termination are not eligible.

If the grant is terminated for breach of the obligation to submit reports, the coordinator may not submit any report after termination.

If the granting authority does not receive the report within the deadline, only costs and contributions which are included in an approved periodic report will be taken into account (no costs/contributions if no periodic report was ever approved).

Termination does not affect the granting authority's right to reduce the grant (see Article 28) or to impose administrative sanctions (see Article 34).

The beneficiaries may not claim damages due to termination by the granting authority (see Article 33).

After termination, the beneficiaries' obligations (in particular Articles 13 (confidentiality and security), 16 (IPR), 17 (communication, dissemination and visibility), 21 (reporting), 25 (checks, reviews, audits and investigations), 26 (impact evaluation), 27 (rejections), 28 (grant reduction) and 42 (assignment of claims)) continue to apply.

(b) for **beneficiary termination**:

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a **report on the distribution of payments** to the beneficiary concerned

(ii) a **termination report** from the beneficiary concerned, for the open reporting period until termination, containing an overview of the progress of the work, the financial

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statement, the explanation on the use of resources, and, if applicable, the certificate on the financial statement (CFS; see Articles 21 and 24.2 and Data Sheet, Point 4.3)

(iii) a **request for amendment** (see Article 39) with any amendments needed (e.g. reallocation of the tasks and the estimated budget of the terminated beneficiary; addition of a new beneficiary to replace the terminated beneficiary; change of coordinator, etc.).

The granting authority will calculate the amount due to the beneficiary on the basis of the report submitted and taking into account the costs incurred and contributions for activities implemented before termination takes effect (see Article 22). Costs relating to contracts due for execution only after termination are not eligible.

The information in the termination report must also be included in the periodic report for the next reporting period (see Article 21).

If the granting authority does not receive the termination report within the deadline, only costs and contributions included in an approved periodic report will be taken into account (no costs/ contributions if no periodic report was ever approved).

If the granting authority does not receive the report on the distribution of payments within the deadline, it will consider that:

- the coordinator did not distribute any payment to the beneficiary concerned and that
- the beneficiary concerned must not repay any amount to the coordinator.

If the request for amendment is accepted by the granting authority, the Agreement is **amended** to introduce the necessary changes (see Article 39).

If the request for amendment is rejected by the granting authority (because it calls into question the decision awarding the grant or breaches the principle of equal treatment of applicants), the grant may be terminated (see Article 32).

After termination, the concerned beneficiary's obligations (in particular Articles 13 (confidentiality and security), 16 (IPR), 17 (communication, dissemination and visibility), 21 (reporting), 25 (checks, reviews, audits and investigations), 26 (impact evaluation), 27 (rejections), 28 (grant reduction) and 42 (assignment of claims)) continue to apply.

SECTION 3 OTHER CONSEQUENCES: DAMAGES AND ADMINISTRATIVE SANCTIONS

ARTICLE 33 — DAMAGES

33.1 Liability of the granting authority

The granting authority cannot be held liable for any damage caused to the beneficiaries or to third parties as a consequence of the implementation of the Agreement, including for gross negligence.

The granting authority cannot be held liable for any damage caused by any of the beneficiaries or other participants involved in the action, as a consequence of the implementation of the Agreement.

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33.2 Liability of the beneficiaries

The beneficiaries must compensate the granting authority for any damage it sustains as a result of the implementation of the action or because the action was not implemented in full compliance with the Agreement, provided that it was caused by gross negligence or wilful act.

The liability does not extend to indirect or consequential losses or similar damage (such as loss of profit, loss of revenue or loss of contracts), provided such damage was not caused by wilful act or by a breach of confidentiality.

ARTICLE 34 — ADMINISTRATIVE SANCTIONS AND OTHER MEASURES

Nothing in this Agreement may be construed as preventing the adoption of administrative sanctions (i.e. exclusion from EU award procedures and/or financial penalties) or other public law measures, in addition or as an alternative to the contractual measures provided under this Agreement (see, for instance, Articles 135 to 145 EU Financial Regulation 2018/1046 and Articles 4 and 7 of Regulation 2988/95[21]).

SECTION 4 FORCE MAJEURE

ARTICLE 35 — FORCE MAJEURE

A party prevented by force majeure from fulfilling its obligations under the Agreement cannot be considered in breach of them.

'Force majeure' means any situation or event that:

- prevents either party from fulfilling their obligations under the Agreement,
- was unforeseeable, exceptional situation and beyond the parties' control,
- was not due to error or negligence on their part (or on the part of other participants involved in the action), and
- proves to be inevitable in spite of exercising all due diligence.

Any situation constituting force majeure must be formally notified to the other party without delay, stating the nature, likely duration and foreseeable effects.

The parties must immediately take all the necessary steps to limit any damage due to force majeure and do their best to resume implementation of the action as soon as possible.

CHAPTER 6 FINAL PROVISIONS

ARTICLE 36 — COMMUNICATION BETWEEN THE PARTIES

36.1 Forms and means of communication — Electronic management

[21] Council Regulation (EC, Euratom) No 2988/95 of 18 December 1995 on the protection of the European Communities financial interests (OJ L 312, 23.12.1995, p. 1).

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EU grants are managed fully electronically through the EU Funding & Tenders Portal ('Portal').

All communications must be made electronically through the Portal, in accordance with the Portal Terms and Conditions and using the forms and templates provided there (except if explicitly instructed otherwise by the granting authority).

Communications must be made in writing and clearly identify the grant agreement (project number and acronym).

Communications must be made by persons authorised according to the Portal Terms and Conditions. For naming the authorised persons, each beneficiary must have designated — before the signature of this Agreement — a 'legal entity appointed representative (LEAR)'. The role and tasks of the LEAR are stipulated in their appointment letter (see Portal Terms and Conditions).

If the electronic exchange system is temporarily unavailable, instructions will be given on the Portal.

36.2 Date of communication

The sending date for communications made through the Portal will be the date and time of sending, as indicated by the time logs.

The receiving date for communications made through the Portal will be the date and time the communication is accessed, as indicated by the time logs. Formal notifications that have not been accessed within 10 days after sending, will be considered to have been accessed (see Portal Terms and Conditions).

If a communication is exceptionally made on paper (by e-mail or postal service), general principles apply (i.e. date of sending/receipt). Formal notifications by registered post with proof of delivery will be considered to have been received either on the delivery date registered by the postal service or the deadline for collection at the post office.

If the electronic exchange system is temporarily unavailable, the sending party cannot be considered in breach of its obligation to send a communication within a specified deadline.

36.3 Addresses for communication

The Portal can be accessed via the Europa website.

The address for paper communications to the granting authority (if exceptionally allowed) is the official mailing address indicated on its website.

For beneficiaries, it is the legal address specified in the Portal Participant Register.

ARTICLE 37 — INTERPRETATION OF THE AGREEMENT

The provisions in the Data Sheet take precedence over the rest of the Terms and Conditions of the Agreement.

Annex 5 takes precedence over the Terms and Conditions; the Terms and Conditions take precedence over the Annexes other than Annex 5.

Annex 2 takes precedence over Annex 1.

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ARTICLE 38 — CALCULATION OF PERIODS AND DEADLINES

In accordance with Regulation No 1182/71[22], periods expressed in days, months or years are calculated from the moment the triggering event occurs.

The day during which that event occurs is not considered as falling within the period.

'Days' means calendar days, not working days.

ARTICLE 39 — AMENDMENTS

39.1 Conditions

The Agreement may be amended, unless the amendment entails changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

Amendments may be requested by any of the parties.

39.2 Procedure

The party requesting an amendment must submit a request for amendment signed directly in the Portal Amendment tool.

The coordinator submits and receives requests for amendment on behalf of the beneficiaries (see Annex 3). 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 and
- for a change of coordinator without its agreement: the opinion of the coordinator (or proof that this opinion has been requested in writing).

The granting authority may request additional information.

If the party receiving the request agrees, it must sign the amendment in the tool within 45 days of receiving notification (or any additional information the granting authority has requested). If it does not agree, it must formally notify its disagreement within the same deadline. The deadline may be extended, if necessary for the assessment of the request. If no notification is received within the deadline, the request is considered to have been rejected.

An amendment **enters into force** on the day of the signature of the receiving party.

An amendment **takes effect** on the date of entry into force or other date specified in the amendment.

[22] Regulation (EEC, Euratom) No 1182/71 of the Council of 3 June 1971 determining the rules applicable to periods, dates and time-limits (OJ L 124, 8/6/1971, p. 1).

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ARTICLE 40 — ACCESSION AND ADDITION OF NEW BENEFICIARIES

40.1 Accession of the beneficiaries mentioned in the Preamble

The beneficiaries which are not coordinator must accede to the grant by signing the accession form (see Annex 3) directly in the Portal Grant Preparation tool, within 30 days after the entry into force of the Agreement (see Article 44).

They will assume the rights and obligations under the Agreement with effect from the date of its entry into force (see Article 44).

If a beneficiary does not accede to the grant within the above deadline, the coordinator must — within 30 days — request an amendment (see Article 39) to terminate the beneficiary and make any changes necessary to ensure proper implementation of the action. This does not affect the granting authority's right to terminate the grant (see Article 32).

40.2 Addition of new beneficiaries

In justified cases, the beneficiaries may request the addition of a new beneficiary.

For this purpose, the coordinator must submit a request for amendment in accordance with Article 39. It must include an accession form (see Annex 3) signed by the new beneficiary directly in the Portal Amendment tool.

New beneficiaries will assume the rights and obligations under the Agreement with effect from the date of their accession specified in the accession form (see Annex 3).

Additions are also possible in mono-beneficiary grants.

ARTICLE 41 — TRANSFER OF THE AGREEMENT

In justified cases, the beneficiary of a mono-beneficiary grant may request the transfer of the grant to a new beneficiary, provided that this would not call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

The beneficiary must submit a request for **amendment** (see Article 39), with

- the reasons why
- the accession form (see Annex 3) signed by the new beneficiary directly in the Portal Amendment tool and
- additional supporting documents (if required by the granting authority).

The new beneficiary will assume the rights and obligations under the Agreement with effect from the date of accession specified in the accession form (see Annex 3).

ARTICLE 42 — ASSIGNMENTS OF CLAIMS FOR PAYMENT AGAINST THE GRANTING AUTHORITY

The beneficiaries may not assign any of their claims for payment against the granting authority to

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any third party, except if expressly approved in writing by the granting authority on the basis of a reasoned, written request by the coordinator (on behalf of the beneficiary concerned).

If the granting authority has not accepted the assignment or if the terms of it are not observed, the assignment will have no effect on it.

In no circumstances will an assignment release the beneficiaries from their obligations towards the granting authority.

ARTICLE 43 — APPLICABLE LAW AND SETTLEMENT OF DISPUTES

43.1 Applicable law

The Agreement is governed by the applicable EU law, supplemented if necessary by the law of Belgium.

Special rules may apply for beneficiaries which are international organisations (if any; see Data Sheet, Point 5).

43.2 Dispute settlement

If a dispute concerns the interpretation, application or validity of the Agreement, the parties must bring action before the EU General Court — or, on appeal, the EU Court of Justice — under Article 272 of the Treaty on the Functioning of the EU (TFEU).

For non-EU beneficiaries (if any), such disputes must be brought before the courts of Brussels, Belgium — unless an international agreement provides for the enforceability of EU court judgements.

For beneficiaries with arbitration as special dispute settlement forum (if any; see Data Sheet, Point 5), the dispute will — in the absence of an amicable settlement — be settled in accordance with the Rules for Arbitration published on the Portal.

If a dispute concerns administrative sanctions, offsetting or an enforceable decision under Article 299 TFEU (see Articles 22 and 34), the beneficiaries must bring action before the General Court — or, on appeal, the Court of Justice — under Article 263 TFEU.

For grants where the granting authority is an EU executive agency (see Preamble), actions against offsetting and enforceable decisions must be brought against the European Commission (not against the granting authority; see also Article 22).

ARTICLE 44 — ENTRY INTO FORCE

The Agreement will enter into force on the day of signature by the granting authority or the coordinator, depending on which is later.

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SIGNATURES

For the coordinator

For the granting authority

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ANNEX 1

Horizon Europe (HORIZON)

Description of the action (DoA)

Part A

Part B

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DESCRIPTION OF THE ACTION (PART A)

COVER PAGE

Part A of the Description of the Action (DoA) must be completed directly on the Portal Grant Preparation screens.

PROJECT *Grant Preparation (General Information screen) — Enter the info.*	
Project number:	101095672
Project name:	PHYSICS INFORMED MACHINE LEARNING-BASED PREDICTION AND REVERSION OF IMPAIRED FASTING GLUCOSE MANAGEMENT
Project acronym:	PRAESIIDIUM
Call:	HORIZON-HLTH-2022-STAYHLTH-02
Topic:	HORIZON-HLTH-2022-STAYHLTH-02-01
Type of action:	HORIZON-RIA
Service:	HADEA/A/03
Project starting date:	fixed date: 1 January 2023
Project duration:	36 months

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PROJECT SUMMARY

Project summary

Grant Preparation (General Information screen) — Provide an overall description of your project (including context and overall objectives, planned activities and main achievements, and expected results and impacts (on target groups, change procedures, capacities, innovation etc)). This summary should give readers a clear idea of what your project is about.

Use the project summary from your proposal.

The incidence of undiagnosed diabetes accounts for 36% European adults, while 541M adults worldwide have Impaired Glucose Tolerance (IGT), an important risk factor for further T2D development. Both IGT and/or Impaired Fasting Glucose (IFG) are intermediate glucose mishandling (i.e. intermediate conditions in the healthy-T2D transition) and are manifestations of the so-called prediabetes condition. Prediabetes itself is not an extensively studied condition compared to the overt T2D, but it is also a condition that can be reversed without the prescription usage to not proceed into T2D. The aim of our project is to develop a prototype tool for the real-time prediction of the prediabetic risk based on a series of patient-specific mathematical models (firstly developed during the FP7 MISSION-T2D project) that simulate metabolism, pancreas hormone production, microbiome metabolites, inflammatory process and immune system response. The prediction algorithm will be based on a “physics-informed machine learning” approach. A rich dataset of real-life data will be combined with a mathematical model to overcome the limits of a “black-box” ML approach, while reducing the computational time for simulating the solutions of a heavy mathematical models and improving its prediction performances.We will collect the necessary training data (e.g., diet questionnaire, physical activity, blood metabolites and microbiome) from already existing clinical studies (used as retrospective trials) which are representative of the real-life scenarios of a prediabetes/diabetes risk insurgence in adulthood (20-80y): family history, Metabolic Syndrome, Liver disease and obesity. A newly dedicated multicentric pilot prospective observational study will be also performed, during which we will also equip the participants with wearable sensors (e.g. glucose monitoring, bioimpedance, heart rate, accelerometer).

LIST OF PARTICIPANTS

PARTICIPANTS

Grant Preparation (Beneficiaries screen) — Enter the info.

Number	Role	Short name	Legal name	Country	PIC
1	COO	SPXL	SPINDOX LABS SRL	IT	903350816
2	BEN	CNR	CONSIGLIO NAZIONALE DELLE RICERCHE	IT	999979500
3	BEN	EDI	ELEKTRONIKAS UN DATORZINATNU INSTITUTS	LV	997829883
4	BEN	EURO	EURONET CONSULTING	BE	907542089
5	BEN	SdR	SCUOLA DI ROBOTICA	IT	951668747
6	BEN	CHK	CHECKHEALTH SWEDEN AB	SE	900926010
7	BEN	FIF	FONDAZIONE ITALIANA FEGATO ONLUS	IT	997492808
8	BEN	MUG	MEDIZINISCHE UNIVERSITAT GRAZ	AT	999836231
9	BEN	HKL	HK3 LAB S.R.L.	IT	895500121
10	BEN	UNIL	LATVIJAS UNIVERSITATE	LV	999871830
11	AP	SUPSI	SCUOLA UNIVERSITARIA PROFESSIONALE DELLA SVIZZERA ITALIANA	CH	999587620

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LIST OF WORK PACKAGES

Work packages

Grant Preparation (Work Packages screen) — Enter the info.

Work Package No	Work Package name	Lead Beneficiary	Effort (Person-Months)	Start Month	End Month	Deliverables
WP1	Project Management & coordination	1 - SPXL	59.00	1	36	D1.1 – Minutes of General Assembly D1.2 – Project quality plan, including risk contingency plan D1.3 – Project management report 1.1 D1.4 – Project management report 1.2 D1.5 – Data Mangement Plan (DMP) _ v1 D1.6 – Data Mangement Plan (DMP) _ v2
WP2	High-dimensional data: acquisition, stratification and drift analytics	6 - CHK	132.00	1	36	D2.1 – Study Initiation Package for the Retrospective analysis of clinical data, including ethical requirements clinical study D2.2 – Initial set of relevant research results and technologies D2.3 – Report of ethical requirement for the system usage D2.4 – PRAESIIDIUM framework requirements, KPIs and success criteria D2.5 – Report on the status of posting results for clinical data acquisition and preprocessing V 1 D2.6 – Report on the status of posting results for clinical data acquisition and preprocessing V 2 D2.7 – Definition of rules and algorithms for endophenotypes stratification and tracking drift along time and domains V1 D2.8 – Definition of rules and algorithms

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Work packages

Grant Preparation (Work Packages screen) — Enter the info.

Work Package No	Work Package name	Lead Beneficiary	Effort (Person-Months)	Start Month	End Month	Deliverables
						for endophenotypes stratification and tracking drift along time and domains V2
WP3	Multi-scale physics-informed ML for T2D modelling	11 - SUPSI	118.00	1	36	D3.1 – Report on the PI-ML model D3.2 – Report on X-ML model development D3.3 – Report on Data Drift prototype service
WP4	Modelling metabolic dysregulation and inflammation	2 - CNR	66.00	1	32	D4.1 – Report on first data generation D4.2 – Report on integration of microbiota model D4.3 – Report on integration with sensors data D4.4 – Report on model calibration, validation and final data generation
WP5	Development and demonstration to multiple stakeholders of interpretable physicsinformed ML-solutions.	1 - SPXL	142.00	1	36	D5.1 – A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - v1 D5.2 – A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - v2 D5.3 – PRAESIDIIUM platform
WP6	Acquisition of bio-clinical data from clinical study	7 - FIF	139.00	4	27	D6.1 – Study initiation package D6.2 – Mid-term reporting D6.3 – Report on the status of posting results D6.4 – Validated Predictive Biomarkers Report

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Work packages

Grant Preparation (Work Packages screen) — Enter the info.

Work Package No	Work Package name	Lead Beneficiary	Effort (Person-Months)	Start Month	End Month	Deliverables
WP7	Exploitation, dissemination and communication: paving the way for PRAESIIDIUM's acceptance	4 - EURO	83.00	1	36	D7.1 – Communication Plan for Dissemination and Exploitation D7.2 – Dissemination Plan and follow-up reports - v1 D7.3 – Dissemination Plan and follow-up reports - v2 D7.4 – Business Plan and Exploitation Strategy - v1 D7.5 – Business Plan and Exploitation Strategy - v2 D7.6 – Project Website

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Work package WP1 – Project Management & coordination

Work Package Number	WP1	Lead Beneficiary	1. SPXL
Work Package Name	Project Management & coordination		
Start Month	1	End Month	36

Objectives

(i)To coordinate the financial and administrative reporting requirements and communication EC partners.
(ii) To coordinate the scientific activities, monitor progress, ensure effective operation and timely delivery of results.
(iii) To undertake risk management.
(iv) To ensure gender equality and address ethical issues.
PRAESIIDIUM management structure comprises: Project Coordinator with responsibility for the successful development of the project, scientific and technological management and to ensure achievement of project objectives. SPXL Projects Office (PO) will oversee the day-to-day management tasks of the project and will give support to the project coordinator.

Description

Tasks T1.1: Overall administrative, contractual, and financial management (SPXL, all) [M1-M36]. The Project Coordinator will be the official intermediary between the consortium and the EC and will chair the General Assembly. Its responsibility will be to carry out all the contractual tasks related to the implementation of the EC contract and the project, considering the rules set up in the Consortium Agreement (CA). Besides the CA, the Project Coordinator will design the Project Quality Plan to define the communication procedures within the consortium, establish templates for all deliverables and reports, detailed annual work-plan and documentation standards to guaranty the coherence, design homogeneity and quality of the outcomes. Besides the periodic reports requested by the EC, there will be internal reports every 12 months detailing the progress of the project (technical and financial) and explaining delays and the plan for the next period.

T1.2: Coordination, monitoring and communication flows management (SPXL) [M1-M36]. The General Assembly, chaired by the Project Coordinator, will meet every 12 months, starting with a two-days kick-off meeting to launch the project (M1-13-25-36). The Project Coordinator will be responsible for the organization of these meetings, propose the agenda and circulate the minutes to all partners and the EC. The agenda will be focused on strategic project orientation, validation of global technical reports, risks and results assessment, and milestones follow-up. In case of critical issues (i.e., partner exclusion or mayor delays in planned work-plan, for instance), exceptional meetings could be organized. Communication flow: the PI will set-up a secure repository (M3) to facilitate the internal and external communication and as resource database. The website (M4) will be used to store and exchange documents, create mailing lists, generate newsletters for partners, publicize press releases related to the project, workshop announcement and hold public reports.

T1.3: Risk contingency plan (SPXL, all) [M1-M36]. The Project Coordinator, with the assistance of Scientific Coordinator, Exploitation and Dissemination Managers and all partners' contributions, will identify the risks related to the project to define the Risk Contingency Plan. This Plan will be part of the Project Quality Plan that will complement the Consortium Agreement, to guarantee the professional management of PRAESIIDIUM. The first set of risks has been identified and included in Part B section 3.2.2.

T1.4: Data Management (SPXL, all) [M1-M36]. A Data Management Plan will be prepared to detail the archiving strategies to be followed within the project for all data collected and generated during the project. SPXL will work on product data feeding into the PRAESIIDIUM catalogue and the protection of the data generated in the project. This task will also analyse all the issues related to security and privacy to guarantee compliance with the GDPR regulations and ethical guidelines.

T1.5: Ethics assessment and requirements (SdR, all) [M1-M36]. The present task will take care of all the possible ethical issues for which clinical studies and app development are concerned. The Ethics Steering Committee will provide the Ethical Self-Assessment and will overview all the processes for ethical requests to the relative commissions, the development and end-user guidance of the app.

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Work package WP2 – High-dimensional data: acquisition, stratification and drift analytics

Work Package Number	WP2	Lead Beneficiary	6. CHK
Work Package Name	High-dimensional data: acquisition, stratification and drift analytics		
Start Month	1	End Month	36

Objectives

WP2 will define the clinical context and provide the data (and data acquisition's solutions) which will be ingested in the PRAESIIDIUM tool, enabling its training through the entire project's lifespan. The main objectives will be achieved by performing the following activities: 1) Review, assessment and enabling technologies analysis for the relevant application domain; 2) Highlight of major barriers of the current State-ofthe-Art (SotA) and State of Practice (SoP) and definition of mitigation approaches to overcome them; 3) Definition of the PRAESIIDIUM clinical case-study scenarios and ingestion of clinical data from already/existing retrospective studies; 4) Identification of relevant ethics requirements for retrospective studies and definition of the multicentric pilot prospective observational study protocol; 5) Definition of KPIs and success criteria, especially in view of the pilot observational study; 6) Identification of possible data-related issues and definition of pre-processing techniques for data ingestion.

Description

T2.1: Review and acquisition of enabling technologies (CHK, SPXL, EDI, HKL) [M1-M6]. To provide the required knowledge basis for the activities especially related to wearable sensor and patients monitoring during the project, a review and evaluation of existing methodologies - hardware technologies as well as software systems - will be conducted. The activity will be carried out with the support of the project technology developers and providers due to their deep knowledge of the respective fields of specialization. This task is essential to exploit existing state-of-the-art solutions (SoA) and available standards as starting points for the project innovations, guaranteeing extensive industrial adoption and exploitation of the project results. The activity of review will cover, among others, the following specific domains fundamental for the project: Wearable sensors for physical activity monitoring as well as for fat-mass calculation, non-invasive glycaemic monitoring already available in the market; State-of-the-art sensors for diabetes and metabolism monitoring that are under development but not already in the market; Mobile apps for patients remote monitoring and diabetes prevention with particular attention to diet, physical activity, and patient education. In particular, we will consider some of the technologies developed by EDI, such as: 1) Accelerometer sensors integrated in a shape sensing fabric [https://www.edi.lv/en/solutions/smartfabric/];
2) Physical activity recognition from accelerometer data: EDI has developed energy-efficient methods for on-board physical activity classification, validated against the widely used Actigraph devices, and published it as open-source code [https://github.com/atiselsts/feature-group-selection] and a Machine learning-models for energy-efficient activity classification [https://github.com/atiselsts/onboard-activity-classification].
T2.2: Clinical case studies definition and retrospective data ingestion (FIF, MUG, UNIL, CNR, SdR, SUPSI) [M1-M12]. The clinical partners assisted by SdR will define the protocol for the retrospective analysis of the clinical studies, which will provide the first wave of data ingestion. Inclusion criteria based on clinical and biochemical requirements dictated by the math modelling (see T4.1) and review steps (see T2.1) will be defined. During the first three months of the project, ethical requests for retrospective data analysis will be presented to each relative ethical commission (M1-M3). After obtaining the ethical commissions' approval, clinical-studyspecific input data (e.g., demographic, clinical, biochemical data, food frequency questionnaire for dietary preferences and physical activity monitoring) will be collected, transferred, and prepared for data pre-processing and subsequent steps. The data transfer will be facilitated according to the Data Management Plan and GDPR and safety compliance will be secured (M4-12).
T2.3: Requirements Elicitation and consolidation (SPXL, EDI, CHK, SUPSI, CNR, SdR) [M4-M9]. The object of this task is to identify relevant functional and non-functional requirements for all the PRAESIIDIUM components and math modelling, gathered during the T1.2. The definition of a common terminology, as well as the templates that will be used to document all the requirements and metrics baselines, will be provided to the involved partners. A first elicitation phase will serve as a starting point to define the system specifications, architecture and development of the final demonstrators and will be related to different aspects of the PRAESIIDIUM framework: 1) Technical requirements of the system components; 2) Ethical Requirement Roadmap on the ethical sensitive aspects of the mobile app and clinical studies; 3) Definition of the evaluation

metrics in order to provide quantitative and qualitative KPIs and to establish the project success criteria. Finally, a consolidation phase will be conducted as a follow-up activity to review, fine-tune and map all the identified requirements and metrics into the final demonstrators that will be developed during the project.
T2.4: Data acquisition, drift analytics and endo-phenotypes stratification (HKL, CNR) [M4-M36]. The aim of this task is to develop new tools to curate and harmonize the retrospective datasets from various sources and settings to enable subsequent training of algorithms, considering the adoption of modern procedures for stratification and drift analytics. Besides routine technical adjustments (e.g., data formats, units of measure), this task will define a core set of features for diabetes risk characterization as well as context-/case study- specific features, providing inputs to T3.2-3 and T3.7. Particular attention will be given to harmonization of data from EU and non-EU settings and to longitudinal datasets (e.g., CPCSSN) and patient's trajectories. Methods for unsupervised stratification and data drift analysis will be explored for integrative T2D data, and further refined with inputs from T3.7.

Work package WP3 – Multi-scale physics-informed ML for T2D modelling

Work Package Number	WP3	**Lead Beneficiary**	11. SUPSI
Work Package Name	Multi-scale physics-informed ML for T2D modelling		
Start Month	1	**End Month**	36

Objectives

WP3 is aimed at the development of (i) a PI-ML dynamical model featuring lower computational requirements and higher accuracy than the original MT2D model and (ii) a ML-based, explainable rule mapping the evolution of several system variables to a T2D risk index. The first objective (i) will be dealt with in Tasks T3.3 and T3.5, which are devoted to the development of an intermediate MT2D model surrogate (reproducing the same input/output behaviour of the MT2D model, at a fraction of the original model's computational requirements and with higher flexibility in terms of time-interval covered by the simulations) and the final PI-ML model (which will combine information from the surrogate with fresh data from the PRAESIIDIUM clinical trials to produce more accurate simulations, at the same computational cost of the surrogate), respectively. Methods for generic model distillation, considering potential subtype data structures and longitudinal data drift will be also explored and applied as a baseline comparison, The second objective (ii) will be tackled in T3.3 and T3.6 by replacing the fixed (empirical) rule for risk- index prediction devised in the EU-FP7 MISSION-T2D7 project with more powerful and flexible data-driven rules and ML explanations. In particular, the risk prediction task will be cast to time series classification problem. To train the classifier, historical clinical data together with the surrogate model and different input data (diet, physical activity, …) will be used to generate abundant (synthetic) data corresponding to the health-to-disease transition. The generated trajectories of informative variables for T2D detection will then be used as features to predict a target describing the health/disease condition. T3.7 will deliver a general solution for long-term monitoring of domain shift as a service, supporting the real-world adoption of the model

Description

T3.1: Literature review (SUPSI, CNR, SPXL) [M1-M6] This task is devoted to a literature review about (i) PIML methodologies and (ii) physical models of diabetes (with focus on the MT2D model). This task has great importance for the successful completion of WP3 for the following reasons: 1) While SUPSI and other partners are actively involved in PI-ML research, the field is new and rapidly evolving, with novel breakthrough discoveries being published virtually on a daily basis. To be updated with the latest developments, a careful review of the recent PI-ML literature will be performed during the first months of PRAESIIDIUM. 2) While CNR is highly knowledgeable in diabetes modelling (notably, CNR is the main developer of the MT2D model), SUPSI and SPXL need to consolidate their notions in this area to understand the most important driving mechanisms, causal relationships and connections among key variables.
T3.2: Preliminary dynamical analysis on selected mathematical models from literature (SUPSI, SPXL)[M7-M10] It is well known that the glucose dynamics changes abruptly from periodic regime to chaos at the transition point between health state and diabetic condition. We will first review literature models describing the glucoseinsulin dynamics. We will then analyse the trajectories of glucose and insulin obtained by the MT2D model to identify joint evolution patterns discriminating between healthy and prediabetic conditions. The information

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acquired from the glucose-insulin dynamics will be used to build the risk score in the final PI-ML algorithm.
T3.3: Surrogate model building (SUPSI, HKL) [M11-M16] This task is devoted to the development of a machine-learning surrogate of the MISSION-T2D model. The surrogate model is aimed at reproducing the input/output behaviour of the MISSION-T2D model, while drastically reducing the computational and memory cost required to run (long-term) simulations, which was recognised as one of the main limiting factors of model. Moreover, the surrogate model will allow to obtain simulations that are more flexible in terms of analyzed time-intervals. A first (synthetic) dataset for training the surrogate model will be constructed by using short, mid and long-term simulations generated by the original MISSION-T2D model with different initial conditions and input trajectories (diet, physical activity, ...). Active learning methodologies such as Bayesian Optimization will be utilised to efficiently sample the output space of interest, and thus to minimise the number of simulations required to construct an informative dataset covering all relevant configurations. This sampling process will be performed in collaboration with WP4 (T4.1). The dataset will then be used to train the surrogate model, by minimising a regression loss that penalises the difference between the MISSION-T2D and the surrogate model quantitative outputs. To capture the dynamical nature of the learning problem, the surrogate will be based on machine-learning architectures for sequential data such as Recurrent and 1-D Convolutional Neural Networks. The most appropriate model structure among a set of candidates will be determined using cross-validation techniques. The results from the data stratification analysis will inform the definition of the cross-validation design and monitoring by drift analytics will be put in place to analyze promptly possible accuracy deviations due to data shifts (based on T2.4; further developed in T3.7). Finally, the surrogate model will be fine-tuned using the simulations obtained from the improved MISSION-T2D model, which will be developed in Task T4.4 and available at month M30.
T3.4: ML-based risk prediction (SUPSI) [M15-M25] This task is meant to improve the accuracy of the rule mapping quantitative outputs of the MISSION-T2D (or the surrogate) model to a risk score representing, for instance, the probability of transition from health to prediabetes within a given time horizon. In the MISSIONT2D project, an empirical ad-hoc rule defining the risk as a deterministic function of three system variables (namely, the level of insulin resistance, the level of inflammatory cytokines, and the pro-inflammatory cell counts) at a given time was devised. Within PRAESIIDIUM, we aim to develop a more flexible and accurate rule - possibly based on the time evolution of several system variables - by means of supervised machine-learning techniques. The surrogate model will be fed with patient data from the historical dataset, and time trajectories of relevant system quantities will be extracted by running (short- and mid-length) simulations. Using these trajectories as features and the patient's status as target, a time series classification problem will be instantiated. To tackle this problem, deep-learning architectures such as Temporal Convolutional Networks (TCNs) will be applied. The trained TCN classifier's prediction probability will then be used as the risk score. To define a simple (and thus easily interpretable) rule, feature selection techniques will be used to identify the smallest subset of features (i.e., system variable trajectories) required for accurate risk prediction, and the TCN network will be restricted to those features accordingly. A challenge arising in this data-driven learning of the decision rule could be the lack of informative data exhibiting the health-to-disease transition. In fact, most of the patients in the historical dataset are expected to lie either in the healthy or in the disease category for the whole duration of the clinical observation. This may limit the classifier's prediction accuracy in the presence of new data occurring at the boundary between the two states. To overcome this limitation, the surrogate model will also be used for data augmentation purposes, by running long-term simulations of the relevant patients' variables - beyond the duration of the clinical observation - and thus producing different future scenarios for each patient, where the transition may or may not occur, also according to the choice of input variables (food, physical exercise).
T3.5: PI-ML model development (SUPSI) [M16-M30]. In this task, the surrogate model developed during T1 will be improved based on the new data collected in the PRAESIIDIUM clinical studies (WP6). The objective is to overcome the limitations and simplifications used in MISSION-T2D by constructing a physics-informed machine-learning (PI-ML) model able to predict the evolution of the variables of interest over time with superior accuracy, while keeping the low computational budget of the surrogate model developed in T1. Training will be performed by minimising a properly defined trade-off loss promoting adherence of the PI-ML model with the new experimental data and penalising the deviation of the PI-ML model with respect to the surrogate model. The rationale is to obtain a model that fits the experimental data without diverging too much from the behaviour of the surrogate model (which in turn is representative of the dynamics of the MISSION-T2D model). Thus, penalising the discrepancy between the PI-ML and the surrogate acts as a regularisation term that promotes consistency with the assumptions of the MISSION-T2D model. This prior knowledge is expected to bias the model learning process towards physically plausible dynamics, and thus to reduce the risk of overfitting and enhance the prediction capability of the PI-ML model. Training of the PI-ML model will be performed in a cross-validation setting and the performance in predicting the health/disease patients status will be assessed on a validation set, i.e., a subset of the data collected during the clinical studies that will not be used for training the models, in terms of ROC AUC, accuracy, precision and recall.

T3.6: EXplainable ML (X-ML) model development (CNR, HKL) [M12-M36].The aim of this task is to develop, using a range of XAI techniques, intelligible models able to describe the individual risk of developing prediabetes and diabetes and to identify, based on the explainable models derived, personalized measures to reduce the risk on an individual basis. X-ML models will be built both using longitudinal data from retrospective and existing datasets as well as using the surrogate and PI-ML models. The range of XAI approaches will include both natively transparent models (e.g., models able to generate intelligible rules, e.g. decision tree, logic learning machine) and model-specific/model-agnostic post-hoc explanations with various output formats (e.g., rules, numbers, text, or visualizations) to provide a comprehensive characterization of the role of input features and their value ranges in determining the risk of developing prediabetes and diabetes and the likelihood of reversing prediabetes. In addition to supervised classification models, combined with the preliminary stratification analysis from WP2, unsupervised techniques will also be used (e.g., clustering, support vector data description) to characterize the multi-dimensional feature space for healthy, prediabetic, and diabetic individuals and the transitions between states/regions. Such unsupervised approaches will also be used as a basis to generate counterfactual explanations, i.e., to determine perturbations in factual (patient) data (biomarkers, lifestyle, modifiable risk factors) able to change the status of the data point (e.g., from prediabetic or diabetic to healthy), all unmodifiable variables being unaltered (e.g., age, sex, family history, other unmodifiable risk factors), and that can therefore be used as a basis to determine personalized recommendations to reduce the individual risk. In [M30-M36] the model will be further optimized for implementation and user validation in the final App.
T3.7 Impact of Data Drift (HKL) [M12-M36] The task will customize for T2D longitudinal multidomain data a model-agnostic data drift monitoring model. A prototype system delivering service-based analytics will be developed on a generic distilled model and tested on the specific PIML model, providing real-time impact assessment due to domain shifts due to known subtype data structures (inizialization, e.g. from T2.4), resulting from model design (from T3.3), or inducted from novel data (e.g incoming longitudinal data), Feedback to the potential impacts on the cross-validation design and on simulated use in real-world condition will be also returned

Work package WP4 – Modelling metabolic dysregulation and inflammation

Work Package Number	WP4	**Lead Beneficiary**	2. CNR
Work Package Name	Modelling metabolic dysregulation and inflammation		
Start Month	1	**End Month**	32

Objectives

This WP4 will focus on i) the MT2D model used to generate data suitable to the construction of the surrogate model and successively the PI-ML (WP3), ii) improve the MT2D model itself by exploiting the microbiota compartment (developed by partner SPXL), sensors data and retrospective trial data coming from WP2 and iii) finally calibrate and further validate the upgraded version of the model. As a final exploitable result of the WP the upgraded MT2D model will generate data suitable for the statistical analysis ending up in the surrogate model and the PI-ML model (WP3).

Description

T4.1 First data set generation (CNR, SUPSI) [M1-M11] MT2D model data generation simulating healthy individuals, individuals at risk of type 2 diabetes and pre-diabetes individuals following different lifestyles; we will be simulating user specific parameters such as gender, body weight, height, body mass index (BMI), age, fitness class, fasting glucose, microbiota composition, inflammatory cytokine levels (in blood), daily meals (in terms of grams of carbs, proteins and fat), daily duration and intensity of physical activity sessions. The simulation tool MT2D produces very detailed information about the kinetics of metabolic (including glucose level), inflammatory (e.g., IL-6 and other inflammatory cytokines) and anthropometric (e.g., body weight) variables. Such
variables are typically used to make an expert assessment of the health condition of an individual.This data will be used by partner SUPSI to construct a preliminary version of the surrogate model in WP3.

T4.2 Integration of microbiota model (CNR, SPXL) [M6-M12]. This task regards the integration of the microbiota model. Developed by partner SPXL with the MT2D model to account for the influence of the microbiota to the level of the low-grade systemic inflammation which is at the basis of type 2 diabetes.

T4.3 Integration with sensor data (CNR, CHK) [M12-M17]. Data collected through sensors (e.g., PA, weight, glucose,

etc.) in WP2 will be processed to suitable formats ready to be used as input data from the MT2D model to follow closely (and more realistically) the lifestyle patterns of physical activity and other physiological measures. Data needs to be collected, processed, transformed into a ready-to-be-read format and then set together with other input parameters for a patient-tailored simulation of the past and present period to forecast future conditions.

T4.4 Model calibration, validation and generation of the second data set (CNR, SUPSI, HKL) [M18-M30].
This task includes model calibration and validation with data coming from trial data of pre-diabetic individuals collected in WP2. This will eventually lead to an improvement of MT2D model estimated parameters and a better fit to trial data. This task also possibly includes adaptation of the MT2D model to account for liver problems, that is, to possibly modify the parameters of the metabolic reaction terms in the liver compartment of the metabolic sub-model of MT2D. The outcome is a calibrated and validated version of the MT2D model able to generate the second, refined data set for the final surrogate model. Such results will be also exploited by upgrading the algorithm on the online server http://t2dm.iac.cnr.it.

Work package WP5 – Development and demonstration to multiple stakeholders of interpretable physicsinformed ML-solutions.

Work Package Number	WP5	**Lead Beneficiary**	1. SPXL
Work Package Name	Development and demonstration to multiple stakeholders of interpretable physicsinformed ML-solutions.		
Start Month	1	**End Month**	36

Objectives
This WP is devoted to the development of the technology involved into the project. PRAESIDIIUM aims at developing a wrist-worn wearable device with bioimpedance sensing, a LinkWatch platform for remote monitoring and self-management of patients during clinical trials, and the final web-based applications developed by SPXL that will integrate the PI-ML model and data in order to give a real time risk prediction of developing prediabetes

Description
T5.1 Development of a prototype of a wrist-worn wearable device with bioimpedance sensing and signal processing capabilities (EDI) [M1-M36]. In the initial phase of the project [M1-M12], the end goal is a construction of a prototype of the wrist-worn wearable device with bioimpedance sensing and signal processing capabilities. This end prototype will be suitable for pilot deployments in the main clinical trial (M12). In the middle phase of the project [M12-M24] our goal is to test the device in real-life conditions using the clinical trial, and compare its data with data from other, already validated sensors, to validate the accuracy of the device in real-life conditions, as well as to collect feedback about user experiences. In the final phase of the project [M24-M36], our goal is to produce a new version of the device that adds improvements considering the lessons learned in the clinical trial, as well as help to integrate the device in the final application with the mathematical model. T5.2 Development of a LinkWatch platform for remote monitoring and self-management of patients during clinical trials (CHK)[M1-M12]. The LinkWatch platform for remote monitoring and self-management of patients will be adapted to the requirements of PRAESIDIIUM as defined in WP2. New sensor type will be added using the FHIR (Fast Healthcare Interoperability Resources) for data transfer and exchange. FHIR Observation Resource types need to be defined for each new sensor type added. For activity and behavioural tracking we need to integrate with the cloud API provided by FitBit or other supplier depending on the chosen bracelets. This involves subscribing to events when FitBit user account is updated with new data and storing the information in the LinkWatch cloud database. Furthermore, for questionnaries for collection of PROMS (Patient Reported Health Outcomes) need to be specified for the particular case of pre-diabetes. We will also integrate the bioimpedance sensor developed in task 5.1. The underlying database will be a Postgres SQL hosted in a cloud environment. T5.3 Technologies integration for the final App (SPXL, EDI) [M24-M36] This task will focus on the integration of the PI-ML algorithm in the backend system of the application to serve predictions according to the user inputs and configuration. An ad-hoc layer for serving versioned model instances will be provided to ensure optimal inferences capabilities over a well-known and reusable interface. The first version of the PI-ML model should be ready

for integration at M29, a more refined version will then be integrated at M32. In this task the sensors developed by EDI will be integrated into the platform, based on the specification provided. A first version of bioimpedance sensor (T5.1, EDI) will be ready at M12, afterwards EDI will work on creating a bioimpedance sensor access library for mobile devices and integration with the app [M13-M24]. For direct connectivity over mobile device, a dedicated integration will be provided ensuring connectivity, communication and interaction is effectively available to the end users both from a technical and user experience perspective. Iteratively, test will be conducted to ensure the system performs accordingly to the requirements. We will also consider the integration of other sensors selected during the scouting phase (T2.1).

T5.4 Infrastructure development (SPXL)[M24-M36]. The final outcome of the project will be a Web based platform to be used by doctors where, for each patient, it will be possible to collect data (to be added manually and/or collected by sensors) and to run the PI-ML model that will furnish a real-time Risk Parameter associated with the probability of developing Prediabetes. A mobile app will be used by the patients, who can see their profile (personal information and graphs representing historical data) and integrate new data. The app will be compatible for the acquisition of data from some commercial sensors, depending on the outcomes of the scouting phase in T2.1 (mainly for measuring: hearth rate, BMI, percentage of fat in the body, VO2max, glucose), and it will takethe advantage of the integration with the new developed sensor of bioimpedance (T5.1-T5.4). This task will setup and configure the technical infrastructure required to run the applications such as the backend services, databases and computing runtime. In particular, the system will be configured in three main areas: 1) Frontend services: provide the user with an overview of the available data and allow the interrogation of the PI-ML model in order to obtain a prediction of a patient's T2D-risk. The doctor will see and manage data from each patient and will be able to insert particular type of data such as measurement coming from blood and other clinical analysis. The dashboard will show data elaboration and a synthetic view. Each user (doctor and patient) will be able to insert other type of personal data and to acquire data from the connected sensors. They will interrogate the PI-ML model any time, selecting a time window in which they wish to have a prevision of the T2D risk. 2) Backend services: they offer frontend application interfaces from which information can be retrieved in order to interact with the PIML model. Given the importance of data privacy, a Gateway API and authentication system is set up to ensure that access to information is only by authorized personnel. 3) The PI-ML model engineering process, which is the set of steps necessary to use the PI-ML model (provided by SUPSI) to be trained on the available data (data injected by the doctor and the patient and acquired from sensors). It consists in several steps: data selection and cleaning, training on such data, risk index prediction for different time-windows. The API shows a catalogue of the fields required by the model as input for the calculation of the T2D risk index. A model-based specific API interface produces in response the probability that the patient will develop the prediabete in a certain time window. The system will not impose strong constraints on the presence of data, but it is important to point out that a greater completeness of the same greatly improves the prediction of the model.

Work package WP6 – Acquisition of bio-clinical data from clinical study

Work Package Number	WP6	**Lead Beneficiary**	7. FIF
Work Package Name	Acquisition of bio-clinical data from clinical study		
Start Month	4	**End Month**	27

Objectives
The objective of the present WP is to conduct newly-dedicated clinical studies to: 1) acquire more bio-clinical data to ingest in the math model as a second wave data ingestion; 2) assess the prediabetic risk of the participants at baseline with a prototype version of the mobile app; 3) equip participants with commerciallyavailable wearable sensors for a continuous data ingestion and 4) test the newly-dedicated wearable sensor in a controlled manner on a smaller group of participants

Description
T6.1: Individuation of Blood-Based Inflammatory Biomarkers in metabolic risks cohorts (FIF) [M4-M14]. The in-silico approach will be constituted by an initial systematic literature search, in which Pubmed medical database will be queried sequentially using several medical subject headings (MeSH) of our interest. We will retrieve all the scientific articles containing transcriptomics datasets of our interest. Then the retrieved literature will be screened, and additional selection

filters will be used (considering filters for specie, type of sample, cohort clinics, etc.). The articles and their transcriptome reported datasets, meeting the eligibility criteria, will be
downloaded from specific databases (GEO, ArrayExpress, HPA) and the selected transcriptome datasets, once uniformly processed and normalized, will be subjected to the meta-analysis, obtaining the differentially expressed genes for the interesting condition and further use in the in-silico strategy described before. Meta-transcriptome
datasets from the studies retrieved during the sequentially queries will be included, and among other selection criteria, secreted protein-coding genes associated with the inflammatory process or implicated in key molecular pathways in prediabetes/T2DM will be used. Qualification/Verification of the putative biomarkers [M14-
M27]. During the verification phase, the abundance of the selected candidates will be quantified in an initial collection of 100 plasma samples (balanced for sex and age) from NAFLD biopsy-proven bariatric patients stratified according to the diabetes condition (no diabetes, prediabetes and T2D). Candidates' abundances in
plasma samples will be tested with two different standardised ELISA commercial kits following a systematic approach to generate high-quality data. Standardisation and harmonisation of the commercial ELISA kits will involve calibration curve verification, determination of the algorithm to fit the calibration curve, evaluation of
assay selectivity, matrix interference, dilution, linearity and parallelism evaluation among other parameters. The diagnostic performance for prediabetes/T2DM classification using the novel biomarkers will be assessed by receiver operating characteristic (ROC) curves. The sensitivity, specificity, PPV and NPV for relevant cut-offs will also be calculated.

T6.2: Clinical study 1: Patients with low risk of prediabetes (MUG) [M12-M27]. Detailed inclusion and exclusion criteria for participants, study protocol, ethics clearance and clinical trial registration data will be provided in D2.2 and specification of the clinical studies were described in the Methodology section. Adult participants with normal weight will enroll in the observational study and will be followed for about 4 months.
Assessment of their prediabetes risks will be performed with the prototype app (T5.3), along with other biochemical measurements. Diet and physical activity will be monitored. Biological samples will be obtained three times during the study (at baseline, in the mid and at the end of the study). Compliance to physical activity
intervention will be recorded by commercially- available wearable sensors and continuous glucose monitors provided by CHK (T5.2); compliance to dietary recommendations and adherence to the study protocol will be monitored during regular remote consultations with dietician and study staff.

T6.3: Clinical study 2: Patients with metabolic risk factors (UNIL) [M12-M27]. Detailed inclusion and exclusion criteria for participants, study protocol, ethics clearance and clinical trial registration data will be provided in D2.2. Specification of the clinical studies were described in the Methodology section. Adult overweight/obese participants will be recruited and followed-up for about 4 months. Assessment of their
prediabetes risks will be performed with the prototype app (T5.3), along with other measurements. Dietary analysis will be performed using Latvian nutritional databases provided by Institute of Food Safety, Animal health and Environment (https://www.bior.lv/en). Patients will be consulted by a nutrition specialist and exercise physiologist based on their nutritional intake and physical activity test results and a personalized physical activity with simple and safe physical activity profiles (such as brisk walking, Nordic walking etc) and nutritional programme (e.g., Nordic diet with person-specific modifications) will be suggested. Compliance to physical activity intervention will be recorded by newly developed wearables (provided by EDI, T5.1); compliance to dietary recommendations and adherence to the study protocol will be monitored during regular remote consultations with nutrition specialist and study nurse.

T6.4: Clinical study 3: Plasma bio-banking and clinical data collection (FIF) [M12-M27]. Biological samples from patients affected with NAFLD stratified according to diabetes condition (healthy, prediabetes and T2DM) will be collected. At FIF, plasma/serum samples from obese patients will be collected almost during the total period of the project (28 months). The new samples and the clinical associated data will enlarge the sample collection at FIF (actual number of samples n = 250). We are collecting samples from obese patients at a rate of 50 samples/year. We expect to extend our collection to 350-360 samples for a full validation phase of the most adapted biomarkers in the period covering the last 8 months of the project.

Work package WP7 – Exploitation, dissemination and communication: paving the way for PRAESIIDIUM's acceptance

Work Package Number	WP7	**Lead Beneficiary**	4. EURO
Work Package Name	Exploitation, dissemination and communication: paving the way for PRAESIIDIUM's acceptance		

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Start Month	1	End Month	36

Objectives
Developing a global strategy for dissemination and exploitation of PRAESIIDIUM results. Key outcomes from other WPs will be obtained and used as a basis for the preparation of a sound business plan and exploitation strategy. Stemming from them early marketing and business development actions will be identified. Furthermore, this WP will take care of effectively communicating the results of the project in relevant events and disseminate key outcomes to the scientific community, making them available and fully accessible.

Description
T7.1: Business Plan and Exploitation strategy (Lead: EURO, Contributors: All partners) [M1-M36] This Task aims at fostering PRAESIIDIUM adoption in the market. To this extent, the following actions are envisaged: - Analysis of the market and of the competitive environment to identify market segmentation, market trends (both historical and expected), as well as key opportunities and threats for PRAESIIDIUM. The market analysis will be coupled with an environment assessment and value chain analysis to support an effective go-to-market strategy; -Non-economic viability and liability analysis to identify and quantify the main non-economic aspects relevant for the successful implementation and operation of the proposed solution, including IPR potential issues; - Drafting of a risk analysis to map the main economic and non-economic risks linked to PRAESIIDIUM and identify main actions to avoid/mitigate them; - Preparation of an Overall Business Plan quantifying key assumptions over a 5 to 10 years period, to obtain a long-term cash-flow prediction of the PRAESIIDIUM solution; - Design of an Exploitation Strategy (incl. Implementation Roadmap development) aimed at defining key strategy and drivers for the exploitation activities and solution adoption; - In addition, the use cases will be strongly leveraged to identify and analyse PRAESIIDIUM impacts, including an assessment of approximate costs benefits. T7.2: Scientific Dissemination (Lead: FIF, Contributors: All partners) [M1-M36] A detailed dissemination plan will be prepared to ensure the scientific target audiences and specific messages, focusing on global publication of papers, international workshops using open-source resources, and a wider public dissemination of the project. . T7.3: Communication and dissemination (Lead: SPXL, Contributors: All partners) [M4-M36] This task will be focused on the definition, coordination and implementation of the Communication Strategy to develop the unique visual identity, virtual presence, and physical presence of PRAESIIDIUM. A dedicated website will be created, to showcase the project and its achievements. To update the stakeholders network, a series of e-Newsletters will be programmed, and to reach a wider public will be used institutional social networks (Twitter, LinkedIn) and traditional media (press, radio, TV). While networking with scientific communities and other EU projects will be a key task to be able to create synergies and cooperate for common benefit. The networking and collaboration are aimed at considering the results of other projects and state of the art thinking in the chosen communities. This will enable a more agile and unique contribution to the project.

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

STAFF EFFORT

Staff effort per participant

Grant Preparation (Work packages - Effort screen) — Enter the info.

Participant	WP1	WP2	WP3	WP4	WP5	WP6	WP7	Total Person-Months
1 - SPXL	20.00	6.00	6.00	10.00	60.00		17.00	119.00
2 - CNR	3.00	16.00	40.00	45.00			2.00	106.00
3 - EDI	3.00	12.00			58.00	6.00	2.00	81.00
4 - EURO	3.00					8.00	37.00	48.00
5 - SdR	12.00	4.00					2.00	18.00
6 - CHK	3.00	24.00			24.00		2.00	53.00
7 - FIF	3.00	12.00				52.00	13.00	80.00
8 - MUG	3.00	12.00				30.00	2.00	47.00
9 - HKL	3.00	24.00	24.00	9.00			2.00	62.00
10 - UNIL	3.00	18.00				43.00	2.00	66.00
11 - SUPSI	3.00	4.00	48.00	2.00			2.00	59.00
Total Person-Months	59.00	132.00	118.00	66.00	142.00	139.00	83.00	739.00

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

LIST OF DELIVERABLES

Deliverables

Grant Preparation (Deliverables screen) — Enter the info.

The labels used mean:

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	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D1.1	Minutes of General Assembly	WP1	1 - SPXL	R — Document, report	C-UE/EU-C - EU Classified	36
D1.2	Project quality plan, including risk contingency plan	WP1	1 - SPXL	R — Document, report	C-UE/EU-C - EU Classified	4
D1.3	Project management report 1.1	WP1	1 - SPXL	R — Document, report	C-UE/EU-C - EU Classified	13
D1.4	Project management report 1.2	WP1	1 - SPXL	R — Document, report	C-UE/EU-C - EU Classified	25
D1.5	Data Mangement Plan (DMP) _ v1	WP1	1 - SPXL	DMP — Data Management Plan	C-UE/EU-C - EU Classified	6
D1.6	Data Mangement Plan (DMP) _ v2	WP1	1 - SPXL	DMP — Data Management Plan	C-UE/EU-C - EU Classified	24
D2.1	Study Initiation Package for the Retrospective analysis of clinical data, including ethical requirements clinical study	WP2	7 - FIF	R — Document, report	C-UE/EU-C - EU Classified	3
D2.2	Initial set of relevant research results and technologies	WP2	9 - HKL	R — Document, report	C-UE/EU-C - EU Classified	6
D2.3	Report of ethical requirement for the system usage	WP2	5 - SdR	R — Document, report	C-UE/EU-C - EU Classified	6
D2.4	PRAESIIDIUM framework requirements, KPIs and success criteria	WP2	6 - CHK	R — Document, report	C-UE/EU-C - EU Classified	9

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Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D2.5	Report on the status of posting results for clinical data acquisition and preprocessing V 1	WP2	2 - CNR	R — Document, report	C-UE/EU-C - EU Classified	12
D2.6	Report on the status of posting results for clinical data acquisition and preprocessing V 2	WP2	2 - CNR	R — Document, report	C-UE/EU-C - EU Classified	32
D2.7	Definition of rules and algorithms for endophenotypes stratification and tracking drift along time and domains V1	WP2	9 - HKL	R — Document, report	C-UE/EU-C - EU Classified	12
D2.8	Definition of rules and algorithms for endophenotypes stratification and tracking drift along time and domains V2	WP2	9 - HKL	R — Document, report	C-UE/EU-C - EU Classified	32
D3.1	Report on the PI-ML model	WP3	11 - SUPSI	R — Document, report	C-UE/EU-C - EU Classified	30
D3.2	Report on X-ML model development	WP3	2 - CNR	R — Document, report	C-UE/EU-C - EU Classified	34
D3.3	Report on Data Drift prototype service	WP3	9 - HKL	R — Document, report	C-UE/EU-C - EU Classified	34
D4.1	Report on first data generation	WP4	2 - CNR	R — Document, report	C-UE/EU-C - EU Classified	12
D4.2	Report on integration of microbiota model	WP4	2 - CNR	R — Document, report	C-UE/EU-C - EU Classified	24
D4.3	Report on integration with sensors data	WP4	2 - CNR	R — Document, report	C-UE/EU-C - EU Classified	24
D4.4	Report on model calibration, validation and final data generation	WP4	2 - CNR	R — Document, report	C-UE/EU-C - EU Classified	32

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Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D5.1	A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - v1	WP5	3 - EDI	R — Document, report	C-UE/EU-C - EU Classified	12
D5.2	A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - v2	WP5	3 - EDI	R — Document, report	C-UE/EU-C - EU Classified	36
D5.3	PRAESIDIIUM platform	WP5	1 - SPXL	DEM — Demonstrator, pilot, prototype	C-UE/EU-C - EU Classified	35
D6.1	Study initiation package	WP6	7 - FIF	R — Document, report	C-UE/EU-C - EU Classified	12
D6.2	Mid-term reporting	WP6	10 - UNIL	R — Document, report	C-UE/EU-C - EU Classified	20
D6.3	Report on the status of posting results	WP6	7 - FIF	R — Document, report	C-UE/EU-C - EU Classified	27
D6.4	Validated Predictive Biomarkers Report	WP6	7 - FIF	R — Document, report	C-UE/EU-C - EU Classified	27
D7.1	Communication Plan for Dissemination and Exploitation	WP7	1 - SPXL	R — Document, report	PU - Public	6
D7.2	Dissemination Plan and follow-up reports - v1	WP7	7 - FIF	R — Document, report	C-UE/EU-C - EU Classified	18
D7.3	Dissemination Plan and follow-up reports - v2	WP7	7 - FIF	R — Document, report	C-UE/EU-C - EU Classified	34

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

Deliverables

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Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D7.4	Business Plan and Exploitation Strategy - v1	WP7	4 - EURO	R — Document, report	C-UE/EU-C - EU Classified	18
D7.5	Business Plan and Exploitation Strategy - v2	WP7	4 - EURO	R — Document, report	C-UE/EU-C - EU Classified	34
D7.6	Project Website	WP7	1 - SPXL	DEC —Websites, patent filings, videos, etc	PU - Public	6

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

Deliverable D1.1 – Minutes of General Assembly

Deliverable Number	D1.1	Lead Beneficiary	1. SPXL
Deliverable Name	Minutes of General Assembly		
Type	R — Document, report	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	36	Work Package No	WP1

Description
Minutes of General Assembly - written & update at M1, M13, M25, M36 and submitted on M36

Deliverable D1.2 – Project quality plan, including risk contingency plan

Deliverable Number	D1.2	Lead Beneficiary	1. SPXL
Deliverable Name	Project quality plan, including risk contingency plan		
Type	R — Document, report	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	4	Work Package No	WP1

Description
Project quality plan, including risk contingency plan

Deliverable D1.3 – Project management report 1.1

Deliverable Number	D1.3	Lead Beneficiary	1. SPXL
Deliverable Name	Project management report 1.1		
Type	R — Document, report	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	13	Work Package No	WP1

Description
Project management report v1.1

Deliverable D1.4 – Project management report 1.2

Deliverable Number	D1.4	Lead Beneficiary	1. SPXL
Deliverable Name	Project management report 1.2		
Type	R — Document, report	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	25	Work Package No	WP1

Description
Project management report v 1.2

Deliverable D1.5 – Data Mangement Plan (DMP) _ v1

Deliverable Number	D1.5	Lead Beneficiary	1. SPXL
Deliverable Name	Data Mangement Plan (DMP) _ v1		
Type	DMP — Data Management Plan	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	6	Work Package No	WP1

Description
Data management plan report _ v1

Deliverable D1.6 – Data Mangement Plan (DMP) _ v2

Deliverable Number	D1.6	Lead Beneficiary	1. SPXL
Deliverable Name	Data Mangement Plan (DMP) _ v2		
Type	DMP — Data Management Plan	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	24	Work Package No	WP1

Description
Data Management Plan _ v2

Deliverable D2.1 – Study Initiation Package for the Retrospective analysis of clinical data, including ethical requirements clinical study

Deliverable Number	D2.1	Lead Beneficiary	7. FIF
Deliverable Name	Study Initiation Package for the Retrospective analysis of clinical data, including ethical requirements clinical study		
Type	R — Document, report	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	3	Work Package No	WP2

Description
Study Initiation Package for the Retrospective analysis of clinical data, including ethical requirements clinical study

Deliverable D2.2 – Initial set of relevant research results and technologies

Deliverable Number	D2.2	Lead Beneficiary	9. HKL
Deliverable Name	Initial set of relevant research results and technologies		
Type	R — Document, report	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	6	Work Package No	WP2

Description

Initial set of relevant research results and technologies

Deliverable D2.3 – Report of ethical requirement for the system usage

Deliverable Number	D2.3	**Lead Beneficiary**	5. SdR
Deliverable Name	Report of ethical requirement for the system usage		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	6	**Work Package No**	WP2

Description
Report of ethical requirement for the system usage

Deliverable D2.4 – PRAESIIDIUM framework requirements, KPIs and success criteria

Deliverable Number	D2.4	**Lead Beneficiary**	6. CHK
Deliverable Name	PRAESIIDIUM framework requirements, KPIs and success criteria		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	9	**Work Package No**	WP2

Description
PRAESIIDIUM framework requirements, KPIs and success criteria

Deliverable D2.5 – Report on the status of posting results for clinical data acquisition and preprocessing V 1

Deliverable Number	D2.5	**Lead Beneficiary**	2. CNR
Deliverable Name	Report on the status of posting results for clinical data acquisition and preprocessing V 1		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	12	**Work Package No**	WP2

Description
Report on the status of posting results for clinical data acquisition and preprocessing version 1

Deliverable D2.6 – Report on the status of posting results for clinical data acquisition and preprocessing V 2

Deliverable Number	D2.6	**Lead Beneficiary**	2. CNR
Deliverable Name	Report on the status of posting results for clinical data acquisition and preprocessing V 2		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	32	**Work Package No**	WP2

Description
Report on the status of posting results for clinical data acquisition and preprocessing version 2

Deliverable D2.7 – Definition of rules and algorithms for endophenotypes stratification and tracking drift along time and domains V1

Deliverable Number	D2.7	**Lead Beneficiary**	9. HKL
Deliverable Name	Definition of rules and algorithms for endophenotypes stratification and tracking drift along time and domains V1		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	12	**Work Package No**	WP2

Description
Definition of rules and algorithms for endophenotypes stratification and tracking drift along time and domains version 1

Deliverable D2.8 – Definition of rules and algorithms for endophenotypes stratification and tracking drift along time and domains V2

Deliverable Number	D2.8	**Lead Beneficiary**	9. HKL
Deliverable Name	Definition of rules and algorithms for endophenotypes stratification and tracking drift along time and domains V2		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	32	**Work Package No**	WP2

Description
Definition of rules and algorithms for endophenotypes stratification and tracking drift along time and domains version 2

Deliverable D3.1 – Report on the PI-ML model

Deliverable Number	D3.1	**Lead Beneficiary**	11. SUPSI
Deliverable Name	Report on the PI-ML model		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	30	**Work Package No**	WP3

Description
Report on the PI-ML model

Deliverable D3.2 – Report on X-ML model development

Deliverable Number	D3.2	**Lead Beneficiary**	2. CNR
Deliverable Name	Report on X-ML model development		

Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	34	**Work Package No**	WP3

Description
Report on X-ML model development

Deliverable D3.3 – Report on Data Drift prototype service

Deliverable Number	D3.3	**Lead Beneficiary**	9. HKL
Deliverable Name	Report on Data Drift prototype service		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	34	**Work Package No**	WP3

Description
Report on Data Drift prototype service

Deliverable D4.1 – Report on first data generation

Deliverable Number	D4.1	**Lead Beneficiary**	2. CNR
Deliverable Name	Report on first data generation		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	12	**Work Package No**	WP4

Description
Report on first data generation

Deliverable D4.2 – Report on integration of microbiota model

Deliverable Number	D4.2	**Lead Beneficiary**	2. CNR
Deliverable Name	Report on integration of microbiota model		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	24	**Work Package No**	WP4

Description
Report on integration of microbiota model

Deliverable D4.3 – Report on integration with sensors data

Deliverable Number	D4.3	**Lead Beneficiary**	2. CNR
Deliverable Name	Report on integration with sensors data		

Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	24	**Work Package No**	WP4

Description
Report on integration with sensors data

Deliverable D4.4 – Report on model calibration, validation and final data generation

Deliverable Number	D4.4	**Lead Beneficiary**	2. CNR
Deliverable Name	Report on model calibration, validation and final data generation		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	32	**Work Package No**	WP4

Description
Report on model calibration, validation and final data generation

Deliverable D5.1 – A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - v1

Deliverable Number	D5.1	**Lead Beneficiary**	3. EDI
Deliverable Name	A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - v1		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	12	**Work Package No**	WP5

Description
A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - version 1

Deliverable D5.2 – A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - v2

Deliverable Number	D5.2	**Lead Beneficiary**	3. EDI
Deliverable Name	A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - v2		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	36	**Work Package No**	WP5

Description
A document set describing the know-how on the design and applications of a bioimpedance sensing capable wearable device - version 2

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

Deliverable D5.3 – PRAESIDIIUM platform

Deliverable Number	D5.3	Lead Beneficiary	1. SPXL
Deliverable Name	PRAESIDIIUM platform		
Type	DEM — Demonstrator, pilot, prototype	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	35	Work Package No	WP5

Description
PRAESIDIIUM platform final version at M35

Deliverable D6.1 – Study initiation package

Deliverable Number	D6.1	Lead Beneficiary	7. FIF
Deliverable Name	Study initiation package		
Type	R — Document, report	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	12	Work Package No	WP6

Description
Study initiation package

Deliverable D6.2 – Mid-term reporting

Deliverable Number	D6.2	Lead Beneficiary	10. UNIL
Deliverable Name	Mid-term reporting		
Type	R — Document, report	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	20	Work Package No	WP6

Description
Mid-term reporting

Deliverable D6.3 – Report on the status of posting results

Deliverable Number	D6.3	Lead Beneficiary	7. FIF
Deliverable Name	Report on the status of posting results		
Type	R — Document, report	Dissemination Level	C-UE/EU-C - EU Classified
Due Date (month)	27	Work Package No	WP6

Description
Report on the status of posting results

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

Deliverable D6.4 – Validated Predictive Biomarkers Report

Deliverable Number	D6.4	**Lead Beneficiary**	7. FIF
Deliverable Name	Validated Predictive Biomarkers Report		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	27	**Work Package No**	WP6

Description
Validated Predictive Biomarkers Report

Deliverable D7.1 – Communication Plan for Dissemination and Exploitation

Deliverable Number	D7.1	**Lead Beneficiary**	1. SPXL
Deliverable Name	Communication Plan for Dissemination and Exploitation		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	6	**Work Package No**	WP7

Description
Communication Plan for Dissemination and Exploitation

Deliverable D7.2 – Dissemination Plan and follow-up reports - v1

Deliverable Number	D7.2	**Lead Beneficiary**	7. FIF
Deliverable Name	Dissemination Plan and follow-up reports - v1		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	18	**Work Package No**	WP7

Description
Dissemination Plan and follow-up reports - version 1 at M18

Deliverable D7.3 – Dissemination Plan and follow-up reports - v2

Deliverable Number	D7.3	**Lead Beneficiary**	7. FIF
Deliverable Name	Dissemination Plan and follow-up reports - v2		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	34	**Work Package No**	WP7

Description
Dissemination Plan and follow-up reports - final version at M34

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

Deliverable D7.4 – Business Plan and Exploitation Strategy - v1

Deliverable Number	D7.4	**Lead Beneficiary**	4. EURO
Deliverable Name	Business Plan and Exploitation Strategy - v1		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	18	**Work Package No**	WP7

Description
Business Plan and Exploitation Strategy - version 1 at M18

Deliverable D7.5 – Business Plan and Exploitation Strategy - v2

Deliverable Number	D7.5	**Lead Beneficiary**	4. EURO
Deliverable Name	Business Plan and Exploitation Strategy - v2		
Type	R — Document, report	**Dissemination Level**	C-UE/EU-C - EU Classified
Due Date (month)	34	**Work Package No**	WP7

Description
Business Plan and Exploitation Strategy - final version

Deliverable D7.6 – Project Website

Deliverable Number	D7.6	**Lead Beneficiary**	1. SPXL
Deliverable Name	Project Website		
Type	DEC —Websites, patent filings, videos, etc	**Dissemination Level**	PU - Public
Due Date (month)	6	**Work Package No**	WP7

Description
Project website

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

LIST OF MILESTONES

Milestones

Grant Preparation (Milestones screen) — Enter the info.

Milestone No	Milestone Name	Work Package No	Lead Beneficiary	Means of Verification	Due Date (month)
1	Ethics Self-Assessment report - version 1	WP1	5-SdR	Report & annual meeting	12
2	Ethics Self-Assessment report - version 2	WP1	5-SdR	Report & annual meeting	24
3	Surrogate model developed	WP3	-	Running code in a dedicated private repository	16
4	ML-based risk prediction model developed	WP3	-	Running code in a dedicated private repository	25
5	X-ML models developed	WP3	2-CNR	Running code in a dedicated private repository	30
6	First data set generated for surrogate model	WP4	2-CNR	File in a dedicated private repository	11
7	Model of the microbiome integrated	WP4	2-CNR	Running code in a dedicated private repository	24
8	Detailed sensor data integrated into MT2D	WP4	2-CNR	File in a dedicated private repository	17
9	Model calibrated, validated and second data set generated	WP4	2-CNR	Running code in a dedicated private repository	30
10	Communication Kit PRAESIIDIUM and website	WP7	1-SPXL	PRAESIIDIUM brochure and website	4

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

LIST OF CRITICAL RISKS

Critical risks & risk management strategy

Grant Preparation (Critical Risks screen) — Enter the info.

Risk number	Description	Work Package No(s)	Proposed Mitigation Measures
1	Not enough data suitable for the training of the PIML model (i) low, (ii) high	WP3	The construction of the surrogate model will be based on simulation data from WP4. Limitations in this WP are linked to those of WP4
2	Ethical and legal issues related to data transfer from local hospitals to a central server located in a different country (i) medium(ii) medium	WP3	A federated learning approach will be used to train the ML models on local data and to share only high-level information to a central server
3	Not enough data suitable for the calibration of the Mathematical Models (i) low, (ii) high	WP4	The first version of the mathematical model MT2D has been developed on literature data and the parameters adapted from previous studies available for all sub-model components. Further refinement of model parameters will require the exploitation of more recent bibliographic resources.
4	Not enough computational resources for generating trajectories (Task 4.1) needed to build the surrogate model (i) medium, (ii) medium	WP4	Borrow in house (Institute for Applied Computing, IAC-CNR) computational resources to increase available CPUs
5	The MT2D model will fail to process when: 1) the metabolic status of the patients is “broken” or 2) there is a dysfunctional liver-pancreas condition. (i) medium, (ii) medium	WP4	There are some mitigation approaches to this issue: 1) set the parameters required properly (under the supervision of a clinical specialist); 2) add new terms into the equations; 3) limit the model to other previously defined cases
6	Recruited patients have problems with connectivity and handling of medical devices and drops out of clinical trials. (i) medium, (ii) medium	WP5	Onboarding processes must be developed to automate the connection the patient devices. Voice-driven intelligent assistants can be used to simplify interaction with the platform
7	Problems with validation of the T5.1 device in the clinical trial due to low-accuracy ground truth data for cardiorespiratory parameter and body composition data. i) low, ii) high	WP5	Select the commercial sensors for the ground-truth in the clinical trial (in T2.1) in a way that maximizes the expected accuracy of these measures.
8	Obsoletion of some of the original goals as low-cost bioimpedance technology successfully	WP5	Pivot the T5.1 research towards data collection and exploration of scientific hypothesis, away for future commercialization goals.

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Critical risks & risk management strategy

Grant Preparation (Critical Risks screen) — Enter the info.

Risk number	Description	Work Package No(s)	Proposed Mitigation Measures
	implemented in off-the-shelf commercial devices. i) low, ii) medium		
9	Low accuracy of the bioimpedance sensor. i) low, ii) medium	WP5	Apply advanced signal processing methods and machine learning methods in T5.1 to interpret the raw data produced by the physical sensor to extract meaningful information even from noisy data
10	Impact of COVID-19 (or other) pandemic on recruitment of subjects. COVID-19 (or other infection) pandemic may lead to national restrictions on outpatients and research facilities if high morbidity is present. In that case, recruitment of subjects for the clinical study might be suspended. Even in the absence of restrictions, high morbidity with COVID-19 (or other infection) might impact subject recruitment and the implementation of the protocol of the clinical study. E.g., patients might miss study visits, change their behaviour and diet due to illness and post-illness syndrome. Clinical and biomarker measurements might be impacted	WP6	To avoid delays in project progress, reasonable number of recruited subjects will be planned for each location of the clinical trial. Also, sufficient time-period for recruitment and observation will be planned. Information about the study will be disseminated in public media and in medical society of recruiting partners to increase recruitment rates. The study protocol will include action plan (such as suspended measurements, postponed study visits etc) in case of Covid and/or other infection during the observation time, to minimize its impact on outcome measures.
11	Low compliance to the clinical study protocol among participants	WP6	Coordination of the clinical studies will include regular contact with recruited subjects for achievement of optimal compliance to the study protocol. To promote motivation and compliance, feedback on the results of investigations (bloodwork, physical tests, nutritional analysis) will be provided to each participant and personalized health goals will be settled
12	Impact of COVID-19 (or other) pandemic on project personnel (i) medium, (ii) medium	WP2, WP3, WP5, WP7, WP1, WP4, WP6	Project team of each partner will include researchers able to substitute each other for the time of the illness. Reasonable timeframe of each work package and regular contact with the project coordinator and consortium will allow for timely adjustments in workplan in such a way that achievement of project deliverables is not impacted.
13	Delays in ethical approval, clinical trial registration and procurements for the clinical studies (i) medium, (ii) medium	WP2, WP6	Preparation of the study protocol, ethics application and clinical trials' registration will be started at the beginning of the project to allow enough time for preparation, submission, correction and approval before the planned start of the clinical studies

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Critical risks & risk management strategy

Grant Preparation (Critical Risks screen) — Enter the info.

Risk number	Description	Work Package No(s)	Proposed Mitigation Measures
14	Not enough ‘omics datasets related to prediabetes/ diabetes condition for blood-based biomarkers individuation. (i) low, (ii) medium	WP6	Direct retrieval of candidates, described as novel markers of prediabetes/T2DM from literature.
15	Not availability of commercial ELISA kits for the selected best 10 protein biomarkers	WP6	Inclusion of a large quantity of ranked candidates from the full list.
16	Poor commercial exploitation. i) low, ii) low	WP7	Key players in charge of exploitation actions are already present in market and aware of market needs. If need, enhance of exploitation actions during the project
17	Business Plan and commercial roadmap reveals failure of market potential i) low, ii) low	WP7	Address market potential and road to market (incl. societal benefits) with strong interaction with end-users, collect inputs from all project partner and relevant end-users contacts for the analysis, if any, Use several data sources.
18	Low level of dissemination and communication and low amplification of the promotion actions i) low, ii) low	WP7	Set up a detailed dissemination Plan at the start of the project to be followed throughout. Ensure impact maximisation through extensive use of social networks under a detailed publication calendar. Engage with readers/followers through social media. Different institutions' communication office contacts will be collected and lists of target stakeholders will be integrated in a common project database. Can detect further gates of communication between consortium partners’ scientists and decision-makers to increase porosity between research finding and society.

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HISTORY OF CHANGES		
VERSION	PUBLICATION DATE	CHANGE
1.0	30.08.2022	Initial version
2.0	31.08.2022	Correction of typos and page summary
3.0	08.09.2022	Corrections to Table 3.1h according to FO/PO comments (pag. 29, 31)
4.0	28.09.2022	Additional corrections requested by FO and PO (pag. 29 – 31)

1. Excellence

1.1 Objectives and ambition

"*Prevention is better than cure*", a maxima which applies in many aspects of the life of an individual, especially when facing the probability of developing a chronic and progressive disease. Noncommunicable diseases (NCDs)[1], including cancer, cardiovascular diseases and diabetes, account for 80% of the disease burden in Europe and are the leading causes of **avoidable premature deaths**[2]. Under the NCDs umbrella, diabetes is a chronic disease occurring when the pancreas no longer produces insulin (or the body is not able to correctly use the secreted insulin[3]), leading to an increased glucose blood level (i.e., *glycaemia*). European prevalence of diabetes in 2021[4] was of 1 in 11 adults (61M), and its incidence is predicted to increase to 69M by 2045. Global management and treatment of diabetes costed 988 billion dollars in 2021; while in Italy, management of diagnosed diabetes cost around 9 billion euro/year most of which costs is allocated to therapy and complications management. Still, diabetes is the third leading cause of death, responsible of a total 6.7M deaths (1.1M only in Europe). Amongst others, **type-2 diabetes** (T2D) accounts for 90% total diabetes cases with an adulthood onset. It is characterised by insulin resistance (i.e., the insulin hormone cannot effectively regulate the blood glucose levels) and/or a failure in compensatory mechanisms for insulin secretion (i.e., the body does not correctly use the insulin produced) [Blo11]. Besides genetic predisposition and

[1] https://ec.europa.eu/health/non-communicable-diseases/overview_en
[2] https://ec.europa.eu/health/non_communicable_diseases/overview_en
[3] Diabetes (who.int)
[4] IDF Diabetes Atlas | Tenth Edition

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family history, metabolic syndrome and obesity increase the risk of T2D development, along with physical inactivity, age, and ethnicity. Despite a management of diabetes is still possible considered all the challenges, taking **effective prevention measures** are mandatory. According to the *IDF Diabetes Atlas* (10th edition)[2], 36% European adults are living with **undiagnosed diabetes**, and such incidence is much higher in low/middle income countries, where 1 in 2 people live with undiagnosed diabetes. Also, 541M adults (20-79 y) worldwide have *Impaired Glucose Tolerance* (IGT), an important risk factor for further T2D development. Both IGT and/or the *Impaired Fasting Glucose* (IFG) are intermediate condition within the "*healthy-to-T2D transition*" and are manifestations of the so-called **prediabetes** condition. For the sake of completeness, the definitions of IGT and IFG are: 1) *Impaired Glucose Tolerance* (IGT) occurs when "glycaemia is higher than normal, but not high enough to be classified as diabetes" [May15]: blood glucose level of 140 to 200 mg/dL 2 hours after a 75g oral intake of glucose (during oral glucose tolerance test)[5]. 2) *Impaired Fasting Glucose* (IFG) happens when "glycaemia level is consistently higher than normal ranges in the fasting state, but not high enough to be classified as diabetes" [May15]: fasting blood glucose level of 100 to 125 mg/dL[5]. In 2021, around 25,600 European adults had IFG, and this number is set to increase close to 27,000 by 2045[6]. As for T2D, family history and ethnicity are important risk factors for prediabetes. Moreover, prediabetes can occur because of the metabolic syndrome (MetS), i.e., presence of high body fat (central obesity), non-alcoholic fatty liver disease (e.g., steatosis) and insulin resistance. Unlike overt T2D, **prediabetes** is still an early-stage, intermediate condition that **can be reversed**; in fact, "*the rate of T2D progression within 3 years can be decreased by approx. 58% with a lifestyle modification*" [May15]. **Physical activity** should be performed for minimum 30-54 minutes at least 2-5 days/week, and a **healthy diet** is also strongly recommended (2014 WHO and IDF recommendations[7,8]). As T2D prevention strategy, effort has been made in developing **non-invasive diabetes risk prediction models** - usable either by healthcare professionals or patients themselves - based on clinically available parameters, as reviewed in [Nob11]; although none of these models function at the present as a *consensus* method. One algorithm that is worth mentioning for its multi-nations validation and long-term follow-up is the *FINDRISC* [Lin03], an easy-to-use and accurate web-tool to predict the individual risk of T2D. The *FINDRISC* relies on a multivariate logistic regression method to assign to each variable (i.e., age, BMI, waist circumference, physical activity, history of hypertension and/or high blood glucose and diet preferences) a score. The resulting diabetes risk score is the sum of the individual scores. As it is based on easily obtainable input variables, this score is suitable for large screenings; however, it lacks a cardinal involvement of the biological system as a whole. Underlying T2D onset, in fact, there are complex mechanisms acting in a multi-scale approach starting from molecular, tissue and organ levels, leading up to the physiological processes' dysfunction. In fact, chronic inflammatory biomarkers play a pivotal role in the T2D pathogenesis [Don11]. Considering such a multi-level approach is also a step towards the **personalized diagnosis** of the disease. Still there are some challenges regarding the *modelling of a* "*healthy-to-prediabetes transition*", both from a case study and methodology perspectives, that are reported in Table 1.

Table 1 Challenges in the modelling and prediction of a "healthy-to-prediabetes" transition:

Clinical case study-related challenges:	**Methodology-specific challenges:**
C1) How to define a risk index associated to the development of prediabetes based on the analysis of bio-clinical data? C2) How to ensure a patient-centred approach in predicting the risk of a "health-to-disease" transition? C3) Lack of longitudinal data describing the individual "health-to-prediabetes" transition C4) How to develop the patient trust in using computer-aided diagnosis (CAD)? C5) How to guide a pre-diabetic patient engaged in a clinical trial devoted to the observation of a reversion of the disease?	M1) How to ensure reproducibility of a data-driven prediction system? M2) How to enhance the interpretability and trustworthiness of machine learning (ML) solutions? M3) How to improve a risk prediction accuracy while reducing the computation time? M4) How to integrate data attributes, such as completeness, fairness, quality requirements into a computer aided diagnosis (CAD)? M5) How to ensure that the general design of the project is compliant with ethical requirements from the outset? M6) How to ensure that clinical investigations are designed to be compliant with all ethical and societal requirements?

Mathematical biology aims at understanding biological phenomena that are too complex to an analysis without the use of the exact sciences. Through **mathematical or computational modelling**, observations obtained through experiments in "conventional" laboratories are rather described by quantitative traits. Adherence to the experimental

[5] Definition and diagnosis of diabetes mellitus and hyperglycemia (WHO consultation at 9241594934_eng.pdf (who.int))
[6] Europe diabetes report 2000 — 2045 (diabetesatlas.org)
[7] Prevention (idf.org)
[8] Framework-for-Action-on-Sugar-010615.pdf (idf.org)

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data is the necessary condition for the mathematical model, while the predictive power of the latter is its added value. The multi-level complexity of a biological phenomenon might be modelled at the mesoscopic level through mathematical formulations, either continuous (i.e., ordinary, or partial differential equations) or discrete (agent-based models). These models describe the functional relationships amongst entities and allow tracking the changes over time and (the anatomical) space. At a molecular level instead, complex biological systems might be represented and mathematically analysed as computable networks (e.g., using graph theory). Based on these assumptions, a multi-scale, hybrid computational model of the human metabolic and inflammatory status was developed by CNR during the EU-FP7 project **MISSION-T2D**[9] (MT2D), with the purpose of providing the user with an indication of the risk of T2D. While the MT2D prototype simulator is already functional, there are still some fundamental and computational challenges that need to be addressed. Therefore, the core partners joint their efforts and expertise in this proposal to tackle the challenges (Table 1). The ***PRAESIIDIUM*** project will exploit and optimize some of the outcomes of the MT2D project, along with the integration of a new research area called "*physics-informed machine learning*" (**PIML)** [Kar21, Rai19] to develop an easy-to-use, reliable, and efficient tool for the prediction of the prediabetes risk. Thus, the aim of the ***PRAESIIDIUM*** project (i.e., in Latin "*praesidium*" means "protection") is:

To develop a tool aimed at providing a **real-time prediction of the prediabetic risk of an individual**. The prediction algorithm will be based on a "*physics-informed machine learning*" approach: a **rich dataset of real-life data**, obtained from already existing previous and a new clinical trial with continuous data ingestion through wearable sensors, will be combined with mathematical models and eXplainable AI (XAI) techniques, to overcome the limits of "*black-box*" ML approaches while improving the prediction performances and reducing the computational time of the risk calculation based on the simulations of the mathematical model. The final algorithm will be implemented in a web-based platform, where medical doctors and patients can inject data from several sources (acquisition form connected sensors and manual insertion) and obtain a real time analysis of the risk to develop the prediabetic condition over time.

Table 2 summarizes the main **ambitions** of the ***PRAESIIDIUM*** project concerning the challenges listed in Table 1.

Table 2. PRAESIIDIUM's ambitions.

Challenges	Ambitions
C1, C3, C4 M1, M2	*PRAESIIDIUM* will exploit and optimize some modules of the MT2D project (e.g., metabolism, pancreas hormone production, microbiome metabolites, inflammatory process and immune system response), adapt and integrate them with the newly developed modules within the physics-informed machine learning (PIML) framework. The Physics Informed ML algorithm synergistically combines mathematical equations with real-life data through a ML approach. In other words, ML models are trained in a supervised learning setting with constraints provided by a series of mathematical equations (such as ordinary differential equations, ODE, and an agent-based system, ABS). Thanks to a PIML model and eXplainable AI methods, including natively transparent methods and post- hoc explainability techniques, we will overcome prototypical issues of a rather "*black-box*" ML approach such as: 1) lack of interpretability of the outcomes, 2) model reliability and 3) data hungriness. Moreover, the nature of the mathematical equations themselves (according to which biological module are described) will support the identification of the turning point in the "health-to-disease transition".
C2, C3, M5	The PIML model will be trained with real-life data provided by different clinical study-providers: healthcare public foundation, research centres and university hospitals. The first round of data ingestion will be performed from already-existing databases and retrospective clinical studies involving adult (20-80y) participants. Besides data collected from healthy non-diabetic volunteers, the clinical case studies are representative of the real-life scenarios in which the prediabetes can develop e.g., presence of family history, metabolic risk factors, liver disease and obesity. A multicentric, prospective, pilot observational study will be conducted specifically during the project with two main aims: 1) to validate the prediabetes PIML-based prediction tool and 2) to obtain new, meaningful, longitudinal data, also, with the support of different wearable sensors and a mobile app for a continuous data acquisition.
C2, C4, M4, M5	*PRAESIIDIUM* data acquisition and architectures will comply with the FAIR principles (findability, accessibility, interoperability, reusability). Besides, data governance mechanisms will be considered to guarantee the quality of the data. Furthermore, to ensure the adherence of *PRAESIIDIUM* outcomes to fairness requirements, including different criteria, such as avoiding any bias, an Ethical Self-Assessment Guidance will be carried out as it will be described in fully

[9] www.mission-t2d.eu/MISSION-T2D/index.html

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	details. Furthermore, a specifically designed Roadmap will be applied to various trials involving other stakeholders under different conditions. The fulfilment of all these requirements, together with safe trajectory planning, real-time feedbacks about the process dynamic, and risk assessment, will allow the deployment of safe systems.
C4, C5, M5	During the pilot prospective observational study, participants will attend at least two focus groups one before the starting of the piloting and one afterwards, to explore the perspectives of patients, their likability of the trial, their opinions, the interest in the perspective piloting and commitment to the experiment, and the prospects and hopes for the outcomes of the experiment. The focus groups qualitative content analysis will offer data regarding recruitment, communication between participants, researchers and health authorities, and evaluation of the same focus group methodology (face-to-face, remotely, etc.). A detailed explanation for the correct usage of the commercial sensors will be ensured at the enrolment with leaflet and during the entire duration of the study (e.g., nurses support etc.). Moreover, an aided compilation of questionnaire will be available thank to the expertise of one stakeholder of the project (CHK).
M3, C1	The definition of a T2D risk index in the project MISSION T2D has not been an easy task: after several attempts, it has been defined as a combination of the level of insulin resistance, the level of inflammatory cytokines, and the pro-inflammatory cell counts. However, within PRAESIIDIUM we will develop a **ML-based risk prediction** with the aim to develop a more flexible and accurate rule - possibly based on the time *evolution* of several system variables - by means of supervised machine-learning techniques. To this aim, we will develop a machine-learning *surrogate* of the MISSION-T2D model, aimed at reproducing the input/output behaviour of the MISSION-T2D model, while drastically reducing the computational and memory cost required to run (long-term) simulations, which was recognised as one of the main limiting factors of model.

The excellence and relevance of the proposed developments are strengthened because they originate from the projects' end-users and are reported together with the project-specific research objectives in

Table 3.

Table 3. PRAESIIDIUM's Objectives.

Scientific Objective 1: ***Physics-informed machine learning.*** This objective will be developed in three main steps. 1) Development of a ML surrogate of the MT2D model based on simulations of the model itself. 2) New analytical tasks to optimize the MT2D project, in order to better describe in mathematical terms, the biological interactions. 3) Improvement of the surrogate model by including real-life data collected from retrospective studies and sensor measurements, to overcome the limitations and simplifications used in MT2D.
KPI: 1) Reduction in time and memory used by the surrogate model by a factor of 10 with respect to the full MT2D model while preserving the same predictive performances. 2) 10% improvement of ROC-AUC (or other measures, e.g., F1, precision, recall, sensitivity, specificity) in predicting disease progression by means of PIML prediction model with respect to the original MT2D model**.** At least three papers published in OA international journals and/or conferences.
Scientific Objective 2: ***Engineering deployment of the validated model.*** *PRAESIIDIUM* will increase the current TRL 3 of the PIML prediction algorithm to TRL 5. In the final part of the project, the PIML algorithm will be implemented in a web-based application where doctors can insert, manage and monitor data inputs from all the patients, who will be equipped with a mobile app able to collect data from several wearable sensors. The PIML algorithm will be able to produce a personalized real time the risk factor based on inputs by doctor and patient, predicting a time window in which the prediabetic condition may be developed.
KPI: Release of an open-source software prototype. At least one paper published in OA international journals and/or conferences.
Scientific Objective 3: ***Acquisition and generation of retrospective and prospective longitudinal datasets representative of the "health-to-disease transition" (prediabetes insurgence).*** Whitin *PRAESIIDIUM*, the availability of longitudinal data representative of the "health-to-prediabetes" transition is essential for the training of the PIML algorithm, and – most importantly – to ensure a patient-centred approach. Therefore, we adopted a multicentric approach of data collection, which will cover the real-life scenarios of prediabetes insurgence. Data will be collected and quality-curated both from already existing large clinical studies/databases and from new dedicated clinical studies. Also, a continuous personal data ingestion approach will be performed through wearable sensors.
KPI: 1) Acquisition of longitudinal data for retrospective analysis from at least 300 health-prediabetic participants.

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2) Prospective multicentric study with at least 150 participants. 3) Monitoring of at least 50 individuals with wearable sensors. 4) At least two OA paper in peer reviewed journal.
Ethical Objective: 1) Selection of participants respecting ethics: The selection and recruitment of participants will respect the gender balance and, as there is a significant literature on the impact of diabetes on non-dual sex, we will try to include participants from this community. Participants will be informed about the objectives and modalities of the trial and will receive appropriate instructions on how to use the device and the app. Initial difficulties in the use of the app will be considered and participants will be guided through the different phases. 2) App development respecting ethical issues: The app will be designed according to the Ethics by Design methodology (see also "Ethics By Design and Ethics of Use Approaches for Artificial Intelligence Ethics By Design and Ethics of Use Approaches for Artificial Intelligence" (2021) and will be compliant with the EC Code of Conduct on privacy for mHealth.
KPI: 1) Design and evaluation of the Ethical self-assessment; 2) Annual meeting of the Ethics Steering committee; 3) Organisation of two focus groups with prospective trial participants, one at the beginning and one at the end of the trial, to collect their opinions on the development of the trial, the use of the device and the impact of the project.
Business Objective: ***Definition of a roadmap for the certification as a medical device app and commercialization of the prediabetes risk prediction app.*** Up to now, there are some commercial solutions (e.g., web and/or mobile apps) for monitoring diet and physical exercises directed towards metabolic syndrome and/or diabetic people. Similarly, there are a few commercially available wearable sensors for (either invasive or non-invasive) glucose monitoring. However, none of these applications are based on real-life data trained PIML prediction algorithm. We expect to deliver the solution as a prototype at TRL 5. Solid actions will be taken to ensure the increase of TRL close to 8/9. In view of the future commercialization, there is the need to define a process for the solution certification. The industrial partners will in fact develop a complete strategy for the certification of the PIML-based to a national/European body under the EU guidelines.
KPI: 1) Creation of dedicated third-party working group to assure the full compliance to international recognised standards for trustworthy AI, mobile health apps labelling and certification. 2) Nomination of a referee will also facilitate communication with regulatory bodies (e.g., ISO, AIFA, EMA's Innovation Task Force and SME office) and ease the process to obtain the required certifications. 3) Scaling-up of the solution with a plan to secure additional fundings from private stakeholders or National/European fundings (e.g., IA fundings). 4) Presentation of the roadmaps to possible investors.

To ensure the timeliness of the project, and to pave the way for a strong and long-lasting impact of the project's outcomes, we will take a case-study-driven approach, where research is guided by, and progress is continuously assessed with respect to **clinical case-studies,** both retrospectively analysed from **already-existing large clinical databases** and from newly-dedicated **prospective observational studies**. These studies are representative of the real-life scenarios of a prediabetes insurgence in **adulthood** (20-80y): e.g., healthy individuals with family history, metabolic risk factors and obese/bariatric population with the highest risk of prediabetes development. In particular, two case studies (#1 and #3) will provide a longitudinal assessment of the "health-to-prediabetes" transition. Two **pilot prospective observational studies** will be performed by the university hospital partners **(UNIL, MUG)** at a later stage of the project. For the sake of clarity, each owner will be responsible for providing data of the case-study assigned; however, owners will also provide retrospective data related to other case-studies and a cross-check analysis will be performed to deliver the most homogenous datasets. The case-studies are detailed in Table 4.

Table 4. PRAESIIDIUM retrospective clinical case studies description.

Case Study 1: Healthy individuals with a family risk of prediabetes - Owner: **MUG.** The BioPersMed Cohort is a biomarker project established at MUG in a collaboration between the Division of Endocrinology and Graz Biobank. Within the Cohort data of people at risk of diabetes are included and they are followed for a period of 5 years in 6-12-month intervals including clinical investigation (biometrics, medical history, medication) and laboratory sampling incl. biobanking material. A dataset of approx. 300 individuals will be available for the project with a balanced gender distribution. The samples meet the requirements of the sample quality standards that were published by the European Committee for Standardization.
Case Study 2: **Liver-disease and obese patients with risk of prediabetes** - Owner: **FIF**. Non-alcoholic fatty liver disease (NAFLD) has a high prevalence in the general adult population (23-25%). NAFLD is diagnosed in 47.3-63.7 % of patients with T2DM and up to 80% of people with obesity. It is interconnected with insulin resistance, and therefore the development of prediabetes and diabetes is the most direct consequence at the extrahepatic level. A dataset of a well clinic-biochemical characterized biopsy-proven NAFLD cohort (250 patients) is available at our institution. For this specific proposal, the cohort can be stratified as follows: 75% without diabetes, 12% with prediabetes (diagnosed as fasting blood sugar 110 to 125 mg/dL –WHO criteria) and overt T2DM (25%). The cohort is gender unbalanced, being most of the patient's females (71%).

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Case Study 3: Trajectory data for health-prediabetes-T2D transitions – Owner**: CNR.** Data from already existing large databases including longitudinal measures in healthy patients and in patients with prediabetes and diabetes will be used to develop models to assess the risk of transition from health to prediabetes and inform the identification of personalized recommendations to prevent or reverse prediabetes. One of the main databases used in *PRAESIIDIUM* is the CPCSSN (Canadian Primary Care Sentinel Surveillance Network, http://cpcssn.ca/), including fully anonymized longitudinal data from primary care electronic medical records from >1.8 million patients in Canada, available through Ryerson University (see Letter of Support by Ryerson University in Annex). The CPCSSN database covers a time span of about 15 years and includes longitudinal measures of lab biomarkers (e.g., fasting blood sugars, glycated haemoglobin, cholesterol, triglycerides), physical examinations (e.g., BMI, blood pressure), risk factors and lifestyle (e.g., smoking, exercise, diet, family history), medications and medical procedures, comorbidities and complications in patients with varying trajectories (e.g., health-to-prediabetes, health-to-T2D, pre-diabetes-to-health, and prediabetes-to-T2D).health-to-prediabetes, health-to-T2D, pre-diabetes-to-health, and prediabetes-to-T2D).

We also set project-wide success criteria: deliverables made available on time, on budget, and with highest quality; milestones reached; at least twenty scientific papers in peer-reviewed international journals or conferences (with support of Open Access); an *ad-hoc* business plan and exploitation strategy definition; at least two dissemination/demonstration activities, and the organization of the *PRAESIIDIUM* workshops. As previously anticipated, *PRAESIIDIUM* plans to advance beyond the state of the art across multiple disciplines. The ambition section discusses specific topics related to *PRAESIIDIUM*, divided by partner, by introducing a subdivision in **State of the art** and **ambition: Modeling metabolic dysregulation and inflammation: Extension of the Mathematical Model in MISSION-T2D (CNR) – State of the art:** The group at CNR-IAC has considerable expertise in mathematical models to study immune-related diseases [Ber01, Cas12]. Moreover, CNR-IAC is involved in computational methods for the reconstruction and analysis of at molecular-level through protein-protein interaction (PPI) networks, gene regulatory networks (GRNs, DNA-DNA and DNA-protein interaction networks), signalling networks (signals transduced within cells or in between cells to form complex signalling networks), metabolic networks and Boolean networks under both synchronous and asynchronous updates. Computational biology also entails creating surrogate statistical models and emulators whose computational cost is negligible compared to fully detailed mathematical models. Given the complexity of the models considered in biology, CNR-IAC has made full use of statistical and machine learning algorithms, from ensemble methods such as Random Forest to Gaussian processes just to name a few, to find the most suitable statistical model in terms of computational cost efficiency and predictive power. In the project MISSION-T2D (MT2D), a multilevel, integrated and patient-specific model for simulation and prediction of metabolic and inflammatory processes and progress of type-2 diabetes has been developed and validated. However, MT2D can be improved both in terms of precision in the prediction of the disease progression and velocity of the simulations. The feasibility of accelerating predictive physical models by replacing complex numerical computations with equivalent real-time deep learning inference (model distillation) has been demonstrated in multiple fields, including operative solutions for nowcasting on complex data [Fra2020]. **Beyond:** The aim of CNR-IAC is to provide, adapt and integrate the MT2D model with newly developed modules within the physics-informed machine learning (PIML) framework. This will constitute the working model at the basis of the PRAESIIDIUM prototype for the real-time prediction of the prediabetic risk. The model MT2D will be improved thanks to the addition of a more sophisticated mathematical model describing the microbiome, while the availability of new data provided by other partners of the project will allow a more precise calibration of its parameters. **EXplainable AI (XAI) to characterise, predict, and prevent T2D (CNR) - State of the art:** In line with the European GDPR that states that there is a need of a "right to explanation" when dealing with automated systems, the CNR-IEIIT group is focused on the development of eXplainable AI (XAI) methods, intelligible analytics aiming to provide humans with understanding and trust in models outcomes therefore supporting domain experts as well as patients/citizens in making informed decisions. The range of XAI models of interest to the CNR-IEIIT team includes natively transparent models (e.g., intelligible rules) and model-specific/model-agnostic post-hoc explanations with various output formats (e.g., rules, numbers, text, or visualizations). The CNR-IEIIT group has developed a variety of XAI-based models to characterize, predict, and prevent chronic diseases from clinical data (including chronic obstructive pulmonary disease, hearing loss and cognitive decline, gestational diabetes and T2D, e.g. [Mon20], [Vac21], [Tas20], [Pag19]). In the field of T2D, CNR-IEIIT has recently developed methods that will support the development of PRAESIIDIUM tools, for example data-driven patient segmentation for T2D prevention through lifestyle change [Mit22, Pag22], individualized preventive recommendations to lower the risk of T2D through changes in biomarkers determined using counterfactual explanations [Len22], and models for prediabetes risk assessment and personalized recommendations to prevent or reverse prediabetes [https://preventdiabetes.ca/]. **Beyond:** Within the PRAESIIDIUM project, CNR-IEIIT will leverage both already existing datasets and newly developed datasets to generate knowledge, through fully interpretable models, about the combination of factors (e.g., clinical, biological, lifestyle, behavioural or environmental) that may determine transitions from health to prediabetes,

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and progression or reversal of prediabetes. Besides the foreseen opportunities for knowledge generation and knowledge transfer (by informing the development of the mobile app and preventive tools), the project will enable methodological advancements of the XAI tools for prediabetes and T2D prevention thanks to new input from the MT2D and PIML models as well as support broader application of these XAI tools towards implementation of EC guidelines to design, develop, and deploy trustworthy AI systems and, specifically, to ensure that key principles of trustworthy AI are met, for example human agency and oversight and accountability (e.g., through explanations, human-machine knowledge integration, and generation of consistent and realistic predictions), technical robustness and safety (e.g., through minimization of false negatives and through safe recommendations), transparency (e.g., through explanations and open science practices). **Physics Informed Machine Learning for Health-to-Disease Transition (SUPSI) – State of the art:** SUPSI is expert in analysing and modelling structured and unstructured data in the medical and life-science domains by means of advanced artificial intelligence (AI) techniques. Among others, SUPSI has strong expertise in ML, deep learning and probabilistic modelling. Our capability of integrating heterogeneous data sources from clinical information systems (e.g., large clinical databases, laboratory tests, electronic health records, unstructured texts) together with expert knowledge - as well as our interest in ethics of AI and interpretable ML - have proven useful in clinical applications [Hal21, Ber21, Gor17]. One active area of research known as physics-informed machine-learning (PIML) deals with the integration of physical knowledge into ML models. In this context, SUPSI has worked on the definition of tailor-made neural model structures for physical systems described in terms of systems of ordinary differential equations (ODEs). In a nutshell, only the uncertain parts of the dynamics are modelled as neural networks, while structural a priori knowledge is retained, whenever it is available. Examples of this modelling approach from the mechanical and electronic domain are presented in [For21], along with algorithms for efficient training based on modern deep-learning tools and concepts. Methods to include partial differential equations (PDEs) into ML models for blood flow estimation are described in [Azz15, Arn19], while the application of a data assimilation technique for fluid dynamics numerical simulations is described in [Gue16]. **Beyond:** Within the project we will integrate our expertise in risk prediction modelling with the one in PIML, thus developing new risk-predicting PIML models. Moreover, the methods will be optimized for the specific application of interest. Both the application of PIML techniques to a large-scale system of differential equations, such as the MT2D model, and the integration of risk prediction with PIML models will be challenges to be faced. **Intelligent digital patient assistants for Patient Empowerment and Involvement in their disease management (CKH)** – **State of the Art:** CKH developed the Linkwatch platform for patient data collection and patients' self-monitoring. It integrates connectivity solutions for medical device measurements (blood pressure monitors, glucometers, weight scales, spirometers, pulse oxymeters etc), activity tracking using bracelets FitBit-like and questionnaires for self-assessments. Data is seamlessly transferred to a cloud solution using the FHIR standard (Fast Healthcare Interoperability Resources). It is available as Open Source. **Beyond:** The prevailing approach to the capture and interpretation of patient-reported outcome and experience measures (PROM/PREM) is largely based on a document/text model using self-questionnaires. This can be effectively complemented by digital assistant technologies based on voice recognition, data capture and storage. Technologies for speech-to-text, text-to-speech, natural language understanding and conversational AI tools as a service, are developing rapidly and there are now several commercial platforms that can be used to design and integrate a conversational user interface into mobile apps, web applications, devices, bots, interactive voice response systems and related uses. The market leading platforms are Google Dialog Flow, Amazon Lex/Connect, Microsoft Azure Bot and IBM Watson Assistant. Moreover, these platforms are starting to provide integration with digital telephony platforms that can be used for automatic digital assistant-based outbound calls to patients to capture PROMS/PREMS data. Within the project PRAESIIDIUM, CKH will exploit and extend the concept of **digital assistants using voice technology for patient interactions and data capture**. This will include the design and evaluation of novel approaches to promote patient dialogues, to convey and collect patient treatment outcomes and various kinds of patient experiences. Data thus obtained will be integrated into the PRAESIIDIUM platform and made available for clinicians. **Wearable sensors for the real-time assessment of impaired glucose and physical performance (EDI) - State of the Art:** EDI is a technological research institute with focus on and extensive experience in both sensor data collection and artificial intelligence. We develop sensors with embedded intelligence and original DSP capabilities to efficiently monitor different environments, and apply them to real-world problems in multiple domains, including healthcare and fitness. Our research in wearable technologies includes ECG, EEG, EMG signal-based interfaces, shape sensing fabric [Herm15] used for posture monitoring in rehabilitation or as a motion tracking device for telemedicine and training purposes, a sensor-based knee rehabilitation device or for prosthetics control, embedded signal processing and machine-learning for activity recognition [Elsts20], as well as research on low-power wireless communication protocols. Our researchers have experience in designing and implementing sensor platforms for running clinical trials [Elsts19]. **Beyond:** In the project *PRAESIIDIUM*, the success of our involvement will be established by the opportunity to construct, test and further improve a prototype of the wrist-worn wearable device with bioimpedance sensing and signal processing capabilities. An early prototype of this device already exists. It integrates nRF5340 next-generation microcontroller with ICM 20948 inertial measurement unit (IMU, includes an accelerometer) and

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MAX30001CWV+ bioimpedance measurement unit. The key parts of the device and/or the bioimpedance signal acquisition algorithm will be patented before the end of 2023. **Prediabetic Prediction and Individuation of Blood-Based Biomarkers in MetS/NAFLD Cohort (FIF) - State of the Art:** Laboratories of FIF are dedicated to both processing and analysis where different experimental in vitro, in vivo animal models, and clinical samples are used. Moreover, all the lab equipment necessary for sample processing, storage and in this case for biomarkers quantification are available. In the last five years, our research involved developing in silico strategies, using the integration of publicly available 'omics datasets (such as GEO, ArrayExpress, HPA, etc.) for the individuation and validation of non-invasive protein biomarkers helpful in diagnosing different stages of the NAFLD disease. **Beyond:** In this project, the success of our involvement will be established by the opportunity to evidence that our in-silico approach could be extended to the discovery of useful non-invasive prediabetes-related biomarkers and test them experimentally, contributing to a better characterization of the transition points from health-to-disease in prediabetes, a pathology highly interconnected with NAFLD. This target will have a major socioeconomic impact. Moreover, a juvenile NAFLD-mouse model developed at our institution might be exploited for the qualification of candidates or other parameters individuated in this project. The candidates can be quantified at gene and protein levels in the tissue of interest (liver, kidney, adipose tissue, muscle, plasma, etc) in this well-characterized mouse model of juvenile NAFLD, showing hyperglycaemia diet-induced, particularly in males. **Prediabetes patients' management and treatment (UNIL) – State of the Art:** The laboratory of Personalized Medicine at the University of Latvia (UL PML) has history of translational clinical studies. For the pilot prospective study, prediabetic patients can be pre-selected based on patient phenotyping (e.g., history of diseases, anthropometric measures, blood and urine chemistry, etc.) and we can provide previous physical activity monitor (through Minnesota leisure-time physical activity questionnaire, IPAQ) and dietary habits evaluation (e.g., diet frequency questionnaire, 3-day diet record or 24h diet survey). A strong collaboration with the Physiology department can provide physical tests (e.g., VO2 max peak test on a treadmill, 5min walking test, muscles strength tests, body composition, ultrasound examination etc.). We also have active collaboration with Latvian Biomedical research and study center and Latvian Genome Database; facilities for storage of biological samples are available and is performed in accordance with international biobanking guidelines. **Beyond:** Participation in the PRAESIIDIUM project will lead to improvement of skills and acquisition of new methods at the UL PML. First, we will exchange experience on clinical studies with other Clinical partners of the project, leading to improved practices at all involved institutions. PRAESIIDIUM project will also be the first experience in conducting a clinical trial with the aid of wearable sensors. **Prediabetes patients' management and treatment (MUG) – State of the Art:** The diabetes outpatient clinic of the Division of Endocrinology and Diabetology offers specialized care for all endocrine diseases and diabetes and its complications. Patient data including biometrics, laboratory parameters and medication are routinely documented in the electronic medical record in a longitudinal manner. Close collaboration with the Graz Biobank and the Institute of Statistics and Bioinformatics enables structured extraction of these data to answer specific research questions. At Graz Biobank facilities to store of biological samples included documentation of clinical data and biometrics are available; sample handling is performed in accordance with international biobanking guidelines. Biobank Graz is one of the largest and most well-known clinical biobanks in the world. Around 20 million individual specimens of body fluids and human tissue from patients with specific diseases and healthy persons are stored here. The Clinical Trial Unit integrated into the Division enables high quality clinical studies (Phase 1-4 clinical trials) including studies for pharmacodynamics and pharmacokinetic assessments of novel therapeutics as well as testing of new developments in the field of diabetes technology incl. Software. The BioPersMed (Biomarkers for Personalized Medicine in Common Metabolic Disorders; collected by the Division and stored at Biobank) Cohort comprises a huge number of samples and data being collected and used since 2010 (still ongoing). The aim is to detect and define specific characteristics and personalized biomarkers of patients at risk for cardiovascular and metabolic diseases and to follow them for future developments. **Beyond:** Within the *PRAESIIDIUM* project, dataset collected within BioPersMed will be used which will contribute to sustainability and visibility of the BioPersMed Cohort and Graz Biobank. By participating in the *PRAESIIDIUM* project MUG will strengthen its position as clinical trial centre for innovative technologies and early adopter of novel technologies. **– SPXL:** Deploying ML applications on the edge requires specific competences which cover several fields, and application developers face several challenges regardless of the scenario they are targeting. **Beyond**; Within *PRAESIIDIUM*, the role of SPXL will be to implement a Web based platform to be used by doctors where, for each patient, it is possible to collect data (to be added manually or collected by sensors) and to run the PIML model that furnishes a real-time Risk Parameter associated with the probability of developing Prediabetes. The doctor/user can set different time intervals for the prediction. We will also develop a mobile app where the patient can see his profile (personal information and graphs representing historical data) and integrate new data (the doctor will see the data added by patients). The app will be compatible for the acquisition of data from some commercial sensors (mainly for measuring: hearth rate, BMI, percentage of fat in the body, VO2 max, glucose) and will be integrate with the newly developed sensor of bioimpedance (T5.1). **Data stratification and Data Shift in Precision Medicine (HKL) – State *of the Art:*** There is an ideal connection between the most recent key guiding principles for good machine learning practice for precision medicine from integrated data and efforts for scientific

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reproducibility of predictive biomarkers, on which HKL has long-term experience of collaboration with the US FDA. Recent scientific work [Soi22] as well as EU and US FDA directives identify the relevance of well-designed frameworks to mitigate the impact of subtypes and data drifts between training and operation data (e.g., covariate, or target label shift), proposing integrative methods for monitoring domain shifts (e.g., different data providers or devices) along the AI Life Cycle. HKL scientists have combined unsupervised data reduction and clustering methods to support the distillation of medical decision algorithms by deep learning models [Mag18] and collaborate with the Mount Sinai Hospital for developing stratification tools on digital medical data [Lan20]. ***Beyond:*** the project will adopt for the first time on the integrative prediabetes data provided by clinical partners an internal platform capable of automatic stratification and Domain Drift monitoring. Multimodal drift identification and monitoring will be proposed on longitudinal trajectories, also adopting ultra-fast methods formerly applied on longitudinal time series for radar-based weather nowcasting. An explainable AI approach will be developed to analyse the impact of drift and stratification on the model, supporting its life cycle as additional data (including real-world data) are added in the project, and in the expected operational phases. This component will have high value for the expected regulatory path of the solution, and it will also become an asset for similar projects. Beyond the specific use in *PRAESIIDIUM*, HKL will aim at developing a general model-agnostic and platform-agnostic, centralized system data stratification and drift for biomedical research and digital biomarker services.

1.2 Methodology

The methodology of this project follows two main directions both approaching the same objective: developing an algorithm able to predict a patient-specific risk associated to *health-to-disease* transition in type-2 prediabetes, i.e., the probability a patient has to develop prediabetes in a certain time window. On the one hand, we point at the usage of the technique called Physics Informed Machine Learning (PIML), that integrates data and mathematical models to incorporate domain knowledge into ML algorithms. On the other hand, we aim at creating an accurate mathematical model describing the inflammatory processes involved in the transition from health to prediabetics, by combining already existent mathematical models, ML techniques, historical data belonging to clinical studies and sensors measurements. The **starting point of the project** will be based on the acquisition of the Mathematical Model developed in the EU-FP7 **MISSION-T2D**[7] project (MT2D). In the MT2D project, a multilevel, integrated and patient-specific model for simulation and prediction of metabolic and inflammatory processes in the onset and progress of prediabetes has been developed and validated. MT2D is a hybrid continuous/discrete (i.e., ABM-ODEs) multi-scale mathematical model that studies the systemic interactions of the involved biological mechanisms (immunological/inflammatory processes, energy intake/expenditure ratio and cell-cycle rate) in response to a variety of nutritional and metabolic stimuli/stressors. In particular, MT2D is composed by several sub-models (*Table 5*): 1) a model describing the immune activation and inflammation (integrating and extending an agent-based model of the immune system [Ber01,Cas12]); 2) a model for the glucose metabolism (including multiple tissue compartments); 3) a model to account for the effects of physical activity on the hormones' regulation [Pal18] and on the inflammatory state of the individual [Mor17]; 4) a model describing the food ingestion; 5) a model of energy intake-expenditure balance; 6) a model for adipogenesis due to excessive calorie intake inducing the secretion of inflammatory cytokines such as tumour necrosis factor alpha (TNFalfa), interleukin-6 (IL-6), and interleukin-1beta (IL-1b) [Pra19]. All these *modules* are merged into a single integrated simulation tool with the purpose of providing the user with an indication of the risk of type-2 diabetes and ultimately to proactively prevent the disease based on the subjects-specific characteristics to achieve greater generalization and user-customization. We integrated in our model a previously validated system model of the effects of exercise on plasma IL-6 dynamics in healthy humans, combining the contributions of both adipose tissue and skeletal muscle [Mor17].

What is Physics Informed Machine Learning? With the term "*Physics-informed machine learning*" (PIML) scientists intend a set of strategies focused on the use of a prior knowledge of the physical system underlying the problem to help training machine-learning models like neural networks and gaussian processes, making them more efficient. Machine Learning (ML) – a branch of artificial intelligence (AI) - has the best potential to exploit large digital data availability to build decision algorithms needed for precision medicine and tools in the simulation of biological, medical and physical problems. However, ML solutions are often perceived as a "*black box*" tools, being less interpretable and explainable than other basic statistical approaches; moreover, concerns regarding results' reproducibility have been raised. Additionally, training deep-learning models requires large-scale datasets, not always available. Instead, PIML models can be trained on smaller sets of data, by integrating additional information obtained from physical laws. Indeed, PIML approaches allow convenient integration of data and physical a priori knowledge within neural networks or other (e.g., kernel-based) machine-learning models. Moreover, it may be possible to design specialized model architectures that automatically satisfy some of the physical invariants for better accuracy, faster training and improved generalization. PIML has the potential to allow scientists to tackle problems they could not address before. For example, it can lead to the design of better drugs by helping reduce the size of the design space and by guiding the choice of new experiments [Moo22]; it can lead to a better prediction of fluid flow,

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which appears almost everywhere, from blood vessels to river waters, by improving simulations in complex geometries, which traditionally have been very expensive [Que21]. There are different ways to embed physical knowledge into machine-learning models: 1) Soft constraint. Include the mismatch between the physical and the machine-learning-model as a penalty in the loss function to be minimized. In training, the overall loss will thus be a trade-off between reconstructing the measurements (fitting goal) and satisfying a priori assumptions (consistency goal). This approach has been first popularized in the context of partial differential equations by [Rai19]. Nowadays, it has become extremely popular due to its flexibility and (relatively) simple implementation. 2) Hard constraint. We may instead define tailor-made machine-learning architectures where physical knowledge is embedded in the model structure. In these models, flexible machine-learning function approximation is used only to describe the most uncertain model components, while physical knowledge is retained whenever it is possible. Even for the uncertain component, certain rough, yet relevant properties, (e.g., positiveness, monotonicity, admissible range, etc.), could be embedded. In our case, the embedding of physical knowledge by means of soft constraints could be easily adapted to the ML surrogate model [Rai19], however we will consider both possibilities.

Added value of a PIML model: The embedding of mathematical models into ML can seamlessly integrate data and the governing physical laws, including models with partially missing physics, in a unified way. In addition, the integration of physics models into data-driven solutions underlines the fact that the validation of a ML model with some analytical model relates to the concept of trustworthy ML, since the support of mathematical equations contributes to the repeatability and explainability of the final model.

What do we mean by T2D risk index? The definition of a T2D risk index in the project MISSION T2D has not been an easy task: after several attempts, it has been defined as a combination of the level of insulin resistance, the level of inflammatory cytokines, and the pro-inflammatory cell counts. These observables are, among others, used in the introduced mathematical description of the complex interdependencies among metabolism and pancreatic control as well as among adipose tissue components and inflammation [Sto20]. Within *PRAESIIDIUM*, we aim to develop a more powerful and flexible rule to compute the risk index leveraging ML tools. In particular, the risk prediction task will be cast to a classification problem of time series and longitudinal data. To train the classifier, clinical data together with the surrogate model will be used to generate time trajectories of relevant variables for T2D detection to be used as *features*, while the patient's status in the dataset will be used as *target*. The risk score will then be defined as the probability of transition to prediabetes within a given amount of time, which will be obtained as output of the trained classifier in response to a new trajectory. Table *7* reports how the partners will implement the methodology towards *PRAESIIDIUM's* objective.

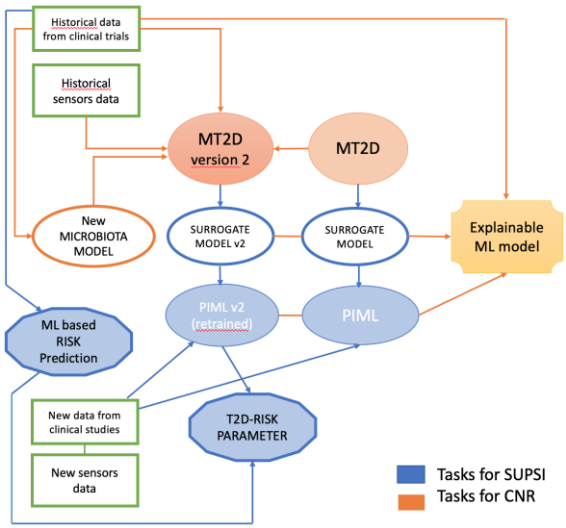

Figure 1: schematic description of the passage from MT2D to PI-ML model

From the MT2D model to the PIML model: the mathematical core of the project. The flux conducting to the mayor outcomes of the project PRAESIIDIUM can be schematized through the following steps (*Figure 1*): **1)** While historical data (previous clinical studied and sensors) are collected and preprocessed, a first surrogate model (SUPSI) accompanied by a deep learning model called *model distillation* (HKL) will be performed, by analyzing the trajectories generated by the original version of the model MT2D (CNR). **2)** A more refined version of the MT2D model (MT2D-v2) will be obtained: 2.1) from historical data and sensors data by a parameter tuning, 2.2) by introducing a detailed mathematical model describing the microbiota (CNR+SPXL). **3)** An improved version of the surrogate model (surrogate-v2) will be performed from the MT2D-v2, accompanied by model distillation (SUPSI+HKL). **4)** An improved version of the PIML model (PIML-v2) will be obtained by the surrogate-v2 and the new data coming from the clinical studies (in WP6). As mitigation risk of this step, we will consider a back-up version of the PIML model obtained by combining the surrogate model and data from the new clinical studies. **5)** A ML based risk prediction will be obtained from the analysis of historical data (SUPSI). **6)** Explainable ML(X-ML) techniques will improve the accuracy of the ML based risk prediction (CNR). X-ML models will be built both using longitudinal data from retrospective and existing datasets as well as using the surrogate and PIML models. **7)** From the PIML-v2, the ML based risk prediction and the X-ML, we will be able to formulate the most relevant mathematical result of our project: **the T2D-risk parameter**.

Table 5. How the partners will implement the methodology towards PRAESIIDIUM's objectives.

How to speed up the MT2D simulation tool? The strategy used in PRAESIIDIUM will be the development of a ML surrogate model (**MLSM**) of the MT2D model based on simulations of the model itself, in order to obtain faster simulations of the trajectories, and more flexibility on the length of the simulations. This step will contribute to the development of the PIML model. The MLSM will be trained on short-, mid- and long-term simulations of the original MT2D model by minimizing a properly defined loss function. The input parameters of the simulations used to train the MLSM will be sampled in the original input space by means of Bayesian optimization techniques in order to properly cover the output space of interest. **KPI :** reduction in time and memory used by the surrogate model by a factor of 10 with respect to the MT2D model while keeping the same predictive performances. **Main involved partners: SUPSI, CNR.**
How improve the qualitative description of the MT2D model? One of the objectives of the project PRAESIIDIUM is to enhance the MT2D model by describing better and more robustly causal relationships between the patient's microbiome and its impact on the regulation of inflammatory pathways which may play a critical role in the onset of the inflammation and eventually of type 2 diabetes. The MT2D model is equipped with a detailed mechanism for the lymphocytes T helper differentiation between pro-inflammatory (I.e., Th1, Th2, Th17) and anti-inflammatory (i.e., Treg) phenotype. In the actual version of the MT2D model, this differentiation mechanism is described as a Boolean Gene Regulatory Network (GRN) of a set of genes such as Foxp3, GATA3, STAT1 and Tbet among forty genes. The activation of key genes determines the differentiation fate of a T lymphocytes during the set-up of a chronic inflammation. The model of microbiota that is currently implemented, links the gene Foxp3 with the level of butyric acid (butyrate), that is produced during the digestion by specific strains of commensal bacteria present in our gut. Therefore, given the distribution and relative abundances of bacterial species in the microbiota and the abundance of certain meal elements (i.e., PUFA, saturated fatty acids, CLA fatty acids, trans fatty acids, vegetable proteins, animal proteins, total proteins, prebiotics, sugars, total carbohydrates, fiber) the model determines the level of butyrate produced, hence the likelihood of a systemic class switch for T helper cells toward the Treg phenotype. T-regulatory lymphocytes then produce anti-inflammatory cytokines that lower the inflammatory state. This is the logic linking ingested food with the emergence of an inflammatory state mediated by patients' specific microbiota and gene expression levels. Through a metagenomics approach, it is also possible to derive the bacterial species specifically involved in short-chain fatty-acids (SCFA, including butyrate) production (i.e., which induces an anti-inflammatory response through epigenetic modification) and their related genes and metabolic pathways. Moreover, interaction networks coupled with co-occurrence analysis will further strengthen the linkage between bacterial species abundance, SCFA production and food ingested. To reach this goal, the availability of already published datasets (e.g., Human Microbiome Project 2, HMP2) and new data furnished by several parners or the project (UNIL, MUG, FIF, CHK, CNR), will be paramount. Indeed, new data will be needed to fit the parameters of the improved version of the MT2D model. **Main involved partners: CNR, SUPSI, SPXL.**
How to improve the predictive precision of the MT2D model? To obtain in real time the risk parameter, we plan to write a Physics Informed Machine Learning (**PIML**) algorithm, i.e., to combine data with the surrogate mathematical model. We will incorporate physical knowledge derived by the full MISSION-T2D model into a real-time PIML model to predict the patient-specific risk of disease transition. The prediction model will be based on a surrogate model approximating the full MISSION-T2D mathematical model and will integrate patients' data (diet, fitness, and disease progression) collected during the clinical study. On the one hand, the surrogate model will provide real-time predictions on different time scales overcoming the current computational complexity limitations, while preserving the reliability of the MISSION-T2D model. On the other hand, the incorporation of patients' data collected during the clinical study will improve the MISSION-T2D model in predicting the patient-specific risk of disease transition. The physics-informed risk prediction model will be trained on both simulations of the original model and patients data collected during the clinical study, e.g., diet, fitness, and disease progression, by minimising a fitting criterion based on adherence to both the mathematical model and the data, e.g., a linear combination of a model-related loss and a data-related one. This approach could be seen as a soft constrained PIML method. **KPI**: 10% improvement of ROC AUC (or other measures, e.g., F1, precision, recall, sensitivity, specificity) in predicting disease progression by means of PIML prediction model with respect to MT2D model. **Main involved partners: SUPSI, HKL**
How to decipher the means of 'omics and the chronic inflammation factors triggering the health-to-prediabetes transition? An original *in-silico* funnel strategy was designed to discover non-invasive biomarkers able to diagnose liver fibrosis in NAFLD (https://doi.org/10.3390/ijms23052813). The FIF approach will be adapted for this proposal to the discovery of protein markers, as candidates for the prediction/diagnosis of prediabetes/T2D. To do this, open 'omics datasets retrieved in the literature related to prediabetes and T2D disease-transcriptomic datasets, NAFLD-related transcriptomic datasets, liver, and pancreas tissue-specific transcriptomic among others; will be combined with transcriptomic datasets from the Human Protein Atlas (HPA) database, in

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which protein-coding genes have been categorized as housekeeping, secreted and/or plasma protein components. The protein candidates that meet our selection criteria (around 5 candidates) will be ranked and selected for entering in the qualification/verification experimental phase and ultimately, they could potentially be included the mathematical models. **Main involved partners: FIF**

How to collect a representative dataset for the development of the PIML model? Three clinical partners, with proved history of clinical and research experience in endocrinology and gastroenterology, will provide e.g., clinical, biochemical, dietary, and physical-activity-related data from already existing databases/retrospective studies, which cover the three main clinical case-studies of the project (e.g., healthy individuals, family history, metabolic risks/obesity and liver disease adult patients). Moreover, access to a large database (CPCSSN) will be provided by colleagues at CNR. Two dedicated pilot prospective observational studies will be performed at a later stage of the project by MUG and UNIL (M12-M26), to collect more necessary data for the prediction tool validation, including a continuous data ingestion by wearable sensors and recording via mobile app. Ethical commission approvals will be performed during the first year of the project and statistical power calculation will be performed. However, from a first round interviews with clinicians and according to the capacity of conducting a clinical study with diet and physical activity monitoring, the following scheme summarized the proposed clinical observational studies. **Main involved partners: FIF, MUG, UNIL, HKL, CNR, SUPSI.**

	UNIL	**MUG**
N participants	75	75
Age Range	35-65 years	35-65 years
Body Mass Index	25-40 kg/m2 (overweight/obese grade I and II)	19-25 kg/m2 (normal weight)
Exclusion criteria	already prediabetic or diabetic (based on OGTT); cardiovascular disease; other NCDs increasing inflammation	
Intervention	Diet and physical activity (wearable sensors monitored)	
Medical Assessment	Nutritional intake; physical activity; aerobic capacity; metabolic flexibility and inflammation; medical history	
Physical assessment	VO2 peak (3 times); peak power output; shift in substrate oxidation, max fat oxidation, intensity for max fat oxidation	
Nutritional assessment	3-day weighing protocols, measurements of dishes used; 24-hour diet recall and diet frequency questionnaire (followed by dietician)	
Biological samples	Urine, blood and faeces 3 times during the study	
Biological measurements	Fasting glucose, cholesterol and metabolic profiles, IL-6/hsCRP;	

What is the strategy used for collecting *meaningful and representative data* during the retrospective study (or clinical trial)? The data will be first injected in one shared data lake formed by a set of heterogeneous data sources (relational databases and semi-structured data). Provenance of sources and persistence of the original data, before and after transformations, will be maintained by a data and feature versioning system. Automatic tools will be developed for *(i) Quality Check and imputation; (ii) Data stratification; and (iii) Domain Shift evaluation.* The analysis of missing/null/invalid data and their imputation will evaluate random or non-random effects, considering clinical information or analytical methods, e.g., by random forest regression models. Computational statistics tools will be applied to explore the variable correlation structure among variables, or potential bias, including tracking aspects of "data disparity" of impact for model fairness (e.g., gender imbalance). Data will be stratified after a dimensionality reduction and unsupervised machine learning analysis. The stratification will be enriched by explainability procedures. The design of the QC process and the explainability features will be based on interaction among data scientists and clinicians. Of notice, a set of Domain Shift algorithms will be made available to identify issues on the potential difference in statistical distribution of the datasets from different clinical providers, or between the retrospective and prospective datasets, supporting the use on real-world data of the model. All the results will be made available to the team modelling the PIML method as well as to the clinical team enrolling for patients during the prospective observational trials. **Main involved partners: HKL, CNR, SPXL.**

How to help patients to collect proper data during the prospective study? We will development of a LinkWatch platform for remote monitoring and self-management of patients during clinical trials. The idea is to capture and interpret patient-reported outcome and experience measures by digital assistant technologies based on voice recognition, data capture and storage. Within the project *PRAESIIDIUM*, CKH will exploit and extend the concept of digital assistants using voice technology for patient interactions and data capture. This will include the design and evaluation of novel approaches to promote patient dialogues, to convey and collect patient treatment outcomes and various kinds of patient experiences. **Main involved partners: CHK**

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What are the achievements that we expect from the realization of the observational study? 1)The patients engaged into the pilot observational study will obtain a prediction of their recovery from prediabetes by means of the already developed PIML model. 2) The data collected during the clinical trial will be used for a further improvement of the PIML model. The sensors developed by EDI will be tested during the clinical trial and integrated in the web app developed at the end of the project. 4) A specific platform will be developed by CHK to optimize the quality of data collected and integrate various sensors data: our aim is that this will enhance the quality of the collected dataset, to allow the PIML model to give a very precise prediction. **Main involved partners: CNR, SUPSI, EDI, CHK, SPXL.**

National and international research projects. The goals of *PRAESIIDIUM* are beyond the scope of any of the projects listed below. We believe that with our consortium, we are uniquely well placed to tackle the ambitious tasks that we have set out. The consortium is involved in several other research projects, although due to a limited space we included only the most important for this project (Table 6).

Table 6. National and International Projects

SUPSI - 1) *SPEARHEAD* *(2021-2024)* Innosuisse flagship project in collaboration with University Hospital of Basel, Geneva and Lausanne, Novartis, Swiss RE, Resistell AG: development of a clinical decision support system based on ML models to provide data-driven insights for antibiotic prescriptions and to predict patient-specific clinical risk of antibiotics resistance. **2) *DEALING*** *(2021)* Small project funded by the Swiss HASLER STIFTUNG foundation to pursue fundamental research on deep learning for dynamical systems modelling. **3) *SpineReg*** (2020-2021) in collaboration with Istituto Ortopedico Galeazzi: development and deployment of an interpretable ML model, based on explainable AI methods, to stratify patients undergoing spinal lumbar arthrodesis to support clinicians in the surgery strategy definition. **4) *Life-ON*** *(2019-2022)* in collaboration with Ente Ospedaliero Cantonale (EOC): development of ML models for early risk prediction of perinatal depression in pregnant women.
CNR – 1) EU-IMI2 project ERA4TB. The main objective of the EU-IMI2 project ERA4TB is to create a European open platform to accelerate the development of new regimens for the treatment of tuberculosis. In this project we use the "inflammation" component of the MT2D model mentioned above to describe the immune response to mycobacterium tuberculosis. **2) JPI-AMR MAGIcIAN.** This project focuses on developing computational tools to describe the emergence of antibiotic resistance in a population. In this activity we are using the same mathematical methodology by describing the individuals in the contact-network as discrete agents (agent-based modelling). **3) SCI-PHI** (2020-21, Segment-based Collective Intelligence for Population Health Improvement), pilot project funded by Nesta to develop AI-based diabetes prevention intervention using data from electronic medical records to segment patients with Type 2 Diabetes based on behaviours to deliver tailored interventions to promote lifestyle change and reduce the risk of complications.
EDI – 1) CONVERGENCE. ERA-NET project "Frictionless Energy Efficient Convergent Wearables For Healthcare and Lifestyle Applications". EDI role was the development of full-body motion tracking suit using Inertial Measurement Unit (IMU) sensors. Includes development of a custom sensing solution, and validation on 50 test subjects. **2) I-MECH**. H2020 ECSEL RIA project "Intelligent Motion Control Platform for Smart Mechatronic Systems". 32 partners from 11 countries. EDI role was development of Industrial low latency real-time wireless sensor (and model of it for MiL simulations); SoC based platform for smart sensors with advanced data processing. Included development of a custom sensing solution, and successful cooperation with a wide range of European partners.
UNIL – 1) Mutual funds Taiwan – Latvia - Lithuania cooperation project 2018-2021. Novel biomarkers of diabetic retinopathy: epigenetic modifications of genes of ubiquitine-proteasome system, telomere length and proteasome concentration. **2) EEA grants 2021-2023**. Integrated model for personalized diabetic retinopathy screening and monitoring using risk-stratification and automated AI-based fundus image analysis (PerDiRe). **3) Collaboration within InterDiane consortium** (www.finndiane.fi). **4) Collaboration with University of Vienna**, group of Ina Bergheim (Dept. of Nutritional Sciences, Molecular Nutritional Science), in the area of intestinal permeability in hepatic steatosis in type-1 diabetes. **5). ERDF project "Postdoctoral research aid", Nr. 1.1.1.2/16/I/001. 2020-2023.** Intestinal inflammation as a potentially modifiable risk factor for complications in type 1 diabetes. **6). Project of Latvian Science Council program of Fundamental and applied research projects 2021-2023.** "Dissecting the associations between glucose variability, intestinal derangements and progression of diabetic nephropathy in type 1 diabetes".
CHK - 1) PICASO H2020—689209. http://www.picaso-project.eu. PICASO (A Personalised Integrated Care Approach for Service Organisations and Care Models for Patients with Multi-Morbidity and Chronic Conditions) aims to develop an ICT platform, which will support the coordination of care plans across different sectors for people diagnosed with co-occurring chronic diseases. PICASO addresses three main challenges in Europe's healthcare systems: managing multi-morbidities; coordinating care and treatment across organisational silos and

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adapting e-health solutions to existing care models and plans. **2) Swedish National Health Account.** Hälsa För Mig (Health For Me) was a free, personal health account available every Swedish citizen aged 18, to save, review and share digital information about your health. **3) H2020 MyAirCoach 2015-2018.** Delivery of a holistic asthma monitoring system based on personalised mHealth capabilities, an ergonomic, compact, and efficient sensor-based inhaler, intuitive user interfaces and a personalized guidance system. **4) FP7 IP Reaction.** The project developed techniques for minimally invasive wearable sensors, multi-parametric monitoring, data fusion analysis of physiological signs as well as context data for patients with diabetes.

MUG - 1) Hypo-RESOLVE (IMI2) (Hypoglycaemia - REdefining SOLutions for better liVEs). The overall objective of Hypo-RESOLVE is to alleviate the burden and consequences of hypoglycaemia, to be achieved by answering several key questions through a unique public-private partnership. **2) INNODIA-Harvest (IMI2)** - Translational approaches to disease modifying therapy of type 1 diabetes related to INNODIA (call IMI2-2014-01-01, Grant Agreement No. 115797), to advance in a decisive way how we predict, stage, evaluate and prevent the onset and progression of Type 1 Diabetes (T1D). **3) BioPersMed (FFG – Austrian Research Promotion Agency)** - Biomarkers for Personalised Medicine in Common Metabolic Disorders. This prospectively collected cohort comprises samples and data being collected since 2010 (ongoing). Aim is to detect and define characteristics and personalized biomarkers of asymptomatic individuals at risk for cardiovascular and metabolic diseases and to follow them for future developments.

SPXL – 1) "COD19: AI for healthcare". The project aimed at creating a platform (www.cod19.it) to screen patients with COVID-19 directly at home through previsional models to estimate the progress of the illness. **2)"Noncado".** This project aimed at selection biomedical parameters and indicators of motor performance; identifying wearable technologies for the collection of useful data; designing a system for aggregation and reading of such data remotely, with the possibility to insert alert mechanisms in case of exceeding threshold values; implementing a prototype to test in a simulated home environment.

FIF – 1) INTERREG Italia-Slovenia. Cross-border platform for an efficient management of biobanks. The project aims to build a standardized, harmonized, and integrated biobank for liver and blood specimens in chronic liver diseases, among healthcare centres of Italy and Slovenia. **2) Progetto Fegato Grasso (ProFeGra)**, funding by Fondazione CRtrieste. The project aims to generate molecular information on the progression of non-alcoholic fatty liver disease, to individuate using in silico strategies accurate biomarkers, and validate them for the non-invasive diagnosis of inflammation and fibrosis in the liver, and to disseminate the obtained knowledge.

HKL – PathologAI is a multistage deep learning framework for preclinical digital pathology commissioned by the FDA NCTR centre. The goal of the AI solution is to support experts in the identification of drug-related liver lesions. Efficient deep learning models are used for stratification and classification: the transformation through a GAN embedding of very large-scale data is used to provide inputs for neural network classifiers, The framework provides a stratification into subtypes of intermediated progressive severity leading to cell necrosis and integration with microarray gene expression data. All computing is based on cloud resources.

Interdisciplinarity. The *PRAESIIDIUM* welcomes a multi-disciplinary approach, with the involvement of humanities, medicine, biology, computer technologies, mathematical and engineering sciences cooperating each other to timely and successfully deliver the objectives of the project itself. In particular, the Consortium includes healthcare professionals (FIF, UNIL, MUG) and researchers specialized in bioinformatics (CNR), Machine Learning (SUPSI, SPXL. CNR, HKL), data analysis (CHK), wearable sensors (EDI, CHK) but also in Project Management (SPXL), and ethics (SdR). The *PRAESIIDIUM* project requires fundamental insights in medical aspects, issues related to ethics and technical aspects of AI-ML approaches like biases absence, robustness, computer science; but also, user experience and safety for which the wearable sensors are concerned.

Role of social science and humanities. Social Sciences and Humanities (SSH) have a cross-cutting role in the *PRAESIIDIUM* for improving our assessment and response to complex societal issues. The SSH disciplines in the project include: (i) Social and behavioural sciences (mainly economics but approaches from other disciplines are also applied), (ii) Journalism and information (documentation techniques), (iii) Business and administration (management, public and institutional administration, public relations), (iv) Law (Complying with legislation and standardization), and (v) Humanities (native languages, interpretation and translation, ethics).

Gender equality. Gender diversity is a cardinal topic within the *PRAESIIDIUM* project, with the adoption of *Gender Aspects* in recruitment as well as in the decision-making level. According to Articles 2 & 3 of the Treaty of Amsterdam (1997) and other EU-policy directives and reports (EUR 20022), the Consortium is committed to incorporate principles of *gender mainstreaming* across all project levels and especially for which the clinical case-studies and pilot prospective observational study are concerned. For the sake of clarity, *type-2 diabetes* (T2D) has a higher global prevalence in males compared to females (221M vs. 204M cases, according to the IDF 2018 atlas[10]).

[10] https://diabetes.atlas.org/resources/2017-atlas.html

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However, such gender prevalence must be weighted across lifespan. Females have in fact a higher T2D prevalence in youth (< 18y) [Hue19], probably due to the different hormonal influx and related comorbidities such as the polycystic ovary syndrome (PCOS). It is also worth mentioning that woman may experience the *gestational diabetes* – i.e., high blood sugars level during pregnancy - which usually resolves after giving birth; however, it is a predisposition cause for a later T2D onset, other than mother/infant health complications. For which concerns *prediabetes*, according to the CDC survey[11], males have still a higher age-adjusted prevalence of prediabetes compared to females (41% vs. 32%), although prediabetes awareness was higher in females than males (19.4% vs. 15.9%). For inclusiveness reasons, it is important to highlight that the LGBTQI community is at a high risk of diabetes development, especially those people undergoing gender-affirming hormone therapy[12]. Whitin *PRAESIIDIUM*, every possible effort will be implemented to ensure that the work packages and related tasks contribute to gender equality wherever possible. Moreover, no activities within the project will contribute to or aggravate such existing gender inequalities. Within the consortium, in fact, Scuola di Robotica (SdR) will specifically monitor any existing and possibly emerging gender issues related to the design of the pilot prospective observational study and development of the *PRAESIIDIUM* system, working with the WP leaders for the definition of the study protocols, a dedicated gender plan and for the assessment of the results. The following objectives underpin the **Gender Action Plan**: 1) Ensuring that women and men have equal opportunities to benefit of project results and to participate in the various parts of the project; 2) In addressing diversity, the work plan will take account of the different situations needs and interests of women and men; 3) The work plan will contribute to reducing inequalities between women and men. To this extent, the consortium promotes and welcome the effective participations of woman scientist and STEM experts in the project; 4) Active measures will be taken to ensure that women scientists are well represented in the partner's organizations and that women scientists lead elements of the project; 5) Opportunities for mobility within the project will take account of the different needs of women and men to enhance participation by women scientists and workers. It should be noted at this point that all partners involved in this proposal are firm believers in equal opportunities for both genders and inclusiveness. We have included both female and male staff collaborating in the development of the project under equal qualifications and competences. Hiring of female researchers and support to diversity will be considered by the Consortium, when possible, to ensure gender balance within the early-stage researchers and postdocs (at least 40% of female researchers).

Open science. Open Science aims to make scientific research freely available to other scholars and to society. It makes the whole research process more transparent and ensures, through peer review, that the research done is of high-quality. Next to that, the impact of the research will be a lot higher as the whole of Europe can benefit from and build upon the results of the research done and the same topics to not have to be investigated repeatedly. Open science includes open access for publications and sounds data management. Because of the various benefits, the consortium of *PRAESIIDIUM* fully supports the open science practices: any publication will be open access and data management will follow the principles explained in "Data Management" section.

Data management. Within *PRAESIIDIUM*, *'data'* refers to the means of information (e.g., datasets or user findings) collected, examined, and considered for the basis of reasoning, discussion, or calculation (e.g., statistics, results of experiments, measurements, observations resulting from surveys and from wearable sensors, etc.). The main principles for research data management within the *PRAESIIDIUM* consortium are: **I)** Research data must be stored and documented in a safe, secure and sustainable manner - in this way data can be retrieved and accessed by the project partner, that gathered the data, when needed: i) Metadata of research data will be registered to ensure findability of the data. ii) Deletion (if required) or changes of the data will be justified and documented. **II)** Data-related documentation will be maintained, monitored, and tracked to support audit trials. After the end of the research, **III)** relevant research data will be retained for a minimum of 10 years in a safe, secure, and sustainable way for purposes of reproducibility and verification. As for potential reuse, which the Consortium considers essential, and for which the best effort will be allocated to make relevant data available for reuse purposes. **IV)** All research is carried out in accordance with and considering *PRAESIIDIUM* contractual agreements, local legislation, regulations, and guidelines or possible exploitation potential. The consortium will ensure full compliance to international and country-specific ethical guidelines. Data management plays a pivotal role in the project. In addition to the innovative research area of the "*physics-informed machine learning*" and stimulating cross-partner collaborations in a multi-disciplinary environment, *PRAESIIDIUM* will enable the team to reach its expected outcomes on time and successfully. The Consortium will create and follow a strategic **Data Management Plan (DMP)** for the *valorization* and the *promotion* of results, which it will be constantly updated along the way to ensure that we will be commercially and scientifically successful afterwards. Most importantly, this framework will clearly define the best *data management practices*, so that all partners clearly understand "why and how" to manage the data generated and collected (from retrospective and prospective studies) throughout the project. Additional metadata will also be stored for each recording session (e.g., date and time; devices used; algorithms and parameters used to process data;

[11] Appendix | Diabetes | CDC
[12] TFIE-35_LGBT-Diabetes-Brief_final2_pages.pdf (lgbtqiahealtheducation.org)

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semantic metadata (manually added, or automatically derived; unprocessed data (used for comparison with newer versions of the algorithms). Moreover, state-of-the-art methods will be applied to avoid the potential risks of personal data loss or theft. Measures such as pseudonymization, encryption, personal feature obscuration will be used to ensure the *confidentiality* and *integrity* of personal data collected. Such measures will enable the consortium members to access the data in a timely and straightforward manner for processing needs. *PRAESIIDIUM'*s DMP will exploit Open Data Commons Licensing.

Ethics. The PIML-based algorithm for the prediabetes prediction developed within the *PRAESIIDIUM* project, at the present, is addressed towards an adult population. Both for which the means of retrospectively curated clinical and personal data, and the second-wave data ingestion from a pilot observational prospective study are concerned. Within the pilot observational study, participants will be monitored by commercially available wearable sensors, moreover a newly developed wearable sensor will be tested on a smaller cohort of participants. To this extent, *PRAESIIDIUM* will not involve any drugs products testing. Each partner has a local ethics committee – which is represented by ethics commission of the hospitals and public health-foundation, and for the remaining partners is represented by their legal offices. Within PRAESIIDIUM, a dedicated Ethics Board and a Data Protection Board will be implemented as a part of the Steering Committee, since not all partners and entities have an already in place ethics and data protection board. Under the supervision of SdR, they will always be asked to provide clearance before the start of any activity that raises ethical issues (e.g., ethnicity and gender balance). An Ethical Self-Assessment Guidance will be carried out, to: 1) ensure compliance with applicable international, EU and national law; 2) contribute to the responsible implementation of the project so increasing its social acceptance; 3) allow the results of the project to be published more easily in internationally refereed journals. The Ethical Self-Assessment Guidance will secure: a) the respect for persons and for human dignity; b) fair distribution of benefits and burden; c) the rights and interests of the participants; d) the need to ensure participants' free informed consent (with particular attention to vulnerable categories of individuals such as children, patients, discriminated people, minorities, persons unable to give consent, etc.).

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2. Impact

2.1 Project's pathways towards impact

PRAESIIDIUM will allow a personalised approach in the **prediction of the prediabetes risk** to determine the predisposition to this disease and deliver timely and targeted prevention measures.

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***PRAESIIDIUM* will develop easy-to-use, reliable, efficient and innovative tools (esp., web/ mobile app, mathematical models, wearable sensors) for the personalized management and real-time prediction of the prediabetic risk. This goal will result in benefits for affected citizens, their families, hospitals, different industries, scientific community, governments/ policy-makers, and environment.**

2.1.1 Impact from the Call topic and unique project contribution

The table below reports the contribution our project results will make towards the topic outcomes and the destination impacts, identifying also Target Groups (**PR**=professionals, **IN**=industry, **EU**=End-users, **CZ**=citizens, **SC**=scientific community, **PM**=policy makers), Type of Outcome/Impact (Technological/ Economic (**TE/EC**), Societal **(SO)**, Scientific (**SC**) Outcome), Link with project objectives (as in the Excellence) and KPIs**.**

Expected outcomes		
Researchers and medical professionals understand the chronic inflammation factors triggering the health-to-disease transition and subsequently provide optimal counselling to citizens for improving their health.		
PRAESIIDIUM will allow researchers, medical professionals and citizens to use trustworthy AI-based solutions to better predict the prediabetes risk and its progression. The prototype (mobile app) based on AI technology will be able to inform medical professionals about key inflammation factors involved in health-to-disease transition, alerting them when those markers reach a threshold, which will be determined and validated by training the most appropriate mathematical models with ad hoc patients' datasets. The project will develop in silico 'omics strategies to individuate inflammatory markers related to prediabetes in the onset of liver diseases and performing an experimental pilot validation of the markers. The validation through accurate quantification of the inflammatory markers in plasma samples of obese patients with non-alcoholic fatty liver disease will be used in determining the diagnostic performance (optimal cut-offs and accuracy) associated to the inflammatory state in prediabetes and T2DM conditions. The inclusion of the individuated markers in the mathematical models of the AI prototype will support medical doctors in clinical decision-making and to prevent worsening of these NCDs, improving the health of citizens and reducing the impact on the healthcare system. Researchers will be able to adapt the in-silico approaches developed herein to the individuation of attractive targets in other disorders or decide to test the subjected inflammatory markers in mathematical models for pathologies with similar evolution.		
Target groups: All	**Type of outcome*:*** All	**Link with objective(s):** Scientific objectives #1 and #2
KPIs: (i) 5 validated inflammatory markers (optimal cut-off and diagnostic accuracy); (ii) 10% of performance increase of the prediabetes prediction algorithm; (iii) up to 10% of reduction of healthcare costs in 5 years.		
Health care professionals have access to and employ objective health indicators of chronic inflammation for monitoring the health status, establishing personalised prevention measures and improving the health outcomes for citizens.		
PRAESIIDIUM prediction algorithm will be based on a "physics-informed machine learning" approach. A rich dataset of real-life observations (obtained from already existing previous and a new clinical trial with continuous data ingestion through wearable sensors) will be combined with a mathematical model to overcome the limits of "black-box" ML approaches while improving the prediction performances and reducing the computational time of the risk calculation based on the simulations of the mathematical model. Moreover, biological parameters collected by means wearable IoT will allow to define the citizens health status and its fluctuations over time. Thus, personalised prevention measures and improved health outcomes will be generated, e.g.: disease exacerbation reduction; better prognostic assessment; enhancement of patient's autonomy and life expectancy.		
Target groups: All	**Type of outcome*:*** All	**Link with objective(s):** Scientific obj. #1 and #3
KPIs: (i) 8% of patient's health status improvement; ii) 10% of hospitalization reduction in the studied population; iii) 10% improvement of ROC-AUC (or other measures) in predicting disease progression; iv) Reduction in time/ memory used by the surrogate model by a factor of 10 (vs full MT2D model) preserving predictive performances.		
Health care professionals have the scientific evidence and understanding of health-to-disease transition to develop and use improved guidelines for personalised prevention strategies to tackle chronic diseases.		
PRAESIIDIUM project results will add information and contribute to the understanding of which biological processes are a clue in health-to-disease transition, for example, individuating the main tissue source for the inflammatory markers included as parameters in the mathematical models; and explaining when and why they will show an increase or decrease in its plasma abundances. The generated scientific evidence will contribute to a more accurate prediction of prediabetes and a better stratification of subjects considering not only glucose homeostasis impairment but also disorders at the hepatic level.		
Target groups: All	**Type of outcome*:*** All	**Link with objective(s):** Scientific obj. #3 and business obj.
KPIs: (i) Definition of a roadmap for certification and commercialization of the prediabetes risk prediction app;		

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ii) Creation of a third-party working group to assure the full compliance to international recognised standards.		
Citizens are better informed to actively manage their own health, have the tools to maintain their healthy status, improve their health and reduce their risk for developing chronic diseases.		
Disease awareness has been identified, in recent years, as one of the major public health and medical challenges in the detection and management of some NCDs, because of its potential impact on the morbidity and mortality. *PRAESIIDIUM* will allow a real-time prediction of the prediabetic risk, reducing the disease development and improving effective citizens' safety. Among others, thanks to *PRAESIIDIUM*, clinicians and medical professionals will benefit from the application of machine learning and AI tools that will improve the management of prediabetes risk, while citizens will be better informed (through evidence-based facts and figures) on their situation and on related prevention measures, that will be tailored at the patient's level, according to their health status. Therefore, citizens will be able to manage their health and reduce their risk for developing and reduce their risk for developing chronic disease actively and more effectively.		
Target groups: All	**Type of outcome*:*** All	**Link with objective(s):** Business objective
KPIs: (i) 15% of risk reduction for developing diabetes in the studied population; (ii) 70/100 satisfaction for self-assessment of readable IoT parameters; (iii) c. 15% of improvement of citizens' disease awareness thanks to training and implementation of the proposed solution.		
Wider Impacts		
Citizens adopt healthier lifestyles and behaviours, make healthier choices and maintain longer a healthy, independent and active life with a reduced disease burden, including at old ages or in other vulnerable stages of life.		
PRAESIIDIUM will generate scientific evidence to support the inclusion of the correct blood-based parameters in the prediction algorithm. The parameters will follow, for example, the inflammatory/oxidative/dysmetabolic stages in subjects with different comorbidities, lifestyle behaviours, and ages; and will render the most accurate prediction models for subjects' stratification; defining optimal cut-offs and sending alerts to citizens and medical professionals when the parameters indicate an increase of the risk through a less healthy condition of the citizen. *PRAESIIDIUM* will suggested to adopt specific lifestyles and. The project will be especially useful for elderly, frail and low-income citizens that could have difficult access to a specialized center for diabetes prevention.		
Target groups: All	**Type of outcome*:*** All	**Link with objective(s):** Scientific obj. #3; Ethical/ Business obj.
KPIs: i) Selection of at least 5 blood markers/parameters and inclusion in appropriate prediction algorithms during the project; (ii) 15% of increase in the patients' perception of prevention measures; (iii) 25% increase of right and early clinical decisions based on better disease stratification.		
Citizens are able and empowered to manage better their own physical and mental health and well-being, monitor their health, and interact with their doctors and health care providers.		
Thanks to *PRAESIIDIUM* solutions (esp. app and sensors), citizens will be able to interact with a high-level healthcare team (doctor, nurses) to treat and manage their prevention measures, with significant impacts in their everyday-life and mental health. Wearable tools usability, remote patients/physician interaction and algorithm efficacy and safety will be tested during the project.		
Target groups: All	**Type of outcome*:*** All	**Link with objective(s):** Sci. obj. #3 and Business objective
KPIs: i) 4 clinical cases-studies; (ii) 3 clinical observational studies (1 with newly developed wearable sensors).		
Citizens´ trust in knowledge-based health interventions and in guidance from health authorities is strengthened, including through improved health literacy (including at young ages), resulting in increased engagement in and adherence to effective strategies for health promotion, diseases prevention and treatment, including increased vaccination rates and patient safety.		
Scientific evidence towards the individuation of the blood disease indicators will be supported by publication in peer-reviewed journals, participation at international congresses, and dissemination to the scientific-clinical community, as well as to the general society presenting the information at health prevention or public scientific divulgation events at local and European level; doing possible the transference of the knowledge from the medical/health sector to the citizens, and impacting both the health care system and society positively.		
Target groups: All	**Type of outcome*:*** All	**Link with objective(s):** Business objective
KPIs: (i) At least 5 peer-reviewed publications; (ii) At least 3 health promotion/prevention events; (iii) i) 15% improvement of patient' satisfaction in 10 years.		

2.1.1.1 Impact on society as a whole

The International Diabetes Federation (IDF) provides key facts/ figures of **diabetes around the world in 2021**:

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537 million adults are living with diabetes (1 in 10). They are predicted to rise to **643 million** by 2030**.**
Over 3 in 4 adults with diabetes live in low- and middle-income countries.
Diabetes is responsible for **6.7 million deaths** in 2021 (1 every 5 seconds).
Diabetes caused USD **966 billion dollars** in health expenditure (a 316% increase over the last 15 years).
541 million adults have Impaired Glucose Tolerance (IGT), which places them at high risk of type 2 diabetes.

The figure below shows the **geographical distribution of adults with diabetes around the world in 2021**. As it can be noticed, diabetes in Europe represents a key problem, with c. 61 million adults (11% out of the total) affected and 1.1 million of deaths due to this disease. In this Region, the number of adults with diabetes is predicted to rise to 69 million by 2045, an increase of 13%. In this context, a main challenge is posed by undiagnosed cases of diabetes. Globally, 87.5% of all undiagnosed cases of diabetes are in low and middle-income countries, with low-income countries having the highest proportion undiagnosed (50.5%).

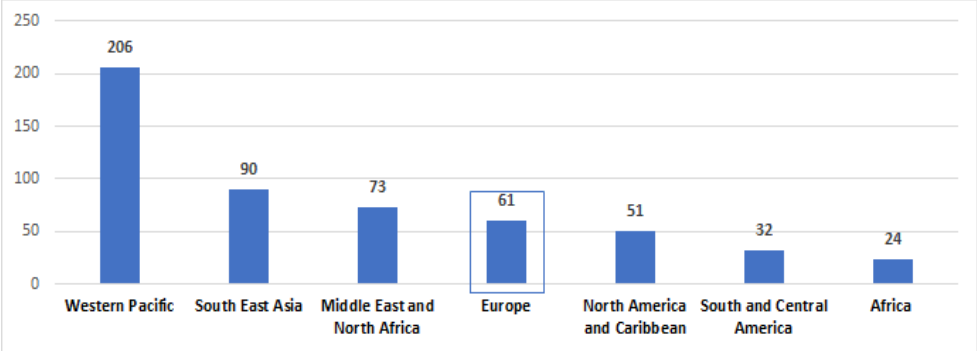

Figure 2: Geographical distribution of adults with diabetes around the world in 2021

However, even in high-income countries, almost a third (28.8%) of people with diabetes have not been diagnosed. This situation is **predicted to impede poverty reduction initiatives**, particularly by increasing household costs associated with health care and expenditure (c. 9% of total spending on adults in 2021). The costs of these diseases will continue to grow, for governments, health systems, businesses, and individuals. This poses a risk of economic loss to health systems, as well as a decrease in life expectancy and quality of life of individuals. Diabetes/ undiagnosed cases of diabetes are key public health problems threatening human health and health systems.

Hence, *PRAESIIDIUM* will allow to diagnose as early as possible the prediabetic risk to prevent or delay complications, reduce premature death and improve quality of life. Moreover, people with prediabetes/ diabetes diagnosed earlier are likely to use less healthcare services due to lower likelihood of diabetes complications, avoiding an added burden on healthcare systems already under pressure. Assuming as hypothesis an annual reduction of 1% in health expenditure and 2% in deaths thanks to *PRAESIIDIUM* adoption, in 2021 c. USD 9.9 billion dollars could have been saved and 134,000 deaths avoided, globally.

2.1.1.2 Impact on Consortium and other stakeholders

Impact on Consortium. The table below summarises the impact of *PRAESIIDIUM* for each Consortium member, with a preliminary exploitation path by entity (while for Consortium impact and exploitation, refer to section 2.2.2).

SPXL: *PRAESIIDIUM* outcomes will be exploited through various vectors for communication and integration in Spindox Labs' service portfolio.
EDI: EDI will use the technological know-how developed in the project in subsequent Horizon Europe projects and other international and national projects. It will also develop it for higher TRL in nationally and privately funded commercialization projects.
CNR: An optimised model for the prediction of the risk of T2D resulting from the *PRAESIIDIUM* project will be exploited by updating the simulation server already available at this link. CNR exploits outcomes in education network, towards competence centres in AI and in ICT sectors and through contacts with national/ international companies and participation of CNR team members in standardization committees.
SUPSI: SUPSI will directly exploit the competencies developed within *PRAESIIDIUM* in other (new and already-running) medical/industrial research projects. *PRAESIIDIUM* activities will constitute an important source of inspiration to pursue fundamental research in physics-informed ML, and thus publish novel methodological results in reputable peer-reviewed journals. Finally, the project outcomes not subject to IPR will be integrated into data science and artificial intelligence courses taught at SUPSI.

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EURO: The methodology followed in performing the EURO tasks in the project will be used in other company's projects. The knowledge acquired (e.g., on tools for decentralised intelligence and swarms and on specific use cases) combined with the know-how in AI-based applications was/ will be fruitful in further projects. EURO will leverage the information acquired to provide new consultancy services to interested customers.
SdR: SdR produced the Euron Roboethics Roadmap, which proposed to tackle the ethical problems on the basis of an applicative taxonomy. Since then, it has participated in numerous projects and initiatives on specific application fields. Participation in this project will allow to deepen some issues of AI applied to diagnosis, allowing it to expand the knowledge in the medical field, as well as to establish fruitful collaborations with leading European institutions in view of further interdisciplinary studies.
CHK: The main product offered by CHK is LinkWatch, a platform for patient data collection and self-monitoring using our medical device gateway and federated cloud. Our plan is to extend our platform with the new data types handled in *PRAESIIDIUM* and the new device types integrated. We will also disseminate results from the project on our website and LinkedIn pages. We plan to participate in the Vitalis fair, a major e-health event in Scandinavia every year and the E-Hälsa Fair for digital health innovations.
FIF: The approaches followed by FIF to achieve its task objectives in the project could be used or adapted to other partners' projects. The information/knowledge generated could be exploited to predict the progression of FIF's interested diseases or models for diagnosing and prognosis better chronic liver disorders.
MUG: MUG will provide existing data sets to develop an AI tool for risk prediction and subsequently test the AI tool in a clinical trial. The AI tool will be subsequently integrated in the electronic medical record of the hospital provider and will be integrated in routine care. This will enable to promote MUG's position as clinical test center and co-developer of software for clinical use. The knowledge acquired will be useful for future projects. MUG will also benefit from publication activities to further increase the visibility in the field.
UNIL: During the project UNIL will develop its capacity as a clinical research unit. Experience gained during planning and implementation of the clinical study will be used in further projects. Collaboration within the consortium will contribute to development of new skills of the UNIL personnel. Dissemination of the project results will increase UNIL visibility as an international collaborator, leading to new projects.
HKL: The advance in ML/AI stratification and Shift Detection models developed in PREASIDIIUM will be used for the development of new analytical services. IP from the project will be considered for stand-alone products (MD certification), and for data-centric marketplaces (e.g., MS Azure, SnowFlake), or in collaboration with AI Service companies specialized in AI governance.

Impact on other stakeholders. Besides the benefits brought by the proposed solution to people with undiagnosed cases of diabetes, their families, governments, healthcare system, scientific community and society as a whole, *PRAESIIDIUM* could foster market growth and produce positive impacts on public entities and private enterprises. Among them, first of all **public/ private hospitals** (first in Europe, then globally) could be interested in the proposed solution. Moreover, **pharma companies** (e.g., Novo Nordisk, Sanofi, Merck) and, as a third step, **manufacturers of wearable devices** (e.g., Apple or Google) represent key beneficiaries of the project outcomes. To a larger extent, all the **digital and/or AI-based health services/solutions providers** (e.g., SPX, HKL, CheckHealth) could be positively impacted by the *PRAESIIDIUM* results. To ensure a future commercialization of the solution, the CNR-IEIIT have links with Italian, European and International (ISO) committees and working groups in mobile apps labelling and assessment, including an ongoing CSA. *PRAESIIDIUM* consortium itself will also nominate a referee for facilitating the relationships between the stakeholder and the certification regulatory bodies. It is important to mention that the *PRAESIIDIUM* stakeholders will follow the WHO "health-for-all" policy (6NovSven (who.int)). Therefore, the *PRAESIIDIUM* solution will be also validated using data mainly from ethnicity living in low-income regions at a high-risk of diabetes development (e.g., Africa, South Asia) and the solution could be provided at affordable prices to low/middle income countries.

2.1.2 Overcoming barriers for impact

Barrier 1	**Barriers to implementation into clinical practice**

The web or mobile app for prediabetes risk prediction developed in the project is not used by medical personnel. *Mitigation* measures: To promote progressive adoption of the developed algorithm into clinical practice, work with stakeholders will be performed during and beyond the project duration. The algorithm will be presented to the medical society. The interest to the project results is expected to rise due to increased understanding of the value of preventive medicine and preserving health in contemporary medicine.

Barrier 2	**Lack of acceptance by clinicians and patients**

Public is not informed about the web or mobile app for prediabetes risk prediction developed in the project. The tools developed may not be widely accepted by clinicians and patients as they are based on AI and ML methodologies,

which are sometimes perceived as "black-bokes" by people not trained in these fields. Mitigation measures: The use of physics-informed ML techniques is expected to improve explainability, as PIML models can be designed to satisfy a priori certain modelling assumptions specified by field experts (i.e., clinicians). Moreover, strategies aiming at improving AI acceptability and building trust towards AI have been planned. The project solution will be illustrated on different channels/ profiles on social media (like LinkedIn and Twitter), having the opportunity to assess the level of acceptance of the technology and to address any concern or complaint. Regular communication of project information will increase public awareness of the health risks associated with prediabetes, and options to detect these risks and to handle them with diet and physical activity.

Barrier 3	**Health data regulations**

Existing legislation in Europe still does not favour the adoption of AI in hospitals. Moreover, European countries can set different derogations under the GDPR. Member States often have additional (and differing) laws relating to the use of medical records and EHRs. This can create problems for international research projects. Some European countries have national legislation/rules about health and research data in addition to GDPR. Mitigation measures: *PRAESIIDIUM* will ensure that failsafe modes are implemented in the technological systems and adopt measures for trustworthy medical AI. The trust in data management and AI/ML model life cycle shall comply with requests by authorities and certification bodies, in particular for achieving high level of the operational safety and provide adoption of the PRAESIDIUM technology on a large scale. The social, ethical and legal issues will be continuously monitored during and beyond the project, avoid getting into conflict with these issues.

Barrier 4	**Clinical trust in real world data**

Clinicians might not trust data generated from patients to take clinical decisions. Objective measurements regarding sleep, weight loss, pulse during the day are needed. Mitigation measures: We will validate the devices being used but also gather data related to the environment to ensure the data accuracy. We will also use validated PROMS and PREMS for the specific diseases being managed.

Barrier 5	**High market competition**

Possible barriers for achieving impact may be the fragmentation of the market with a consistent level of competition in which *PRAESIIDIUM* aims to enter. Among the main players in this market, we can find small companies as well as to very big players. Mitigation measures: *PRAESIIDIUM* can gain a competitive advantage in relation to alternatives: i) starting its roll-out from Europe; ii) adopting a convenient pricing strategy and maintain the costs as low as possible, iii) stressing its unique value proposition and its potential impact; iv) supporting the EU effort for a wider adoption of AI and innovative tools to predict the prediabetes risk.

Barrier 6	**Barriers for further TTL steps**

The TRL evolution towards industrialization needs a proper guidance for the application of the technologies, which, in turn, needs a clear assessment with proved achievable performance. The large heterogeneity of the involved sectors (AI, safety, security, green and ethics) makes providing such a guidance a hard task. Mitigation measures: That is where the project comes into play. How and where such a heterogeneity may let the evolution of the technology is the final goal to pursue. Either a suitable balance is found to define safe, secure, and ethical deployment of the proposed solutions, thus letting further TRL steps in the near future, or clear and concrete limitations are found to re-think AI and steer technology in a human perspective.

2.1.3 Scale and significance of the project's contribution

Forecasts (KPIs) identified in 2.1 well represented the scale and significance of the project. They are based on clinical studies and consortium experience matured in the field and previous projects/research activities. **Scale of the project**: On top of those identified above, additional business insights based on market reports, research studies and interviews with stakeholders (e.g., Consortium companies) are: (i) at least 15 products and/or services improved within the consortium; (ii) at least 100 number of stakeholders identified as potential customers and users of *PRAESIIDIUM* solution(s); (iii) at least 120 number of expected jobs created in Europe (by 2030); (iv) c. 42 million of turnover created by the project in 2037. **Significance of the project**: Improvement in prediabetes risk prediction and their progression represents the main goal of the project, therefore the significance of the project is summarised by the consequent reduction of mortality and complications, improvement of patient's health status and quality of life, reduction of costs supported by individuals, health systems and businesses and an improvement of prediabetes risk management in time of crisis, e.g., during Covid-19 (for quantitative indicators, please refer to KPIs in 2.1.1). As estimated above, thanks to *PRAESIIDIUM* adoption, only in 2021 c. USD 9.9 billion dollars could have been saved and 134,000 deaths avoided, globally. At the same time, the project will be able to create positive impacts on research community, governments, medical units or associations, and society as a whole. The provided estimates are preliminary and will be reviewed in collaboration with Consortium members and stakeholders.

2.2 Measures to maximise impact - Dissemination, exploitation and communication

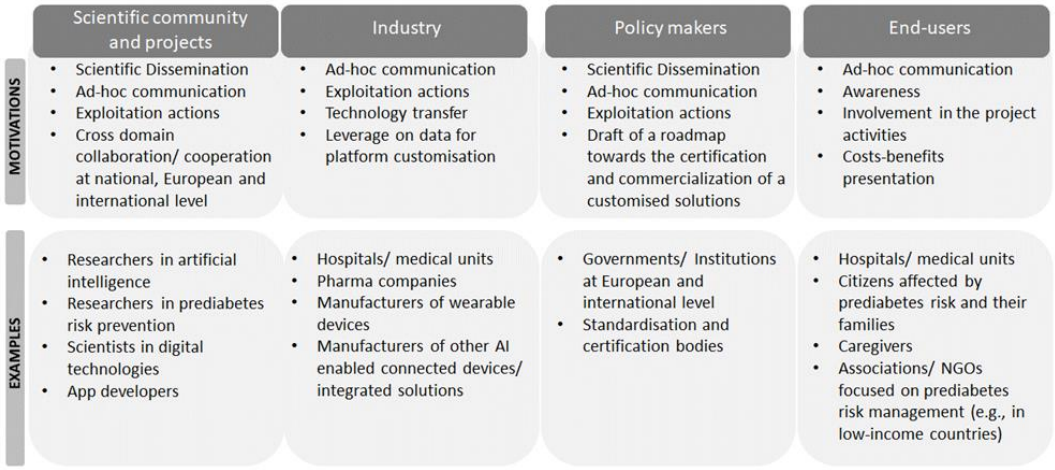

Figure 3: Stakeholders identification

PRAESIIDIUM will combine numerous communications, dissemination, and exploitation actions to achieve its expected impacts and maximise its societal, scientific and technological repercussions. These actions will be targeted to the main stakeholder clusters of the project which are summarized in the figure 3

2.2.1 Dissemination

Dissemination activities will be undertaken as a part of an overall strategy composed by three types of actions: **i) Scientific dissemination**: publication of papers in highly relevant international conferences and peer-reviewed journals (possibly with an Open Access policy). Research results shall be published in peer-reviewed open access journals in accordance with the principles of Open Science. Similarly, research data not suitable for commercial use will be publicly available in an open repository in accordance with the principles of Open Data. **ii) Organization of and participation in international workshops and communities**: international workshops will be organized around the topic addressed within *PRAESIIDIUM* for face-to-face contact of the partners. The workshops organized by *PRAESIIDIUM* may also be open to interested third parties, stakeholders, outside researchers and students. Patients' organisations will have a representative in the project. In addition, the participation in selected workshops will be leveraged in a view of bringing additional value to the scientific activities. Moreover, the institutions involved in the project intend to participate at dissemination events such as the Trieste Next meeting https://www.triestenext.it/ sponsored by Trieste municipality, Trieste University and ItalyPost. Trieste Next is a "showcase of innovation and applied research" where researchers and entrepreneurs present their experiences and interchange their experience, improving technological transfer of the most advanced research to originate new solutions. It is a place in which scientist, young researchers, businesspeople, science communicators and the lay public from all over Europe communicate together interchanging knowledge about the most advanced discoveries and tech applications. **iii) Public dissemination** of the project outcomes. An additional opportunity is represented by all outputs that can be shared freely with the public that will also become available at the websites of proposal participants through press releases, news updates, and posts shared in the official social media pages of consortium members involved and all the media available (described in section 2.2.3). Specific budget has been considered for publishing the key scientific papers using Open Access. It is envisaged that "gold" open access will be the preferred option, whereby the partners will publish in peer-reviewed scientific journals that, already, are committed to solely open access methods or that can foresee (under payment) this option. The public technical reports and other communicative documents will be archived within the project website, in the repository section "Documents and reports", with free access ("green" open access). To measure the quality of the dissemination activity, the following KPIs have been identified.

KPI description	***KPI target***
Scientific publications to journals supporting project's approach	At least 10 journals/ 20 conference papers
Impact factor of journals considered for publications	Greater than 1; at least 30% in Q1
Number of workshops attended/organized	At least 20/3 (one per year)
Percentage of ISI indexed journal	90%
Ranking of conferences	90% must belong to tier 1 A or tier B2

A preliminary list of main target events and target academic journals/ conferences are identified below.

Table 7 Scientific events

Event name (frequency, if available)	**Ranking**
International Liver Congress (yearly)	NA
Euroscience Open Forum, ESOF (biennial)	NA
Diabetes Technology Meeting	NA

ACM/IEEE SenSys (1 time per year	A*

Table 8 Target journals and magazines.

Journal (Ranking JCR)	Popular scientific magazines
Nature (JCR 1/73 Multidisciplinary Sciences)	WIRED
Science (JCR 2/73 Multidisciplinary Sciences)	New Scientist
American Proceedings of the National Academy of Sciences (SCOPUS 4/110 Multidisciplinary Sciences)	Cosmos Magazine
PlOS Computational Biology (Multidisciplinary Sciences)	

2.2.2 Exploitation strategy and preliminary roadmap

Market assessment. The *PRAESIIDIUM* framework aims to connect various applications, such as the ***PRAESIIDIUM* web platform and mobile app** (enhanced by our "distilled" mathematical model) and **sensors**. These solutions will be designed and conceive mainly for **healthcare industry**, and specifically **the mHealth**[13] **market**. 1) Global market forecasts. The global **mHealth market size is predicted to be worth around USD 126.6 billion by 2030,** expanding growth at a CAGR of 10% during the period 2022 to 2030[14]. 2) Global trends. Increasing government initiatives towards the digitalization of healthcare service are registered worldwide. The rising focus on improving personal health and fitness using smart devices and wearables is the major factor accelerating market growth. Besides, increasing penetration of the internet and smartphones (in 2021, c. 3.9 billion smartphone users worldwide) and growing adoption of mHealth technology and platforms by physicians and patients are also anticipated to propel market growth. Furthermore, rising penetration of digital health services for remote patient monitoring is also increasing the demand for mobile health apps. **The global mHealth apps market size was valued at USD 38.2 billion in 2021 and is expected to expand at a CAGR of 12% from 2022 to 2030**[15]. The growing interest of the users to use health applications for chronic disease management is expected to increase the adoption of mobile health applications. In addition, increasing recommendations of healthcare professionals to use mobile applications for better patient care is also another factor anticipated to accelerate the mHealth app adoption. 3) Geographies. In mHealth market, North America is a leading region with a revenue share of 38.2% in 2021. However, European mHealth market is also expected to grow fast and reach USD 38.4 billion by 2027. According to Mordor Intelligence[16], a major issue fostering the growth of the European mHeatlh market will be the increasing number of people affected by diabetes and related deaths. Notably, blood glucose monitors are expected to have the largest share in device type segment. 4) Key customer segments. A key segment for *PRAESIIDIUM* will be the healthcare primary providers staring from **hospitals in Europe** (c. 24,318 in 2021)[17]. Primary health care accounts for around 13% of health spending on average across EU countries[18], ranging from less than 10% in the Slovak Republic and Romania to more than 17% in Lithuania and Estonia. Activities delivered in hospitals account for the largest proportion of health care expenditure in almost all EU countries. In 2018, hospitals received 39% of health system funding on average across EU countries. After hospitals, the second-largest category of care providers are ambulatory providers.

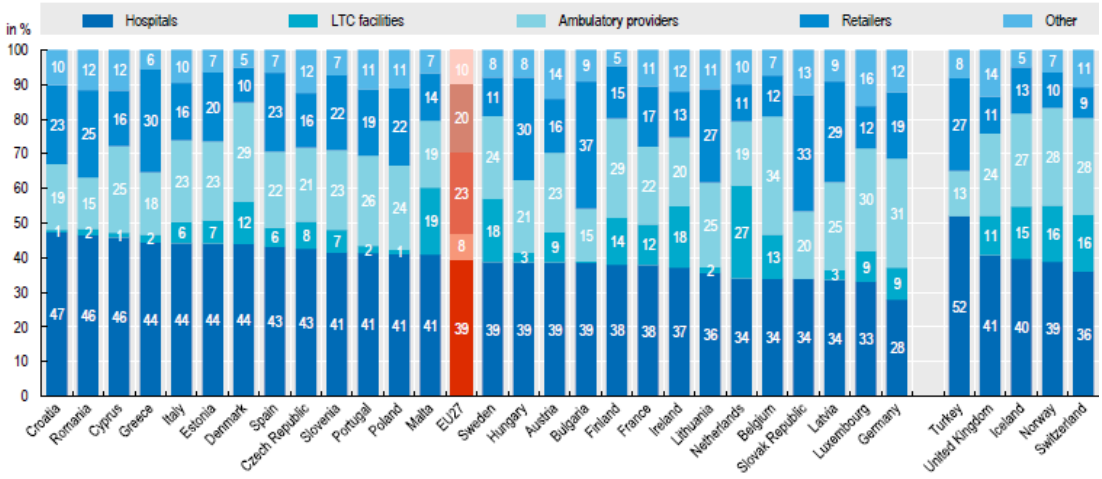

Figure 4: Health expenditure by provider, 2018

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[13] WHO defines mHealth as "medical and public health practice supported by mobile".
[14] Biospace, mHealt market size, 2022
[15] https://www.grandviewresearch.com/industry-analysis/mhealth-app-market
[16] https://www.marketdataforecast.com/market-reports/europe-mobile-health-market
[17] https://www.statista.com/forecasts/1166223/hospital-count-forecast-in-europe
[18] https://ec.europa.eu/health/system/files/2020-12/2020_healthatglance_rep_en_0.pdf

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On top of hospitals, **pharma companies are also a relevant** (but secondary) **customer segment**, especially for purchase of sensors protype and its further development against a license. Worldwide pharmaceutical industry is quite huge (USD 1.27 trillion in 2020 only in Europe), however focusing on the selected disease and based on the antidiabetic revenues, the top 10 antidiabetics pharmaceutical companies in the world are[19]: Novo Nordisk (DK), Eli Lilly (USA), Sanofi (FR), Merck (GE), Boehringer Ingelheim (GE), AstraZeneca (UK), Johnson & Johnson (USA), Bayer (GE) and Takeda Pharmaceutical (Japan). Europe is a key geography also within this segment.

Competitive assessment. A distinction should be made between *PRAESIIDIUM*: i) mobile app (including the PIML model); and ii) sensors. Starting from the web/ mobile app, several providers exist. Among them, those offering similar/ alternative solutions are: **Brainomix** (UK)**, Imbio** (US), **Siemens** (GE) and **Sophia Genetics** (US). It is worth mentioning that there are also R&D projects as well as open access tools (e.g., **Findrisk**) that are being developed. Moving to health sensors for wearables, main comparable providers are **AURA Strap** (US), **PKvitality** (FRA). However, actually, **available solutions seem**: i) **fragmented** and not allowing the full list of functionalists that *PRAESIIDIUM* aims to provide; ii) not focused on **prediabetes risk prediction**.

***PREASIIDIUM* can have a concrete competitive advantage as it allows interaction with several devices, allowing full interoperability, unique functionalities and a specific focus on prediabetes risk. Hence, it can be considered the leading-edge market solution both in term of system differentiator (no comparable technologies are present in the market) and in terms of value added brought to customers and society.**

Preliminary Business Model. A preliminary business model Canvas for the *PRAESIIDIUM* is presented. As shown in the Canvas, first of all *PRAESIIDIUM* mobile app (enhanced by the mathematical model) will be commercialised. It will be provided **through a Business to Business** (B2B) approach. During the project it will be evaluated either the possibility that **a Consortium partner will commercialise the solution or that a new commercial entity (a NewCo) will be set up and supported by all the involved partners**. The Consortium members will leverage their experience, their presence across multiple countries and their contacts with different user communities. They will continue to work together to guarantee the availability and reliability of the services and to support the potential NewCo in the exploitation strategy.

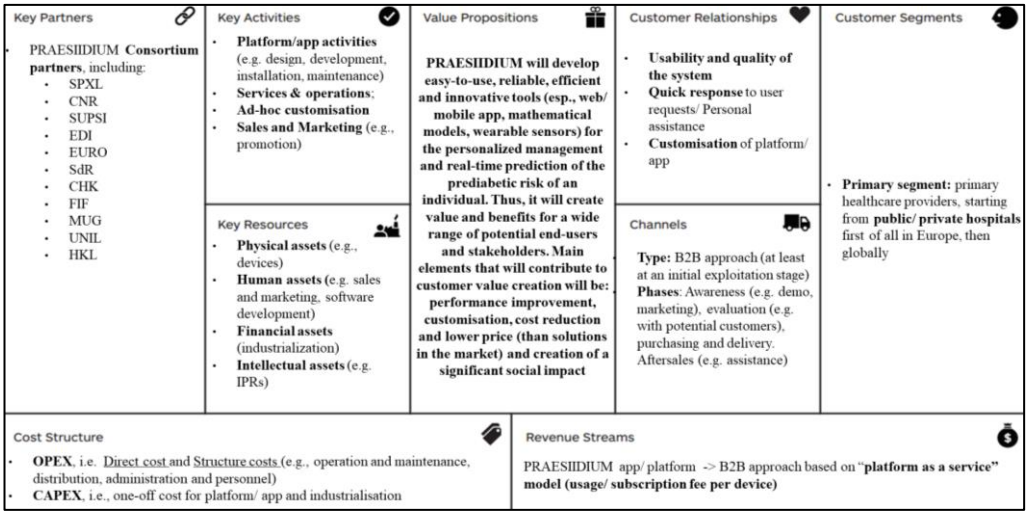

Figure 5 Business Model Canvas for PRAESIIDIUM initiative.

Preliminary revenues assessment. The table below summarizes the assumptions used to estimate the revenues of the initiative over the period 2027-2037 (timeframe).

Key items	Key figures
Market	Primary healthcare providers, starting from hospitals (Europe first, then globally)
Commercial offer	Platform as a service, incl. ad-hoc models (e.g., PIML model), adaptation/integration services and customer support.
New customers	From 3 new customers in 2027 to 57 new customers in 2037
Target price	€450 per month per device on which the web app/platform will be installed (on average, from c. 5 devices per customer in 2027 to 25 devices per customer in 2037, targeting small-medium hospitals in the first years and bigger players since 2033). Healthcare providers offering the mobile app to patients (free of charge).

Based on these assumptions, revenues can reach c. €0.1 million already in 2027. In the next years of activity (up to 2037), the Consortium expects to propose *PRAESIIDIUM* to all relevant stakeholders in the target industries exploiting direct contacts and partnerships as well as dissemination/ awareness activities. This effort will support the Consortium to reach c**. €41.7 million revenues in 2037**. Over the years considered, c. 300 hospitals could purchase

[19] https://www.marketresearchreports.com/blog/2019/06/10/top-10-antidiabetics-pharma-companies-world

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the solution, especially in Europe (at least an initial stage of the solution adoption, e.g., first 5/6 years).

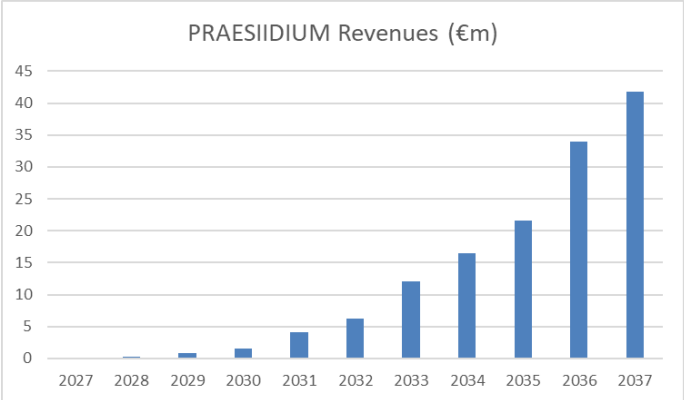

Figure 6 Revenues (€m) for PRAESIIDIUM

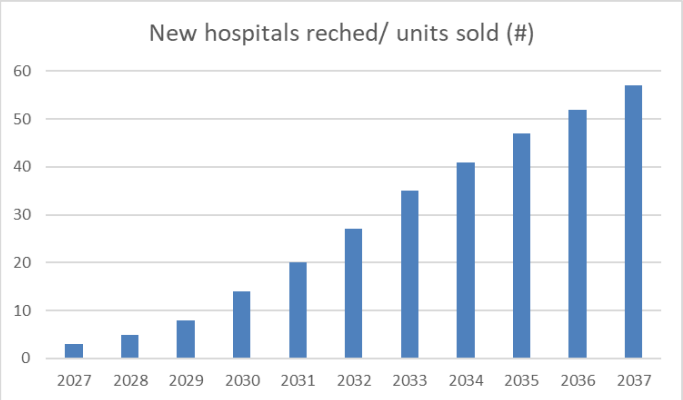

Figure 7 Hospitals/ Sales (#) for PRAESIIDIUM

On top of these results, during the project, the business plan will take into consideration also the **commercialisation of our sensors, improving the economic impact**. This potential exploitation path will ensure the overall viability of the solution also after the project end and, at the same time, the possibility to differentiate the pricing strategy and customise it, offering the developed solutions at affordable prices also to low-income countries facing the increasing challenge of diabetes. Also, *PRAESIIDIUM* will aim not only to create an economic impact, but also to **reduce the social costs caused by diabetes**, as already explained in section 2.1. All these estimates are preliminary as they will be further improved during the project' in collaboration with stakeholders.

Preliminary roadmap. *PRAESIIDIUM* needs firstly to position itself clearly towards the respective target groups. To this end, dedicated actions in the period 2026-2027 will be done to bring *PRAESIIDIUM* to TRL 8/9, i.e.: validation of the mobile game application and dashboard solution with demonstration of the prototypes in operational environment. Moreover, *PRAESIIDIUM* exploitation strategy will foresee a dedicated roadmap towards certification and commercialization and a calibrated effort starting the roll-out from key geographies, i.e., Europe (e.g., Italy, Germany, France, Scandinavian countries, Spain and Portugal). Consortium network and experience will be a key lever to promote the solution first of all in Europe and then globally.

Knowledge management and IPR strategy. The *PRAESIIDIUM* consortium is expected to generate new knowledge that qualifies for Intellectual Property (IP) protection. To disseminate results according to open access rules and obligations, whilst safeguarding at the same time the rights of the partners to protect their IP, a strategy aimed to a proper management of the generated knowledge will be developed. The output of such activity will lead to several actions addressing needs coming from the Consortium to protect the existing IP, such as a Register document for protection of the existing know-how; protection of the results, such as outlining IP that need protection and rights; contingency plan; report of invention; and patents. The procedures for the IP management will consider the principles set in the Model Grant Agreement (GA) and in the Consortium Agreement (CA). General principles are: i) **Ownership of results**: results are owned by the beneficiary that generates them; ii) **Joint ownership by several beneficiaries**: whenever results have been jointly generated by two or more beneficiaries and it is not possible to establish the respective contribution of each beneficiary, or separate them for the purpose of applying for, obtaining or maintaining their protection, such results shall be jointly owned by the beneficiaries which generated them; iii) **Agreement on background**: the beneficiaries will identify and agree (in writing) on the background for the action ('agreement on background'). Background will be clearly identified within the CA, which will be concluded among the partners before the GA is signed; iv) **Access rights**: the beneficiaries will give each other access – on a royalty-free basis – to background needed to implement their own tasks under the action. The beneficiaries will moreover give each other access – under fair and reasonable conditions – to background needed for exploiting their own results, unless the beneficiary that holds the background has – before acceding to the GA – informed the other beneficiaries that access to its background is subject to legal restrictions or limits.

2.2.3 Communication

For a systematic and successful communication of the project progress and outcomes, a communication strategy will be defined and formalized into a Dissemination and Communication Plan (D&CP) to highlight the achievements of *PRAESIIDIUM*. The plan will be developed at the beginning of the project (within M6) by dedicated communication experts. The planned comprehensive communication strategy will aim to fulfil the following objectives: i) to **raise awareness** on projects topics; ii) to **communicate on how the *PRAESIIDIUM*** derived solutions will **impact** diverse industries across Europe; iii) to actively **engage with stakeholders**; iv) to set the basis for the **successful implementation** of the technological solutions generated by *PRAESIIDIUM*; v) to show how European collaborations through the consortium in research projects like *PRAESIIDIUM* promote the development of

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technological innovations that can build more resilient societies. To reach these objectives different types of actions with related main messages will be put in place: **1) Phase I: Analysis** (**up to M12**). In this preliminary phase of the project's presentation, the Consortium will analyze the project's framework, with a special attention to internal and external barriers that could slow down the communication and dissemination activities, defining the priorities for the first year of the project and aligning them with the needs of the stakeholders, creating general awareness about the project's objectives and expected results. The first set of promotional material produced in the frame of *PRAESIIDIUM* communication plan will be prepared and delivered: **guidelines for the** implementation of communication and dissemination actions (messages to convey, internal reporting rules, etc.); **corporate identity**, tools needed to implement successful communication activities; **communication materials** (website, brochures, e-newsletters, videos). **2) Phase II: Increase impact** (**M13-M30**). The main objective of Phase II is to increase the impact and awareness generated during Phase I and to expose the project achievements. In this phase, we will work to properly find the right means to engage and collaborate with the target groups. This will help increase the potential impact of the project's results. Participation in workshops, organizations of ad hoc events as demonstration workshops, as well as the organization of tutorials/webinars will boost the dissemination process. Specific PR material will be also produced. All of this will help increase the potential impact of the project's results. **3) Phase III: Adoption** (**M30-M36**). This phase will leverage the general awareness raised in Phase I and Phase II, attracting more potential users of *PRAESIIDIUM* project's results and maximizing their impact. This phase will define the main activities that could increase the impact also beyond the project's lifetime, reaching the main target, the public, such as continuing use of events, participation in workshops and conferences, contributions to publications in targeted specific media online and research journals, general public engagement (e.g., the public could be involved with a web app quiz to learn at what level is their know-how in terms of prevention and how can they improve it). A Final Event will be organized to bring together all the partners, the stakeholders and the citizens, and to show the project's achievements and showcase the strength of the network. To sum up, communication will address the following activities and will be designed to reach out to the highest number of and different Target Groups (TGs) identified as: professionals (PR), industry (IN), End-users (EU), citizens (CZ), scientific community (SC), policy makers (PM).

Communication activities	***TGs***	***KPI target***
Communication KIT: production of materials that contribute to the creation of identity, consistency and awareness of the project. Contents will be personalized based on the target groups.	PR, IN, EU, CZ, SC, PM.	Project Logo, Colours and fonts, templates for project documents and presentations, flyer – **M2**
Project website will include general information for project institutional description, progress and achievement and will be linked to major websites and portals, including additional specific initiatives supported by the European Commission.	PR, IN, EU, CZ, SC, PM.	Project Website – **M4** 500,000 unique vistors
Social media channels to increase exposure of the project and create a large online community of interested parties. Creation of a LinkedIn group and a Project Twitter account to maximize the communication of hints about the project	PR, SC, PM.	Creation of LinkedIn group – **M4** Creation of Twitter account – **M4** Expected to reach **300+** members/followers at the end of the project.
Project Documentation and Technical Publications: Documentation material in the form of public deliverables on the results achieved will be used to contribute to technical blog, articles, and books.	PR, IN, SC.	nr. 6 articles on traditional media channels
Newsletter: the website will have a dedicated section with the news, that will be published following an editorial plan. That news, together with other content will be included in a periodical newsletter	PR, IN, EU, CZ, SC, PM.	News on the website: **each month** (based on the editorial plan starting from **M6**) Newsletter: 4 for the whole project (**every 8 months**)
Infographics: basic concept and advancement about the project will be translated into infographics to make them more intelligible to a wider audience.	PR, IN, EU, CZ, SC, PM.	at least **1 infographic** for each solution developed
Traditional print for distribution at conferences and trade shows will be generated with information about the project to be distributed by the partners and in networking activities.	IN, CZ, SC	4 project leaflets (of which at least 1 dedicated to the mobile app and 1 to sensor) and 3 updated banners Expected to reach 350+
Events organization: At least 2 focus groups and 1	PR, IN, EU, CZ, SC, PM	At least 3 events – M36

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hybrid final event open to a wider public to show the outcomes of the project, with external speakers		Expected attendances 500+

2.3 Summary

Specific Needs	Expected Results	D & E & C Measures
Need for: • Define a risk index associated to the development of prediabetes based on the analysis of bio-clinical data • Non invasive tool for the real time prediction of the prediabetes risk	• **Successful trials** of the solution for people with prediabetes risk. • **Creation of a NewCo** to commercialise the technologies developed within the project, building on meaningful partnerships with first of all hospitals. • **New products**: web/ mobile app, mathematical models, wearable sensor • **Scientific publications**: Publications of scientific discovery on importance of diabetes prevention and role of AI/digital technologies to prevent disease development	• **Dissemination towards the scientific community and healthcare industry**: Scientific community: publications with the results of the planned trials; Participation at relevant conferences; Organisation of thematic workshops. Healthcare industry: Participation to relevant industry tradeshows, leveraging as well on meaningful relationship and increase networking activities; participation to EC project portfolios to disseminate the results as part of a group to maximise project's visibility; • **Exploitation**: Patenting the developed solutions. Provision of services throughout NewCo and usage/ subscription fee to major healthcare primary providers in the field of diabetes prevention. • **Communication towards a wide audience**: actions to present the project, raise awareness through ad-hoc messages and to maximize the impact of results and foster the implementation/ exploitation of outcomes within the main targeted industries. Organisation of a final workshop open to wider public.
Target Group	**Outcomes**	**Impact**
• **Main potential customers** – healthcare primary providers (esp. hospitals); other segments: pharma companies, manufacturers of wearable devices; • **Main potential users** – citizens with prediabetes risks • **Indirect uptake** - Uptake of PRAESIIDIUM solution in closed environments such as hospitals, GP and other wellbeing environment (indirect)	• **A new commercial entity** (PREASIIDIUM NewCo) that will bring to the addressable market the developed solutions and services. • Major healthcare primary providers exploit/use the new solutions. • When possible (as subject to patenting activity), **High use of the scientific discovery published** (measured with the relative rate of citation index of project publications).	• **Scientific**: New breakthrough scientific discovery on PIML trustworthiness methods. New methods for developing PIML. Novel approach based on XAI method for continuous improvement of safety. • **Economic/Technological**: A new market for trustworthy AI, such as assisted living devices; job creation with the creation of new commercial entity (NewCo); 100 number of expected jobs created in Europe through the project (by 2030). • **Societal**: Prevent or delay complications, reduce premature death and improve quality of life of citizens with prediabetes risks, with a potential yearly reduction of 1% and 2% namely in healthcare expenditure and expected deaths (in 2021 c. USD 9.9 billion dollars could have been saved and 134,000 deaths avoided, globally, just to mention some key impacts).

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		• **Environmental**: greener AI with reduction of the overall energy consumption (with consequent lower impacts on the environment)

3. Quality and efficiency of the implementation

3.1 Work plan and resources

Considering the project overall goals, to guarantee the objectives achievement and to manage the project efficiently and effectively, a coherent work-plan, over **36 months**, has been devised. PRAESIIDIUM work-plan is organized through 7 work-packages (WPs). WP2 will set the reference context for the project, collect all the technical requirements to develop the PRAESIIDIUM framework and will be devoted to data acquisition and preprocessing, adopting best practices for reproducibility and monitoring of data drift. It will also support the design of the clinical case studies to be performed in WP6. WP3 and WP4 will be devoted to the mathematical part of the project: In WP3 we will improve the mathematical model previously developed in MT2D, in order to have a more detailed model of the metabolic dysregulation and inflammation, while WP3 will produce a PIML model by combining the mathematical model in WP3 and the data collected and pre-processed in WP2. WP5 will be focused on the development of the technological part of PRAESIIDIUM. A wrist-worn wearable device with bioimpedance sensing will be developed, together with a LinkWatch platform for remote monitoring and self-management of patients during clinical trials. The final web-based applications developed by SPXL will then integrate the PIML model and collected data in order to furnish a real time risk prediction of developing prediabetes. WP6 will have as objective the conduction of newly-dedicated clinical studies on participants affected by prediabetes. These studies will be finalised at 1) the acquisition of more bio-clinical data, also measured by sensors, in order to further improve the PIML model; 2) the prediction of the recovery time for the patients, by using the newly developed PIML algorithm, and 4) the testing of the newly-dedicated wearable sensor in a controlled manner on a smaller group of participants. WP7, impact creation, exploitation and dissemination, and WP1, project management, will run in parallel throughout the other project WPs. The temporal evolution of PRAESIIDIUM project is represented by the Gantt diagram in Figure 9. The temporal evolution of PRAESIIDIUM project is represented by the Gantt diagram in Fig. 9.

Fig. 8 Gantt diagram

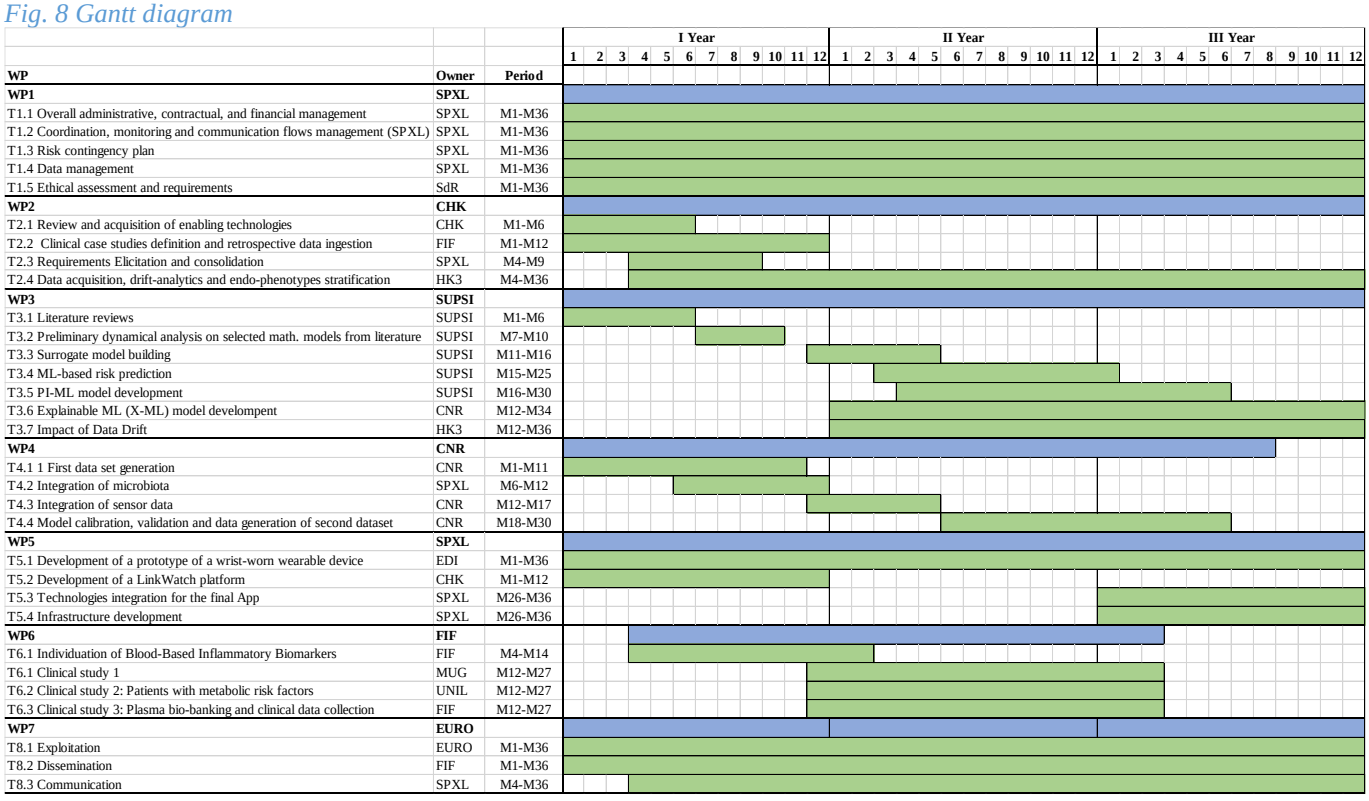

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Table 3.1h: 'Purchase costs' items (travel and subsistence, equipment, and other goods, works and services)

Participant 2 - CNR		
	Cost (€)	**Justification**
Travel and subsistence	32.000,00	Travel costs are for the project meetings, international conferences and workshops, during the 3 years, for CNR members. Average cost per travel = 800 euro/person.
Equipment	30.000,00	Only depreciation costs are here declared: server with specific NVIDIA with CUDA for parallel processing on GPU (20.000 euro), PC purchase for research tasks (10.000 euro).
Other goods, works and services	29.000,00	Publication costs/Open Access fees: 25.000 euro, Audit certificate: 4.000 euro
Total	91.000,00	

Participant 7 - FIF		
	Cost (€)	**Justification**
Travel and subsistence	20.000,00	Travel costs for the project meetings during the 3 years: (6 meetings – 2 persons involved): €10.000 6 travels for conference meeting (3 USA conferences and 3 EU conferences - 1 persons involved): €10.000
Equipment	50.000,00	Only depreciation costs are here declared: -Freezer -80° (fully equipped with freezing racks for the storage of the samples collected for the project): €18.000 -alarm detection system for monitoring freezer temperature (to guarantee the preservation on the samples under certificated conditions): €4.000 -barcode camera rack reader (for sample tracking): €9.000 -refrigerated centrifuge (for sample processing under certified conditions): €6.000 -NanoDrop spectrophotometer: €13.000
Other goods, works and services	75.000,00	Marketed ELISA kits for at least 10 biomarkers validation: €20.000 disposable laboratory material (plasticware, dpi, chemicals, biological reagents): €32.000 publication fees: €18.000 audit costs: €5000
Total	145.000,00	

Participant 8 - MUG		
	Cost (€)	**Justification**
Travel and subsistence	14.700,00	Travel costs are for the project meetings during the 3 years: 6 travels to project meetings for 2 persons and 3 conferences (e.g., EASD, ATTD and ÖDG) for 1 person.
Equipment		
Other goods, works and services	135.800,00	For all studies that are more than just routine data use, MUG reimburses subjects. For 75 subjects, MUG calculated 100 euro/month (for a total of 4 months, not considering dropouts) plus potential travel costs of 100 euro, if participants are not living in Graz (37.500 euro). Costs for clinical study of 75 participants: 1200 (8 sensors/patient) glucose sensors at 36.000 euro (60 euro/unit) plus 33 sensors in case of replacement. Blood sampling consumables (2.300 euro). Insurance (8.000 euro), Biobank costs (25.0000 euro), Audit costs 10.000 euro; eCRF 15.000 euro.
Total	150.500,00	

3.2 Capacity of participants and consortium as a whole

The consortium consists of 11 members, three of which are companies, and the rest are universities or research institutes. The members come from five EU countries and one Swiss Associated Partner.. In assembling the consortium, care has been taken to ensure that the skills of the various consortium members complement each other and together meet the needs of the call. Within the consortium, partners blend theoretical and practical knowledge in formal methods, mathematical modelling, explainability of ML models, collection of medical data via clinical trials and their analysis, to address the project's enabling objectives.

Spindox Labs srl is the research and development center of Spindox Sp.a Mission of Spindox Spa is to support the process of digital transformation of their customers, by developing new technology and providing consultancy in five strategic domains: cloud computing, hybrid and native mobile applications, artificial intelligence, big data & analytics and internet of things. Being the R&D soul of the group, Spindox Labs collaborates with Italian and international universities and research centers carrying out innovation projects related to Artificial Intelligence and Artificial Vision, Internet of Things and 3D modelling. SPXL will coordinate the proposal and it will lead both WP1 and WP5.

The **National Research Council** of Italy (CNR) is a public organization; its duty is to carry out, promote, spread, transfer and improve research activities in the main sectors of knowledge growth and of its applications for the scientific, technological, economic and social development of the country. The Istitute IAC "M. Picone" (Istituto per le Applicazioni del Calcolo (www.iac.cnr.it) is specialized in developing highly advanced mathematical, statistical and computational methods to solve problems with strong relevance to society and industry. The IAC-CNR group will be responsible for the improvement of the MISSION-T2D predictive mathematical/computational model describing the effects of nutrition and physical exercise to prevent the onset of type 2 diabetes, and to estimate parameters from experimental data generated by other members of the consortium. The Institute of Electronics, Information Engineering and Telecommunications IEIIT (www.ieiit.cnr.it) performs research activity in the fields related to information technology, systems engineering, electronics, and biomedical engineering. In the field of diabetes modeling and prevention, IEIIT has recently coordinated a pilot project SCI-PHI (Segment-based Collective Intelligence for Population Health Improvement) aimed at using AI on data from electronic medical records to segment patients with Type 2 Diabetes based on behaviors in order to deliver tailored interventions to promote lifestyle change and reduce the risk of complications. Moreover, IEIIT is part of the PREVENT project (https://preventdiabetes.ca/), aimed at delivering AI-based prediabetes risk identification and personalized recommendations to decrease the risk of developing prediabetes and Type 2 Diabetes. The group will be responsible for the development of XAI models to characterize, predict, and prevent transitions from a healthy status to prediabetes and from prediabetes to healthy status or diabetes. The IEIIT group will leverage data and knowledge extracted from a large database of electronic medical records including longitudinal data from >1.8 million patients in Canada (http://cpcssn.ca/), available through an ongoing agreement with Ryerson University, Toronto.

Euronet Consulting EEIG is a pan-European group of cutting-edge consultancy companies and a global network consisting of partners in Official Development Assistance (ODA) countries. The group was established in 1990 as a coordination hub for managing joint operations in a broad number of thematic sectors. Over time it evolved to become a means by which services of member companies have been made readily available to major international donors, primarily the Commission of the European Union. EURONET is responsible for the Exploitation Activities and Strategy, Route to the Market, and Costs-Benefits Analysis (Task 8.1). In addition, it will consult the partners on business matters and compose a viable business plan for various operations of the project.

SUPSI-IDSIA SUPSI-IDSIA is a Swiss research institute that distinctively combines multiple Artificial Intelligence competencies that are central to PRAESIIDIUM. SUPSI-IDSIA has pioneering expertise in mathematical modelling and optimization, machine learning, and advanced statistics, which are core to work packages 3 and 4. Furthermore, SUPSI-IDSIA will lead WP3 about multi-scale physics informed machine learning. Furthermore, SUPSI-IDSIA will lead WP3 about multi-scale physics informed machine learning. SUPSI-IDSIA is one of the most prominent European research institutes in AI, with extensive experience in distributed systems, control of swarm intelligence, Bayesian methods, optimization, and machine learning. In PRAESIIDIUM, SUPSI will develop a Physics Informed Machine Learning algorithm that, combining the physical knowledge of the biomedical system described by a complex set of mathematical equations and agent-based models with a dataset belonging to clinical studies and sensors measurements, will largely contribute in improving the performances and accuracy prediction of the predictive tool

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developed in the previous project MISSION-T2D. As SUPSI is a Swiss Associated Partner, its participation within the project will be funded and provided by SEFRI.

The Medical University of Graz (MUG) is the second largest Medical University of Austria with over 2,500 academic and general staff members and around 4,500 students. MUG has a strong track-record in clinical research including coordination and participation in numerous EU-funded projects. The Division of Endocrinology and Diabetology offers extensive outpatient services and a 21-bed inpatient ward. Research areas of the Division are: analysis of real-world data, assessment of risk prediction tools, biomarker research, design, evaluation and use of diabetes technology incl. software, hypoglycaemic clamp experiments, new pharmaceutical approaches for the treatment of diabetes mellitus. With MUG's expertise in clinical research, we will contribute to ethics assessment and requirements (Task 1.5). Within PRAESIIDIUM, MUG will provide data from BioPersMed, a cohort of people at risk of prediabetes for developing the PIML model (Task 2.4). Subsequently MUG will be responsible to perform a validation study (Task 6.2).

HKL Lab HKL Lab (HKL) develops research assets for the new season of AI, where the availability of predictive models is vital for any organization, from corporates to public agencies and individuals. HKL has expertise based on more than 20 years of international research in machine learning, including highly cited papers in deep learning, predictive biomarkers, model distillation, and model reproducibility. H3K Lab provides solutions & consulting services in machine learning, data science and their applications, with a focus on Life Sciences. In PRAESIIDIUM, HKL will co-coordinate WP2 for data ingestion, developing the core analytics functions for data stratification and data drift detection (T2.4), contributing to the distillation of the surrogate model (PIML) in T3.3. It will also be responsible for developing an experimental real-time data drift monitoring service to support the trustworthy use on real-world data of the model.

EDI is a public state research institute conducting fundamental and applied research in the broad area of Smart Embedded Cooperative Systems. Currently, EDI is the highest rated scientific institution in Latvia specializing in engineering research. The key driving force of EDI scientific activities is its economic and social impact, therefore we apply our expertise in mobility, industry, health, digital life and space domains. Meanwhile, we are focusing on following research directions: extremely precise event timing; remote sensing and space data processing; robotics and machine perception; signal processing and embedded intelligence; smart sensors and IoT. Our expertise is complemented by close collaboration with 300+ international partners. EDI have coordinated and participated in numerous EU projects (H2020, ECSEL, ERA-NET, COST). For this project, EDI will involve researchers from the Discrete Signal Processing laboratory. Discrete Signal Processing laboratory focuses on research on acquisition, representation, and manipulation of signals for a wide range of practical applications, including biometric and acceleration signals, as well as wearable devices and other kinds of smart sensors.

CheckHealth is an innovative medtech company developing and marketing solutions to help care organisations implement customised remote patient monitoring programmes. Personnel and key persons at CheckHealth has participate in numerous of international and national R&D projects which have resulted in exploitable results leading to commercial products now being marketed by CheckHeath. CheckHealth offers LinkWatch, a cloud based platform for patient data collection and self-monitoring, RheumaCloud a service for self management of rheumatic patients with cardiovascular complications using our medical device gateway and federated cloud and VoiveRPM, an Intelligent Digital Voice Assistant for Remote Patient Monitoring. In PRAESIDIIUM Checkhealth will provide the platform for integrating patient data collected through sensors, wearables and questionnaries. We will lead WP2 "High-dimensional data: acquisition, ingestion, and pre-processing" and task 5.2 and adapt the LinkWatch platform for the requirements of the clinical trials of RAESIDIIUM.

Scuola di Robotica is a non-profit association founded in 2000 by a group of robotics and human science scholars. The main objective of Scuola di Robotica is the promotion of culture through education, training, education and dissemination of the arts and sciences involved in the process of development of robotics and new technologies.Over the years Scuola di Robotica has become a national and international reference point for many research activities and application of robotics in the most varied sectors of society such as didactics, ecology and disabilities. Scuola di Robotica is a partner of many European projects and since 2009 has been certified as a training

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body by the Ministry of Education, University and Research for the updating of teaching staff. In the project PRAESIIDIUM, SdR will take care of all the Ethical issues regarding the treatment of human data.

The Italian Liver Foundation (Fondazione Italian Fegato (FIF)–ONLUS) is a no-profit research center in Trieste, Italy, specialized in translational research and educational training of researchers and clinical personnel in liver-related diseases. Its additional strength lies in the vast network of collaborators with research centers, universities, hospitals (more than 30) located worldwide (Italy, US, EU, Indonesia, Philippines, Argentina, Vietnam). The Foundation's staff ranges from senior scientists and researchers, PostDocs and PhD students, including the visiting researchers and a significant number of ungraduated students performing their daily research activity. One research line developed ten years ago is dedicated to studying metabolic associated liver disorders and chronic liver diseases, and currently, the team counts on expertise/skills/tools and models for the investigation of the liver diseases.

University of Latvia (UNIL) is one of the largest comprehensive and leading research universities in the Baltics. University of Latvia is continuously developing — expanding horizons of the academic work and scientific research by collaborating internationally, increasing the number of international study programmes, strengthening its cooperation with industrial partners. The newly built Academic Centres for Natural Sciences ('The House of Nature' and 'the House of Science') has become an excellent environment for research-based study process and multidisciplinary research opportunities.Within the years to come, th e University of Latvia campus will expand further.Laboratory for Personalized medicine, Faculty of Medicine has experience in running national and international scientific projects in the area of diabetes and endocrinology. The project *PRAESIIDIUM* will benefit from the expertise of the UNIL in translational studies and its collaboration with University hospitals, outpatient clinics in Latvia, allowing a good access to patients. In addition, close collaboration of UNIL with Latvian Genome database (national biobank) allows for high-quality sample collection and preservation protocols. Thus, UNIL will be actively involed in retrospective data provision (task 2.2) and performance of the clinical study (task 6.3).

4. Ethics

4.1 Ethical dimension of the objectives, methodology and likely impact

Objectives: The project objectives do not involve studies on vulnerable or at-risk populations. The clinical studies (both retrospective and prospective) do not involve children. Sensitive data, mainly concerning the health status of volunteers will be stored by Spindox Labs and processed according to the GDPR: 1) Volunteers will be informed thoroughly about the objectives and modalities of the project and will be asked for their informed consent. 2) The analysis of the ethical impact on the participants will be carried out in all phases of exploration, selection, collaboration and implementation. Therefore, in the application it is explained in detail how we will inform and reach out to participants and the number of participants that will be reached.
Methodology: The selection of volunteers will be free from any bias or stigmatisation of particular social groups. The selection and recruitment of participants for the clinical prospective will 1) respect the gender balance and, as there is a significant literature on the impact of diabetes on non-dual sex, we will try to include participants from this community. 2) The prospective clinical studies, also involving the usage of wearable sensors, will take place in a controlled envinronment. 3) Surveys and gradibility ratings will be collected, anonymously. Any focus groups will be anonymous.
The potential impact of the activities: The project and research does not foresee any particular environmental impacts. It does not provide for political or financial adverse consequences and misuse since the device cannot be used otherwise (no dual use). From a cost/benefit and sustainability point of view, a cost/benefit analysis of the project device compared to other products will be carried out.

4.2 Compliance with ethical principles and relevant legislations

The *PRAESIIDIUM* framework will comply with the EU GDPR and will also consider the ongoing activities aiming at defining an EU ePrivacy regulation and guidelines on automatic processing of personal data. The consortium is conscious that interviews, focus groups, stakeholder workshops, surveys and observational clinical studies can raise ethical issues related to informed consent and privacy. For adequately addressing any ethical issues that could arise in the project related to privacy and consent, we will ensure that the data collected and processed during focus groups, by surveys and during retrospective data collection and from the observational clinical studies are only processed in the way described in the following. All participants in *PRAESIIDIUM* clinical prospective observational studies will be informed of all aspects of the research that might reasonably be expected to influence willingness to participate.

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Ethical approvals will be obtained from each ethical commissions before the initiation of the retrospective data collection. Participants will have the right to withdraw from the research at any time, and to withdraw retrospectively any consent given and to demand that their personal data be destroyed. The project will avoid situations where participants feel pressurized to take part in the observational studies. The project will maintain transparency, i.e., it will never intentionally deceive, mislead or withhold information from participants as to the purpose and nature of the investigation. Once complete, or at suitable stages throughout the project when appropriate, results will be collated and circulated to the consortium members. Data directly or indirectly related to people involved in the *PRAESIIDIUM* clinical studies will never be provided to subjects not directly involved in the consortium. Data provided to third parties, included the ones included in project deliverables, will be duly anonymized or at least pseudo-anonymized, depending on the requirements. Confidentiality and data protection: At the start of the project, a Data Protection Officer (DPO) for the project will be appointed within Consortium members, for handling management of personal data in accordance with the GDPR and other relevant EU and national legislations. The responsibilities of the DPO will be in line with Article 39 of the GDPR and will include, at a minimum, the following: advise the data controller and processors within the project on the processing of personal data and data privacy issues, training of researchers and assignment of responsibility; provide support on the performance and tracking of impact assessment; assist in risk assessment of personal data processing; cooperate with any national or European supervisory authority and act as a contact point for the project with such authorities; act as contact point for the data subjects concerned and for the purposes of consent and be responsible for ensuring all partners address the need for compliance with the national and EU regulation.
Oversight and responsibilities: The overall oversight will lay with the project coordinator SPXL as part of WP1 Management. All partners will be required to fulfil all Ethics related responsibilities via specific guidelines that will be included as part of the Consortium Agreement and related *PRAESIIDIUM* project management handbook. Privacy policy for project website: The project will also make sure that the public project web site will present a privacy and cookie policy that is compliant with the legislation, and that the web server will restrict its log files to what is allowed by law as well as stated in the privacy policy. Develop the app respecting ethical issues: The app will be designed according to the Ethics by Design methodology (see “Ethics By Design and Ethics of Use Approaches for Artificial Intelligence Ethics By Design and Ethics of Use Approaches for Artificial Intelligence” (2021), and will be compliant with the EC Code of Conduct on privacy for mHealth.

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ANNEX 2

ESTIMATED BUDGET FOR THE ACTION

	Estimated eligible[1] costs (per budget category)										Estimated EU contribution[2]			
	Direct costs								Indirect costs	Total costs	EU contribution to eligible costs			Maximum grant amount[6]
	A. Personnel costs			B. Subcontracting costs	C. Purchase costs			D. Other cost categories	E. Indirect costs[3]		Funding rate %[4]	Maximum EU contribution[5]	Requested EU contribution	
	A.1 Employees (or equivalent) A.2 Natural persons under direct contract A.3 Seconded persons		A.4 SME owners and natural person beneficiaries	B. Subcontracting	C.1 Travel and subsistence	C.2 Equipment	C.3 Other goods, works and services	D.2 Internally invoiced goods and services	E. Indirect costs					
Forms of funding	Actual costs	Unit costs (usual accounting practices)	Unit costs[7]	Actual costs	Actual costs	Actual costs	Actual costs	Unit costs (usual accounting practices)	Flat-rate costs[8]					
	a1	a2	a3	b	c1	c2	c3	d2	e = 0,25 * (a1 + a2 + a3 + c1 + c2 + c3)	f = a + b + c + d + e	U	g = f * U%	h	m
1 - SPXL	654 500.00	0.00	0.00	0.00	20 000.00	30 000.00	40 000.00	0.00	186 125.00	930 625.00	100	930 625.00	930 625.00	930 625.00
2 - CNR	551 200.00	0.00	0.00	0.00	32 000.00	30 000.00	29 000.00	0.00	160 550.00	802 750.00	100	802 750.00	802 750.00	802 750.00
3 - EDI	405 000.00	0.00	0.00	0.00	10 000.00	2 000.00	40 000.00	0.00	114 250.00	571 250.00	100	571 250.00	571 250.00	571 250.00
4 - EURO	325 000.00	0.00	0.00	0.00	11 000.00	0.00	0.00	0.00	84 000.00	420 000.00	100	420 000.00	420 000.00	420 000.00
5 - SdR	72 600.00	0.00	0.00	0.00	9 000.00	0.00	0.00	0.00	20 400.00	102 000.00	100	102 000.00	102 000.00	102 000.00
6 - CHK	439 900.00	0.00	0.00	0.00	24 000.00	0.00	8 000.00	0.00	117 975.00	589 875.00	100	589 875.00	589 875.00	589 875.00
7 - FIF	369 273.00	0.00	0.00	0.00	20 000.00	50 000.00	75 000.00	0.00	128 568.25	642 841.25	100	642 841.25	642 841.00	642 841.00
8 - MUG	310 529.00	0.00	0.00	0.00	14 700.00	0.00	135 800.00	0.00	115 257.25	576 286.25	100	576 286.25	576 286.00	576 286.00
9 - HKL	372 000.00	0.00	0.00	0.00	12 000.00	17 000.00	5 000.00	0.00	101 500.00	507 500.00	100	507 500.00	507 500.00	507 500.00
10 - UNIL	465 591.00	0.00	0.00	0.00	14 700.00	15 000.00	37 200.00	0.00	133 122.75	665 613.75	100	665 613.75	665 613.00	665 613.00
11 - SUPSI														
Σ consortium	3 965 593.00	0.00	0.00	0.00	167 400.00	144 000.00	370 000.00	0.00	1 161 748.25	5 808 741.25		5 808 741.25	5 808 740.00	5 808 740.00

[1] See Article 6 for the eligibility conditions. All amounts must be expressed in EUR (see Article 21 for the conversion rules).
[2] The consortium remains free to decide on a different internal distribution of the EU funding (via the consortium agreement; see Article 7).
[3] Indirect costs already covered by an operating grant (received under any EU funding programme) are ineligible (see Article 6.3). Therefore, a beneficiary/affiliated entity that receives an operating grant during the action duration cannot declare indirect costs for the year(s)/reporting period(s) covered by the operating grant, unless they can demonstrate that the operating grant does not cover any costs of the action. This requires specific accounting tools. Please immediately contact us via the EU Funding & Tenders Portal for details.
[4] See Data Sheet for the funding rate(s).
[5] This is the theoretical amount of the EU contribution to costs, if the reimbursement rate is applied to all the budgeted costs. This theoretical amount is then capped by the 'maximum grant amount'.
[6] The 'maximum grant amount' is the maximum grant amount decided by the EU. It normally corresponds to the requested grant, but may be lower.
[7] See Annex 2a 'Additional information on the estimated budget' for the details (units, cost per unit).
[8] See Data Sheet for the flat-rate.

ANNEX 2a

ADDITIONAL INFORMATION ON UNIT COSTS AND CONTRIBUTIONS

SME owners/natural person beneficiaries without salary (Decision C(2020) 7115[1])

Type: unit costs

Units: days spent working on the action (rounded up or down to the nearest half-day)

Amount per unit (daily rate): calculated according to the following formula:

{EUR 5 080 / 18 days = **282,22**}
multiplied by
{country-specific correction coefficient of the country where the beneficiary is established}

The country-specific correction coefficients used are those set out in the Horizon Europe Work Programme (section Marie Skłodowska-Curie actions) in force at the time of the call (see Portal Reference Documents).

HE and Euratom Research Infrastructure actions[2]

Type: unit costs

Units[3]: see (for each access provider and installation) the unit cost table in Annex 2b

Amount per unit*: see (for each access provider and installation) the unit cost table in Annex 2b

* Amount calculated as follows:

For trans-national access:

$$\frac{\text{average annual total trans-national access costs to the installation (over past two years[4])}}{\text{average annual total quantity of trans-national access to the installation (over past two years[5])}}$$

For virtual access:

$$\frac{\text{total virtual access costs to the installation (over the last year[6])}}{\text{total quantity of virtual access to the installation (over the last year[7])}}$$

Euratom staff mobility costs[8]

Monthly living allowance

Type: unit costs

---

1 Commission Decision of 20 October 2020 authorising the use of unit costs for the personnel costs of the owners of small and medium-sized enterprises and beneficiaries that are natural persons not receiving a salary for the work carried out by themselves under an action or work programme (C(2020)7715).

2 Decision of 19 April 2021 authorising the use of unit costs for the costs of providing trans-national and virtual access in Research Infrastructure actions under the Horizon Europe Programme (2021-2027) and the Research and Training Programme of the European Atomic Energy Community (2021-2025).

3 Unit of access (e.g. beam hours, weeks of access, sample analysis) fixed by the access provider in proposal.

4 In exceptional and duly justified cases, the granting authority may agree to a different reference period.

5 In exceptional and duly justified cases, the granting authority may agree to a different reference period.

6 In exceptional and duly justified cases, the granting authority may agree to a different reference period.

7 In exceptional and duly justified cases, the granting authority may agree to a different reference period.

8 Decision of 15 March 2021 authorising the use of unit costs for mobility in co-fund actions under the Research and Training Programme of the European Atomic Energy Community (2021-2025).

Units: months spent by the seconded staff member(s) on research and training in fission and fusion activities (person-month)

Amount per unit*: see (for each beneficiary/affiliated entity and secondment) the unit cost table in Annex 2b

* Amount calculated as follows from 1 January 2021:
{**EUR 4 300** multiplied by
country-specific correction coefficient** of the country where the staff member is seconded}[9]

**Country-specific correction coefficients as from 1 January 2021[10]

EU-Member States[11]

Country / Place	Coefficient (%)
Bulgaria	59,1
Czech Rep.	85,2
Denmark	131,3
Germany Bonn Karlsruhe Munich	101,9 95,8 98 113,9
Estonia	82,3
Ireland	129
Greece	81,4
Spain	94,2
France	120,5
Croatia	75,8
Italy Varese	95 90,7
Cyprus	78,2
Latvia	77,5
Lithuania	76,6
Hungary	71,9
Malta	94,7
Netherlands	113,9
Austria	107,9
Poland	70,9
Portugal	91,1
Romania	66,6
Slovenia	86,1

[9] Unit costs for living allowances are calculated by using a method of calculation similar to that applied for the secondment to the European Commission of seconded national experts (SNEs).

[10] ⚠ For the financial statements, the amount must be adjusted according to the actual place of secondment.
The revised coefficients were adopted in the Decision authorising the use of unit costs for the Fusion Programme co-fund action under the Research and training Programme of the European Atomic Energy Community 2021-2025. They are based on the 2020 Annual update of the remuneration and pensions of the officials and other servants of the European Union and the correction coefficients applied thereto (OJ C 428, 11.12.2020) to ensure purchasing power parity. The revised coefficient are applied as from 1 January 2021 through an amendment to the grant agreement.

[11] No correction coefficient shall be applicable in Belgium and Luxembourg.

Slovakia	80,6
Finland	118,4
Sweden	124,3

Third countries

Country/place	Coefficient (%)
China	82,2
India	72,3
Japan	111,8
Russia	92,7
South Korea	92,3
Switzerland	129.2
Ukraine	82.3
United Kingdom	97.6
United States	101,4 (New-York) 90,5 (Washington)

Mobility allowance

Type: Unit costs

Units: months spent by the seconded staff member(s) on research and training in fission and fusion activities (person-month)

Amount per unit: **EUR 600** per person-month; see (for each beneficiary/affiliated entity and secondment) the unit cost table in Annex 2b

Family allowance

Type: unit costs

Units: months spent by the seconded staff member(s) on research and training in fission and fusion activities (person-month)

Amount per unit: **EUR 660** per person-month; see (for each beneficiary/affiliated entity and secondment) the unit cost table in Annex 2b

Education allowance

Type: Unit costs

Units: months spent by the seconded staff member(s) on research and training in fission and fusion activities (person-month)

Amount per unit*: see (for each beneficiary/affiliated entity and secondment) the unit cost table in Annex 2b

*Amount calculated as follows from 1 January 2021:
{EUR 283.82 x number of dependent children[12]**}**

[12] For the estimated budget (Annex 2): an average should be used. (⚠ For the financial statements, the number of children (and months) must be adjusted according to the actual family status at the moment the secondment starts.)

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

CONSIGLIO NAZIONALE DELLE RICERCHE (CNR), PIC 999979500, established in PIAZZALE ALDO MORO 7, ROMA 00185, Italy,

hereby agrees

to become beneficiary

in Agreement No 101095672 — PRAESIIDIUM ('the Agreement')

between SPINDOX LABS SRL (SPXL) **and** the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 39.

By signing this accession form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

SIGNATURE

For the beneficiary

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

ELEKTRONIKAS UN DATORZINATNU INSTITUTS (EDI), PIC 997829883, established in DZERBENES IELA 14, RIGA 1006, Latvia,

hereby agrees

to become beneficiary

in Agreement No 101095672 — PRAESIIDIUM ('the Agreement')

between SPINDOX LABS SRL (SPXL) **and** the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 39.

By signing this accession form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

SIGNATURE

For the beneficiary

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

EURONET CONSULTING (EURO), PIC 907542089, established in 43 RUE SAINT CHRISTOPHE, BRUSSELS 1000, Belgium,

hereby agrees

to become beneficiary

in Agreement No 101095672 — PRAESIIDIUM ('the Agreement')

between SPINDOX LABS SRL (SPXL) **and** the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 39.

By signing this accession form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

SIGNATURE

For the beneficiary

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

SCUOLA DI ROBOTICA (SdR), PIC 951668747, established in STUDIO MARTINETTO, VIA FIESCHI 20/9, GENOVA 16149, Italy,

hereby agrees

to become beneficiary

in Agreement No 101095672 — PRAESIIDIUM ('the Agreement')

between SPINDOX LABS SRL (SPXL) **and** the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 39.

By signing this accession form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

SIGNATURE

For the beneficiary

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

CHECKHEALTH SWEDEN AB (CHK), PIC 900926010, established in SVARDVAGEN 3 A, DANDERYD 182 33, Sweden,

hereby agrees

to become beneficiary

in Agreement No 101095672 — PRAESIIDIUM ('the Agreement')

between SPINDOX LABS SRL (SPXL) **and** the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 39.

By signing this accession form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

SIGNATURE

For the beneficiary

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

FONDAZIONE ITALIANA FEGATO ONLUS (FIF), PIC 997492808, established in AREA SCIENCE PARK, BLDG Q, SS14, KM 163.5, TRIESTE 34149, Italy,

hereby agrees

to become beneficiary

in Agreement No 101095672 — PRAESIIDIUM ('the Agreement')

between SPINDOX LABS SRL (SPXL) **and** the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 39.

By signing this accession form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

SIGNATURE

For the beneficiary

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

MEDIZINISCHE UNIVERSITAT GRAZ (MUG), PIC 999836231, established in AUENBRUGGERPLATZ 2, GRAZ 8036, Austria,

hereby agrees

to become beneficiary

in Agreement No 101095672 — PRAESIIDIUM ('the Agreement')

between SPINDOX LABS SRL (SPXL) **and** the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 39.

By signing this accession form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

SIGNATURE

For the beneficiary

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

HK3 LAB S.R.L. (HKL), PIC 895500121, established in VIA PARTELI 19, ROVERETO 38068, Italy,

hereby agrees

to become beneficiary

in Agreement No 101095672 — PRAESIIDIUM ('the Agreement')

between SPINDOX LABS SRL (SPXL) **and** the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 39.

By signing this accession form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

SIGNATURE

For the beneficiary

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 3

ACCESSION FORM FOR BENEFICIARIES

LATVIJAS UNIVERSITATE (UNIL), PIC 999871830, established in RAINIS BOULEVARD 19, RIGA 1586, Latvia,

hereby agrees

to become beneficiary

in Agreement No 101095672 — PRAESIIDIUM ('the Agreement')

between SPINDOX LABS SRL (SPXL) **and** the **European Health and Digital Executive Agency (HADEA)** ('EU executive agency' or 'granting authority'), under the powers delegated by the European Commission ('European Commission'),

and mandates

the coordinator to submit and sign in its name and on its behalf any **amendments** to the Agreement, in accordance with Article 39.

By signing this accession form, the beneficiary accepts the grant and agrees to implement it in accordance with the Agreement, with all the obligations and terms and conditions it sets out.

SIGNATURE

For the beneficiary

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

FINANCIAL STATEMENT FOR [PARTICIPANT NAME] FOR REPORTING PERIOD [NUMBER]

	Eligible[1] costs (per budget category)																EU contribution[2]				Revenues
	Direct costs															Indirect costs	Total costs	EU contribution to eligible costs			Total requested EU contribution	Income generated by the action
	A. Personnel costs			B. Subcontracting costs	C. Purchase costs			D. Other cost categories								E. Indirect costs[2]		Funding rate %[3]	Maximum EU contribution[4]	Requested EU contribution		
	A.1 Employees (or equivalent) A.2 Natural persons under direct contract A.3 Seconded persons		A.4 SME owners and natural person beneficiaries	B. Subcontracting	C.1 Travel and subsistence	C.2 Equipment	C.3 Other goods, works and services	[D.1 Financial support to third parties]	D.2 Internally invoiced goods and services	[D.3 Transnational access to research infrastructure unit costs]	[D.4 Virtual access to research infrastructure unit costs]	*[OPTION for HE PCP/PPI:* D.5 PCP/PPI procurement costs*]*	*[OPTION for Euratom Programme Cofund Actions:* D.6 Euratom Cofund staff mobility costs*]*	*[OPTION for HE ERC Grants:* D.7 ERC additional funding*]*	*[OPTION for HE ERC Grants:* D.8 ERC additional funding (subcontracting, FSTP and internally invoiced goods and services)*]*	E. Indirect costs						
Forms of funding	Actual costs	Unit costs (usual accounting practices)	Unit costs[5]	Actual costs	Actual costs	Actual costs	Actual costs	[Actual costs]	Unit costs (usual accounting practices)	[Unit costs[5]]	[Unit costs[5]]	[Actual costs]	[Unit costs[5]]	[Actual costs]	[Actual costs]	Flat-rate costs[6]						
	a1	a2	a3	b	c1	c2	c3	[d1a]	d2	[d3]	[d4]	[d5]	[d6]	[d7]	[d8]	e = 0,25 * (a1 + a2 + a3 ~~+b+~~ c1 +c2 + c3 ~~+d1a + d2 + d3 + d4 [+ d5][+ d6]~~ [+d7] ~~[+ d8]~~)	f = a+b+c+d+e	U	g = f*U%	h	m	n
XX – [short name beneficiary/affiliated entity]																						

The beneficiary/affiliated entity hereby confirms that:

The information provided is complete, reliable and true.

The costs and contributions declared are eligible (see Article 6).

The costs and contributions can be substantiated by adequate records and supporting documentation that will be produced upon request or in the context of checks, reviews, audits and investigations (see Articles 19, 20 and 25).

For the last reporting period: that all the revenues have been declared (see Article 22).

① Please declare all eligible costs and contributions, even if they exceed the amounts indicated in the estimated budget (see Annex 2). Only amounts that were declared in your individual financial statements can be taken into account lateron, in order to replace costs/contributions that are found to be ineligible.

[1] See Article 6 for the eligibility conditions. All amounts must be expressed in EUR (see Article 21 for the conversion rules).

[2] If you have also received an EU operating grant during this reporting period, you cannot claim indirect costs - unless you can demonstrate that the operating grant does not cover any costs of the action. This requires specific accounting tools. Please contact us immediately via the Funding & Tenders Portal for details.

[3] See Data Sheet for the reimbursement rate(s).

[4] This is the *theoretical* amount of EU contribution to costs that the system calculates automatically (by multiplying the reimbursement rates by the costs declared). The amount you request (in the column 'requested EU contribution') may be less.

[5] See Annex 2a 'Additional information on the estimated budget' for the details (units, cost per unit).

[6] See Data Sheet for the flat-rate.

Associated with document Ref. Ares(2022)7741659 - 09/11/2022

ANNEX 5

SPECIFIC RULES

CONFIDENTIALITY AND SECURITY (— ARTICLE 13)

Sensitive information with security recommendation

Sensitive information with a security recommendation must comply with the additional requirements imposed by the granting authority.

Before starting the action tasks concerned, the beneficiaries must have obtained all approvals or other mandatory documents needed for implementing the task. The documents must be kept on file and be submitted upon request by the coordinator to the granting authority. If they are not in English, they must be submitted together with an English summary.

For requirements restricting disclosure or dissemination, the information must be handled in accordance with the recommendation and may be disclosed or disseminated only after written approval from the granting authority.

EU classified information

If EU classified information is used or generated by the action, it must be treated in accordance with the security classification guide (SCG) and security aspect letter (SAL) set out in Annex 1 and Decision 2015/444[1] and its implementing rules — until it is declassified.

Deliverables which contain EU classified information must be submitted according to special procedures agreed with the granting authority.

Action tasks involving EU classified information may be subcontracted only with prior explicit written approval from the granting authority and only to entities established in an EU Member State or in a non-EU country with a security of information agreement with the EU (or an administrative arrangement with the Commission).

EU classified information may not be disclosed to any third party (including participants involved in the action implementation) without prior explicit written approval from the granting authority.

ETHICS (— ARTICLE 14)

Ethics and research integrity

The beneficiaries must carry out the action in compliance with:

- ethical principles (including the highest standards of research integrity)

[1] Commission Decision 2015/444/EC, Euratom of 13 March 2015 on the security rules for protecting EU classified information (OJ L 72, 17.3.2015, p. 53).

and

- applicable EU, international and national law, including the EU Charter of Fundamental Rights and the European Convention for the Protection of Human Rights and Fundamental Freedoms and its Supplementary Protocols.

No funding can be granted, within or outside the EU, for activities that are prohibited in all Member States. No funding can be granted in a Member State for an activity which is forbidden in that Member State.

The beneficiaries must pay particular attention to the principle of proportionality, the right to privacy, the right to the protection of personal data, the right to the physical and mental integrity of persons, the right to non-discrimination, the need to ensure protection of the environment and high levels of human health protection.

The beneficiaries must ensure that the activities under the action have an exclusive focus on civil applications.

The beneficiaries must ensure that the activities under the action do not:

- aim at human cloning for reproductive purposes
- intend to modify the genetic heritage of human beings which could make such modifications heritable (with the exception of research relating to cancer treatment of the gonads, which may be financed)
- intend to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer, or
- lead to the destruction of human embryos (for example, for obtaining stem cells).

Activities involving research on human embryos or human embryonic stem cells may be carried out only if:

- they are set out in Annex 1 or
- the coordinator has obtained explicit approval (in writing) from the granting authority.

In addition, the beneficiaries must respect the fundamental principle of research integrity — as set out in the European Code of Conduct for Research Integrity[2].

This implies compliance with the following principles:

- reliability in ensuring the quality of research reflected in the design, the methodology, the analysis and the use of resources
- honesty in developing, undertaking, reviewing, reporting and communicating research in a transparent, fair and unbiased way

[2] European Code of Conduct for Research Integrity of ALLEA (All European Academies).

- respect for colleagues, research participants, society, ecosystems, cultural heritage and the environment

- accountability for the research from idea to publication, for its management and organisation, for training, supervision and mentoring, and for its wider impacts

and means that beneficiaries must ensure that persons carrying out research tasks follow the good research practices including ensuring, where possible, openness, reproducibility and traceability and refrain from the research integrity violations described in the Code.

Activities raising ethical issues must comply with the additional requirements formulated by the ethics panels (including after checks, reviews or audits; see Article 25).

Before starting an action task raising ethical issues, the beneficiaries must have obtained all approvals or other mandatory documents needed for implementing the task, notably from any (national or local) ethics committee or other bodies such as data protection authorities.

The documents must be kept on file and be submitted upon request by the coordinator to the granting authority. If they are not in English, they must be submitted together with an English summary, which shows that the documents cover the action tasks in question and includes the conclusions of the committee or authority concerned (if any).

VALUES (— ARTICLE 14)

Gender mainstreaming

The beneficiaries must take all measures to promote equal opportunities between men and women in the implementation of the action and, where applicable, in line with the gender equality plan. They must aim, to the extent possible, for a gender balance at all levels of personnel assigned to the action, including at supervisory and managerial level.

INTELLECTUAL PROPERTY RIGHTS (IPR) — BACKGROUND AND RESULTS — ACCESS RIGHTS AND RIGHTS OF USE (— ARTICLE 16)

Definitions

Access rights — Rights to use results or background.

Dissemination — The public disclosure of the results by appropriate means, other than resulting from protecting or exploiting the results, including by scientific publications in any medium.

Exploit(ation) — The use of results in further research and innovation activities other than those covered by the action concerned, including among other things, commercial exploitation such as developing, creating, manufacturing and marketing a product or process, creating and providing a service, or in standardisation activities.

Fair and reasonable conditions — Appropriate conditions, including possible financial terms or royalty-free conditions, taking into account the specific circumstances of the request for access, for example the actual or potential value of the results or background to which access is requested and/or the scope, duration or other characteristics of the exploitation envisaged.

FAIR principles — 'findability', 'accessibility', 'interoperability' and 'reusability'.

Open access — Online access to research outputs provided free of charge to the end-user.

Open science — An approach to the scientific process based on open cooperative work, tools and diffusing knowledge.

Research data management — The process within the research lifecycle that includes the organisation, storage, preservation, security, quality assurance, allocation of persistent identifiers (PIDs) and rules and procedures for sharing of data including licensing.

Research outputs — Results to which access can be given in the form of scientific publications, data or other engineered results and processes such as software, algorithms, protocols, models, workflows and electronic notebooks.

Scope of the obligations

For this section, references to 'beneficiary' or 'beneficiaries' do not include affiliated entities (if any).

Agreement on background

The beneficiaries must identify in a written agreement the background as needed for implementing the action or for exploiting its results.

Where the call conditions restrict control due to strategic interests reasons, background that is subject to control or other restrictions by a country (or entity from a country) which is not one of the eligible countries or target countries set out in the call conditions and that impact the exploitation of the results (i.e. would make the exploitation of the results subject to control or restrictions) must not be used and must be explicitly excluded from it in the agreement on background — unless otherwise agreed with the granting authority.

Ownership of results

Results are owned by the beneficiaries that generate them.

However, two or more beneficiaries own results jointly if:

- they have jointly generated them and
- it is not possible to:
    - establish the respective contribution of each beneficiary, or
    - separate them for the purpose of applying for, obtaining or maintaining their protection.

The joint owners must agree — in writing — on the allocation and terms of exercise of their joint ownership ('**joint ownership agreement**'), to ensure compliance with their obligations under this Agreement.

Unless otherwise agreed in the joint ownership agreement or consortium agreement, each joint owner may grant non-exclusive licences to third parties to exploit the jointly-owned results (without any right to sub-license), if the other joint owners are given:

- at least 45 days advance notice and
- fair and reasonable compensation.

The joint owners may agree — in writing — to apply another regime than joint ownership.

If third parties (including employees and other personnel) may claim rights to the results, the beneficiary concerned must ensure that those rights can be exercised in a manner compatible with its obligations under the Agreement.

The beneficiaries must indicate the owner(s) of the results (results ownership list) in the final periodic report.

Protection of results

Beneficiaries which have received funding under the grant must adequately protect their results — for an appropriate period and with appropriate territorial coverage — if protection is possible and justified, taking into account all relevant considerations, including the prospects for commercial exploitation, the legitimate interests of the other beneficiaries and any other legitimate interests.

Exploitation of results

Beneficiaries which have received funding under the grant must — up to four years after the end of the action (see Data Sheet, Point 1) — use their best efforts to exploit their results directly or to have them exploited indirectly by another entity, in particular through transfer or licensing.

If, despite a beneficiary's best efforts, the results are not exploited within one year after the end of the action, the beneficiaries must (unless otherwise agreed in writing with the granting authority) use the Horizon Results Platform to find interested parties to exploit the results.

If results are incorporated in a standard, the beneficiaries must (unless otherwise agreed with the granting authority or unless it is impossible) ask the standardisation body to include the funding statement (see Article 17) in (information related to) the standard.

Additional exploitation obligations

Where the call conditions impose additional exploitation obligations (including obligations linked to the restriction of participation or control due to strategic assets, interests, autonomy or security reasons), the beneficiaries must comply with them — up to four years after the end of the action (see Data Sheet, Point 1).

Where the call conditions impose additional exploitation obligations in case of a public emergency, the beneficiaries must (if requested by the granting authority) grant for a limited period of time specified in the request, non-exclusive licences — under fair and reasonable conditions — to their results to legal entities that need the results to address the public emergency and commit to rapidly and broadly exploit the resulting products and services at fair and reasonable conditions. This provision applies up to four years after the end of the action (see Data Sheet, Point 1).

Additional information obligation relating to standards

Where the call conditions impose additional information obligations relating to possible standardisation, the beneficiaries must — up to four years after the end of the action (see Data Sheet, Point 1) — inform the granting authority, if the results could reasonably be expected to contribute to European or international standards.

Transfer and licensing of results

Transfer of ownership

The beneficiaries may transfer ownership of their results, provided this does not affect compliance with their obligations under the Agreement.

The beneficiaries must ensure that their obligations under the Agreement regarding their results are passed on to the new owner and that this new owner has the obligation to pass them on in any subsequent transfer.

Moreover, they must inform the other beneficiaries with access rights of the transfer at least 45 days in advance (or less if agreed in writing), unless agreed otherwise in writing for specifically identified third parties including affiliated entities or unless impossible under the applicable law. This notification must include sufficient information on the new owner to enable the beneficiaries concerned to assess the effects on their access rights. The beneficiaries may object within 30 days of receiving notification (or less if agreed in writing), if they can show that the transfer would adversely affect their access rights. In this case, the transfer may not take place until agreement has been reached between the beneficiaries concerned.

Granting licences

The beneficiaries may grant licences to their results (or otherwise give the right to exploit them), including on an exclusive basis, provided this does not affect compliance with their obligations.

Exclusive licences for results may be granted only if all the other beneficiaries concerned have waived their access rights.

Granting authority right to object to transfers or licensing — Horizon Europe actions

Where the call conditions in Horizon Europe actions provide for the right to object to transfers or licensing, the granting authority may — up to four years after the end of the action (see Data Sheet, Point 1) — object to a transfer of ownership or the exclusive licensing of results, if:

- the beneficiaries which generated the results have received funding under the grant
- it is to a legal entity established in a non-EU country not associated with Horizon Europe, and
- the granting authority considers that the transfer or licence is not in line with EU interests.

Beneficiaries that intend to transfer ownership or grant an exclusive licence must formally notify the granting authority before the intended transfer or licensing takes place and:

- identify the specific results concerned
- describe in detail the new owner or licensee and the planned or potential exploitation of the results, and
- include a reasoned assessment of the likely impact of the transfer or licence on EU interests, in particular regarding competitiveness as well as consistency with ethical principles and security considerations.

The granting authority may request additional information.

If the granting authority decides to object to a transfer or exclusive licence, it must formally notify the beneficiary concerned within 60 days of receiving notification (or any additional information it has requested).

No transfer or licensing may take place in the following cases:

- pending the granting authority decision, within the period set out above
- if the granting authority objects
- until the conditions are complied with, if the granting authority objection comes with conditions.

A beneficiary may formally notify a request to waive the right to object regarding intended transfers or grants to a specifically identified third party, if measures safeguarding EU interests are in place. If the granting authority agrees, it will formally notify the beneficiary concerned within 60 days of receiving notification (or any additional information requested).

Granting authority right to object to transfers or licensing — Euratom actions

Where the call conditions in Euratom actions provide for the right to object to transfers or licensing, the granting authority may — up to four years after the end of the action (see Data Sheet, Point 1) — object to a transfer of ownership or the exclusive or non-exclusive licensing of results, if:

- the beneficiaries which generated the results have received funding under the grant
- it is to a legal entity established in a non-EU country not associated to the Euratom Research and Training Programme 2021-2025 and
- the granting authority considers that the transfer or licence is not in line with the EU interests.

Beneficiaries that intend to transfer ownership or grant a licence must formally notify the granting authority before the intended transfer or licensing takes place and:

- identify the specific results concerned
- describe in detail the results, the new owner or licensee and the planned or potential exploitation of the results, and
- include a reasoned assessment of the likely impact of the transfer or licence on EU interests, in particular regarding competitiveness as well as consistency with

ethical principles and security considerations (including the defence interests of the EU Member States under Article 24 of the Euratom Treaty).

The granting authority may request additional information.

If the granting authority decides to object to a transfer or licence, it will formally notify the beneficiary concerned within 60 days of receiving notification (or any additional information requested).

No transfer or licensing may take place in the following cases:

- pending the granting authority decision, within the period set out above
- if the granting authority objects
- until the conditions are complied with, if the granting authority objection comes with conditions.

A beneficiary may formally notify a request to waive the right to object regarding intended transfers or grants to a specifically identified third party, if measures safeguarding EU interests are in place. If the granting authority agrees, it will formally notify the beneficiary concerned within 60 days of receiving notification (or any additional information requested).

Limitations to transfers and licensing due to strategic assets, interests, autonomy or security reasons of the EU and its Member States

Where the call conditions restrict participation or control due to strategic assets, interests, autonomy or security reasons, the beneficiaries may not transfer ownership of their results or grant licences to third parties which are established in countries which are not eligible countries or target countries set out in the call conditions (or, if applicable, are controlled by such countries or entities from such countries) — unless they have requested and received prior approval by the granting authority.

The request must:

- identify the specific results concerned
- describe in detail the new owner and the planned or potential exploitation of the results, and
- include a reasoned assessment of the likely impact of the transfer or license on the strategic assets, interests, autonomy or security of the EU and its Member States.

The granting authority may request additional information.

Access rights to results and background

Exercise of access rights — Waiving of access rights — No sub-licensing

Requests to exercise access rights and the waiver of access rights must be in writing.

Unless agreed otherwise in writing with the beneficiary granting access, access rights do not include the right to sub-license.

If a beneficiary is no longer involved in the action, this does not affect its obligations to grant access.

If a beneficiary defaults on its obligations, the beneficiaries may agree that that beneficiary no longer has access rights.

Access rights for implementing the action

The beneficiaries must grant each other access — on a royalty-free basis — to background needed to implement their own tasks under the action, unless the beneficiary that holds the background has — before acceding to the Agreement —:

- informed the other beneficiaries that access to its background is subject to restrictions, or

- agreed with the other beneficiaries that access would not be on a royalty-free basis.

The beneficiaries must grant each other access — on a royalty-free basis — to results needed for implementing their own tasks under the action.

Access rights for exploiting the results

The beneficiaries must grant each other access — under fair and reasonable conditions — to results needed for exploiting their results.

The beneficiaries must grant each other access — under fair and reasonable conditions — to background needed for exploiting their results, unless the beneficiary that holds the background has — before acceding to the Agreement — informed the other beneficiaries that access to its background is subject to restrictions.

Requests for access must be made — unless agreed otherwise in writing — up to one year after the end of the action (see Data Sheet, Point 1).

Access rights for entities under the same control

Unless agreed otherwise in writing by the beneficiaries, access to results and, subject to the restrictions referred to above (if any), background must also be granted — under fair and reasonable conditions — to entities that:

- are established in an EU Member State or Horizon Europe associated country

- are under the direct or indirect control of another beneficiary, or under the same direct or indirect control as that beneficiary, or directly or indirectly controlling that beneficiary and

- need the access to exploit the results of that beneficiary.

Unless agreed otherwise in writing, such requests for access must be made by the entity directly to the beneficiary concerned.

Requests for access must be made — unless agreed otherwise in writing — up to one year after the end of the action (see Data Sheet, Point 1).

Access rights for the granting authority, EU institutions, bodies, offices or agencies and national authorities to results for policy purposes — Horizon Europe actions

In Horizon Europe actions, the beneficiaries which have received funding under the grant must grant access to their results — on a royalty-free basis — to the granting authority, EU institutions, bodies, offices or agencies for developing, implementing and monitoring EU policies or programmes. Such access rights do not extend to beneficiaries' background.

Such access rights are limited to non-commercial and non-competitive use.

For actions under the cluster 'Civil Security for Society', such access rights also extend to national authorities of EU Member States for developing, implementing and monitoring their policies or programmes in this area. In this case, access is subject to a bilateral agreement to define specific conditions ensuring that:

- the access rights will be used only for the intended purpose and
- appropriate confidentiality obligations are in place.

Moreover, the requesting national authority or EU institution, body, office or agency (including the granting authority) must inform all other national authorities of such a request.

Access rights for the granting authority, Euratom institutions, funding bodies or the Joint Undertaking Fusion for Energy — Euratom actions

In Euratom actions, the beneficiaries which have received funding under the grant must grant access to their results — on a royalty-free basis — to the granting authority, Euratom institutions, funding bodies or the Joint Undertaking Fusion for Energy for developing, implementing and monitoring Euratom policies and programmes or for compliance with obligations assumed through international cooperation with non-EU countries and international organisations.

Such access rights include the right to authorise third parties to use the results in public procurement and the right to sub-license and are limited to non-commercial and non-competitive use.

Additional access rights

Where the call conditions impose additional access rights, the beneficiaries must comply with them.

COMMUNICATION, DISSEMINATION, OPEN SCIENCE AND VISIBILITY (— ARTICLE 17)

Dissemination

Dissemination of results

The beneficiaries must disseminate their results as soon as feasible, in a publicly available format, subject to any restrictions due to the protection of intellectual property, security rules or legitimate interests.

A beneficiary that intends to disseminate its results must give at least 15 days advance notice to the other beneficiaries (unless agreed otherwise), together with sufficient information on the results it will disseminate.

Any other beneficiary may object within (unless agreed otherwise) 15 days of receiving notification, if it can show that its legitimate interests in relation to the results or background would be significantly harmed. In such cases, the results may not be disseminated unless appropriate steps are taken to safeguard those interests.

Additional dissemination obligations

Where the call conditions impose additional dissemination obligations, the beneficiaries must also comply with those.

Open Science

Open science: open access to scientific publications

The beneficiaries must ensure open access to peer-reviewed scientific publications relating to their results. In particular, they must ensure that:

- at the latest at the time of publication, a machine-readable electronic copy of the published version or the final peer-reviewed manuscript accepted for publication, is deposited in a trusted repository for scientific publications

- immediate open access is provided to the deposited publication via the repository, under the latest available version of the Creative Commons Attribution International Public Licence (CC BY) or a licence with equivalent rights; for monographs and other long-text formats, the licence may exclude commercial uses and derivative works (e.g. CC BY-NC, CC BY-ND) and

- information is given via the repository about any research output or any other tools and instruments needed to validate the conclusions of the scientific publication.

Beneficiaries (or authors) must retain sufficient intellectual property rights to comply with the open access requirements.

Metadata of deposited publications must be open under a Creative Common Public Domain Dedication (CC 0) or equivalent, in line with the FAIR principles (in particular machine-actionable) and provide information at least about the following: publication (author(s), title, date of publication, publication venue); Horizon Europe or Euratom funding; grant project name, acronym and number; licensing terms; persistent identifiers for the publication, the authors involved in the action and, if possible, for their organisations and the grant. Where applicable, the metadata must include persistent identifiers for any research output or any other tools and instruments needed to validate the conclusions of the publication.

Only publication fees in full open access venues for peer-reviewed scientific publications are eligible for reimbursement.

Open science: research data management

The beneficiaries must manage the digital research data generated in the action ('data') responsibly, in line with the FAIR principles and by taking all of the following actions:

- establish a data management plan ('DMP') (and regularly update it)

- as soon as possible and within the deadlines set out in the DMP, deposit the data in a trusted repository; if required in the call conditions, this repository must be federated in the EOSC in compliance with EOSC requirements

- as soon as possible and within the deadlines set out in the DMP, ensure open access — via the repository — to the deposited data, under the latest available version of the Creative Commons Attribution International Public License (CC BY) or Creative Commons Public Domain Dedication (CC 0) or a licence with equivalent rights, following the principle 'as open as possible as closed as necessary', unless providing open access would in particular:

    - be against the beneficiary's legitimate interests, including regarding commercial exploitation, or

    - be contrary to any other constraints, in particular the EU competitive interests or the beneficiary's obligations under this Agreement; if open access is not provided (to some or all data), this must be justified in the DMP

- provide information via the repository about any research output or any other tools and instruments needed to re-use or validate the data.

Metadata of deposited data must be open under a Creative Common Public Domain Dedication (CC 0) or equivalent (to the extent legitimate interests or constraints are safeguarded), in line with the FAIR principles (in particular machine-actionable) and provide information at least about the following: datasets (description, date of deposit, author(s), venue and embargo); Horizon Europe or Euratom funding; grant project name, acronym and number; licensing terms; persistent identifiers for the dataset, the authors involved in the action, and, if possible, for their organisations and the grant. Where applicable, the metadata must include persistent identifiers for related publications and other research outputs.

Open science: additional practices

Where the call conditions impose additional obligations regarding open science practices, the beneficiaries must also comply with those.

Where the call conditions impose additional obligations regarding the validation of scientific publications, the beneficiaries must provide (digital or physical) access to data or other results needed for validation of the conclusions of scientific publications, to the extent that their legitimate interests or constraints are safeguarded (and unless they already provided the (open) access at publication).

Where the call conditions impose additional open science obligations in case of a public emergency, the beneficiaries must (if requested by the granting authority) immediately deposit any research output in a repository and provide open access to it under a CC BY licence, a Public Domain Dedication (CC 0) or equivalent. As an exception, if the access would be against the beneficiaries' legitimate interests, the beneficiaries must grant non-exclusive licenses — under fair and reasonable conditions — to legal entities that need the research output to address the public emergency and commit to rapidly and broadly exploit the resulting products and services at fair and reasonable conditions. This provision applies up to four years after the end of the action (see Data Sheet, Point 1).

Plan for the exploitation and dissemination of results including communication activities

Unless excluded by the call conditions, the beneficiaries must provide and regularly update a plan for the exploitation and dissemination of results including communication activities.

SPECIFIC RULES FOR CARRYING OUT THE ACTION (— ARTICLE 18)

Implementation in case of restrictions due to strategic assets, interests, autonomy or security of the EU and its Member States

Where the call conditions restrict participation or control due to strategic assets, interests, autonomy or security, the beneficiaries must ensure that none of the entities that participate as affiliated entities, associated partners, subcontractors or recipients of financial support to third parties are established in countries which are not eligible countries or target countries set out in the call conditions (or, if applicable, are controlled by such countries or entities from such countries) — unless otherwise agreed with the granting authority.

The beneficiaries must moreover ensure that any cooperation with entities established in countries which are not eligible countries or target countries set out in the call conditions (or, if applicable, are controlled by such countries or entities from such countries) does not affect the strategic assets, interests, autonomy or security of the EU and its Member States.

Recruitment and working conditions for researchers

The beneficiaries must take all measures to implement the principles set out in the Commission Recommendation on the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers[3], in particular regarding:

- working conditions
- transparent recruitment processes based on merit, and
- career development.

The beneficiaries must ensure that researchers and all participants involved in the action are aware of them.

Specific rules for access to research infrastructure activities

Definitions

Research Infrastructures — Facilities that provide resources and services for the research communities to conduct research and foster innovation in their fields. This definition includes the associated human resources, and it covers major equipment or sets of instruments; knowledge-related facilities such as collections, archives or scientific data infrastructures; computing systems, communication networks, and any other infrastructure, of a unique nature and open to external users, essential to achieve excellence in research and innovation. Where relevant, they may be used beyond research, for example

[3] Commission Recommendation 2005/251/EC of 11 March 2005 on the European Charter for Researchers and on a Code of Conduct for the Recruitment of Researchers (OJ L 75, 22.3.2005, p. 67).

for education or public services, and they may be 'single-sited', 'virtual' or 'distributed'[4]:

When implementing access to research infrastructure activities, the beneficiaries must respect the following conditions:

- for transnational access:
  - access which must be provided:

    The access must be free of charge, transnational access to research infrastructure or installations for selected user-groups.

    The access must include the logistical, technological and scientific support and the specific training that is usually provided to external researchers using the infrastructure. Transnational access can be either in person (hands-on), provided to selected users that visit the installation to make use of it, or remote, through the provision to selected user-groups of remote scientific services (e.g. provision of reference materials or samples, remote access to a high-performance computing facility).

  - categories of users that may have access:

    Transnational access must be provided to selected user-groups, i.e. teams of one or more researchers (users).

    The majority of the users must work in a country other than the country(ies) where the installation is located (unless access is provided by an international organisation, the Joint Research Centre (JRC), an ERIC or similar legal entity).

    Only user groups that are allowed to disseminate the results they have generated under the action may benefit from the access (unless the users are working for SMEs).

    Access for user groups with a majority of users not working in a EU Member State or Horizon Europe associated country is limited to 20% of the total amount of units of access provided under the grant (unless a higher percentage is foreseen in Annex 1).

  - procedure and criteria for selecting user groups:

    The user groups must request access by submitting (in writing) a description of the work that they wish to carry out and the names, nationalities and home institutions of the users.

    The user groups must be selected by (one or more) selection panels set up by the consortium.

[4] See Article 2(1) of the Horizon Europe Framework Programme Regulation 2021/695.

The selection panels must be composed of international experts in the field, at least half of them independent from the consortium (unless otherwise specified in Annex 1).

The selection panels must assess all proposals received and recommend a short-list of the user groups that should benefit from access.

The selection panels must base their selection on scientific merit, taking into account that priority should be given to user groups composed of users who:

- have not previously used the installation and
- are working in countries where no equivalent research infrastructure exist.

It will apply the principles of transparency, fairness and impartiality.

Where the call conditions impose additional rules for the selection of user groups, the beneficiaries must also comply with those.

- other conditions:

The beneficiaries must request written approval from the granting authority for the selection of user groups requiring visits to the installations exceeding 3 months (unless such visits are foreseen in Annex 1).

In addition, the beneficiaries must:

- advertise widely, including on a their websites, the access offered under the Agreement
- promote equal opportunities in advertising the access and take into account the gender dimension when defining the support provided to users
- ensure that users comply with the terms and conditions of the Agreement
- ensure that its obligations under Articles 12, 13, 17 and 33 also apply to the users
- keep records of the names, nationalities, and home institutions of users, as well as the nature and quantity of access provided to them

- for virtual access:

  - access which must be provided:

The access must be free of charge, virtual access to research infrastructure or installations.

'Virtual access' means open and free access through communication networks to digital resources and services needed for research, without selecting the users to whom access is provided.

The access must include the support that is usually provided to external users.

Where allowed by the call conditions, beneficiaries may in justified cases define objective eligibility criteria (e.g. affiliation to a research or academic institution) for specific users.

- other conditions:

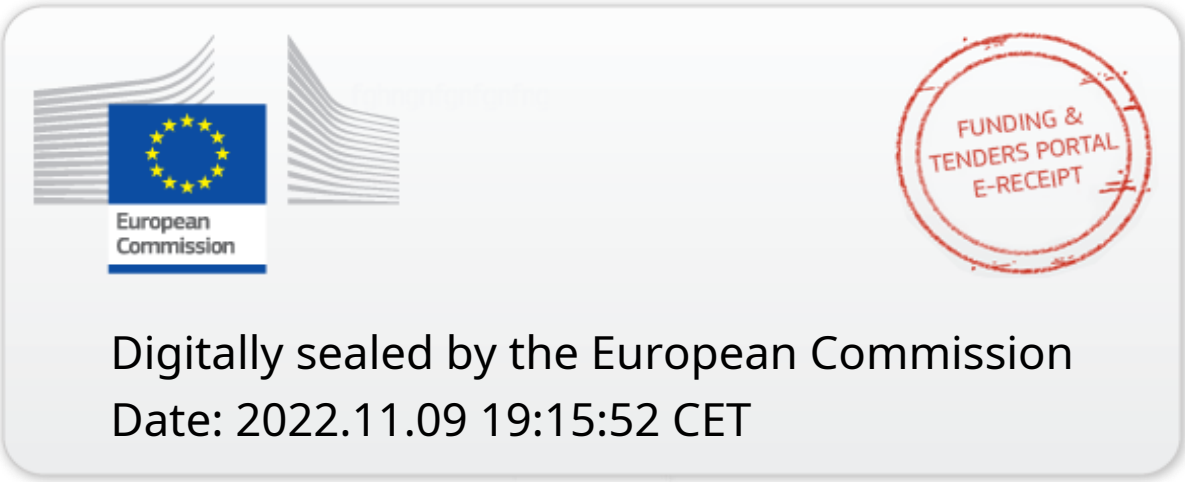
  The beneficiaries must have the virtual access services assessed periodically by a board composed of international experts in the field, at least half of whom must be independent from the consortium (unless otherwise specified in Annex 1). For this purpose, information and statistics on the users and the nature and quantity of the access provided, must be made available to the board.

  The beneficiaries must advertise widely, including on a dedicated website, the access offered under the grant and the eligibility criteria, if any.

  Where the call conditions impose additional traceability[5] obligations, information on the traceability of the users and the nature and quantity of access must be provided by the beneficiaries.

These obligations apply regardless of the form of funding or budget categories used to declare the costs (unit costs or actual costs or a combination of the two).

[5] According to the definition given in ISO 9000, i.e.: "Traceability is the ability to trace the history, application, use and location of an item or its characteristics through recorded identification data." The users can be traced, for example, by authentication and/or by authorization or by other means that allows for analysis of the type of users and the nature and quantity of access provided.



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