EUROPEAN HEALTH AND DIGITAL EXECUTIVE AGENCY (HADEA)

HADEA.A – Health and Food

**A.3 – Health research**

## GRANT AGREEMENT Project 101080251 — TRUSTING

## 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,**

### ‘the coordinator’:

**ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG)**, PIC 999914801, established in HANZEPLEIN 1, GRONINGEN 9713 GZ, Netherlands,

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

1. **UNIVERSIDAD POMPEU FABRA (UPF)**, PIC 999867077, established in PLACA DE LA MERCE, 10-12, BARCELONA 08002, Spain,
2. **UNIVERSITETET I TROMSOE - NORGES ARKTISKE UNIVERSITET (UiT)**, PIC 999874643, established in HANSINE HANSENS VEG 14, TROMSO 9019, Norway,
3. **IZMIR DE DOKUZ EYLUL UNIVERSITESI\*DOKUZ EYLUL UNIVERSITY OF IZMIR UNIVERSITE DOKUZ EYLUL D'IZMIR FACULTY OF LAW DEU HUKUK FAKULTESI DEKANLIG (DEU)**, PIC 999871636, established in CUMHURIYET BULVARI 144, ALSANCAK IZMIR 35210, Turkiye,
4. **NARODNI USTAV DUSEVNIHO ZDRAVI (NIMH)**, PIC 999462684, established in TOPOLOVA 748, KLECANY 250 67, Czechia,
5. **GLOBAL ALLIANCE OF MENTAL ILLNESS ADVOCACY NETWORKS EUROPE AISBL (GAMIAN)**, PIC 951109251, established in RUE DU TRONE 60, BRUXELLES 1050, Belgium,
6. **ASSOCIATION EUROPEENNE DE PSYCHIATRIE (EPA)**, PIC 918282705, established in AVENUE DE LA LIBERTE 15, STRASBOURG 67000, France,
7. **SYREON KUTATO INTEZET KORLATOLT FELELOSSEGU TARSASAG (SRI)**, PIC 952715183, established in MEXIKOI UT 65/A, BUDAPEST 1142, Hungary,
8. **ROYAL COLLEGE OF SURGEONS IN IRELAND (RCSI)**, PIC 999867368, established in ST STEPHEN'S GREEN 123, DUBLIN 2, Ireland,

### 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 action1 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](https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/how-to-participate/reference-documents). 2 Template published on [Portal Reference Documents](https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/how-to-participate/reference-documents). 3 Template published on [Portal Reference Documents](https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/how-to-participate/reference-documents).

## TERMS AND CONDITIONS

**TABLE OF CONTENTS**

[GRANT AGREEMENT 1](#_bookmark0)

[PREAMBLE 1](#_bookmark1)

[TERMS AND CONDITIONS 3](#_bookmark0)

[DATASHEET 8](#_bookmark0)

[CHAPTER 1 GENERAL 13](#_bookmark2)

[ARTICLE 1 — SUBJECT OF THE AGREEMENT 13](#_bookmark3)

[ARTICLE 2 — DEFINITIONS 13](#_bookmark4)

[CHAPTER 2 ACTION 14](#_bookmark5)

[ARTICLE 3 — ACTION 14](#_bookmark6)

[ARTICLE 4 — DURATION AND STARTING DATE 14](#_bookmark7)

[CHAPTER 3 GRANT 14](#_bookmark8)

[ARTICLE 5 — GRANT 14](#_bookmark9)

* 1. [Form of grant 14](#_bookmark10)
  2. [Maximum grant amount 15](#_bookmark11)
  3. [Funding rate 15](#_bookmark12)
  4. [Estimated budget, budget categories and forms of funding 15](#_bookmark13)
  5. [Budget flexibility 15](#_bookmark14)

[ARTICLE 6 — ELIGIBLE AND INELIGIBLE COSTS AND CONTRIBUTIONS 16](#_bookmark0)

* 1. [General eligibility conditions 16](#_bookmark15)
  2. [Specific eligibility conditions for each budget category 17](#_bookmark16)
  3. [Ineligible costs and contributions 21](#_bookmark17)
  4. [Consequences of non-compliance 22](#_bookmark18)

[CHAPTER 4 GRANT IMPLEMENTATION 23](#_bookmark0)

[SECTION 1 CONSORTIUM: BENEFICIARIES, AFFILIATED ENTITIES AND OTHER PARTICIPANTS 23](#_bookmark19)

[ARTICLE 7 — BENEFICIARIES 23](#_bookmark20)

[ARTICLE 8 — AFFILIATED ENTITIES 25](#_bookmark21)

[ARTICLE 9 — OTHER PARTICIPANTS INVOLVED IN THE ACTION 25](#_bookmark22)

* 1. [Associated partners 25](#_bookmark23)
  2. [Third parties giving in-kind contributions to the action 26](#_bookmark24)
  3. [Subcontractors 26](#_bookmark25)
  4. [Recipients of financial support to third parties 26](#_bookmark26)

[ARTICLE 10 — PARTICIPANTS WITH SPECIAL STATUS 27](#_bookmark0)

* 1. [Non-EU participants 27](#_bookmark27)
  2. [Participants which are international organisations 27](#_bookmark28)
  3. [Pillar-assessed participants 27](#_bookmark29)

[SECTION 2 RULES FOR CARRYING OUT THE ACTION 30](#_bookmark30)

[ARTICLE 11 — PROPER IMPLEMENTATION OF THE ACTION 30](#_bookmark31)

* 1. [Obligation to properly implement the action 30](#_bookmark32)
  2. [Consequences of non-compliance 30](#_bookmark33)

[ARTICLE 12 — CONFLICT OF INTERESTS 30](#_bookmark34)

* 1. [Conflict of interests 30](#_bookmark35)
  2. [Consequences of non-compliance 30](#_bookmark36)

[ARTICLE 13 — CONFIDENTIALITY AND SECURITY 30](#_bookmark37)

* 1. [Sensitive information 30](#_bookmark38)
  2. [Classified information 31](#_bookmark39)
  3. [Consequences of non-compliance 32](#_bookmark27)

[ARTICLE 14 — ETHICS AND VALUES 32](#_bookmark40)

* 1. [Ethics 32](#_bookmark41)
  2. [Values 32](#_bookmark42)
  3. [Consequences of non-compliance 32](#_bookmark43)

[ARTICLE 15 — DATA PROTECTION 32](#_bookmark44)

* 1. [Data processing by the granting authority 32](#_bookmark45)
  2. [Data processing by the beneficiaries 32](#_bookmark46)
  3. [Consequences of non-compliance 33](#_bookmark47)

[ARTICLE 16 — INTELLECTUAL PROPERTY RIGHTS (IPR) — BACKGROUND AND RESULTS —](#_bookmark48) [ACCESS RIGHTS AND RIGHTS OF USE 33](#_bookmark48)

* 1. [Background and access rights to background 33](#_bookmark49)
  2. [Ownership of results 34](#_bookmark50)
  3. [Rights of use of the granting authority on materials, documents and information received for policy, information, communication, dissemination and publicity purposes 34](#_bookmark31)
  4. [Specific rules on IPR, results and background 35](#_bookmark51)
  5. [Consequences of non-compliance 35](#_bookmark52)

[ARTICLE 17 — COMMUNICATION, DISSEMINATION AND VISIBILITY 35](#_bookmark53)

* 1. [Communication — Dissemination — Promoting the action 35](#_bookmark54)
  2. [Visibility — European flag and funding statement 35](#_bookmark55)
  3. [Quality of information — Disclaimer 36](#_bookmark56)
  4. [Specific communication, dissemination and visibility rules 36](#_bookmark57)
  5. [Consequences of non-compliance 36](#_bookmark58)

[ARTICLE 18 — SPECIFIC RULES FOR CARRYING OUT THE ACTION 36](#_bookmark59)

* 1. [Specific rules for carrying out the action 37](#_bookmark0)
  2. [Consequences of non-compliance 37](#_bookmark60)

[SECTION 3 GRANT ADMINISTRATION 37](#_bookmark61)

[ARTICLE 19 — GENERAL INFORMATION OBLIGATIONS 37](#_bookmark62)

* 1. [Information requests 37](#_bookmark63)
  2. [Participant Register data updates 37](#_bookmark64)
  3. [Information about events and circumstances which impact the action 37](#_bookmark65)
  4. [Consequences of non-compliance 37](#_bookmark66)

[ARTICLE 20 — RECORD-KEEPING 38](#_bookmark67)

* 1. [Keeping records and supporting documents 38](#_bookmark68)
  2. [Consequences of non-compliance 39](#_bookmark69)

[ARTICLE 21 — REPORTING 39](#_bookmark70)

* 1. [Continuous reporting 39](#_bookmark71)
  2. [Periodic reporting: Technical reports and financial statements 39](#_bookmark72)
  3. [Currency for financial statements and conversion into euros 40](#_bookmark73)
  4. [Reporting language 40](#_bookmark74)
  5. [Consequences of non-compliance 41](#_bookmark0)

[ARTICLE 22 — PAYMENTS AND RECOVERIES — CALCULATION OF AMOUNTS DUE 41](#_bookmark75)

* 1. [Payments and payment arrangements 41](#_bookmark76)
  2. [Recoveries 41](#_bookmark77)
  3. [Amounts due 41](#_bookmark78)
  4. [Enforced recovery 47](#_bookmark79)
  5. [Consequences of non-compliance 48](#_bookmark80)

[ARTICLE 23 — GUARANTEES 49](#_bookmark81)

[ARTICLE 24 — CERTIFICATES 49](#_bookmark82)

* 1. [Operational verification report (OVR) 49](#_bookmark83)
  2. [Certificate on the financial statements (CFS) 49](#_bookmark84)
  3. [Certificate on the compliance of usual cost accounting practices (CoMUC) 49](#_bookmark85)
  4. [Systems and process audit (SPA) 49](#_bookmark86)
  5. [Consequences of non-compliance 50](#_bookmark87)

[ARTICLE 25 — CHECKS, REVIEWS, AUDITS AND INVESTIGATIONS — EXTENSION OF](#_bookmark88) [FINDINGS 50](#_bookmark88)

* 1. [Granting authority checks, reviews and audits 50](#_bookmark89)
  2. [European Commission checks, reviews and audits in grants of other granting authorities 52](#_bookmark90)
  3. [Access to records for assessing simplified forms of funding 52](#_bookmark91)
  4. [OLAF, EPPO and ECA audits and investigations 52](#_bookmark92)
  5. [Consequences of checks, reviews, audits and investigations — Extension of results of reviews, audits or investigations 52](#_bookmark93)
  6. [Consequences of non-compliance 54](#_bookmark94)

[ARTICLE 26 — IMPACT EVALUATIONS 54](#_bookmark95)

* 1. [Impact evaluation 54](#_bookmark96)
  2. [Consequences of non-compliance 54](#_bookmark97)

[CHAPTER 5 CONSEQUENCES OF NON-COMPLIANCE 54](#_bookmark98)

[SECTION 1 REJECTIONS AND GRANT REDUCTION 54](#_bookmark99)

[ARTICLE 27 — REJECTION OF COSTS AND CONTRIBUTIONS 54](#_bookmark100)

* 1. [Conditions 54](#_bookmark101)
  2. [Procedure 55](#_bookmark15)
  3. [Effects 55](#_bookmark102)

[ARTICLE 28 — GRANT REDUCTION 55](#_bookmark103)

* 1. [Conditions 55](#_bookmark104)
  2. [Procedure 55](#_bookmark105)
  3. [Effects 56](#_bookmark106)

[SECTION 2 SUSPENSION AND TERMINATION 56](#_bookmark107)

[ARTICLE 29 — PAYMENT DEADLINE SUSPENSION 56](#_bookmark108)

* 1. [Conditions 56](#_bookmark109)
  2. [Procedure 56](#_bookmark110)

[ARTICLE 30 — PAYMENT SUSPENSION 56](#_bookmark111)

* 1. [Conditions 56](#_bookmark112)
  2. [Procedure 57](#_bookmark113)

[ARTICLE 31 — GRANT AGREEMENT SUSPENSION 57](#_bookmark114)

* 1. [Consortium-requested GA suspension 57](#_bookmark115)
  2. [EU-initiated GA suspension 58](#_bookmark116)

[ARTICLE 32 — GRANT AGREEMENT OR BENEFICIARY TERMINATION 59](#_bookmark117)

* 1. [Consortium-requested GA termination 59](#_bookmark118)
  2. [Consortium-requested beneficiary termination 60](#_bookmark119)
  3. [EU-initiated GA or beneficiary termination 61](#_bookmark120)

[SECTION 3 OTHER CONSEQUENCES: DAMAGES AND ADMINISTRATIVE SANCTIONS 65](#_bookmark121)

[ARTICLE 33 — DAMAGES 65](#_bookmark12)

* 1. [Liability of the granting authority 65](#_bookmark122)
  2. [Liability of the beneficiaries 65](#_bookmark33)

[ARTICLE 34 — ADMINISTRATIVE SANCTIONS AND OTHER MEASURES 65](#_bookmark123)

[SECTION 4 FORCE MAJEURE 65](#_bookmark124)

[ARTICLE 35 — FORCE MAJEURE 65](#_bookmark125)

[CHAPTER 6 FINAL PROVISIONS 66](#_bookmark126)

[ARTICLE 36 — COMMUNICATION BETWEEN THE PARTIES 66](#_bookmark127)

* 1. [Forms and means of communication — Electronic management 66](#_bookmark42)
  2. [Date of communication 66](#_bookmark128)
  3. [Addresses for communication 67](#_bookmark50)

[ARTICLE 37 — INTERPRETATION OF THE AGREEMENT 67](#_bookmark129)

[ARTICLE 38 — CALCULATION OF PERIODS AND DEADLINES 67](#_bookmark130)

[ARTICLE 39 — AMENDMENTS 67](#_bookmark131)

* 1. [Conditions 67](#_bookmark132)
  2. [Procedure 67](#_bookmark133)

[ARTICLE 40 — ACCESSION AND ADDITION OF NEW BENEFICIARIES 68](#_bookmark134)

* 1. [Accession of the beneficiaries mentioned in the Preamble 68](#_bookmark135)
  2. [Addition of new beneficiaries 68](#_bookmark136)

[ARTICLE 41 — TRANSFER OF THE AGREEMENT 68](#_bookmark137)

[ARTICLE 42 — ASSIGNMENTS OF CLAIMS FOR PAYMENT AGAINST THE GRANTING](#_bookmark138) [AUTHORITY 69](#_bookmark138)

[ARTICLE 43 — APPLICABLE LAW AND SETTLEMENT OF DISPUTES 69](#_bookmark139)

* 1. [Applicable law 69](#_bookmark140)
  2. [Dispute settlement 69](#_bookmark141)

[ARTICLE 44 — ENTRY INTO FORCE 70](#_bookmark142)

## DATA SHEET

**1.  General data**

Project summary:

Schizophrenia affects a staggering 21 million people worldwide, with 80% of these citizens suffering from a relapsing disease, putting their health and safety at enormous risk. Timely detection of these psychotic relapses would require very frequent contact with clinicians, which is neither desirable nor feasible. An accurate online relapse predictor could alert clinicians of subtle deterioration, which enables timely intervention and allow safe discontinuation of long-term medication, which so many affected citizens desire. Our Consortium demonstrated that subtle alterations in speech carry a predictive signal for psychosis onset. This project will develop an AI monitoring system that leverages spoken language processing (SLP) and natural language processing (NLP) of speech recorded at home to calculate the relapse risk. The monitoring tool we develop will be validated retrospectively in a longitudinal cohort, cross-sectionally, across six languages, after which it will be tested prospectively in a multicenter randomized trial, with the end goal of improving functional and clinical outcomes of those affected by schizophrenia. Developing such a system for exceptionally vulnerable people requires ‘buy-in’ from clinicians and mental health care service users, namely trust. A lack of trust is the biggest obstacle to the real-world implementation of a speech-based monitoring system. TRUSTING will develop a framework that systematically ensures addressing all the criteria for trustworthy AI put forward by the EU. This will ensure an empirically based and validated tool that can reliably detect pending relapse. As the core philosophy of trustworthiness is part of every aspect of the project, it will be a system more likely to be welcomed and embraced by service users and their carers. TRUSTING generates the scientific and social foundation for disruptive technology to deliver the unmet promise of an equitable and just form of healthcare for people at risk of relapse.

Project summary

Keywords:

* Psychology (including human - machine relations)
* Psychology, special (including therapy for learning, speech, hearing, visual and other physical and mental disabilities)
* Natural Language Processing, Spoken language processing, Speech, Psychosis, Schizophrenia, Relapse prevention, Human-in-the-loop, AI-tool, Online-monitoring

Project number: 101080251

Project name: A TRUSTworthy speech-based AI monitorING system for the prediction of relapse in individuals with schizophrenia

Project acronym: TRUSTING

Call: HORIZON-HLTH-2022-STAYHLTH-01-two-stage Topic: HORIZON-HLTH-2022-STAYHLTH-01-04-two-stage

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 July 2023

Project end date: 31 December 2028 Project duration: 66 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 | UMCG | ACADEMISCH ZIEKENHUIS GRONINGEN | NL | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 1.1 | AE | RBV | UMCG RESEARCH BV | NL | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 2 | BEN | UPF | UNIVERSIDAD POMPEU FABRA | ES | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 3 | BEN | UiT | UNIVERSITETET I TROMSOE - NORGES ARKTISKE UNIVERSITET | NO | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 4 | BEN | DEU | IZMIR DE DOKUZ EYLUL UNIVERSITESI\*DOKUZ EYLUL UNIVERSITY OF IZMIR UNIVERSITE DOKUZ EYLUL D'IZMIR FACULTY OF LAW DEU HUKUK FAKULTESI DEKANLIG | TR | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 5 | BEN | NIMH | NARODNI USTAV DUSEVNIHO ZDRAVI | CZ | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 6 | BEN | GAMIAN | GLOBAL ALLIANCE OF MENTAL ILLNESS ADVOCACY NETWORKS EUROPE AISBL | BE | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 7 | BEN | EPA | ASSOCIATION EUROPEENNE DE PSYCHIATRIE | FR | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 8 | BEN | SRI | SYREON KUTATO INTEZET KORLATOLT FELELOSSEGU TARSASAG | HU | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 9 | BEN | RCSI | ROYAL COLLEGE OF SURGEONS IN IRELAND | IE | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 10 | AP | UZH | UNIVERSITAT ZURICH | CH | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 11 | AP | UNIGE | UNIVERSITE DE GENEVE | CH | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 12 | AP | SUT | SWINBURNE UNIVERSITY OF TECHNOLOGY | AU | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **Total** | | | | | | **VYMAZÁNO** | **VYMAZÁNO** |

**Coordinator:**

* ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG)

**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)** |
| **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |

**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)
* 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)

1. **Reporting, payments and recoveries**
   1. **Continuous reporting** (art 21)

**Deliverables:** see Funding & Tenders Portal Continuous Reporting tool

* 1. **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 | Interim payment | 90 days from receiving periodic report |
| 3 | 37 | 54 | Periodic report | 60 days after end of reporting period | Interim payment | 90 days from receiving periodic report |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reporting** | | | | | **Payments** | |
| **Reporting periods** | | | **Type** | **Deadline** | **Type** | **Deadline (time to pay)** |
| **RP No** | **Month from** | **Month to** |  |  |  |  |
| 4 | 55 | 66 | 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) | 2 399 804.00 |

**Reporting and payment modalities** (art 21, 22): Mutual Insurance Mechanism (MIM): Yes

MIM contribution: 5% of the maximum grant amount (299 975.50), retained from the initial prefinancing

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

NL31INGB0652785212

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)

1. **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

**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)

## 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 2018/10464 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]:

1. 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)];
2. 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”.

### 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 2017/13715 and Article 1 of the Convention on the protection of the European Communities’ financial interests, drawn up by the Council Act of 26 July 19956, 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 2988/957.

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 **101080251** — **TRUSTING** (‘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

## Form of grant

The grant is an action grant8 which takes the form of a budget-based mixed actual cost grant (i.e. a

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).

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”.

### 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).

## Maximum grant amount

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

## Funding rate

The funding rate for costs is 100% of the action’s eligible costs. Contributions are not subject to any funding rate.

## 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.

## 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
    - other changes require an amendment or simplified approval, if specifically provided for in Article 6.2
    - flexibility caps: not applicable.

9 See Article 125 EU Financial Regulation 2018/1046.

## 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.

## General eligibility conditions

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

### for actual costs:

* + - 1. they must be actually incurred by the beneficiary
      2. 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)
      3. they must be declared under one of the budget categories set out in Article 6.2 and Annex 2
      4. they must be incurred in connection with the action as described in Annex 1 and necessary for its implementation
      5. 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
      6. they must comply with the applicable national law on taxes, labour and social security and
      7. they must be reasonable, justified and must comply with the principle of sound financial management, in particular regarding economy and efficiency
    1. for unit costs or contributions (if any):
       1. they must be declared under one of the budget categories set out in Article 6.2 and Annex 2
       2. 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
       3. the number of units must be identifiable and verifiable, in particular supported by records and documentation (see Article 20)
    2. for flat-rate costs or contributions (if any):
       1. they must be declared under one of the budget categories set out in Article 6.2 and Annex 2
       2. 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)
    3. for lump sum costs or contributions (if any):
       1. they must be declared under one of the budget categories set out in Article 6.2 and Annex 2
       2. the work must be properly implemented by the beneficiary in accordance with Annex 1
       3. 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)
    4. for unit, flat-rate or lump sum costs or contributions according to usual cost accounting practices (if any):
       1. they must fulfil the general eligibility conditions for the type of cost concerned
       2. the cost accounting practices must be applied in a consistent manner, based on objective criteria, regardless of the source of funding
    5. 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’).

## Specific eligibility conditions for each budget category

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

**Direct costs**

**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- 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.
  1. 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:

### 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

* + 1. 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.

1. **4** The work of **SME owners** for the action (i.e. owners of beneficiaries that are small and medium- sized enterprises10 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.

1. **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 of the costs actually incurred, fulfil the general eligibility conditions and are awarded using the

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.

### 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’).

1. **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.

1. **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.

1. **Other cost categories**
2. **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**

1. **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

## Ineligible costs and contributions

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

* + 1. costs or contributions that do not comply with the conditions set out above (Article 6.1 and 6.2), in particular:
       1. costs related to return on capital and dividends paid by a beneficiary
       2. debt and debt service charges
       3. provisions for future losses or debts
       4. interest owed
       5. currency exchange losses
       6. bank costs charged by the beneficiary’s bank for transfers from the granting authority
       7. excessive or reckless expenditure
       8. deductible or refundable VAT (including VAT paid by public bodies acting as public authority)
       9. costs incurred or contributions for activities implemented during grant agreement suspension (see Article 31)
       10. in-kind contributions by third parties: not applicable
    2. 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:
       1. Synergy actions: not applicable
       2. if the action grant is combined with an operating grant11 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
    3. 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)
    4. costs or contributions (especially travel and subsistence) for staff or representatives of EU institutions, bodies or agencies
    5. other :
       1. country restrictions for eligible costs: not applicable
       2. costs or contributions declared specifically ineligible in the call conditions.

## 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”.

## 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:

### Each beneficiary must:

* + - 1. keep information stored in the Portal Participant Register up to date (see Article 19)
      2. 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)
      3. 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
      4. submit via the Portal data and information related to the participation of their affiliated entities.
    1. The coordinator must:
       1. monitor that the action is implemented properly (see Article 11)
       2. 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)
       3. 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.”

### 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

The following entities which are linked to a beneficiary will participate in the action as ‘affiliated entities’:

* **UMCG RESEARCH BV (RBV)**, PIC 902794618, linked to ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG)

### Affiliated entities can charge costs and contributions to the action under the same conditions as the beneficiaries and must implement the action tasks attributed to them in Annex 1 in accordance with Article 11.

Their costs and contributions will be included in Annex 2 and will be taken into account for the calculation of the grant.

The beneficiaries must ensure that all their obligations under this Agreement also apply to their affiliated entities.

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 affiliated entities.

Breaches by affiliated entities will be handled in the same manner as breaches by beneficiaries. Recovery of undue amounts will be handled through the beneficiaries.

If the granting authority requires joint and several liability of affiliated entities (see Data Sheet, Point 4.4), they must sign the declaration set out in Annex 3a and may be held liable in case of enforced recoveries against their beneficiaries (see Article 22.2 and 22.4).

## ARTICLE 9 — OTHER PARTICIPANTS INVOLVED IN THE ACTION

## Associated partners

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

* + - **UNIVERSITAT ZURICH (UZH)**, PIC 999976396
    - **UNIVERSITE DE GENEVE (UNIGE)**, PIC 999974650
    - **SWINBURNE UNIVERSITY OF TECHNOLOGY (SUT)**, PIC 949273235

### 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.

## 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

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

## 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/EC13
    - 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).

## Participants which are international organisations

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).

## 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.

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).

### ‘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:

* 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)
* 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

## 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.

## 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

## 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.

## 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

## 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:

* + 1. need to know it in order to implement the Agreement and
    2. 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:

1. this is necessary to implement the Agreement or safeguard the EU financial interests and
2. the recipients of the information are bound by an obligation of confidentiality. The confidentiality obligations no longer apply if:
3. the disclosing party agrees to release the other party
4. the information becomes publicly available, without breaching any confidentiality obligation
5. 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.

## Classified information

The parties must handle classified information in accordance with the applicable EU, international or national law on classified information (in particular, Decision 2015/44414 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.

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).

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

## 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.

## 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 15 — DATA PROTECTION

## 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 2018/172515.

## Data processing by the beneficiaries

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).

### 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 2016/67916).

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.

## 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

## 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:

* + 1. held by the beneficiaries before they acceded to the Agreement and
    2. needed to implement the action or exploit the results.

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).

### 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.

## 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.

## 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:

* + 1. **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)
    2. **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 by any channel, public display or presentation, communicating through press information services, or inclusion in widely accessible databases or indexes)
    3. **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)
    4. **translation**
    5. **storage** in paper, electronic or other form
    6. **archiving**, in line with applicable document-management rules
    7. 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
    8. **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.”

## Specific rules on IPR, results and background

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

## 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.

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

## 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.

## Quality of information — Disclaimer

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

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.”

## Specific communication, dissemination and visibility rules

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

## Specific rules for carrying out the action

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

## SECTION 3 GRANT ADMINISTRATION

## ARTICLE 19 — GENERAL INFORMATION OBLIGATIONS

## 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.

## 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.

## Information about events and circumstances which impact the action

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

* + 1. **events** which are likely to affect or delay the implementation of the action or affect the EU’s financial interests, in particular:
       1. 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)
       2. linked action information: not applicable
    2. **circumstances** affecting:

### the decision to award the grant or

* + - 1. compliance with requirements under the Agreement.

## 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

## 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:

* + 1. 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
    2. 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
    3. for the following simplified costs and contributions: the beneficiaries do not need to keep specific records on the actual costs incurred, but must keep:
       1. for unit costs and contributions (if any): adequate records and supporting documents to prove the number of units declared
       2. 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
       3. 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
    4. 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:

* + 1. 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
    2. 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.

## 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

## 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).

### 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.

## 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.

## 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.

## 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).

## 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.

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).

* 1. **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).

* + 1. **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 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.

* + 1. **Interim payments**

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).

* + 1. **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: 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, 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:

1. 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

1. 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.

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.

* + 1. **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.

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.

## Enforced recovery

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

1. 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.

1. financial guarantee(s): not applicable
2. joint and several liability of beneficiaries: not applicable
3. by holding affiliated entities jointly and severally liable (if any, see Data Sheet, Point 4.4)
4. 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 2015/236617 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).

## Consequences of non-compliance

* + 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.

* + 1. If the coordinator breaches any of its obligations under this Article, the grant may be reduced (see Article 28) and the grant or the coordinator may be terminated (see Article 32).

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).

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

## ARTICLE 23 — GUARANTEES

Not applicable

## ARTICLE 24 — CERTIFICATES

## Operational verification report (OVR)

Not applicable

## 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:

* + 1. be provided by a qualified approved external auditor which is independent and complies with Directive 2006/43/EC18 (or for public bodies: by a competent independent public officer)
    2. 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).

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

Not applicable

## Systems and process audit (SPA)

Beneficiaries which:

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).

### 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).

## 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

* 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.

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.

## 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.

## 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.

## OLAF, EPPO and ECA audits and investigations

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

* + - the European Anti-Fraud Office (OLAF) under Regulations No 883/201319 and No 2185/9620
    - 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.

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

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 2185/96 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).

## 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.

* + 1. **Extension from other grants**

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

* + - 1. 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
      2. 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:

### an invitation to submit observations on the list of grants affected by the findings

1. the request to submit revised financial statements for all grants affected
2. 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:
   1. considers that the submission of revised financial statements is not possible or practicable or
   2. does not submit revised financial statements.

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

### an invitation to submit observations on the list of grants affected by the findings and

1. 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).

## 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

## 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 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.

## 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.

## 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

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

* + 1. 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:
       1. substantial errors, irregularities or fraud or
       2. 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
    2. 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.

## 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:

* + 1. the required report (see Article 21) has not been submitted or is not complete or additional information is needed
    2. there are doubts about the amount to be paid (e.g. ongoing audit extension procedure, queries about eligibility, need for a grant reduction, etc.) and additional checks, reviews, audits or investigations are necessary, or
    3. there are other issues affecting the EU financial interests.

## 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:

* + 1. 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:
       1. substantial errors, irregularities or fraud or
       2. 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
    2. 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.

## Procedure

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

* 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.

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).

* 1. **EU-initiated GA suspension 31.2.1 Conditions**

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

* + 1. 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:
       1. substantial errors, irregularities or fraud or
       2. 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
    2. 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
    3. other:
       1. linked action issues: not applicable
       2. 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

* + 1. **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 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

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

* 1. **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:

1. a **report on the distribution of payments** to the beneficiary concerned

### 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)

1. 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).

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.

* 1. **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:

1. one or more beneficiaries do not accede to the Agreement (see Article 40)
2. 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)
3. 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
4. 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
5. 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.)
6. a beneficiary (or person with unlimited liability for its debts) is in breach of social security or tax obligations
7. 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
8. 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
9. 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)
10. a beneficiary (or person having powers of representation, decision-making or control, or person essential for the award/implementation of the grant) has committed:
    1. substantial errors, irregularities or fraud or
    2. 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.)
11. 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)
12. 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
13. other:
    1. linked action issues: not applicable
    2. 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
       1. **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:

* + - * 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**

1. 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.

1. for **beneficiary termination**:

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

* 1. a **report on the distribution of payments** to the beneficiary concerned

### 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)

* 1. 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

## 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.

## 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 2988/9521).

## 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,

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).

### 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

## Forms and means of communication — Electronic management

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.

## 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.

## 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.

## ARTICLE 38 — CALCULATION OF PERIODS AND DEADLINES

In accordance with Regulation No 1182/7122, 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).

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).

### 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.

## ARTICLE 40 — ACCESSION AND ADDITION OF NEW BENEFICIARIES

## 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).

## 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 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

## 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).

## 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.

SIGNATURES

For the coordinator For the granting authority

**VYMAZÁNO** **VYMAZÁNO**

Associated with document Ref. Ares(2023)2437294 - 04/04/2023



**ANNEX 1**



**Horizon Europe (HORIZON) Description of the action (DoA)**

**Part A Part B**

**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:** | 101080251 |
| **Project name:** | A TRUSTworthy speech-based AI monitorING system for the prediction of relapse in individuals with schizophrenia |
| **Project acronym:** | TRUSTING |
| **Call:** | HORIZON-HLTH-2022-STAYHLTH-01-two-stage |
| **Topic:** | HORIZON-HLTH-2022-STAYHLTH-01-04-two-stage |
| **Type of action:** | HORIZON-RIA |
| **Service:** | HADEA/A/03 |
| **Project starting date:** | fixed date: 1 July 2023 |
| **Project duration:** | 66 months |

# TABLE OF CONTENTS

[Project summary 3](#_bookmark0)

[List of participants 3](#_bookmark143)

[List of work packages 5](#_bookmark144)

[Staff effort 16](#_bookmark144)

[List of deliverables 17](#_bookmark144)

[List of milestones (outputs/outcomes) 29](#_bookmark144)

[List of critical risks 30](#_bookmark145)

[Project reviews 33](#_bookmark144)

**PROJECT SUMMARY**

Schizophrenia affects a staggering 21 million people worldwide, with 80% of these citizens suffering from a relapsing disease, putting their health and safety at enormous risk. Timely detection of these psychotic relapses would require very frequent contact with clinicians, which is neither desirable nor feasible. An accurate online relapse predictor could alert clinicians of subtle deterioration, which enables timely intervention and allow safe discontinuation of long-term medication, which so many affected citizens desire. Our Consortium demonstrated that subtle alterations in speech carry a predictive signal for psychosis onset. This project will develop an AI monitoring system that leverages spoken language processing (SLP) and natural language processing (NLP) of speech recorded at home to calculate the relapse risk. The monitoring tool we develop will be validated retrospectively in a longitudinal cohort, cross-sectionally, across six languages, after which it will be tested prospectively in a multicenter randomized trial, with the end goal of improving functional and clinical outcomes of those affected by schizophrenia. Developing such a system for exceptionally vulnerable people requires ‘buy-in’ from clinicians and mental health care service users, namely trust. A lack of trust is the biggest obstacle to the real-world implementation of a speech-based monitoring system. TRUSTING will develop a framework that systematically ensures addressing all the criteria for trustworthy AI put forward by the EU. This will ensure an empirically based and validated tool that can reliably detect pending relapse. As the core philosophy of trustworthiness is part of every aspect of the project, it will be a system more likely to be welcomed and embraced by service users and their carers. TRUSTING generates the scientific and social foundation for disruptive technology to deliver the unmet promise of an equitable and just form of healthcare for people at risk of relapse.

**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.*

**LIST OF PARTICIPANTS**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **PARTICIPANTS**  *Grant Preparation (Beneficiaries screen) — Enter the info.* | | | | | |
| **Number** | **Role** | **Short name** | **Legal name** | **Country** | **PIC** |
| 1 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 1.1 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 2 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 3 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 4 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 5 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 6 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 7 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |

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| --- | --- | --- | --- | --- | --- |
| **PARTICIPANTS**  *Grant Preparation (Beneficiaries screen) — Enter the info.* | | | | | |
| **Number** | **Role** | **Short name** | **Legal name** | **Country** | **PIC** |
| 8 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 9 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 10 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 11 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| 12 | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |

**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 | Develop speech-based prediction model: psychotic relapse prediction with SLP/NLP | 1 - UMCG | 56.60 | 1 | 36 | D1.1 – Top predicting classifier D1.2 – Validation in separate dataset D1.3 – Test-retest reliability  D1.4 – Sensitivity analyses D1.5 – Medication  D1.6 – Model enhancement |
| WP2 | Validation of an SLP/NLP-based psychosis classifier across languages, tasks and sociodemographic groups | 2 - UPF | 70.60 | 4 | 36 | D2.1 – Generalizability report D2.2 – Validation report  D2.3 – Report on construct validity |
| WP3 | Creating a trustworthy AI monitoring system based on the speech biomarker | 3 - UiT | 137.14 | 1 | 66 | D3.1 – User-needs assessment results D3.2 – e-health course  D3.3 – Alpha AI tool version D3.4 – Beta AI tool version  D3.5 – Technical service for the AI tool D3.6 – Technical service for the AI tool final |
| WP4 | Clinical application: Testing the efficacy of the TRUSTING AI monitoring system for psychosis relapse prevention in a randomized clinical trial | 10 - UZH | 569.40 | 13 | 66 | D4.1 – Study initiation package D4.2 – Midterm recruiting report  D4.3 – Report on the status of posting results  D4.4 – Report on relapse rates D4.5 – Report on trustworthiness |
| WP5 | Health economic evaluation | 8 - SRI | 50.00 | 1 | 66 | D5.1 – Health economic model D5.2 – Net Present Value model |

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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** |
| WP6 | Dissemination, Communication, and Exploitation Activities | 6 - GAMIAN | 38.45 | 1 | 66 | D6.1 – DEC plan  D6.2 – DEC Plan report D6.3 – IP Update  D6.4 – Website |
| WP7 | Project Management | 1 - UMCG | 75.85 | 1 | 66 | D7.1 – Data Management Plan D7.2 – Ethics plan  D7.3 – Data Management Plan report |
| WP8 | Ethics requirements | 1 - UMCG | 0.00 | 1 | 66 | D8.1 – NEC - POPD - AI - H - OEI -  Requirement No. 1  D8.2 – POPD - AI - NEC - H - OEI -  Requirement No. 2  D8.3 – POPD - H - OEI - NEC - AI -  Requirement No. 3  D8.4 – OEI - NEC - AI - POPD - H -  Requirement No. 4  D8.5 – H - AI - POPD - NEC - OEI -  Requirement No. 5 |

## Work package WP1 – Develop speech-based prediction model: psychotic relapse prediction with SLP/NLP

|  |  |  |  |
| --- | --- | --- | --- |
| **Work Package Number** | WP1 | **Lead Beneficiary** | 1. UMCG |
| **Work Package Name** | Develop speech-based prediction model: psychotic relapse prediction with SLP/NLP | | |
| **Start Month** | 1 | **End Month** | 36 |

Main objective: To create an accurate speech-based predictor for psychotic relapse. Associated subordinate objectives:

* 1. To create an accurate speech-based relapse predictor using an existing database.
  2. To establish generalizability of the relapse predictor in an independent sample of the same language.
  3. To establish test-retest reliability in people who had multiple relapses
  4. To adjust and improve accuracy of relapse prediction in both genders and in other sociodemographic subgroups
  5. To assess the impact of antipsychotic medication on speech-based features.
  6. To assess the predictive accuracy of the speech-based features when combined with clinical measures.

**Objectives**

**Description**

This study follows participants with a psychotic disorder over time, measuring speech at baseline, 3, 6, 12 and 24 months. At each visit, relapse was assessed retrospectively. Inclusion for this study is always during remission after a first psychotic episode. This means that the baseline recording will contain speech of the individual when he/she has no or only minimal psychotic symptoms. Comparing speech of each individual to his/her own speech during remission in a longitudinal analysis will help reduce heterogeneity and increase the power to detect deviations. We will use hidden Markov models41 to predict relapse within one month. The input for these Markov models will be provided by analysing the speech with SLP and NLP software, using acoustic, BERT models and graph-theoretical models respectively. The hidden Markov model will be trained on the Utrecht and validated in the Groningen dataset (now at 265 and 140 inclusions respectively).

Generalizability of the trained model will be validated in the Groningen database of this cohort. Using a separate testing and training set is considered the gold standard in ML, as it prevents overfitting.

Since HAMLETT has a long follow-up time, many participants have more than one relapse. SLP/NLP features that were able to predict a first relapse will be tested for accuracy to predict a second (or third etc) relapse.

Given gender differences in both psychotic relapse and speech, we intend to perform gender-specific sensitivity analyses. We will train separate classifiers for men and women from the Utrecht and Groningen database together. If overlap in best predicting features is less than 80%, we will decide to build gender-specific predicting models for WP4.

Sensitivity analyses will also be performed for the following subgroups: 1. Citizens who received less than 10 years of education, 2. Citizens with a migration background, 3. Citizens from different age groups. Accuracy of the model will be tested in these subgroups and if retrieved values are significantly lower than for majority groups, the model will be adjusted for these subgroups to provide adequate accuracy.

We expect that performance of the model can improve if clinical and demographic information of the participants is integrated in the model, as several factors are well-known to increase the risk for relapse. Largest impact on relapse was found for medication non-adherence, persistent substance use and poorer premorbid adjustment109, but we will also assess other demographic and clinical measures for their potential to increase accuracy of relapse prediction when combined with speech-based features. If the addition of such information can significantly enhance accuracy, we will also use this in the RCT of WP4.

## Work package WP2 – Validation of an SLP/NLP-based psychosis classifier across languages, tasks and sociodemographic groups

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| **Work Package Number** | WP2 | **Lead Beneficiary** | 2. UPF |
| **Work Package Name** | Validation of an SLP/NLP-based psychosis classifier across languages, tasks and sociodemographic groups | | |
| **Start Month** | 4 | **End Month** | 36 |

Main objective: To validate the classifiers of relapse from WP1 for forwarding to WPs 3 and 4. Specific objectives:

* 1. Data preparation of cross-sectional speech data.
  2. Replicate accuracy of the classifiers developed in WP1 for generalizability as a psychosis predictor in a cross- sectional setting of harmonized cross-linguistic data.
  3. Evaluate interpretability, explainability, methods-dependence, bias, sensitivity to subgroups, and construct validity of this classifier.
  4. Test performance of classifiers across different speech elicitation tasks.

**Objectives**

**Description**

Description of work:

Task 2.1: Prepare DISCOURSE data. Lead: UPF. Partners involved: 3. Month 1-12.

Curate, de-identify, and pre-process speech data from participating sites of the DISCOURSE consortium.

Task 2.2: Co-develop the classifiers developed in WP1 with the purpose of replication of accuracy and generalizability in a cross-sectional setting of harmonized cross-linguistic data. Partners involved: 1, 3. Lead: UPF. Month 4-24.

We will test the classifiers developed for the longitudinal data in WP1 in their function as a predictor of psychosis in a cross-sectional and cross-linguistic setting, based on data obtained with different speech elicitation tasks (picture description, open speech as per WP1 and story recall) from DISCOURSE (www.discourseinpsychosis.org). The specific purpose is to check generalizability across harmonized and independent data, with maximally similar methods (minimally adapting analysis tools such as parsers, insofar as they are language-specific), and across the different language available in DISCOURSE including Germanic (Dutch, English and German), Romance (French, Italian, Spanish), Slavic (Czech), and Turkic/Altaic (Turkish), while prioritizing the languages to be used in WP4.

Task 2.3: Evaluate interpretability, explainability, methods-dependence, bias, sensitivity to subgroups, and construct validity of this classifier. Lead: UPF. Partners involved: 1, 3. Month 7-24.

Following the generalization test, we will further scrutinize the model, exploring the effects of changes in parameter settings, pre-processing choices, algorithms, bias, subgroups, and feature selections across linguistic levels. This will involve contextualizing methods used for one speech/language domain, e.g. BERT in the case of semantics, against other word embedding methodologies such as LSA, GLoVE, and CoVec in conjunction with a range of currently available methods for embedding sentences, such as averaging the vectors of the content words in the sentence, using weighted averages (TF-IDF, SIF), or sent2vec. Such contextualization allows determining robustness of results against changes in methods and parameter settings, helping with interpretability. Construct validity will be checked by running regressions between linguistic variables and clinical symptom scores across samples, languages, and tasks. Explainability of the AI methodology will be evaluated by fitting specific language models to specific symptom profiles in a hypothesis-driven fashion, e.g. relating increase of semantic distances between subsequent utterances to loosening of associations or formal thought disorder as clinically evaluated. As a default, we will use random forests for classification, which is a robust classifier allowing to control for overfitting and suitable for relatively small datasets. Similarity analyses between the feature sets, and correlational analyses with clinical psychopathological measures, will also be run.

Task 2.4: Test performance of classifiers across different speech elicitation tasks. Lead: UPF. Partners involved: 1, 3,

4. Months 18-36

Performance in data from free speech (as used in WP1) will be contrasted with performance on a story recall task, as motivated by the good operationalizability of this task for purposes of WP3-4 and previous results on it by partner 3. In addition, for comparability to previous results, data for picture descriptions will be analysed as well.

## Work package WP3 – Creating a trustworthy AI monitoring system based on the speech biomarker

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| **Work Package Number** | WP3 | **Lead Beneficiary** | 3. UiT |
| **Work Package Name** | Creating a trustworthy AI monitoring system based on the speech biomarker | | |
| **Start Month** | 1 | **End Month** | 66 |

Main objective:

**Objectives**

* 1. To develop and implement a remote monitoring system that administers tasks and records speech.
  2. To develop an e-health course.
  3. To develop models of speech with appropriate thresholds for personalized use.
  4. To test the operational functioning of the speech-monitoring system in a sample of 240 participants over a period of 3.5 years.

**Description**

The goal of this WP is to create and operate a technical, legal and ethical information technology infrastructure that enables collection, processing and analysis of speech data across multiple continents, countries and languages. At all stages of this pipeline the data will be collected, processed and stored in a secure manner that conforms with all relevant national and international legislation, and in an ethical manner ensuring the highest level of privacy protection. Human oversight will be a core component of all stages and will be provided 24/7 during the entire RCT period.

Task 3.1 To develop and implement a remote monitoring system that administers tasks and records speech. Lead: UIT. Partners involved: 1, 2, 3, 4, 9 & 10. Month 1-24

A core technical, legal and ethical IT (data) computational and networking infrastructure necessary for the RCT in WP4 will be developed in Norway within the country’s most secure data repository and analysis environment (Services for Sensitive Data - TSD) at the University of Oslo. This infrastructure will enable the (i) secure recording of speech,

(ii) transfer of it automatically to TSD, and (iii) generation of feedback and alerts (of suspected psychosis relapse) for clinicians. Task 3.1 also includes extensive legislative and technical work to ensure compliance with prevailing data protection regulations across the participating countries and the diverse languages (further detail provided in the Clinical Studies annex). Upon this infrastructure, an online system will be developed that enables the remote collection, processing and analysis of speech data across multiple countries and in multiple languages. This will prompt participants to self-administer tasks which will require users to generate naturalistic speech. All partners will be able to securely access the data at TSD that they have permission to access. Access privileges (and their duration) will be determined by the consortium as a whole.

Three main technical considerations will be established in Task 3.1, namely the (i) usability engineering, (ii) data management platform and (iii) clinical interface with alert procedure. This will be achieved as follows: First a user needs assessment (in a broad range of user groups such as citizens with schizophrenia, their families and clinicians) will chart (by month 6) participants’ behaviour regarding online systems notably their tolerance (i.e., for task duration). The survey among citizens with schizophrenia will be performed by GAMIAN and the survey among clinicians performed by the EPA. This will assess current practices around relapse prediction and investigate which methods these stakeholders would, and would not, use so as to inform all aspects of design of WP3, and also provide the foundation for creating a document to educate and empower patients in using the speech-based tool (see Task 3.2 below). The resulting information from this will inform and constrain the subsequent development of the TRUSTING AI tool. Our usability engineering focus will be that the tasks and resulting software should be easy and pleasant to use such that it is acceptable to the participants, and that the data collection will be efficient and sufficiently constrained in how the tasks could be taken such that the data is comparable with in-person testing, and critically that the tool is considered cross-culturally acceptable and appropriate. Previous research54 has shown that participants generally prefer shorter testing sessions. Second, informed by this user needs assessment/survey, the system to collect speech data will be built using progressive web applications. Citizens with schizophrenia and clinicians (via GAMIAN and EPA) will co-design with the partners of this WP regarding all relevant issues such as elements of the task, user friendliness and alert messages. The actual design of the platform and interface for participants’ online interaction will be created according to best practices of usability engineering, with the added challenge of giving participants an enjoyable experience and nurturing retention which is critical to the success of the tool and the RCT. We will design a cross-platform interface accessible through both a web interface and a mobile application that administers a series of language-based interaction tasks (based upon our team’s previous work as well as the findings in the current project, notably from WPs1 and 2). A secure data management platform and infrastructure for confidential data storage, collaborator networking, and authentication of participant identity is essential for the multinational RCT. Concern about privacy issues is a major topic for potential end users of the proposed online service74. While there are mature frameworks for such data management already available, a tailored trustworthy solution for the current application in psychiatry is sorely needed. An effective infrastructure must be compliant under several different legal frameworks. A particular challenge with outpatient and longitudinal procedures is data integrity, namely that we can verify the participant identity over the entire course of the study. We will ensure the participant is the participant we assume they are by employing a combination of voice ID and/or strong authentication procedures that follow those that are the cultural and legal norm of the respective countries. When the (alpha) prototype has been developed (by month 12), it will be reviewed by both GAMIAN and EPA groups for acceptability and pilot tested by the GAMIAN testing panel. Modifications will be made accordingly before the final (beta) system is implemented (at month 24). Third, a pilot study will be conducted in a sample of healthy people in all the participating countries and languages (40 participants from each country). These results will inform the refining of the configuration of the analysis

environment and then the final beta version will be implemented by month 24 for the commencement of the RCT in WP4. This will build on the database from WP2 in terms of the differences in language and add more frequent datapoints than in WP1.

3.2 To develop an e-health course. Lead: UIT. Partner involved: 4, Month 1-12

Informed by the user-needs survey in Task 3.1, an educational course will be developed in all 6 languages. The purpose of this course is to educate, motivate and empower participants (and their families and caretakers/support systems) to ensure that they use the relapse predictor. This course will be developed in concert with the TRUSTING User Board and adapted for use across all testing sites. An important goal of this course is to educate participants about the interpretation of test results. The global population has during the COVID-19 pandemic received a “crash course” in issues around testing such as false alarms and their consequences. Even so, participants will be trained to understand the feedback given in WP4.

Task 3.3 To develop models of speech with appropriate thresholds for personalized use. Lead: UIT. Partners involved: 1, 2, 3, 4. Month 1-24

The goal is to leverage the findings from WP1 and WP2 but increase the scale of operation such that it will be possible to predict relapse from speech collected via the online system built in Task 3.1 that remotely administers questions that thereby generates naturalistic language interactions from individuals with psychosis in out-patient care. Relapse to psychosis will be predicted using the algorithm and features created in WP1 and WP2. Task 3.1 will evaluate the specificity and temporal value of the biomarker to ensure it provides critical information regarding what is about to happen (i.e., that it is relapse versus something else) and when this clinical event will happen (i.e., whether the risk of relapse will happen in a day, in a week or in a month. The clinical interface and alert procedure will be derived from findings from WP1 and WP2 such that feedback can be generated within a 48-hour time-frame. Where possible, the pipeline from task administration to data recording and analysis that generates a clinically actionable inference will be fully automated, specifically the generation of the index regarding risk of relapse.

Task 3.4 To test the operational functioning of the speech-monitoring system in a sample of 240 participants over a period of 3.5 years. Lead: UIT. Partners involved: All Partners. Month 24-66

24 months into the project the interface will be ready to be implemented for the full 3,5 years duration of the RCT (see WP4). Naturalistic speech data will be collected on a weekly basis over the course of one year per participant from the 240 outpatients participating in the RCT (WP4). A select number of language tasks (determined in WPs1 and 2) will be presented to participants orally via their chosen online platform, and they will be prompted to respond verbally to the cue. Their data will contribute to the development of a personalized model of their mental state, which thus will enable detection of a significant change in speech. ‘Significant’ will be established by comparing to traditional clinical ratings (administered by WP4), human ratings of the speech data that are generated, as well as the algorithms that have been developed and fine-tuned in WPs1 and 2. This WP3 will continue to monitor the system to ensure it is fully operationable for the full 3,5 years of the RCT. The ‘human in the loop’ and 'human on the loop' system will function throughout.

## Work package WP4 – Clinical application: Testing the efficacy of the TRUSTING AI monitoring system for psychosis relapse prevention in a randomized clinical trial

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| **Work Package Number** | WP4 | **Lead Beneficiary** | 10. UZH |
| **Work Package Name** | Clinical application: Testing the efficacy of the TRUSTING AI monitoring system for psychosis relapse prevention in a randomized clinical trial | | |
| **Start Month** | 13 | **End Month** | 66 |

Main objectives:

1. To produce a study initiation package 2. To produce a midterm report

1. To report on the on the status of posting results
2. To assess efficacy of the TRUSTING AI monitoring system in reducing psychotic relapse.
3. To evaluate trustworthiness and additional secondary outcomes of the TRUSTING AI monitoring system.

**Objectives**

Task 4.1 To produce a study initiation package. Lead: UZH. Partners involved 1, 2, 5, 6, 7, 8, 11, 12; month 13-24

**Description**

We will obtain a registration number of the clinical study by registering the study at clinicaltrials.gov and produce a final version of study protocol approved by the local ethics committees.

Task 4.2 To produce a midterm report. Lead: UZH. Partners involved 1, 2, 5, 6, 7, 8, 11, 12; month 13-40

This task involves compiling an overview of the number of recruited participants per partner center and document recruitment problems and measures to address delays. We will also compute an interim analysis of outcomes relevant for the health economic evaluation, including efficacy, quality of life and service use (WP5). These interim results will then feed into WP5.

Task 4.3 To report on the status of posting results. Lead: UZH. Partners involved 2; month 66

We will produce a summary report confirming that all results that have been obtained by the end of the study have also been posted to the clinical trials registry (clinical trials.gov).

Task 4.4 To assess efficacy of the TRUSTING AI monitoring system in reducing psychotic relapse. Lead: UZH. Partners involved 1, 2, 5, 6, 7, 8, 12; month 13-66

As per the power analysis described in the Clinical Annex, we computed a required sample size of N = 240, and will thus recruit citizens with schizophrenia at a state of acute psychosis (baseline) and aim to record their individual psychotic speech profiles whenever possible. Once they fulfil remission criteria110 we will record speech again, providing us with digital speech profiles of psychosis and remission for each individual participant (Figure 3.1b1). If speech during psychosis cannot be recorded the AI monitoring system will apply group-level priors for those individuals. Participants, informal caregivers and clinicians will make a personalized relapse-prevention plan, to be activated when imminent relapse is suspected, including a cut-off for the relapse risk (when a clinician will contact the participant for a shared decision appointment) and how to act in case of expected relapse. Participants will then be randomized to two different conditions for the 1-year follow up period: either standard relapse prevention plus speech recording alone (control condition) or standard relapse prevention plus AI speech monitoring (treatment condition). For both conditions, participants will be asked to record a weekly speech sample (speech elicitation task, e.g., recall of a short story) with an app developed in WP3. To be included in the trial participants will need to have access and be familiar with the use of a smartphone or a personal computer. The app will then be installed on what the participant is most familiar with, that is, either a smartphone or a personal computer. For the treatment condition, the speech sample will be analyzed with the AI monitoring system developed in WP3 and a result of this analysis will be sent to the clinician in charge, such that the message will provide the clinician with a relapse risk and confidence interval. When provided with the weekly relapse risk from the speech monitoring system, the clinician in charge will contact the patient whenever the relapse risk interval includes the cut-off estimate from the relapse prevention plan for a shared decision-making appointment. Together, they will then decide the best course of action according to the plan (e.g., watchful waiting, medication increase, rehospitalization etc.). The primary outcome measure is the days until relapse111. We hypothesize that relapses can be significantly reduced with standard relapse prevention plus AI speech monitoring compared to standard relapse prevention plus speech recordings alone during follow up.

Task 4.5 To evaluate trustworthiness and additional secondary outcomes of the TRUSTING AI monitoring system. Lead: UZH. Partners involved 1, 2, 5, 6, 7, 8; 12 month 13-66

To understand how the AI speech monitoring intervention is perceived by end users (i.e., citizens with schizophrenia and clinicians) compared to speech recordings alone we will assess trustworthiness of the procedure (using the General Trust Scale, GTS)29 at every study visit. Additional secondary outcomes, assessed at every study visit, include the WHO- DAS-II disability scale112 Social and Occupational Functioning Assessment Scale (SOFAS), number and duration of psychiatric admissions, rates of self-harm (including suicide, suicide attempts and aggressive incidents) assessed with the Social Dysfunction & Aggression Scale (SDAS)113 Quality of life assessed with the EuroQoL (EQ-5D-5L)113,114. Finally, after the last visit, assessors will be unblinded and have a qualitative interview with the participants and clinical team to assess acceptability and trustworthiness of the intervention. Since we rely on a human-in-the-loop design where the clinician in charge plays a determining role in interpreting and acting upon the messages provided by the monitoring system, we hypothesize that differences in trustworthiness between standard relapse prevention plus AI speech monitoring and standard relapse prevention plus speech recordings alone will be negligible. Thus, we expect our AI-based speech intervention to be perceived as tolerable and trustworthy by citizens with schizophrenia. Together, this WP will provide data on efficacy and trustworthiness of the TRUSTING AI monitoring system which will be the basis for the health economic considerations in WP5.

## Work package WP5 – Health economic evaluation

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| **Work Package Number** | WP5 | **Lead Beneficiary** | 8. SRI |
| **Work Package Name** | Health economic evaluation | | |
| **Start Month** | 1 | **End Month** | 66 |

Objectives:

* 1. To explore target sub-populations, synthesizing medical, economic and reimbursement considerations
  2. To develop economic value frameworks for selected indications and populations
  3. To develop health economic models with sensitivity analyses and with adaptation to selected key EU markets
  4. To estimate Net Present Value of the project that guides future internal GO/NO GO decisions and partnering negotiations

**Objectives**

**Description**

Task 5.1. Exploring potential sub-populations and assessing reimbursement criteria in public financing systems. Lead: SRI. Partners involved: 2, 4, 11. Month 1-12.

In this Task a systematic literature review on the clinical, humanistic, and economic burden of schizophrenia will be conducted. This work will result in an up-to-date synthesis of evidence on disease burden, with a geographic focus on the relevant countries (dealt with in WP3). SRI will explore potential subpopulations (e.g., young people, people with severe schizophrenia), relevant jurisdictions from a health economic perspective. In order to facilitate future access to market of the TRUSTING technology, SRI will carry out a general assessment of processes and criteria of reimbursement of similar medical technologies in the national health systems / statutory health insurance systems of relevant countries. This process will consist of: (i) a review of the relevant literature and websites of organizations responsible for/with stakes in the public reimbursement process; (ii) interviews with key informants, complemented by an expert workshop. Data from the interviews and the workshop will be processed using purpose selected qualitative data analysis methods. The results of this task will be summarized in a report describing the key points of a value dossier and the main lines along which the technology shall get evaluated in relevant health systems.

Task 5.2. Development of value framework for the AI monitoring system. Lead: SRI. Partners involved: 2,4,11. Month 13-36.

SRI will deliver the conceptual modelling framework on recognized value drivers that can be translated to economically meaningful measures for health economic modelling purposes. Typical health economic decision model structures with disease specific health states, established treatment comparator(s), and relevant patient characteristics will be explored to guide the development of an early-phase economic model in Task 5.3. Along the value framework elements, key assumptions on intervention characteristics will be identified in a targeted review of currently available best evidence from scientific literature. Key assumptions on intervention characteristics will be translated into the definition of best case and worst acceptable case scenarios. The selection of the value drivers will be supported by the clinical experts of the consortium.

Task 5.3. Health economic model development and adaptation to selected EU markets. Lead: SRI. Partners involved: 2,4,11. Month 37-54.

Early phase core health economic model will be developed with health states and other model features according to the conceptual modelling framework developed in Task 5.2, in a suitable, user-friendly platform conforming to the selected model type (e.g., Markov cohort, discrete event simulation, decision tree). The model will assess uncertainty in outcomes by performing scenario and sensitivity analyses. The potential differences in the AI monitoring system’s efficacy due to country-specific legislative requirements (see WP3) will be scrutinized. In parallel SRI will perform the validation of the developed model, including examination of internal consistency, transparency and key input parameters, technical verification of model calculations, and assurance of functionality and replicability. Besides the programming syntax, all input data will be verified with their original sources. For model adaptations to various EU markets local input data in selected countries will be collected. Model outputs will allow the estimation of cost-effectiveness, cost-utility, and budget impact for reimbursement decisions on the developed technology, at various target prices. Initial modelling will be carried out on the preliminary outcomes of the RCT (WP4). Model results can be refined once the full dataset is available. Model results will be summarised in the Health Economic Report and circulated for review by all Partners. Task 5.4. Net Present Value estimation. Lead: SRI; Partners involved: 1, 2, 3, 4, 11. Month 55-66.

The Net Present Value (NPV) of the development project, based on educated assumptions of expected development costs, cost of the regulatory and market access activities, device and operational costs and finally costs of commercialization (launch campaign and subsequent sales and marketing costs), timing and success rates in various phases of project development, regulatory approval, public reimbursement, and sales forecasts will be calculated. This NPV valuation will be used to support efficient partnering negotiations and licensing out discussions with potential investors. The NPV approach will also allow to support internal decisions on research continuation (Go / No Go). The NPV estimation platform remains continuously available for the consortium members after the project closure and will allow regular updates whenever new results or assumptions come to our horizon.

## Work package WP6 – Dissemination, Communication, and Exploitation Activities

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| **Work Package Number** | WP6 | **Lead Beneficiary** | 6. GAMIAN |
| **Work Package Name** | Dissemination, Communication, and Exploitation Activities | | |
| **Start Month** | 1 | **End Month** | 66 |

Objectives: The aim of this WP is to ensure uptake and maximization of the impacts of the TRUSTING project. We therefore focus on the creation of a Communication, Dissemination and Exploitation Strategy which will include a Communication Plan, Dissemination Plan and Exploitation Plan as well as the development of an IPR Strategy. The objectives are to establish awareness and credibility of our technology, project progress and results across identified target audiences with strategic, proactive communication measures; set up a roadmap toward future market-creation and commercialisation; proactively manage/protect the IPR generated within the project to secure future exploitation; and ensure sustainability of project outcomes beyond the lifetime of the project. Measures in this WP will be underpinned by an Open Science approach.

**Objectives**

**Description**

Task 6.1 Develop and perform Communication and Dissemination Activities. Lead: GAMIAN. Partners involved: All Partners. Month 1-66.

A detailed, consortium-wide Communication and Dissemination (C&D) Plan will be developed, setting out how we will disseminate the project’s results to defined stakeholder groups, including non-specialized audiences. A first version will be provided as a deliverable in M6. The C&D plan will evolve throughout the project. Communication activities include:

* A project website with sections targeted towards different stakeholders, e.g., researchers/clinicians and service users.
* Social media presence through the EPA and GAMIAN channels.
* Regular newsletters covering the project’s progress and results as well as information sharing with patient organizations via GAMIAN’s newsletters.

• Production of engaging educative materials for various stakeholders such as basic slide sets, flyers, infographics.

• (Online) educational activities, such as webinars with and for the scientific and clinical community as well as activities targeted towards lay audiences such as public talks, events, performance and other forms of science communication including summaries of key scientific publications from the project published on the project’s website.

Dissemination activities will include:

* An active, yet critical dialogue will be promoted between all main stakeholders starting from the project’s early phases, tailored towards the intended audience. This is to achieve maximum awareness and uptake on the project’s guidelines, recommendations and position statements and optimal dissemination, engagement/feedback, public acceptance and best possible implementation of the resulting findings.

• Presentation of the projects’ results at (inter)national conferences in form of abstracts, presentations and posters and in scientific journals in relevant pre-prints and peer-reviewed scientific and medical journals.

* Organization of workshops at EPA congress.
* Setting up meetings with potential partners and key stakeholders for commercialization of the project’s results, including R&D-performing SMEs, service providers, health insurers, health authorities, funders, etc; as well as attending relevant industry events.

Amendment on the role of the service user and clinician user groups in WP6: Besides the role of the service user and clinician user groups in WP3, its members are also incentivized – when suitable- to participate in (strategic) communication in the beginning and during the project. These user groups should advise on the content of the project’s website. Furthermore, they are urged to actively participate in all suitable material targeted to service users and lay audiences.

Task 6.2 Develop and perform exploitation of project results activities. Lead: UiT. Partners involved: All Partners. Month 1-66.

The successful exploitation of the project results to achieve societal, scientific and commercial impact is dependent on a clear exploitation plan and roadmap. Exploitation preparation activities associated with this task will enable the clear identification of exploitable project assets and the pre-requisite conditions needed to position these assets in the market context. This task is dedicated to exploitation preparation activities that will enable the efficient exploitation of these assets post-project. A business strategy will be developed by UiT’s TTO Norinnova. We will model scenarios that allow us to evaluate the different exploitation options based on feasibility, market opportunities, risks involved, investments

required, and profitability, among others. These models will help us to choose the more optimal business strategy and

to optimise our value proposition and commercialisation strategy accordingly.

Stakeholder analysis will be performed, with the objective to identify the most important stakeholders of the TRUSTING solution and find potential partners for business collaborations, further research collaboration and/or future funded proposals. Regulatory strategy – a key component of the Exploitation activities is the identification of all the regulatory requirements to bring to market our solution and the development of a Regulatory strategy. Meetings will be established with Health Authorities to understand the different requirements for different markets. Reimbursement strategy – central to any exploitation strategy is the selection of an appropriate business model to ensure market entry in key target markets. Knowledge of reimbursement pathways is essential to achieve optimal market entry in key target markets.

Task 6.3. Intellectual Property (IP) Management. Lead: UiT. Partners involved: All Partners. Month 1-66.

Continuous scanning of the IP landscape and identification of opportunities for protection of knowledge will be conducted, to ensure protection of existing and attainment of new IP. Freedom to Operate (FTO) practices will continue to be executed to ensure any potential third-party infringement is monitored throughout the project. Opportunities that arise during the project will be monitored and discussed centrally with the WP leads. Prior to the project, background IP will be defined for all partners and documented in the consortium agreement (CA). Joint IP will be generated mostly within the WPs and as such, in each WP an innovation representative will be appointed to safeguard the generation and protection of foreground and joint IP. Each partner will engage its own business development offices to discuss opportunities and discuss together the joint IP issues and settlements. Although patents form the primary deliverable for this task, the partners agree that IP protection will be sought for a variety of intellectual efforts.

## Work package WP7 – Project Management

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| **Work Package Number** | WP7 | **Lead Beneficiary** | 1. UMCG |
| **Work Package Name** | Project Management | | |
| **Start Month** | 1 | **End Month** | 66 |

Objectives: Day-to-day management of the TRUSTING consortium and implementation of the activities. Ensuring the execution of the project in line with the financials and timelines in the Grant Agreement. Interacting with EU authorities to deliver the required documentation such as progress reports, financial reports, and other deliverables.

The organizational structure of TRUSTING is described following the work package.

**Objectives**

Task 7.1: Project coordination. Lead: UMCG. Partners involved: All Partners. Month 1-66.

Liaise between project partners and EC representatives on behalf of the consortium and act as the intermediary for all communications between the beneficiaries and the EC. Monitor that the project is implemented properly. Report and discuss progress and developments with the project team and with members of advisory board. UMCG will lead any negotiations in case of defaulting partners.

Task 7.2: Project and data management. Lead: UMCG. Partners involved: All Partners. Month 1-66.

Organise and prepare the kick-off meeting and project consortium meetings to monitor the progress of the project. Monitor project planning, milestones, and deliverables in line with the Grant Agreement and report to coordinator. Propose amendments of the work plan to the coordinator in case of changes in project planning. Monitor gender aspects and report to coordinator. Collect relevant information (scientific, administrative, financial) and prepare interim and final reports. Prepare concept-minutes of consortium meetings. Request any documents or information required by the EC from all partners and prepare deliverables and reports for submission to the EC. UMCG’s Dr. Koops, as project coordinator, will review all deliverables and reports before submission. UMCG will appoint a Data Management Officer who will prepare a Data Management Plan (DMP) based on input from all partners. The DMP will be discussed during each consortium meeting and updated every 12 months by the Data Management Officer.

Task 7.3: Financial management. Lead: UMCG. Partners involved: All Partners. Month 1-66.

Monitoring budget spent and remaining budget in line with the overall budget and Grant Agreement; Receiving payments from EC according to Grant Agreement; Performing payments to consortium members according to Grant Agreement; Monitoring overall reimbursement of partners as set out in the Grant Agreement; Proposing amendments to the budget in case of significant changes in the work plan and timing; Report the status of the budget and payments performed to

**Description**

the coordinator; Collect relevant financial information, including certified financial statements for submission of reports

to EC.

Task 7.4 Ethics and Risk Management. Lead: UMCG. Partners involved: All Partners. Month 1-66.

In this task, activities will be performed to monitor, prevent, and mitigate project risks, including risks related to ethics. An Ethics Plan will be developed. It will provide a basis to identify, minimise and manage ethical issues, ensuring alignment of the research design with national and international ethics guidelines. The Ethics Manager will monitor ethical issues occurring throughout the project and report to the coordinator. Scientific risk management will focus on identifying and assessing risks to the project and managing those risks to minimise impacts on the project. A Risk Manager (Dr. Koops from partner 1) will be appointed, who will work with the WP Leads to oversee risk management.

**Work package WP8 – Ethics requirements**

|  |  |  |  |
| --- | --- | --- | --- |
| **Work Package Number** | WP8 | **Lead Beneficiary** | 1. UMCG |
| **Work Package Name** | Ethics requirements | | |
| **Start Month** | 1 | **End Month** | 66 |

The objective is to ensure compliance with the 'ethics requirements' set out in this work package.

**Objectives**

This work package sets out the 'ethics requirements' that the project must comply with.

**Description**

**STAFF EFFORT**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Staff effort per participant**  *Grant Preparation (Work packages - Effort screen) — Enter the info.* | | | | | | | | | |
| **Participant** | **WP1** | **WP2** | **WP3** | **WP4** | **WP5** | **WP6** | **WP7** | **WP8** | **Total Person-Months** |
| 1 - UMCG | 49.00 | 8.00 | 8.00 | 36.00 | 2.00 | 2.00 | 51.60 |  | 156.60 |
| 1.1 - RBV |  |  |  |  |  |  | 13.20 |  | 13.20 |
| 2 - UPF | 2.00 | 57.00 | 2.00 |  | 1.00 | 2.00 | 1.00 |  | 65.00 |
| 3 - UiT | 3.60 | 3.60 | 119.40 | 64.00 |  | 9.10 | 2.80 |  | 202.50 |
| 4 - DEU |  |  |  | 42.00 |  |  |  |  | 42.00 |
| 5 - NIMH |  |  |  | 42.00 |  |  |  |  | 42.00 |
| 6 - GAMIAN |  |  | 3.74 |  |  | 13.15 | 2.25 |  | 19.14 |
| 7 - EPA |  |  |  |  |  | 8.20 | 3.00 |  | 11.20 |
| 8 - SRI |  |  |  | 1.00 | 39.00 | 2.00 |  |  | 42.00 |
| 9 - RCSI |  |  |  | 56.40 |  |  |  |  | 56.40 |
| 10 - UZH | 2.00 | 2.00 | 4.00 | 244.00 | 8.00 | 2.00 | 2.00 |  | 264.00 |
| 11 - UNIGE |  |  |  | 42.00 |  |  |  |  | 42.00 |
| 12 - SUT |  |  |  | 42.00 |  |  |  |  | 42.00 |
| **Total Person-Months** | 56.60 | 70.60 | 137.14 | 569.40 | 50.00 | 38.45 | 75.85 | 0.00 | 998.04 |

**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*](https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32015D0444&qid=1586092489803) | | | | | | |
| **Deliverable No** | **Deliverable Name** | **Work Package No** | **Lead Beneficiary** | **Type** | **Dissemination Level** | **Due Date (month)** |
| D1.1 | Top predicting classifier | WP1 | 1 - UMCG | OTHER | SEN - Sensitive | 12 |
| D1.2 | Validation in separate dataset | WP1 | 1 - UMCG | OTHER | SEN - Sensitive | 18 |
| D1.3 | Test-retest reliability | WP1 | 1 - UMCG | R — Document, report | SEN - Sensitive | 21 |
| D1.4 | Sensitivity analyses | WP1 | 1 - UMCG | OTHER | SEN - Sensitive | 27 |
| D1.5 | Medication | WP1 | 1 - UMCG | R — Document, report | PU - Public | 30 |
| D1.6 | Model enhancement | WP1 | 1 - UMCG | OTHER | SEN - Sensitive | 36 |
| D2.1 | Generalizability report | WP2 | 2 - UPF | R — Document, report | SEN - Sensitive | 24 |
| D2.2 | Validation report | WP2 | 2 - UPF | R — Document, report | SEN - Sensitive | 24 |
| D2.3 | Report on construct validity | WP2 | 2 - UPF | R — Document, report | SEN - Sensitive | 36 |
| D3.1 | User-needs assessment results | WP3 | 3 - UiT | R — Document, report | SEN - Sensitive | 6 |
| D3.2 | e-health course | WP3 | 3 - UiT | DEM — Demonstrator, pilot, prototype | PU - Public | 12 |
| D3.3 | Alpha AI tool version | WP3 | 3 - UiT | OTHER | SEN - Sensitive | 12 |
| D3.4 | Beta AI tool version | WP3 | 3 - UiT | OTHER | SEN - Sensitive | 24 |
| D3.5 | Technical service for the AI tool | WP3 | 3 - UiT | OTHER | SEN - Sensitive | 24 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **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*](https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32015D0444&qid=1586092489803) | | | | | | |
| **Deliverable No** | **Deliverable Name** | **Work Package No** | **Lead Beneficiary** | **Type** | **Dissemination Level** | **Due Date (month)** |
| D3.6 | Technical service for the AI tool final | WP3 | 3 - UiT | OTHER | SEN - Sensitive | 66 |
| D4.1 | Study initiation package | WP4 | 10 - UZH | R — Document, report | PU - Public | 24 |
| D4.2 | Midterm recruiting report | WP4 | 10 - UZH | R — Document, report | SEN - Sensitive | 40 |
| D4.3 | Report on the status of posting results | WP4 | 10 - UZH | R — Document, report | PU - Public | 66 |
| D4.4 | Report on relapse rates | WP4 | 10 - UZH | R — Document, report | SEN - Sensitive | 66 |
| D4.5 | Report on trustworthiness | WP4 | 10 - UZH | R — Document, report | SEN - Sensitive | 66 |
| D5.1 | Health economic model | WP5 | 8 - SRI | R — Document, report | SEN - Sensitive | 54 |
| D5.2 | Net Present Value model | WP5 | 8 - SRI | R — Document, report | PU - Public | 66 |
| D6.1 | DEC plan | WP6 | 3 - UiT | R — Document, report | SEN - Sensitive | 6 |
| D6.2 | DEC Plan report | WP6 | 3 - UiT | R — Document, report | SEN - Sensitive | 66 |
| D6.3 | IP Update | WP6 | 3 - UiT | R — Document, report | SEN - Sensitive | 66 |
| D6.4 | Website | WP6 | 6 - GAMIAN | DEC —Websites, patent filings, videos, etc | PU - Public | 3 |
| D7.1 | Data Management Plan | WP7 | 1 - RBV | R — Document, report | PU - Public | 6 |
| D7.2 | Ethics plan | WP7 | 1 - UMCG | R — Document, report | PU - Public | 24 |
| D7.3 | Data Management Plan report | WP7 | 1 - RBV | R — Document, report | PU - Public | 66 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **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*](https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32015D0444&qid=1586092489803) | | | | | | |
| **Deliverable No** | **Deliverable Name** | **Work Package No** | **Lead Beneficiary** | **Type** | **Dissemination Level** | **Due Date (month)** |
| D8.1 | NEC - POPD - AI - H - OEI - Requirement No. 1 | WP8 | 1 - UMCG | ETHICS | SEN - Sensitive | 12 |
| D8.2 | POPD - AI - NEC - H - OEI - Requirement No. 2 | WP8 | 1 - UMCG | ETHICS | SEN - Sensitive | 24 |
| D8.3 | POPD - H - OEI - NEC - AI - Requirement No. 3 | WP8 | 1 - UMCG | ETHICS | SEN - Sensitive | 36 |
| D8.4 | OEI - NEC - AI - POPD - H - Requirement No. 4 | WP8 | 1 - UMCG | ETHICS | SEN - Sensitive | 48 |
| D8.5 | H - AI - POPD - NEC - OEI - Requirement No. 5 | WP8 | 1 - UMCG | ETHICS | SEN - Sensitive | 60 |

**Deliverable D1.1 – Top predicting classifier**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D1.1 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | Top predicting classifier | | |
| **Type** | OTHER | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 12 | **Work Package No** | WP1 |

Provide the best predicting speech-based model

**Description**

**Deliverable D1.2 – Validation in separate dataset**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D1.2 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | Validation in separate dataset | | |
| **Type** | OTHER | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 18 | **Work Package No** | WP1 |

Provide generalizability as calculated in separate validation set

**Description**

**Deliverable D1.3 – Test-retest reliability**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D1.3 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | Test-retest reliability | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 21 | **Work Package No** | WP1 |

Provide test-retest reliability based on second/ third relapses

**Description**

**Deliverable D1.4 – Sensitivity analyses**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D1.4 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | Sensitivity analyses | | |
| **Type** | OTHER | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 27 | **Work Package No** | WP1 |

Provide model accuracy by gender & in sociodemographic groups.

**Description**

**Deliverable D1.5 – Medication**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D1.5 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | Medication | | |
| **Type** | R — Document, report | **Dissemination Level** | PU - Public |
| **Due Date (month)** | 30 | **Work Package No** | WP1 |

Results on impact of antipsychotic medication on speech-based features

**Description**

**Deliverable D1.6 – Model enhancement**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D1.6 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | Model enhancement | | |
| **Type** | OTHER | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 36 | **Work Package No** | WP1 |

Provide the best predicting model plus clinical/ demographic information

**Description**

**Deliverable D2.1 – Generalizability report**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D2.1 | **Lead Beneficiary** | 2. UPF |
| **Deliverable Name** | Generalizability report | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 24 | **Work Package No** | WP2 |

Report on generalizability across samples & languages of WP1 classifiers.

**Description**

**Deliverable D2.2 – Validation report**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D2.2 | **Lead Beneficiary** | 2. UPF |
| **Deliverable Name** | Validation report | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 24 | **Work Package No** | WP2 |

Impact of bias, pre-processing choices, low-level linguistic features, model selection, and task, on classifier performance across linguistic domains.

**Description**

**Deliverable D2.3 – Report on construct validity**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D2.3 | **Lead Beneficiary** | 2. UPF |
| **Deliverable Name** | Report on construct validity | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 36 | **Work Package No** | WP2 |

Report on relations between linguistic variables and clinical dimensions of psychopathology across samples, languages, tasks, and ethnic subgroups.

**Description**

**Deliverable D3.1 – User-needs assessment results**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D3.1 | **Lead Beneficiary** | 3. UiT |
| **Deliverable Name** | User-needs assessment results | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 6 | **Work Package No** | WP3 |

Results from the user needs assessment survey

**Description**

**Deliverable D3.2 – e-health course**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D3.2 | **Lead Beneficiary** | 3. UiT |
| **Deliverable Name** | e-health course | | |
| **Type** | DEM — Demonstrator, pilot, prototype | **Dissemination Level** | PU - Public |
| **Due Date (month)** | 12 | **Work Package No** | WP3 |

E-health course ready

**Description**

**Deliverable D3.3 – Alpha AI tool version**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D3.3 | **Lead Beneficiary** | 3. UiT |
| **Deliverable Name** | Alpha AI tool version | | |
| **Type** | OTHER | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 12 | **Work Package No** | WP3 |

First (alpha) version of the online tool for evaluation and pilot study

**Description**

**Deliverable D3.4 – Beta AI tool version**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D3.4 | **Lead Beneficiary** | 3. UiT |
| **Deliverable Name** | Beta AI tool version | | |
| **Type** | OTHER | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 24 | **Work Package No** | WP3 |

Final (beta) version of the online tool for effective, remote collection of speech data

**Description**

**Deliverable D3.5 – Technical service for the AI tool**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D3.5 | **Lead Beneficiary** | 3. UiT |
| **Deliverable Name** | Technical service for the AI tool | | |
| **Type** | OTHER | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 24 | **Work Package No** | WP3 |

Provide a technical service that enables the collection, processing and analysis of speech data - for duration of the RCT

**Description**

**Deliverable D3.6 – Technical service for the AI tool final**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D3.6 | **Lead Beneficiary** | 3. UiT |
| **Deliverable Name** | Technical service for the AI tool final | | |
| **Type** | OTHER | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 66 | **Work Package No** | WP3 |

Technical service for the AI tool second delivery date

**Description**

**Deliverable D4.1 – Study initiation package**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D4.1 | **Lead Beneficiary** | 10. UZH |
| **Deliverable Name** | Study initiation package | | |
| **Type** | R — Document, report | **Dissemination Level** | PU - Public |
| **Due Date (month)** | 24 | **Work Package No** | WP4 |

Includes registration n of the clinical study, final version of study protocol, regulatory and ethics approvals for the first clinical site

**Description**

**Deliverable D4.2 – Midterm recruiting report**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D4.2 | **Lead Beneficiary** | 10. UZH |
| **Deliverable Name** | Midterm recruiting report | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 40 | **Work Package No** | WP4 |

Delivered when 50% of the study population is recruited. Includes overview of the n of recruited participants by partner, any problems in recruitment plus a detailed description of measures to compensate for incurred delays

**Description**

**Deliverable D4.3 – Report on the status of posting results**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D4.3 | **Lead Beneficiary** | 10. UZH |
| **Deliverable Name** | Report on the status of posting results | | |
| **Type** | R — Document, report | **Dissemination Level** | PU - Public |
| **Due Date (month)** | 66 | **Work Package No** | WP4 |

This report will confirm that a summary of the results obtained have been posted in the applicable registry (clinicaltrials.gov)

**Description**

**Deliverable D4.4 – Report on relapse rates**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D4.4 | **Lead Beneficiary** | 10. UZH |
| **Deliverable Name** | Report on relapse rates | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 66 | **Work Package No** | WP4 |

Report on the difference in relapse rates between usual care and usual care plus speech monitoring

**Description**

**Deliverable D4.5 – Report on trustworthiness**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D4.5 | **Lead Beneficiary** | 10. UZH |
| **Deliverable Name** | Report on trustworthiness | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 66 | **Work Package No** | WP4 |

Report on the difference in trustworthiness between usual care and usual care plus speech monitoring

**Description**

**Deliverable D5.1 – Health economic model**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D5.1 | **Lead Beneficiary** | 8. SRI |
| **Deliverable Name** | Health economic model | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 54 | **Work Package No** | WP5 |

Health economic model report

**Description**

**Deliverable D5.2 – Net Present Value model**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D5.2 | **Lead Beneficiary** | 8. SRI |
| **Deliverable Name** | Net Present Value model | | |
| **Type** | R — Document, report | **Dissemination Level** | PU - Public |
| **Due Date (month)** | 66 | **Work Package No** | WP5 |

Net Present Value model report

**Description**

**Deliverable D6.1 – DEC plan**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D6.1 | **Lead Beneficiary** | 3. UiT |
| **Deliverable Name** | DEC plan | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 6 | **Work Package No** | WP6 |

Dissemination, Exploitation and Communication Plan report

**Description**

**Deliverable D6.2 – DEC Plan report**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D6.2 | **Lead Beneficiary** | 3. UiT |
| **Deliverable Name** | DEC Plan report | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 66 | **Work Package No** | WP6 |

Dissemination, Exploitation and Communication Plan end report

**Description**

**Deliverable D6.3 – IP Update**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D6.3 | **Lead Beneficiary** | 3. UiT |
| **Deliverable Name** | IP Update | | |
| **Type** | R — Document, report | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 66 | **Work Package No** | WP6 |

Updates to IP strategy

**Description**

**Deliverable D6.4 – Website**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D6.4 | **Lead Beneficiary** | 6. GAMIAN |
| **Deliverable Name** | Website | | |
| **Type** | DEC —Websites, patent filings, videos, etc | **Dissemination Level** | PU - Public |
| **Due Date (month)** | 3 | **Work Package No** | WP6 |

Launching website for TRUSTING Project

**Description**

**Deliverable D7.1 – Data Management Plan**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D7.1 | **Lead Beneficiary** | 1. RBV |
| **Deliverable Name** | Data Management Plan | | |
| **Type** | R — Document, report | **Dissemination Level** | PU - Public |
| **Due Date (month)** | 6 | **Work Package No** | WP7 |

Data Management Plan document

**Description**

**Deliverable D7.2 – Ethics plan**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D7.2 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | Ethics plan | | |
| **Type** | R — Document, report | **Dissemination Level** | PU - Public |
| **Due Date (month)** | 24 | **Work Package No** | WP7 |

Ethics plan documentation

**Description**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D7.3 | **Lead Beneficiary** | 1. RBV |
| **Deliverable Name** | Data Management Plan report | | |
| **Type** | R — Document, report | **Dissemination Level** | PU - Public |
| **Due Date (month)** | 66 | **Work Package No** | WP7 |

**Deliverable D8.1 – NEC - POPD - AI - H - OEI - Requirement No. 1**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D8.1 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | NEC - POPD - AI - H - OEI - Requirement No. 1 | | |
| **Type** | ETHICS | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 12 | **Work Package No** | WP8 |

1st report by the external ethics expert and legal expert/Advisory Board

**Description**

**Deliverable D8.2 – POPD - AI - NEC - H - OEI - Requirement No. 2**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D8.2 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | POPD - AI - NEC - H - OEI - Requirement No. 2 | | |
| **Type** | ETHICS | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 24 | **Work Package No** | WP8 |

2nd report by the external ethics expert and legal expert/Advisory Board

**Description**

**Deliverable D8.3 – POPD - H - OEI - NEC - AI - Requirement No. 3**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D8.3 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | POPD - H - OEI - NEC - AI - Requirement No. 3 | | |
| **Type** | ETHICS | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 36 | **Work Package No** | WP8 |

3rd report by the external ethics expert and legal expert/Advisory Board

**Description**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D8.4 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | OEI - NEC - AI - POPD - H - Requirement No. 4 | | |
| **Type** | ETHICS | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 48 | **Work Package No** | WP8 |

**Deliverable D8.5 – H - AI - POPD - NEC - OEI - Requirement No. 5**

|  |  |  |  |
| --- | --- | --- | --- |
| **Deliverable Number** | D8.5 | **Lead Beneficiary** | 1. UMCG |
| **Deliverable Name** | H - AI - POPD - NEC - OEI - Requirement No. 5 | | |
| **Type** | ETHICS | **Dissemination Level** | SEN - Sensitive |
| **Due Date (month)** | 60 | **Work Package No** | WP8 |

5th report by the external ethics expert and legal expert/Advisory Board

**Description**

**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 | Classifiers trained and tested on full cohort | WP1 | 1-UMCG | Accuracy of the classifiers | 12 |
| 2 | Test-retest reliability calculated | WP1 | 1-UMCG | Accuracy of the classifiers | 18 |
| 3 | Sensitivity analyses finished | WP1 | 1-UMCG | Accuracy of the classifiers | 24 |
| 4 | Clinical data added to model | WP1 | 1-UMCG | Accuracy of the classifiers | 36 |
| 5 | Curation and preparation DISCOURSE samples | WP2 | 2-UPF | Availability of data for analysis | 12 |
| 6 | task and language effects calculated | WP2 | 2-UPF | Accuracies for first subset of languages (German, English, Turkish) | 18 |
| 7 | Relation to clinical scores assessed | WP2 | 2-UPF | Regression models | 20 |
| 8 | Task effects calculated | WP2 | 2-UPF | Analyses | 24 |
| 9 | User needs assessment | WP3 | 3-UiT | Data available to inform IT design | 6 |
| 10 | empowering course to use the AI-monitoring tool in 6 languages | WP3 | 3-UiT | Course available for use in alpha test implementation | 12 |
| 11 | Ensuring legislative compliance with prevailing data protection regulations | WP3 | 3-UiT | IT solution(s) determined viable | 12 |
| 12 | Alpha version of (web)app to collect speech data (launched by month 12) | WP3 | 3-UiT | Pilot study completed in 40 participants from each country | 18 |
| 13 | Beta (final) version of (web)app to collect speech data | WP3 | 3-UiT | System thoroughly tested and ready for launching for RCT | 24 |
| 14 | Ethics approval for all centers | WP4 | 10-UZH | Approval confirmation documents | 24 |
| 15 | Inclusion at 50% of target sample | WP4 | 10-UZH | Number of recruited participants | 40 |

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| **Milestones**  *Grant Preparation (Milestones screen) — Enter the info.* | | | | | |
| **Milestone No** | **Milestone Name** | **Work Package No** | **Lead Beneficiary** | **Means of Verification** | **Due Date (month)** |
| 16 | Inclusion at 100% of target sample | WP4 | 10-UZH | Number of recruited participants | 54 |
| 17 | Follow-up finished | WP4 | 10-UZH | Number of recruited participants | 66 |
| 18 | Economic value drivers in selected indications | WP5 | 8-SRI | Economic value drivers in selected indications | 36 |
| 19 | Communication channels created | WP6 | 6-GAMIAN | Project website & SoMe channels | 6 |
| 20 | Exploitation Plan Finalized | WP6 | 6-GAMIAN | Business plan including MDR pathway | 66 |
| 21 | IPR strategy | WP6 | 6-GAMIAN | Business plan including MDR pathway | 66 |
| 22 | Kick-off meeting | WP7 | 1-UMCG | Meeting notes available | 1 |

**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 | A challenge may be that classifiers will not predict relapse successfully. Likelihood: Low / Severity: High | WP1 | A main cause for not being able to predict is insufficient signal in the data. For this reason, collecting sufficient data is a priority. We will make use of algorithms that are relatively robust to noise. We also use intra-individual analyses to reduce heterogeneity in the data. Another technique to maximize classification is the selection of features and optimization of these based on a subset of the data. As we already had pilot data with accuracy of 81% this risk is deemed as low. |
| 2 | A potential problem is that the ASR has a higher | WP1 | If the WER is higher than expected the automatic transcriptions will be manually corrected by |

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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** |
|  | word error rate (WER) than expected. Likelihood:  Medium / Severity: Low |  | using the ASR’s certainty estimates. Words that the ASR is uncertain about will be corrected  first. We will further examine the errors made by the ASR qualitatively, by assessing grammatical part-of-speech classes (POS), most frequently misrecognized words, and their linguistic position within a sentence, to see how we can improve the ASRs performance. |
| 3 | Some selected predicting features (e.g. acoustic measures) may not generalize across languages Likelihood: Medium / Severity: Medium | WP2 | Features will be distributed across domains precisely to mitigate against non-generalizability: some linguistic domains are subject to more crosslinguistic variation than others, and we specifically select one where crosslinguistic variation is not expected (referential meaning). In domains with variability, predicting speech-based features may be given different weighting per languages, so to arrive at optimal predictive power for each language. |
| 4 | A clue in speech may not map in a tight temporal relationship as anticipated or with low practical value such that converting it to a timely warning signal is problematic. Likelihood: Low / Severity: Medium | WP3 | At all stages of this project will we be evaluating the tightness of this relationship and its interaction with contextual variables. Since patients will all be receiving treatment as usual there is no risk to patients if this relationship proves to be less useful than anticipated. Expert clinical oversight will mitigate the resulting consequence. |
| 5 | Undesirable gender discrimination is emerging in clinical applications of artificial intelligence Likelihood: Medium / Severity: Low Medium Risk/ Low severity | WP3 | We will be alert to this risk as well as use the data we collect and compile to create a better database for future personalized medicine purposes, explicitly tagged as a function of gender. If needed, we will train separate classifiers for each gender (also see WP1). |
| 6 | Participants may wish to withdraw consent and retract their data. Likelihood: Low / Severity: Medium | WP3 | The data infrastructure will be designed to enable individual control over one’s own data. |
| 7 | Potential high drop-out rate during follow-up Likelihood: Medium / Severity: Low | WP4 | If the drop-out rate is to become >40%, power problems may threaten the goals of this project. In that case, additional participants will be included through increased recruitment efforts at all clinical sites. |
| 8 | Recruitment difficulties at clinical centers Likelihood: Medium / Severity: Low | WP4 | If a clinical center fails at recruiting the numbers needed in the first year, they will be replaced by a backup center. UMCG and UZH coordinated multi-center trials for citizens with schizophrenia and are well connected to centers experienced in recruiting citizens with schizophrenia. Potential backup centers include academic centers (e.g. University of Berne; German speaking; University of Lausanne; French speaking) and regional clinics in |

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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** |
|  |  |  | Switzerland (e.g. Clienia Schloessli, Sanatorium Kilchberg; German speaking), academic  centers in the Netherlands (e.g., Utrecht University), academic centers in Austria (e.g. University of Innsbruck, University of Vienna). |
| 9 | SUT is not capable of obtaining funding to perform the project (Australian partners are not automatically eligible for EU funding and therefore usually have to participate at their own cost). Likelihood: Medium / Severity: Low | WP4 | This risk has been mitigated by adding RCSI as complementary clinical trial center to enrol English-speaking participants. SUT will apply for Australian funding if TRUSTING is approved. If SUT is not funded, we have brought in enough clinical trial centers to ensure that we reach the minimum power requirements. If SUT is funded, we will have a higher inclusion with more power. In addition, having such high number of participants in the English language could enable subgroup analyses within the language. |
| 10 | Immature clinical data is available from WP4 to feed the economic analysis (WP5) Likelihood: Medium / Severity: Low | WP5 | Consultation with clinical experts on preliminary assumptions to be made on the AI monitoring system’s efficacy to populate the health economic model, until more results become available |
| 11 | Premature publication of results before IPR protection is in place. Likelihood: Medium / Severity: High | WP6 | TTOs involved from initiation, consulting on IPR. All publications such as scientific manuscripts, posters and project website etc to be reviewed for sensitive information related to IPR prior to publication. |

**PROJECT REVIEWS**

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| --- | --- | --- | --- |
| **Project Reviews**  *Grant Preparation (Reviews screen) — Enter the info.* | | | |
| **Review No** | **Timing**  (month) | **Location** | **Comments** |
| RV1 | 20 | Remote/ Brussels, to be decided |  |
| RV2 | 38 | Remote/ Brussels, to be decided |  |
| RV3 | 56 | Remote/ Brussels, to be decided |  |
| RV4 | 66 | Remote/ Brussels, to be decided |  |



**Horizon Europe (HORIZON)**

**Euratom Research and Training Programme (EURATOM)**

**Description of the action (DoA)**

**Part B**

#### 101080251 – TRUSTING

**HORIZON-HLTH-2022-SAYHLTH-01-04-two-stage**

**A TRUSTworthy speech-based AI monitorING system for the prediction of relapse in individuals with schizophrenia**

|  |  |  |
| --- | --- | --- |
| **HISTORY OF CHANGES** | | |
| **VERSION** | **PUBLICATION DATE** | **CHANGE** |
| **1.0** | **12-01-2023** | **Annex changes part A**  Added UMCG Research BV as affiliated entity to Beneficiary UMCG  **Annex changes part B**  Added KPI for SMART objective WP2, table 1.2 p.8 and p.17  Added abbreviations p.3  Addition explainability table 1.1, p.6  Added explanation on AI explainability within project p.15&16  Added association of target KPI values (table 2.2a) to objective Pillar 3 p.20  Improved formulation of several task descriptions figure 3.1a, p.33  Removed UMCG Research BV from subcontracting parties |
| **2.0** | **26-01-2023** | **Annex changes part A**  Added Department and address information of the Research BV - affiliated entity of Beneficiary UMCG  Added UMCG Research BV as carrying out tasks in Deliverables 7.1.(D26) and 7.3.(D28)  Corrected due date of deliverable D7.2 Ethics Plan to M24, as mentioned in the proposal.  Adjusted staff effort of SRI  Added Technical service for the AI tool as second deliverable with due date M66  Changed start date of the Project to 1st July 2023  **Annex changes part B**  Changed wording ‘proposal’ to ‘project’ and where applicable ‘participant’ with ‘beneficiary’ throughout document |

|  |  |  |
| --- | --- | --- |
|  |  | Changed number of Partners in Table 3.1.g. p37 and Table  3.1 h. p37  Removed mention of associated partners table 3.1h. p37  Corrected partner numbers on 5.2. Partners, p47-48 and figure 3.1.c., on p36  Removed the justifications of ‘remaining costs’ in table  3.1.g p37  Added “Subcontracts will be awarded ensuring the best value for money or, if appropriate, the lowest price, ensuring there is no conflict of interests and that all applicable internal and/or national procurement rules have been followed.” in Table 3.1.g. p37  Edited table 3.1.h. per requests by EU officer  Corrected several typo’s throughout proposal (4.ethics, 6. third countries, 5.1.d., 5.3.a)  Added Table 3.1.i p37 Added Table 3.1.j p38 |
| **3.0** |  | **Annex changes part A**  Change in total effort of 998,04 compared to the proposal (986,04), due to total effort addition mistake in the table Staff effort in Part A of the proposal.  Removed subcontracting budget from UMCG; costs moved to personnel costs for affiliated entity RBV.  UPF budget edited to correct discrepancies noted by EU officer  Self-declaration Gender Equality Plan added by partner GAMIAN  Changed the following deliverables to ‘public’ level:1.5, 4.1, 4.3 and 5.2.  **Annex changes part B**  Corrected mistake in History of Changes table: the due date correction was for D7.2, as opposed to D7.3.  Added description and justification of subcontracted tasks in table 3.1g p36  Added certificate on financial statement costs to table 3.1h and edited costs accordingly for partner UPF p37 |

|  |  |  |
| --- | --- | --- |
|  |  | Added specifications for clinical trial costs table 3.1h for partners DEU, NIMH and RCSI p37  Added third party (ICREA) contribution in table 3.1j upon request UPF (partner 2) who noticed this was missing after adding the CFS, this is an administrative issue required due to the PI being an ICREA professor seconded to UPF. p38  Included detailed explanation of the role and planned involvement of UMCG Research BV the tasks in which the third party will be involved etc. p40-41. |
| **4.0** |  | **Annex changes part A**  Research organization changed to ‘no’ by partner GAMIAN, as they are not a research organization.  Added UMCG Research BV PM effort.  **Annex changes part B**  Added partner name and number to table 3.1j. p39  Added additional explanation on third party contribution being free of charge added to table 3.1j. p39  Updated GANTT chart to study start July 1st, including edited timelines for WP2 and WP3, Figure 3.1a. p.36 as follows:   * WP2.1 end date moved to Q3 2024 * WP2.3 end date moved to Q2 2025 * WP3.3 start date moved to Q4 2023 |
| **5.0** | **21-02-2023** | **Annex changes part A**  Adjusted UMCG Research BV PM effort, in relation to UMCG  **Annex changes part B**  Added free of charge third party contribution costs and removed H2020 reference in table 3.1j. p39 |
| **6.0** | **23-02-2023** | **Annex changes part B**  Removed names of subcontractors table 3.1g p.38 |

**CONTENTS**

[Abbreviations 5](#_bookmark146)

1. [Excellence 6](#_bookmark147)

[**1.1.**](#_bookmark148)

1. [Impact 25](#_bookmark149)

[**2.1.**](#_bookmark150)

1. [Quality and efficiency of implementation 34](#_bookmark151)

[**3.1.**](#_bookmark152)

1. [Ethics self-assessment 43](#_bookmark153)

[**4.1.**](#_bookmark154)

1. [Clinical studies. 45](#_bookmark155)

**ABBREVIATIONS.**

AI Artificial Intelligence

ASR Automatic Speech Recognition DALY Disability-Adjusted Life Years

DEC Dissemination Exploitation and Communication DOFI Disclosure of Invention

IP Intellectual Property

KPI Key Performance Indicators

MDR Medical Device Regulation

ML Machine Learning

NLP Natural Language Processing

RCT Randomized Clinical Trial

SLP Spoken Language Processing

TRL Technology Readiness Level

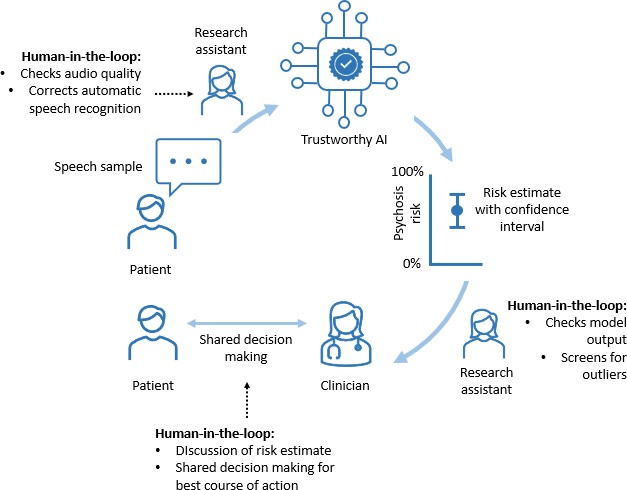
WP Workpackage

1. **EXCELLENCE**
   1. **Objectives and ambition**

**Timely prediction of psychotic relapse: an unmet clinical need**

Schizophrenia is a serious psychiatric disorder that often starts during adolescence and lasts a lifetime. It is characterized by psychosis, which typically has a waxing and waning course with remissions and relapses and is estimated to affect 21 million people worldwide. Schizophrenia contributes 13.4 (9.9–16.7) million years of life lived with disability (DALY) to the burden of disease - the highest DALY among mental and substance-use disorders and ranking 8th place among all diseases1,2 Relapse and associated hospital admissions can be deeply distressing and traumatic for those affected. A psychotic relapse is estimated to cause 9 months lived with disability, and the direct treatment costs are 3 times higher in case of relapse than for those with sustained remission3. Patients with a relapsing course have reduced chances of sustaining relationships, higher risks of unemployment and more severe functional and cognitive decline4. Maintenance treatment with antipsychotic medication is an effective method to prevent relapse5 but has serious side-effects such as metabolic syndrome and parkinsonism, especially when used long term6,7. Over the last decade, society has witnessed a change in attitude and for many patients, maintenance treatment is no longer acceptable8. Many patients want to stop antipsychotic medication after remission, and 56% actually do so9,10. During and after medication discontinuation, relapse risk is very high and frequent monitoring becomes a necessity, which is not feasible with scarce clinical resources. Ground-breaking work from Dr. Spaniel (partner 7) on the temporal aspects of relapse, showed a gradual course of early signs over some 5 weeks5. He also showed that in these early stages, a relapse can be prevented effectively when an individualized relapse prevention plan is activated11. **To accommodate this societal change in medication use, accurate and timely relapse prediction is crucial**, as psychotic relapse can still be prevented using intermittent medication and/or psychosocial interventions, if such actions are taken in time12,13. This is a highly challenging task, given the heterogeneity in clinical presentation of psychotic relapse and the inherent difficulty of monitoring citizens outside the clinic. Thus, there is an urgent need to develop valid and trustworthy predictors of relapse, but no such tools currently exist.

#### Our solution: a speech-based artificial intelligence (AI) monitoring system



**Figure 1.1.** The TRUSTING AI monitoring system concept

TRUSTING will answer this urgent need by creating and validating an AI monitoring system that leverages both audio-based spoken language processing (SLP) which quantifies acoustic aspects of speech and text-based natural language processing (NLP) which quantifies linguistic aspects of speech to provide an accurate quantification of the relapse risk. Many symptoms of psychotic relapse are reflected in speech, and disorganized and impoverished forms of speech carry high clinical significance10. Methodological advances in SLP/NLP have increasingly been applied to psychosis and its risk states. This line of research typically focuses on three main types of language disturbances; disorganized speech (positive thought disorder), poverty of speech (negative thought disorder), bradyphrenia and flat affect14 These are mostly studied using semantic space models and graph-theoretical or syntactic analyses (NLP), and acoustic analyses (SLP), respectively15. We hypothesize that a relapse-predictor based on different types of both

NLP and SLP features will be most accurate, as relapses are heterogeneous and different types of analyses can identify different symptoms. Importantly, work from Dr. Sommer (partner 1) has shown that service users are open to the idea of speech-based predictors in mental health care, as long as their privacy is guaranteed75. Speech is generated almost effortlessly and can be recorded with a personal electronic device independent of time and place. The main principle of TRUSTING is that individuals at risk for relapse record their speech from home on a weekly basis. NLP and SLP analyses will provide a quantified relapse risk plus confidence interval. This will be messaged to the clinician, who integrates this information into the person’s individual context and may invite him/ her and an informal caregiver for shared decision making to discuss if the relapse prevention plan should be activated. During this project, human oversight is implemented at different levels to check audio quality, automatic speech recognition (ASR) for NLP purposes, model accuracy and message content. A simplified scheme of the TRUSTING solution is displayed in Figure 1.1.

|  |
| --- |
| **Why speech?**  Verbal expression affords a spectacular window into the dynamics of mental processes and their pathologies, by reflecting these directly. Apart from *what* content is conveyed, *how* such content is conveyed carries a wealth of information about our fluctuating mental states. This is unsurprising as language does not function in isolation but systematically integrates affect and effectively all other cognitive functions, including executive control, memory, and social cognition. A wave of recent studies demonstrated that SLP and NLP algorithms based on speech can categorize individuals with and without psychosis even when symptom severity is low16,17 and predict which high- risk individuals will go on to develop psychosis with high accuracy (83-100%)18,19. Such high accuracies can  typically not be achieved with brain imaging or blood-based analyses, and such biomarkers are much more burdensome and costly. |

#### An overarching challenge: trust as a key for a speech-based AI monitoring system to be adopted in psychiatry

AI is gaining importance throughout medicine, especially for somatic health applications. Adoption of AI into mental health has been slower as practitioners rely more on soft skills and close relationships to patients20. In psychiatric practice, both ***what*** patients say and ***how*** they say it, is evaluated critically. However, more subtle yet objective features will escape even a trained clinician21. This provides an unprecedented opportunity for a SLP/NLP-based AI algorithm to add a source of quantifiable, clinically relevant information. These methods have achieved stunning technical and empirical success in learning subtle and nuanced features of psychosis in spoken language22. Such a speech-based AI monitoring system has translational potential to (i) improve efficiency and accuracy of illness monitoring, (ii) provide data-driven, quantitative and objective treatment recommendations, (iii) leverage big data to predict optimal and timely interventions, and (iv) prioritize allocation of patients to (scarce) clinicians23–25. As of today, no monitoring system leveraging SLP/NLP analysis of speech has been implemented in psychiatric practice. Indeed, just because something is scientifically viable, does not mean it will translate into practice. For an SLP/NLP- based AI algorithm to become a core part of clinical practice, there are several methodological, legal and ethical hurdles to overcome, notably gaining the trust of critical stakeholders, namely service-users and clinicians. Dr. Elvevåg (partner 4) recently made the case that for AI applications to transform current practice in psychiatry, a **framework that nurtures trustworthiness**26 is essential and the **‘human in the loop’ methodology**27 should be employed, whereby human experts retain system control and thus can approve or deny decisions at all stages, enabling **humans *and* machines** to work towards a common goal. Building on this core infrastructure, TRUSTING will answer an unmet need in psychiatry by creating and validating a speech-based AI monitoring system that leverages ***human in the loop methodology*** and fulfils the European Commission’s criteria for ethical and trustworthy AI (Table 1.1).

**Table 1.1.** In 2019, the European Commission’s High Level Expert Group on AI presented the Ethics Guidelines for Trustworthy Artificial Intelligence. This table summarizes how these 7 requirements are met in TRUSTING.

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| --- |
| **(1) Human agency and oversight** |
| The roles of human agency will change throughout the life of the project such that initially there will be a high level of human oversight (i.e., human-in-command) and as the model proves to become more robust and accurate, oversight will begin to be lifted (i.e., human-in-the-loop) (see Key Concepts – Human oversight).  We will combine ‘human in the loop’ and explainable AI methodology by building a system that incorporates human input and provides information on interpretable features that the AI uses for its decision processes. We will employ a co-design process working with clinicians and patients (as per WP3, WP6) in the creation of the assessments and model outputs, thereby mitigating misinterpretations and strengthening transparency of the  decisions made by the AI. This framework nurtures interpretability, allowing clinicians to make informed decisions on whether to trust and use these predictions or make their own decisions26. |
| **(2) Technical robustness and safety** |

|  |
| --- |
| Our system will employ a pipeline that converts the speech samples into SLP and NLP features, which are then tied to quantitative clinical predictions. We will ensure robustness at each step in the pipeline by thorough evaluation and maximization of the reliability, explainability (feature importance per model, see also (4) Transparency), and consistency of predictions (e.g., test-retest reliability, evaluation of the models’ performance across subgroups defined by age, education, gender, and migration background), and built-in mechanisms to handle data that cannot be interpreted by the model, as per WP2. Diverse data capturing multiple sources of  variation will ensure that the features and models used are accurate across the relevant populations and subgroups and methods will be incorporated so that models are updated and re-evaluated over time as per WP2 and 3. |
| **(3) Privacy and data governance** |
| Speech data are a corruptible type of data that can carry personal information, and human and technical safety mechanisms will alert us to this at all stages of the processing pipeline as per WP3. Compliance with all relevant EU regulations will ensure that privacy of all data is guaranteed (WP3). All participants will be assured that their language samples will not be taken out of context (in the future or misinterpreted) such that they do not fear that  something uttered might be misused at a later date. Importantly, we will ensure that all citizens have the ‘right to be forgotten’. All data will be pseudonymized, namely de-identified and no longer traceable to the individual. |
| **(4) Transparency** |
| We will ensure maximal transparency about the manner in which items and features are used for classification, and demonstrate that we are assessing features that match a specific clinical state (psychotic relapse and remission) as previously rated by expert humans (clinicians). These ratings will also be directly compared with AI-based ratings as per WP2). We will use AI methods that allow for understanding which features drive the classification (as per WPs1-2) and how they will be updated over time (WP3). This includes sharing knowledge of the human demographics in training data, chosen model parameters, pre-processing, and assumptions made about the  relations between chosen features and clinical variables. For explainable AI, we will seek to identify features driving classifications, and select some features based on hypotheses. |
| **(5) Diversity, non-discrimination and fairness** |
| Implementing a digital solution is in keeping with promoting greater equity in health care courtesy of the increased availability and sophistication of recording software interfaces which is important in that data collection can be applied across diverse settings and for diverse populations. We will ensure inclusiveness and equity, guided by the need to identify and mitigate unintended biases in SLP/NLP AI systems, which have already been shown to incur a potential risk of unfair bias in the psychosis context28. We will do this by ensuring the presence of crucial sources of variability in our data (e.g., gender, age, language, education, migration background), analysing their effect on the interpretability of an SLP/NLP based classification, and making our monitoring system fully accessible based on a universal design. WP2 will use the diverse speech data collected by the global DISCOURSE  in Psychosis Consortium (see page 18) and WP4 will include large enough samples across different subgroups to understand how generalizable the models are. |
| **(6) Societal and environmental well-being** |
| Ambulatory testing (WP4) allows for testing from home, and since speech is easy to collect in this way, it is less invasive, requires no traveling and thus has less environmental impact than the process of meeting a doctor in person. To ensure model sustainability, it will need to be continually updated as language and society change, potentially inducing model and data drift. Importantly, global language data collection is starting to show signs of  being democratized (e.g., databases from using voice based virtual assistants such as Siri, Alexa and Google), which provide ample resources for model updating. |
| **(7) Accountability** |
| Accountability will be ensured by building a system that *knows when it does not know*, and that checks data. Initially the expert human and computer rate language transcripts, and when the computer alone is scoring, a certain percentage (i.e.>10%) of transcripts will be selected (randomly or specifically) for their unusual properties  and re-scored by expert humans26,27. |

#### Consortium & Objectives of TRUSTING

The Consortium is composed of 12 partners: University Medical Center Groningen (UMCG – coordinator), University of Zurich (UZH), University Pompeu Fabra (UPF), UiT - The Arctic University of Norway (UiT), University of Geneva (UNIGE), Swinburne University of Technology (SUT), National Institute of Mental Health (NIMH), Dokuz Eylul University (DEU), the Global Alliance of Mental Illness Advocacy Networks-Europe (GAMIAN), the European Psychiatric Association (EPA), Syreon Research Institute (SRI), and the Royal College of Surgeons in Ireland (RCSI). Academic partners UMCG, UZH, UPF, and UiT represent the 4 main R&D partners, who will work together to develop the AI monitoring system. UNIGE, SUT, NIMH, DEU, and RCSI will join the consortium as clinical trial centers (coordinated by UZH) for the AI monitoring system validation. SME SRI will

provide expertise in health economic analysis in view of reimbursement to advance the market readiness of the AI monitoring system. The consortium is complemented by 2 pan-European organizations: GAMIAN, a patient-driven organisation advocating for the interests and rights of persons affected by mental illness, and EPA, the main association representing psychiatry in Europe. The objectives of TRUSTING are described in Table 1.2 below.

**Table 1.2.** SMART objectives of TRUSTING.

|  |  |
| --- | --- |
| **Specific** | **Objective 1. To create an accurate speech-based predictor for psychotic relapse and assess**  **accuracy and validity across subgroups based on gender, age, education and migration background** |
| **Measurable** | Longitudinal predictive AI models for psychotic relapse will be trained on SLP/NLP derived speech-based features using Hidden Markov models using a separate test and train set. We aim for accuracy of 90%, with sensitivity and specificity both >80%. Test-retest reliability is assessed in citizens who experienced 2+ relapses. Sensitivity analyses are performed in sociodemographic subgroups and the effect of medication is assessed. Clinical variables are added to the model to  investigate if it improves classification accuracy. |
| **Achievable** | Dr. Sommer leads the HAMLETT Consortium (see page 17), which follows patients after their first psychosis and documents relapse. Speech samples at baseline (remission) and follow-up time points with information on clinical status (still remitted/relapsed) is available from 380 participants. Dr. Sommer’s team has the expertise and experience to analyse these existing data  using well validated SLP and NLP software (Opensmile, BERT, Alpino Parser). Dr. van Vugt (associated with Dr. Jaeger) is an AI expert, experienced with longitudinal analyses. |
| **Relevant** | This objective will inform which type of speech-based analyses are the best predictors for relapse and informs further WPs how to account for sociodemographic subgroups and clinical  information. |
| **Time-bound** | Given that data from HAMLETT is available, this objective (WP1) can be completed by M36. |
| **Specific** | **Objective 2: To validate an SLP/NLP-based psychosis classifier across 6 languages, 3 different speech tasks and subgroups based on gender, age, education and migration**  **background** |
| **Measurable** | Validation will be measured through accuracy metrics of the classifier developed with WP1, as applied in independent cross-sectional samples across languages, using maximally identical parameter settings, pre-processing, and algorithms (while adapting some of them, such as syntactic parsers, to the specific languages). Generalizability will also be checked at the feature selection level. This will be done in independent cross-sectional psychosis samples in five European languages and Turkish as required for WP4. We will also test generalizability to tasks not used in WP1, to prepare for optimal task selection in WP4. Beyond generalizability in terms of accuracy, interpretability will be measured by varying pre-processing choices and assessing their effect, testing for performance in relevant subgroups, comparing of machine- to human ground truth ratings (in story recall and picture descriptions), relating linguistic variables to symptom dimensions, and contextualizing algorithms against others targeting the same construct (e.g., coherence). This will be based, for the first time, on data collection across languages with a  harmonized speech-elicitation protocol across all participating sites. Accuracy and classifier performance across samples, tasks and languages will be compared and reported. |
| **Achievable** | This is achievable through previously unprecedented availability of speech data within the DISCOURSE consortium, the demonstrated expertise in Dr. Hinzen’s group at UPF in cross- linguistic investigations of speech in psychosis (covering English, peninsular and Chilean Spanish, Turkish and Chinese so far), and the availability of multiple existing algorithms with proven performance across multiple studies, and additional purpose-built ones specifically designed for  generalizability and interpretability. |
| **Relevant** | Generalizability, interpretability, bias assessment, and scrutiny of task effects are all critical components of any new trustworthy speech-based AI system bound for healthcare applications. |
| **Time-bound** | Given expertise within the present project, previous and our own pilot research, and data already being collected within DISCOURSE, WP2 can be time-bound to the first three years. |
| **Specific** | **Objective 3. To build trustworthy AI monitoring system using speech-based features** |
| **Measurable** | An effective AI-mediated clinical monitoring system must be both secure and have computational safeguards in place to protect users at all times. Security will be evaluated and established by  relevant experts in industry to ensure that the technical solution is - at all times during the lifetime of the project - both state of the art, future-proofed and conforms to the highest level of security |

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|  | possible. Computational safeguards will be incorporated into the model by integrating human-in- the-loop ML in the clinical implementation process such that humans will be alerted whenever there are outliers thus prompting review of the data. At the beginning of the project there will be a high level of human oversight (i.e., human-in-command) and as the model becomes more robust  and accurate, oversight will begin to be lifted (i.e., human-in-the-loop). This ensures participants optimal protection from spurious predictions. |
| **Achievable** | UiT’s Dr. Elvevåg has the expertise and experience to build a speech-based AI monitoring system that meets EU’s trustworthiness criteria (see Table 1.1). Dr. Mikaelsen (associated with Dr. Elvevåg) is a machine learning expert experienced in building clinical decision support systems  that predict risk. |
| **Relevant** | Human-in-the-loop methodology affords understanding of ML details, notably where model confidence is low, thus enabling implementation of safeguards to avoid spurious predictions. This allows expert humans to review data where models are unstable or will not generalize. Thus, humans can make informed decisions whether to *trust* predictions. Elvevåg has experience implementing such safeguards (i.e. in automatic scoring of story recall) by evaluating outlier  detection and inductive bias26. |
| **Time-bound** | Given the expertise of the team, and our research developing a secure IT infrastructure and automating a verbal assessment pipeline (i.e. delivering remote assessment, automating data transcription and scoring, and the eventual generation of a clinically actionable inference), this action (WP3) will create the infrastructure necessary for the RCT by 24 months and function  throughout the RCT (month 66). |
| **Specific** | **Objective 4. To assess efficacy of the AI monitoring system in a randomized controlled trial (RCT)** |
| **Measurable** | Efficacy will be measured by comparing time to psychotic relapses in the intervention group and control group. Additional measures include trustworthiness, global assessment of functioning, number and duration of psychiatric admissions, rates of self-harm (including suicide, suicide  attempts and aggressive incidents) and quality of life, all of which will be quantified. |
| **Achievable** | Led by UZH’s Dr. Homan who has substantial expertise in clinical research in schizophrenia,  including clinical trials. All international RCT partners have demonstrated that they can conduct challenging clinical trials in schizophrenia and recruit large numbers of participants. |
| **Relevant** | Clinical efficacy and trustworthiness of the speech-based AI system could directly demonstrate an impact in the real world. |
| **Time-bound** | The team of experienced investigators at different sites ensures that this objective (WP4) can be completed within the timeline. The objective will be completed by the end of the project (M66). |
| **Specific** | **Objective 5. To achieve trust and use by clinicians and service users** |
| **Measurable** | Clinician and service user groups will be set-up by GAMIAN and EPA and their inputs will be used in the design phases of the project. Surveys and information and feedback meetings will be organized throughout the project. Trustworthiness will be assessed in a qualitative interview with service users and clinicians who participate in the RCT. To get a sense of how the speech monitoring intervention is perceived by end users (i.e., service users and clinicians) compared to speech recording alone we will assess trustworthiness of the procedure (using the General Trust Scale, GTS)29 at every visit. In addition, after the last visit, assessors will be unblinded and have a qualitative interview with the participants and clinical team to assess acceptability, tolerability and  trustworthiness of the intervention. |
| **Achievable** | Work from UMCG’s Dr. Sommer has shown that service users welcome the idea of speech-based predictors in mental health care, as long as their privacy is guaranteed. EPA and GAMIAN are uniquely positioned to communicate with a large constituency of service users and clinicians. Their inputs will guide the design of the AI monitoring system for the clinical trial. We will involve AI experts and comply maximally with the EU trustworthy AI guidelines for model development (see Table 1.1). The ‘human-in-the-loop’ methodology will ensure oversight of the speech samples received by the model during the clinical trial and the participant will be always involved in the decision making. Since we rely on a human in the loop design where the clinician in charge plays a determining role in interpreting and acting upon the messages provided by the monitoring system, we hypothesize that differences in trustworthiness between usual care plus speech monitoring and usual care alone will be negligible and that an AI-based speech intervention  will be perceived as equally trustworthy as usual care by service users. |

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| **Relevant** | For an NLP-based AI monitoring system to become part of clinical practice, achieving trust from  clinicians and service users is fundamental. |
| Time-bound | Given the clinical trial timelines, success of the objective can be assessed by project end (M66). |
| **Specific** | **Objective 6. To evaluate the cost-effectiveness of the developed AI monitoring system** |
| **Measurable** | Feeding from the RCT data, we will develop health economic models with sensitivity analyses and adapted to select EU markets. SRI will perform validation of the economic model, including examining internal consistency, transparency and key input parameters, technical verification of  model calculations, and assurance of functionality and replicability. The economic model will be the basis of net present value calculations for the AI monitoring system. |
| **Achievable** | Led by Dr. Zoltán Kaló, Dr. Zoltán Vokó and Dr. Paul Keown, SRI scientists are experts in the interface of clinical research and health burden/economic analysis and have published widely in the area. The health economics group is supported by an economic modelling division led by Dr.  Balázs Nagy with extensive experience in economic evaluation of healthcare interventions. |
| **Relevant** | This is key for the valorization of the outcomes beyond project completion, enabling closing the  gap towards reimbursement and significantly advancing the innovations’ ‘market-readiness’. |
| **Time-bound** | Given the clinical trial timelines, the objective will be achieved by the end of the project (M66). |
| **Specific** | **Objective 7. To define the roadmap for protection and commercialization of the project’s**  **results** |
| **Measurable** | Led by Norinnova (UiT’s TTO) we will develop a business strategy with several commercialization routes, from formation of a spin-off company to licencing to established industry partners. Norinnova will also advice on possible IPR protection strategies and execute prior art or alternatively freedom to operate (FTO) analysis when the technology is more developed (has a higher TRL). The business strategy will integrate key elements for commercialization such as reimbursement (see Objective 6) and regulatory strategies. The  ‘business-readiness’ of the innovation will be assessed through the establishment of meetings with potential exploitation partners and the participation in industry events. |
| **Achievable** | Norinnova has business expertise and will consult market consultants and IP experts. Its role is to handle the commercialization process of research results from UiT and to ensure its realization  into society. SRI will provide support with the reimbursement strategy. |
| **Relevant** | A sound business strategy and tech-to-market plan needs to be developed to ensure the  sustainability of the project outcomes beyond the project. |
| **Time-bound** | All elements will be consolidated into a business plan by project completion (month 66). |

#### Pertinence to the call

Table 1.3 explains how TRUSTING addresses the Horizon Europe Trustworthy AI call requirements.

**Table 1.3.** Pertinence of TRUSTING to the Trustworthy AI call.

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| **Leverage existing high-quality health-relevant data from multiple sources taking into account the**  **individual’s genotypic/phenotypic, medical, life-style, socio-economic, behavioral data etc. and/or generation of new high-quality data necessary for the development of the AI disease-risk tools.** |
| Speech is an underutilized clinical biomarker and a high-quality data source owing to its unique properties (non- invasive, frequent, low barriers to access/generate, close reflection of state of mind)30. A wave of recent studies has demonstrated that SLP/NLP algorithms based on speech can categorize individuals with and without psychosis even when symptom severity is low and predict which high-risk individuals will go on to develop psychosis with high accuracy31,32. Such high accuracy can typically not be achieved with brain imaging or blood-based analyses, and such biomarkers are much more costly and invasive. Existing speech samples will be used (WP1, WP2) to develop the AI monitoring system (WP3), and new samples will be generated (WP4) for validation. We will leverage high-quality data from multiple sources thanks to clinician involvement in interpretation of the system’s outputs. Clinicians have access to the entire participant profile, including data such as lifestyle, socio-economic factors, medication use *etc*., which they will integrate with the speech-based prediction into the shared decision  making and treatment process. |
| **Develop adequate performance metrics to assess the technical robustness of the developed AI tools for risk assessment of disease and/or disease progression and in particular their accuracy, reliability,**  **reproducibility and generalizability33. Assess the possible inherent bias introduced to the AI tools originating from the data quality used for their development.** |
| The core philosophy of TRUSTING is in keeping with the anticipatory ethics approach33 and with principles  underlying trustworthiness, is that at all stages service users and clinicians co-design; in the development of speech tasks, implementation of algorithms and calibration of measures, method of recording and delivery of messages |

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| and payment for each recording. Reproducibility, reliability and generalizability are addressed across 6 clinical centers and across 6 languages (spoken by a total of 1.9 billion people globally, a quarter of the entire population). As SLP/NLP models are only as good as the language they are trained on, to avoid perpetuating bias and discrimination28,34,35, we will systematically identify possible sources of bias relating to gender, language,  educational level, migration background and age, and quantify these in WP1, WP2 and WP4. |
| **Implement proof of concept and/or feasibility studies to validate the AI tools for risk assessment of disease**  **and/or disease progression in a relevant end-users environment and/or real-world setting and assess their performance in comparison to the standard-of-care.** |
| After a development and validation phase prior to and feeding into the RCT, accuracy of the AI monitoring system will be assessed in terms of relapse prediction in the RCT control arm, in terms of false-positives and false- negatives. Six academic centers will recruit a total of 240 participants with a 1-year follow-up (see WP4 and  Clinical Trial Annex). |
| **Develop the criteria to assess the effectiveness of the AI tools for disease risk assessment in terms of**  **improving health outcomes and enabling personalized prevention strategies** |
| The primary criterion (endpoint) to assess the efficacy of the speech-based AI tool is improvement of a crucial health outcome: the time until a psychotic relapse happens during follow-up. Secondary outcomes include level of functioning, use of healthcare resources, and acceptability and trustworthiness for service users and clinicians of this novel AI-mediated intervention. In case of high predicted relapse risk, the personalized prevention strategies  may be activated through involvement of the triad of service user, informal caregiver and clinician. |

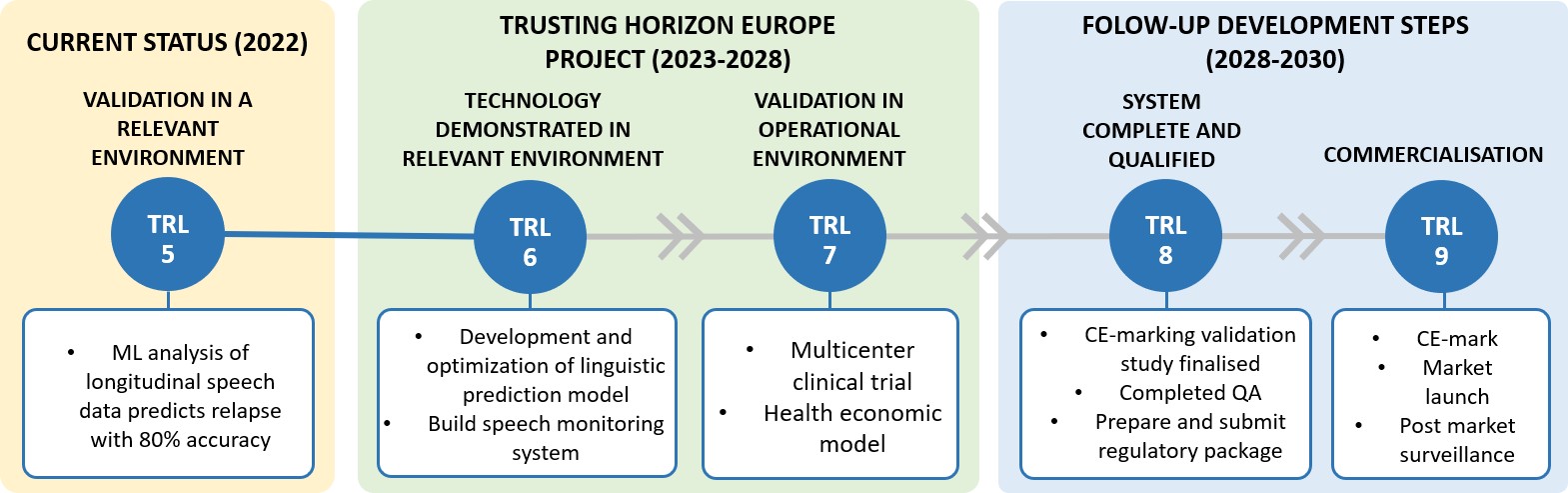
**State-of-the-art relevant to our work:** Thus far, our work and that of many others has shown that speech deviations as quantified with SLP/NLP can categorize those with psychosis from healthy individuals with very high accuracies (i.e., group-wise comparisons)22. NLP can also successfully predict the transition from ultra-high clinical risk states to psychosis18. The field is now making a start exploring sources of variability in existing results across both speech- and language-measures, such as sociodemographic factors and the relation to language28,36,37. SLP/NLP has never been used for relapse prediction so far, but our pilot work (see Section 1.2 - Methodology) demonstrates that this is feasible. Research on relapse prevention has mainly focused on improving treatment adherence as per depot medication or better adherence to oral medication6. However, the changing attitude towards maintenance treatment of both mental health care service users and clinicians calls for a different approach, namely that of timely warnings to provide a window of opportunity for preventive actions. Although digital monitoring of mental health has gained traction in recent years, SLP/NLP has not found its way into clinical application yet. The main reason is that prior studies have mostly been relatively small (with the notable exception of the ground-breaking EU project MONARCA38 which focused on the processing of speech sounds (not language) in bipolar disorder) and did not consider multiple languages; and these prior studies typically also did not consult with potential users of such technologies (individuals with mental illness and clinicians who treat them) to understand and consider their needs. To address this and to convince end users of such technology we propose to consult with them through a User Board during the entire project; and to capitalize on theoretically motivated and explainable AI that is trustworthy.

**Going beyond the state-of-the-art**: This is the first project to use digital phenotyping of spoken language to recognize early warning signs of imminent psychotic relapse. TRUSTING will, for the first time, aim to show that speech-based features hold the key for the transition from ordered (remitted) to disordered (relapsed) state of mind. So far, studies of spoken language often used one type of SLP/NLP software, thereby focusing on specific aspects such as acoustics, semantics, or syntax. TRUSTING will combine and comparatively assess multiple levels of linguistic analyses to accommodate diversity (see Key Concepts “Combining different speech/language analyses”), and develop and test new models specifically designed to help identifying cross-linguistically generalizable patterns of speech in psychosis. This addresses emerging evidence of failures of replication of previous classifiers in other datasets28,35, and in languages other than those for which they were developed36,39, as well as inconsistent and language-specific relations to clinical symptoms36. In addition to comparing groups (citizens with a diagnosis of schizophrenia maintaining remission versus citizens experiencing relapse), we will track individuals longitudinally and compare their speech-based features over time to their own patterns as recorded during psychosis and remission. WP1 will pioneer the implementation of this intra-individual SLP/NLP design to predict psychotic relapse using a large existing cohort and test the best set of predicting speech-based features in an independent longitudinal sample (see Key Concepts “Longitudinal analyses”). We will then for the first time validate this relapse algorithm across different languages, tasks and in specific subgroups in WP2. TRUSTING will further advance the field by building an online speech-based AI monitoring system with human oversight (see Key Concepts “Human oversight”) that meets all national and international legal requirements for handling privacy-sensitive data. Crucially, the project will minimize risk in relapse prevention through the use of novel speech-based relapse prediction while including service- users in a shared decision-making process, in line with the “do no harm” principle40. Finally, we will also go beyond

the state of the art in testing the AI monitoring system for accuracy, efficacy, health-economic benefits, acceptability and trustworthiness in a well-powered international RCT. As the current habits and preferences of service users and clinicians have never been assessed, an important novel step that TRUSTING will take is to identify habits, preferences and dislikes of these stakeholders and collaborate with them to design an acceptable and trustworthy relapse prevention system.

#### Stage of development - Technology Readiness Level (TRL)

While SLP/NLP analysis is easily conducted, the technology readiness level (TRL) for this clinical application of predicting relapse is at level 5 (technology validated in relevant environment, i.e., lab scale). TRUSTING will be the first to concurrently solve the complex legal, privacy and ethical obstacles, *and* create a monitoring system that leverages such analysis of spontaneous speech to be used for 5 European languages and Turkish *and* validate it in a clinical trial. These actions will bring the relapse predictor to TRL 7 (system prototype demonstration in operational environment). Following completion of this project, we will seek progression to TRL 8 (system complete and qualified), which involves pursuing a CE mark in line with EU medical device regulations. For an overview of the remaining TRL steps towards market, see Figure 1.2 below.



# Methodology

**Figure 1.2.** TRL pathway of the TRUSTING AI monitoring system.

#### Key concepts, models and assumptions underpinning our approach

* **Combining different SLP/NLP analyses to improve predictive accuracy:** While previous analysis has shown that we can detect aspects of psychosis in speech, psychotic relapse is a heterogeneous condition and speech deviations that are most characteristic for one person’s relapse may be absent in another person’s relapse. To adapt to this diversity, we will use predictors from 1 SLP analysis (OpenSmile) and 2 NLP analyses (BERT and Alpino Parser) allowing for a large variety of speech features. Previous work from partner 1 showed the SLP- NLP combination to provide higher accuracy41.
* **Choice of AI paradigms: longitudinal individual analyses:** We not only want to know whether a person will relapse, but also when he/she will relapse. In order to give reliable, timely, individual predictions, we will gather repeated samples and use algorithms that are sensitive to longitudinal changes within a single person, which reduces a large source of heterogeneity. In WP1 we will use a hidden Markov model42. Such longitudinal models are well suited for predicting trajectories of time series when the dataset is relatively small, as in the case of HAMLETT which has only five speech samples per participant. In the RCT of WP4, however, we will gather 52 speech samples per participant and expand the longitudinal AI paradigm to Echo State Networks (ESNs) —deep neural networks that are well-suited to make predictions in chaotic time series in larger datasets43. ESN was developed by Dr. Jaeger, who is a close collaborator of partner 1, and is a highly interpretable neural network (<https://www.ai.rug.nl/minds/research/esnresearch/>). Previous work with ESNs has shown that the networks can accurately predict decline in renal function44. Moreover, ESNs have been shown to be able to predict the identity of a speech fragment45, which shows these models are able to detect subtle changes in speech. Finally, and quite relevant for detecting relapse, ESNs could successfully detect emotions in speech46. The RCT will record speech when participants are still psychotic and repeat recordings when in remission. The prediction will start after those two recordings, so that the model can already learn from those two states (i.e., psychotic/remitted). Since the same psychotic symptoms tend to reoccur in a relapse, similar speech deviations as recorded during the initial psychotic episode are expected again with emerging relapse.
* **Human oversight:** In keeping with the WHO’s definition of human oversight of the effective, transparent monitoring of human values and moral considerations, TRUSTING will reduce threats to human agency by

mitigating risks of bias from automation by ensuring that all stages of the project have suitable and timely human oversight in the forms of “human-in-the-loop”, where human experts can approve or deny any action or decision at all stages. We will begin with a high human oversight level (human-in-command) as per the early stage of WP3 (before the RCT starts in month 24) and as the model proves to become more robust and accurate (during WP4), oversight can begin to be lifted (human-in-the-loop) and eventually only needed for extenuating circumstances. During the RCT, human experts will monitor the system at 3 levels: locally (audio quality and ASR correction), centrally (model accuracy and outlier checking) and clinically (integrating predictions with other clinical information). Human oversight will begin with complete checks of all data and will reduce to sampling outliers once accuracy of ASR and the AI model is established. Thus, critically during the RCT, numerous experts will be situated to monitor the system and potentially augment, override or deny AI predictions from affecting the citizen.

#### Preliminary data obtained

* **Relapse prediction**: UMCG analyzed longitudinal speech data of the first 104 HAMLETT participants (ongoing Dutch cohort followed since the 1st psychosis). Speech recordings were made at baseline and after 3, 6, 12 and 24 months. Speech was analyzed only for acoustic features (SLP). The main analysis was the prediction of relapse vs non-relapse within 3 months after a speech recording, with random forest algorithms, using 10-fold cross- validation. 21 participants relapsed within 3 months after a speech recording versus 24 participants who did not relapse within the follow-up period. 31 participants were lost to follow-up, 16 relapsed outside the 3-month time- window and the remaining 12 participants are still within the follow-up period. The relapse vs non-relapse groups did not differ in age (F(1,43)=.719, p=.401), education level (F(1,43)=.009, p=.927), or gender (χ2=1.435, p=.231). We identified an ML classifier that had an 80.8% accuracy in predicting relapse. We checked for overfitting (given the small sample), which was not the case, as shown in area under the curve (0.750) and F1 (0.762) of the classification algorithm in this pilot. The best predicting features included loudness peaks per second - a proxy for speech rate – as well as measures of pitch and tension (spectral slope). Speech rate is often associated with cognitive functioning, and might be a reflection of attention problems people experience with increasing psychotic tendency, while pitch and tension in voice are highly associated with anxiety (most delusions and hallucinations are frightening). This pilot study confirms earlier work from UMCG in which OpenSMILE features were used to recognize positive and negative symptoms16 since there is a large overlap in top-performing features. By combining SLP with NLP software and using a larger training and validation sample, we are confident that the accuracy of relapse prediction can be further improved here.
* **Combining multiple levels of linguistic analyses**: Recent work from UMCG investigating 94 participants with schizophrenia and 73 healthy controls demonstrated accuracy of around 80% for both SLP (i.e. acoustic analyses)

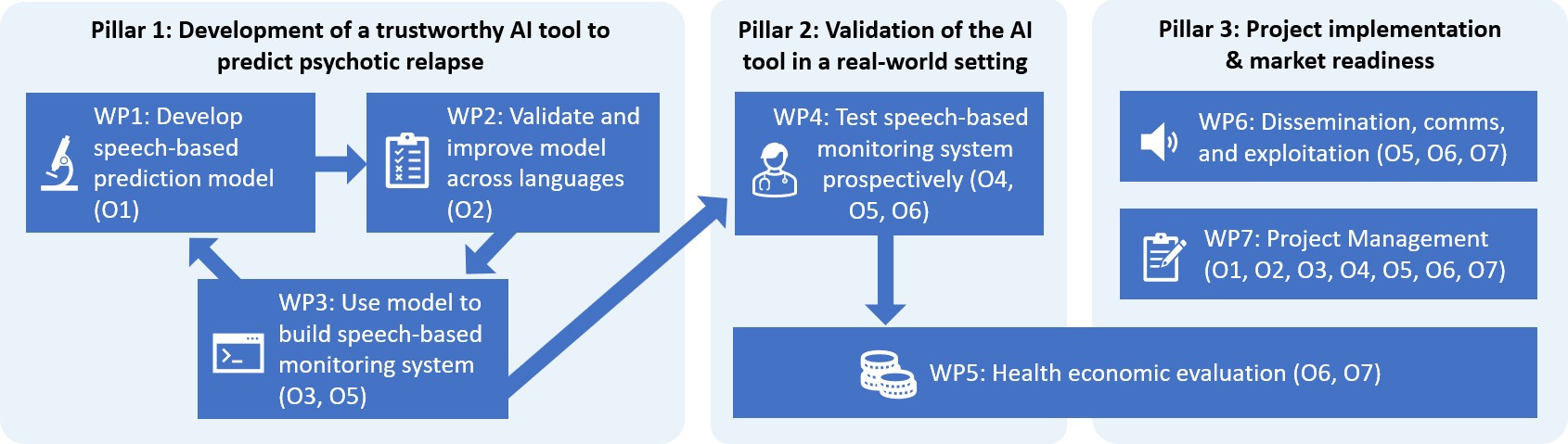
and NLP (i.e. semantic space) analyses, but the accuracy improved to 85% with a combined classifier using features from both tools (SLP and NLP)41. In TRUSTING we aim to further improve accuracy by adding additional SLP/NLP tools.

* **Generalizability of linguistic features relating to psychosis across languages**: While psychosis is nothing language-specific, languages differ across all levels of linguistic organization. Hence automated SLP/NLP systems may not detect linguistic deviations relating to a psychotic process consistently or with similar accuracy across languages36,47. Recent work by UPF has shown across 3 languages from 3 distinct families (English, peninsular Spanish, Turkish) that semantic and temporal aspects of the referential structure of discourse identifies speakers with psychosis, especially those with elevated levels of formal thought disorder, with the same speech- based features48–51.
* **Remote collection of speech samples**: UiT has remotely (and securely) collected speech data from several hundred psychiatric, neurological and healthy control participants52–54. Importantly, the brief and engaging tasks were tolerated well by the diverse users54,55. Participants were prompted to self-administer tasks (by a digital device) or asked over the ubiquitous telephone to listen to and retell specific stories. Then humans listened to the verbal responses and rated them for retelling accuracy, with the goal of creating an automated method of rating recalls that performed as well as experts. First, humans transcribed the response recordings and the semantic similarity of these transcriptions to the original stories was computed using NLP techniques. The same procedure was used on transcripts derived using generic and customized automatic speech recognition (ASR). Although word error rates seemed high, performance of the predictive model was within the level of individual raters demonstrating the robustness of the procedure. The linear model represented the human ratings well. In further work from UiT the word error rate was further (and dramatically) reduced by building in-house customized language models tailored to the specific task. Importantly, audio quality of remotely recorded speech was adequate for all types of SLP/NLP analyses. In conclusion, these story recall tasks reliably engage participants to generate speech, the data are robust and well-suited for full automation (i.e., remote delivery of assessment, ASR and scoring, and subsequent generation of clinically actionable inferences)56. Importantly, UiT has already

evaluated how to implement computational safeguards and human in the loop procedures with the design of these story recall tasks26,56. Finally, frequent assessment requires multiple robust versions of the same speech elicitation task and this research has already generated two dozen comparable stories and confirmed their sensitivity and usefulness for the specific clinical task57.

#### Project methodology

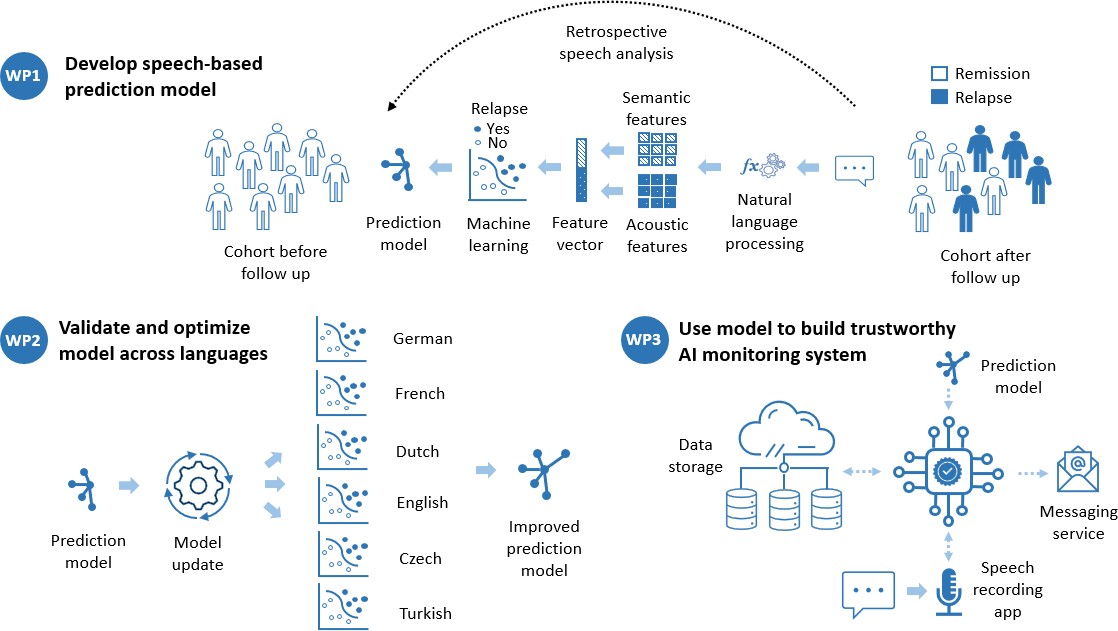
To meet the objectives defined in Table 1.2, we have designed a methodology divided into 3 main pillars, corresponding with the development of the trustworthy AI system, its real-world validation, and the project implementation and market readiness. Figure 1.3 displays these and their relationship with the objectives.



**Figure 1.3.** Overview of the methodology of TRUSTING and relation with the defined project Objectives.

#### Pillar 1: Development of a trustworthy AI monitoring tool for the prediction of psychotic relapse (WP1-3)

The development process of the AI monitoring tool is summarized in Figure 1.4 below.



**Figure 1.4.** TRUSTING AI monitoring system development process overview.

#### Pillar 1: Develop and validate linguistic prediction model for use in a real-world clinical setting (WP1-3)

**To create an accurate speech-based predictor for psychotic relapse and assess accuracy and validity across subgroups based on gender, age, education and migration background (WP1)**

As a preparatory step to the RCT in WP4, data from the ongoing HAMLETT cohort will be used to create a speech- based model to predict relapse. Pilot work from UMCG in a subset of this cohort showed that by using acoustic information in speech, a relapse prediction accuracy of 81% can be reached (see preliminary data obtained). Although we are confident that this accuracy can be increased by modelling intra-individual variation in the full HAMLETT cohort and the sample of the RCT, we will test the predictive power of additional types of NLP-based data in WP1. The reasoning for this is twofold: i) previous work by UMCG showed that the combination of acoustic features with semantic space analysis (NLP) improves classification accuracy41 (Key concepts) ii) it is not yet clear how well

acoustic features (i.e. surface level features) generalize over different languages and over different tasks (which will be further tested in WP2, and see Parola et al 2022)36. Deeper level features at the semantic level are more likely to generalize over languages, which differ most on the surface (i.e., the sounds) and less on the semantic information (i.e. the thoughts) conveyed. A combined SLP/NLP approach using OpenSmile, BERT and Alpino Parser will therefore be first tested in the HAMLETT cohort.

HAMLETT cohort: Speech has been recorded at remission after the first psychotic episode and consecutively after 3, 6, 12 and 24 months. Each speech sample will be divided dichotomously as preceding a relapse (if relapse is documented within a month after recording the speech sample) or not. Relapses are defined as clinical deterioration of a minimum of one week duration, having clinical consequences (re-starting antipsychotic medication, hospital admission) confirmed by a Positive and Negative Symptom Scale (PANSS) positive subscale item score of at least

≥5. HAMLETT currently has 97 documented relapses, but this number will be >150 by the project commencement in 2023.

Interview procedure: Speech is elicited using a five-minute semi-structured interview consisting of predefined neutral open-ended questions (questions provided in16). Speech is recorded on separate channels for participant and interviewer using cardioid head-set microphones, with a sampling rate of 44.1 kHz.

Speech pre-processing: All audio files will be manually checked for acoustic quality (human in-the-loop) using standardized quality assessment forms. Crosstalk is removed by selecting speech segments on the participant’s channel in which interviewer is silent, with the annotate to text grid silences function in PRAAT16.

Acoustic analyses (SLP): Acoustic speech analyses capture a range of speech-related dimensions that have been associated with schizophrenia, including emotion (i.e. flat affect), cognitive abilities (i.e. pausing patterns), as well as speaker characteristics (i.e. gender, age). Previous work on this topic used highly diverse and unsystematic methods as reviewed by15, and it is not yet clear how well these features generalize across languages and language elicitation tasks36 (WP2). Therefore, we will use opensource software and standardized feature sets for acoustic features to ensure easy replication. The acoustic parameters will be extracted with the GeMAPS parameter set developed for the open-source speech analysis toolkit OpenSMILE58, resulting in a total of 88 parameters per participant that describe temporal, frequency, spectrum as well as energy related aspects of speech. For comparability and evaluation of methods, we will also use the open-source Praat-plugin Prosogram 3.0.1 ([h](https://sites.google.com/site/prosogram/))ttps://sites.google.com/site/prosogram/), for automatic acoustic segmentation into acoustic syllables and nuclei, which yields a highly interpretable set of 29 features defining the acoustic-prosodic profile of a speaker. This program is run (i) offline, and (ii) no data from TRUSTING goes out of TRUSTING to Google.

Automatic speech recognition (ASR): ASR technology allows for the quick conversion of speech into text with human-like performance levels for most languages59. An automatic de-identification method60 will be used to de- identify all written text before it is entered in the study database. This includes removal of all names, dates and locations (cities). Although current state-of-the-art ASR tools still make errors, prior research from UiT52,53 showed that word error rates (WER) between 10% and 25% did not affect the performance of the final classification models. In contrast to other fields such as finance, exact transcriptions are not necessary in psychiatric applications since these rely on the statistical properties of whole samples, hence higher WER have little impact on the classification outcome. If the WER is higher than expected (i.e. >25%) the automatic transcriptions will be manually corrected by using the ASR’s certainty estimates. These indicate how certain the tool is about each given word (from 0-100%). Words that the ASR is uncertain about will be corrected first to reduce WER. This will be done using forced alignment, in which the automatically generated transcriptions are aligned with the audio files, making it possible to click on a word in the transcript and listen to the corresponding audio segment (i.e., human-in-the-loop). We will further examine the errors made by the ASR qualitatively, using grammatical part-of-speech classes (POS), most frequently misrecognized words, and their linguistic position within a sentence, to improve ASR performance.

BERT-type models (NLP): Semantic space models (e.g., word2vec, LSA, BERT) aim to capture meaning in language by representing words as mathematical objects (i.e., vectors) in a so-called semantic space. UIT was one of the pioneers of using such models (in this case LSA) to capture disorganization in speech61. Such models have been proven useful in prediction conversion into psychosis in high-risk individuals18,19 and have been associated at the symptom level with formal thought disorder. Bidirectional transformer models such as BERT62 are word embedding models similar to word2vec, but they have the advantage of handling longer input sequences as well as taking into account the relations within these sequences. Therefore, BERT models are better at capturing the (semantic and syntactic) aspects of a certain word as occurring within its contexts (the surrounding words). This enables BERT to find long range dependencies in text, leading to more robust language models for assessing language characteristics63. Unsurprisingly, current NLP research is dominated by BERT-like transformer models. UMCG recently built a large Dutch BERT-type model, belabBERT, to be used for this purpose. BelabBERT outperformed the best BERT-model

for Dutch (RobBERTa) as well as acoustic analyses (OpenSMILE) in the classification of psychiatric disorders (schizophrenia and depression)64.

Graph-theoretic analyses (NLP): For structural language analysis, we will map speech transcribed as text onto different types of networks and analyse these using graph theory. First, parse trees will be generated by inserting transcriptions into a syntax parser (i.e. the Alpino Parser for Dutch), resulting in one parse tree per utterance. Parse trees describe the internal syntactic structure of a sentence. Each place of division in the parse tree (i.e., a word or syntactic category) is recoded as a “node”. Lines between the nodes are coded as “edges”. The resulting syntactic tree will be analyzed as a network using graph theoretic measures. For each utterance, we calculate both local and global graph network measures, including centrality measures, compactness measures and network efficiency. Measures sensitive to sentence length (i.e., diameter, path length and efficiency) will be normalized by the total number of nodes in the graph to control differences in verbosity of participants (i.e., alogia). Second, we will generate networks sensitive to referential information specifically. This is based on the fact that, (i) while languages differ across all levels organization, they (ii) differ less at the structural semantic level, i.e., the referential content or thought conveyed, and (iii) it is this level that plays a crucial role in a clinician’s judgement that speech in psychosis is hard to follow or even incomprehensible. Reference is a universal and primordial feature of language, without which it would not be interpretable or translatable at all – suggesting bias-robustness and generalizability as explored in WP2. Referential anomalies can identify psychosis groups and are not confined to those with formal thought disorder35,39,48,50,51,65. We will therefore construct graphs in which this referential information is captured (i.e., nodes will be referential noun phrases picking out entities in the world that are being talked about, e.g., the speaker’s mother or teacher). Nodes are connected by edges through time, and if a speaker comes back to the same entity during a narrative (i.e., his mother), the edge loops back to the same entity50,51. These graphs therefore capture the dynamic properties of meaning as a narrative progresses from mentioning one entity to mentioning others, and returning to some of these entities within certain limited windows of time. Pilot work from partner 351 has shown in Spanish that these temporal windows of recurrence are enlarged in speech from participants with a psychosis, creating referential confusion interpretable as relating to a distorted thought process and indexing a potential cognitive mechanism underlying it. Concurring with the aim of explainable AI, the resulting models are fully interpretable and theoretically motivated, satisfying recommendations for clarity on *what* we are measuring, *how*, and *wh*y66.

Machine learning analyses: Speech features of all SLP/NLP analyses will be entered as input for the prediction model for relapse. We will first train the classifiers on the separate analysis tools (SLP, BERT and graph-theoretical) to assess the performance of the different types of tools. We plan to use a final set of 10 features for the classifiers in WP1, because a small number of features reduces the risk for overfitting. Previous work by UMCG has shown that using the top-10 features results in similar accuracies as using the full set (>50 features)41 (To select these 10 features, we will use a prototypical constraint-based algorithm (PC) prior to classification to identify dependencies in the selected set of variables to eliminate redundancies, so two measures that are highly correlated will be reduced to one67. In addition, we will check for correlations between the features and symptomatology, to select meaningful features for the model. The best set of predictive speech-based features will be selected using the Utrecht dataset as a training set (now at 255 participants). Its generalizability will be tested on the independent Groningen dataset of this cohort (now at 175 participants). We will compare each new audio recording to that person’s recording at baseline (during remission). As such, these models account for intra-individual variation, which will remove a large source of variation in the data. Based on the combined features of the SLP/NLP algorithms and using a Hidden Markov model we will provide a relapse risk plus confidence interval from each recorded speech sample. Test-retest reliability will be investigated in participants who had two or more relapses during follow-up (currently 37 persons). We will also test accuracy in four sociodemographic subgroups, namely subgroups defined by age, migration background, gender and those with few years of education (<10), to check whether the classifiers systematically mispredicts a certain sociodemographic group. In addition, we will assess the influence of antipsychotic medication and investigate whether the model accuracy increases by adding demographic and clinical information such as age, gender, substance use and disease duration. Asin the health and medical domain there is a performance-explainability tradeoff, machine learning is often used in a purely data-driven fashion without providing mechanistic insight that would explain why and how a predictor works. We will therefore aim not only for accurate but also interpretable predictions, by developing and applying a limited and theory-driven set of speech features. We will report importance of all speech features for models, as well as in-depth interaction where available, such as visualisation of decision trees and Markov models. We will use post-hoc methods to explain more accurate but less explainable black-box methods. To ensure clinical validity, thorough and meticulous testing of trained models, subgroup analysis will be performed.

Output of the WP: The main output of WP1 will be the knowledge on (i) which methods (i.e., SLP (OpenSMILE, Prosogram), and NLP (BERT-type, graph-analysis, referential graphs) deliver the best accuracy for relapse

prediction, (ii) whether models should be trained on different sociodemographic subgroups, (iii) how to account for antipsychotic medication, and (iv) whether to add demographic and clinical information to the final model. Based on this knowledge, in WP2, we will establish which of the methods and features selected in WP1, generalize over the 6 languages and over language elicitation tasks, so as to optimally inform task selection in WPs3-4. In addition, the data used in WP1 (the HAMLETT cohort) will be used for model training in WP3.

#### Validation of the SLP/NLP-based relapse classifier from WP1 across 6 languages, 3 speech elicitation tasks, and subgroups based on gender, age, education and migration background (WP2)

WP2 will co-develop the classifier produced in WP1 and validate it in independent samples in different languages. In addition, its performance on speech data obtained from different speech-elicitation *tasks* will be assessed. For translation of current SLP/NLP into clinical practice, *generalizability* of currently available classifiers has emerged as an important challenge to be addressed15,36,68, and it arises specifically in the setting of our RCT, where different languages will be used (WP4). If indeed certain language changes relate to psychosis, this should be so in all languages, not merely in, say, English. Yet languages differ, and the relation between language and psychosis is necessarily mediated by these differences. Currently, information from large samples using the same recruitment criteria, elicitation tasks, and analysis protocols, is lacking to address this generalizability challenge. We will do this in WP2 by using the largest dataset on speech in citizens experiencing psychosis ever collected, the Psychosis speech bank of the DISCOURSE consortium (<https://discourseinpsychosis.org/>), which was founded in part for this purpose. As longitudinal data are not available cross-linguistically yet, these will be cross-sectional data: if a model is able to recognize schizophrenia in people in remission, it should also do well at recognizing acute psychotic symptoms. Our focus in addressing this generalizability challenge will not merely be to ask “what works?”, but “why it works”, so as to enhance interpretability and build generalizability on it. Challenges to generalizability as currently identified68 can come from: (i) *lack of objectivity* of SLP/NLP measures, which may inherit human bias and deliver signals confounded by factors such as age, education, gender, or ethnic subgroup69; (ii) *lack of interpretability:* e.g. at the semantic level of NLP analysis, we need to know which linguistic patterns measures of coherence or connectivity reflect and how they can be confounded by low-level linguistic factors such as sentence length, repetitions, or pre- processing35,36,39,69,70; (iii) *Construct validity*: SLP/NLP measures purporting to measure psychosis need to relate to clinical and cognitive measures of the latter (e.g. thought disorder, flat affect or incoherence), and such relations have been found to be inconsistent or missing across studies as stated by14,19,36,39,47; (iv) *Methods-dependence*: Automated analyses of some clinical construct (e.g. coherence or tangentiality) can be performed using more than a dozen classifiers purporting to target this construct, but when applied in conjunction, these often yield highly inconsistent results, without the reasons for this being clear (e.g. both increased and decreased average semantic similarity in psychosis groups compared to controls), thus revealing an unexplained dependence on algorithms, parameter settings, modelling decisions, pre-processing, etc.14,35,39; (v) *Task*-*dependence*: Speech can be elicited in many ways with evidence of task-effects70–72, which clinical applications need to be sensitive to.

Addressing these challenges: First we will take the classifier developed as part of WP1 and apply it across the languages of the DISCOURSE dataset with minimal modifications in the methods as required (i.e. using language- specific syntactic parsers as provided by UDPipe, https://bnosac.github.io/udpipe/en/, and language-adapted versions of BERT). Then we will test for the effects on classification accuracy of different pre-processing choices (i.e. removing fillers, repetitions), of low-level unintended linguistic parameters (i.e. sentence-length, which has been shown to independently predict automated coherence measures:14,35,39), of different algorithms targeting the same construct, and of tasks. For construct validity we will check consistency of predictability of clinical symptom profiles across samples and languages from SLP/NLP variables. We will also use human ground truths for assessing interpretability of machine-based classification, i.e. by comparing machine-based rating of story recall to human ratings, making sure they match; and by measuring semantic distances between ground truth descriptions of the pictures used and descriptions of participants with schizophrenia. Effects of socio-demographic variables (age, gender, education, migration background) and medication will be checked by running separate classifiers for subgroups and checking misclassifications for whether they specifically concern particular subgroups73 and by adding these variables to the classifiers so they are taken into account by the classifier, and compare results with and without these additions.

Dataset: For this WP, we will use data from sites of the DISCOURSE consortium that participate in its speech data generation scheme and protocol (currently standing at 11 worldwide). This consortium seeks to overcome the scarcity of available speech data in psychosis, which is striking in a clinical context where provision of health care is almost entirely based on naturally occurring spoken language conversations74. This includes confronting ethical challenges of making such speech data available, on the model of how these have already been successfully overcome in such cases as AphasiaBank and DementiaBank (<https://www.talkbank.org/>), resulting in a new PsychosisBank. Sites will apply for ethics with the specific purpose of using the DISCOURSE protocol and making data available on this

model, a process already successfully completed at several sites including Marburg (Germany) and London, (Ontario). The DISCOURSE protocol also harmonizes technical aspects for how to record, de-identify and transcribe speech data consistently across sites, and which clinical data to provide. This protocol has been designed for this purpose by UPF together with members of the steering committee of the DISCOURSE consortium, of which both UMCG and UPF partners form part.

Speech elicitation tasks: The protocol comprises seven tasks, of which we will specifically focus on speech generated from a free speech task (echoing task elicitation in WP1), a picture description (to have comparability with a majority of previous studies in this field), and a story recall task. Choice of story recall task is motivated by (i) extensive prior work by partner 4 on the use of NLP tools to assess performance on this particular task, and implementing it in a remote-monitoring device52,53, and (ii) the prominence of verbal working memory impairments in schizophrenia. While the HAMLETT dataset from WP1 uses a free speech task to elicit speech, recent work has shown picture descriptions or story retelling tasks could outperform free speech tasks in predicting psychosis70. All naturally or experimentally generated speech reflects language capacities in the context of a particular cognitive task and its specific demands. Picture descriptions demand attention, while story retelling tasks rely more on verbal memory. General cognitive deficits (like memory and attention deficits) are common in schizophrenia. However, cognitive symptoms often persist and are stable over time, while positive symptoms fluctuate and are associated with relapses. Speech tasks with a high cognitive demand may therefore be more suitable for recognizing negative or cognitive symptoms, but perhaps to a lesser degree for recognizing relapse. Since both tasks are readily available in DISCOURSE, and UiT has ample experience with story recall task and automatizing scoring recall, we will evaluate the classifiers on both story recall and a free speech task, while including picture descriptions mainly for consistency and comparability with the majority of previous studies in the field. Based on this we can make the best-informed decisions for implementation in the AI monitoring system developed in WP3 and the RCT in WP4, taking into account its cross-linguistic setting.

Data availability: Within the DISCOURSE consortium, data are currently already being collected, or ethics for collecting them is in progress, across 11 sites in 8 countries, with further sites expected to join the consortium during the coming year. Several sites have successfully passed ethical approval for the DISCOURSE protocol and data sharing, and DISCOURSE offers assistance in ethical applications. Recruitment targets at each of these sites are between 50-100 participants with psychosis, matched to controls, suggesting it will be the largest speech database in psychosis ever collected. We will have access to harmonized data from a total of currently seven languages from at least three different families including those used in the RCT of WP4.

Sample size estimation: Parola’s 2022 meta-analysis of semantic classifiers in SZ 36 reports a mean sample size of participants with schizophrenia in previous studies of n=34. Studies are difficult to compare as they differ across numerous dimensions including sample selection, pre-processing, choice and parameterization of classifiers, and reporting. This makes calculation of expected effect sizes difficult. In WP2, we reckon with samples of n=50-100 in the schizophrenia groups per language/site. This will result in an estimated total sample of people with schizophrenia of at least 300 in total, from each of which we are expecting to obtain at least three speech samples, resulting in at least 900 audio samples and a matched number of control samples.

Output of the WP: This WP2 will deliver information about generalizable and interpretable features and classifiers in specific tasks, in the form of classifier performance metrics, which will optimally inform the choice of a task design in WP3 and afterwards WP4.

#### Creating a trustworthy AI monitoring system using on speech-based features (WP3)

In the first year of the project, a survey among service users (performed by GAMIAN) and among clinicians (performed by EPA) will assess current practices around relapse prediction and investigate which methods these stakeholders would, and would not, use.

Co-design by service users and clinicians: The system will be co-designed by the relevant stakeholders, which are the service users represented by GAMIAN regarding the speech recording part and the clinicians represented by EPA regarding the message receiving part. Our experience is that with excellent user-engineering it is possible to collect high-quality data frequently and maintain participation over time by administering multiple test versions55. In keeping with promoting equity in health, the system to collect speech data will be built using progressive web applications and thus be able to be used regardless of platform (i.e. web or smart device). To ensure participants’ willingness to keep using the system, we will employ short and entertaining tasks. A small monetary incentive per recording will improve motivation to provide the high number of speech samples required for the RCT. This necessitates development of a computational infrastructure to enable the remote monitoring system capable of recording participants’ speech, transferring it automatically to a secure data repository and analysis environment (Services for Sensitive Data; TSD at the University of Oslo, Norway), and generating predictions of suspected relapse (and that

after a full-scale clinical trial in the future could be used as feedback and alerts for relevant people, notably clinicians). When a prototype of the speech-based AI monitoring system has been developed, it will be tested and evaluated by both groups for trustworthiness and user-friendliness. Results from the user and stakeholder evaluation will be integrated into the monitoring system’s design. This WP also includes legislative and technical work to ensure compliance with prevailing data protection regulations across the relevant countries. As our user inquiry indicated75, privacy is of utmost importance and the system will adhere to the strictest privacy rules. TRUSTING will provide built-in safeguards to check for errors and avoid spurious predictions and decisions by enabling a ‘human in the loop’ system that ensures humans review data where models are unstable, bound not to generalize or simply do not make sense clinically. To use the speech-based marker in practice, potential users need to be educated, motivated and empowered. GAMIAN and EPA will create a living document (or interactive video) to fulfil this task.

Output of the WP: This WP will provide the core data collection, transfer and analytic infrastructure for the speech monitoring system for the RCT in WP4 to be conducted with.

#### Pillar 2: Validation of the AI monitoring system in a real-world setting (WP4-5) Testing efficacy of the AI monitoring system in an RCT (WP4)

The finalized AI monitoring system will be used to test real-life efficacy and trustworthiness in a multinational RCT

across the five European languages and Turkish (Fig. 1.5). Qualitative interviews with both user groups who have used the device during the trial provides valuable feedback to ensure acceptability and trustworthiness among service users and clinicians. A recent trial76 that applied digital technology to monitor early warning signs and detect and prevent relapse was found to be feasible, safe, and acceptable.

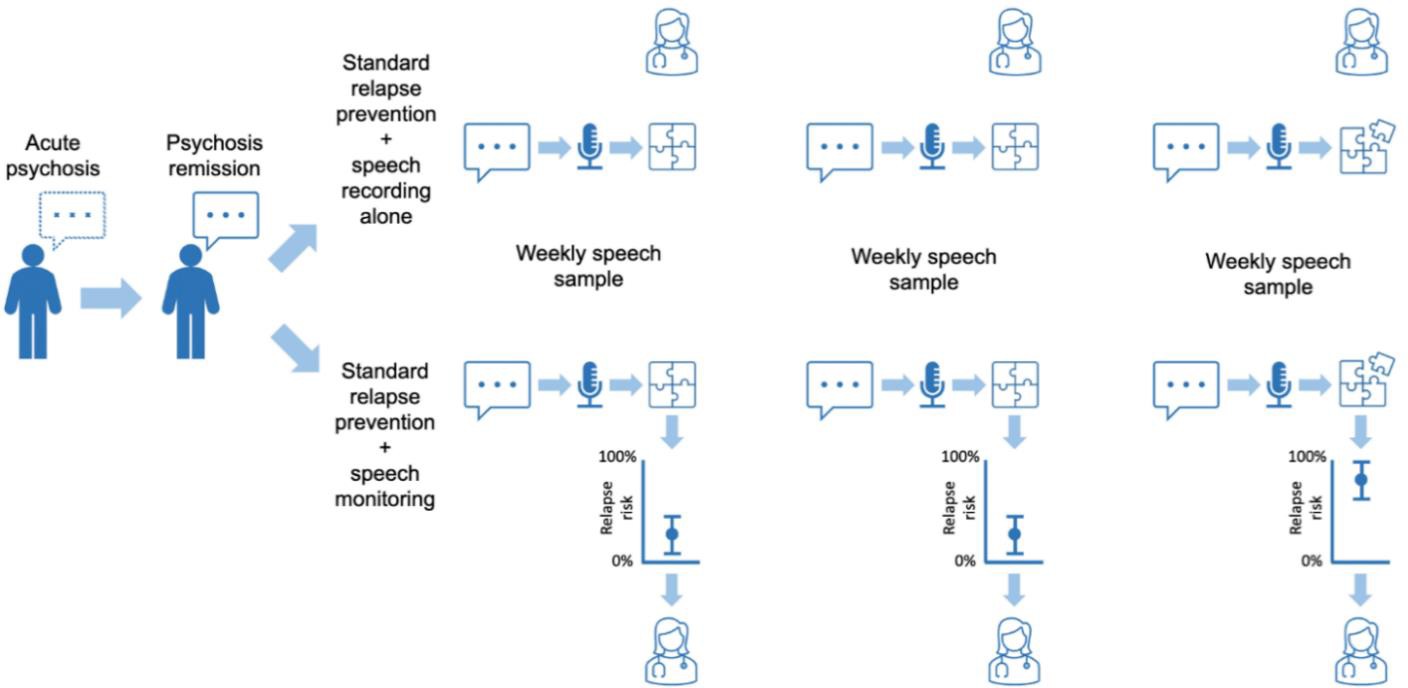
Co-design by service users and clinicians: The RCT will be co-designed by service users who have experienced psychosis and clinicians who treat citizens with psychosis, both part of the TRUSTING User Board. Procedures of visits, outcomes, speech recordings and messages will be confirmed upon dialogue with the User Board. We will also consult with SRI to align outcomes optimally with WP5. An initial meeting will be held to confirm the prototype developed in WP3. Based on this meeting, we will select the most user-friendly speech recording method. In a second board meeting, we will go through the proposed speech elicitation task, fine-tuned and potentially extended in previous work packages (WP1-WP3), and will confirm with the User Board that it is suitable for speech recordings. Outcome measures of the RCT may be adjusted or extended on the initiative of the User Board.

Sample size estimation: We expect an annual relapse rate of about 43% due to a high rate of medication discontinuation, similar to the rate that was found in the HAMLETT cohort from the UMCG partner leading WP1. Based on the effect estimated in a meta-analysis of relapse prevention through early warning signs77 (our power calculation (that also considered a 33% drop-out rate) resulted in 120 inclusions per group, hence N=240 randomized participants in total.

Flow of the RCT: On enrolment, participants, their informal caregivers and their clinicians together will carefully design an individualized relapse prevention plan, including an individual range of relapse risk (within which a clinician will contact the participant for a shared decision appointment, see below) and how to act in case of expected relapse. Potential actions can be to reduce stressful tasks, to increase contact with the caregiver, to increase or reinstall antipsychotic medication or to start psychosocial interventions. We will aim to record participants’ speech already during psychosis so that we can take individual differences in psychotic speech profiles into account; and then again during subsequent remission to provide speech features indicative of these two states. After remission, participants will be randomized to either an intervention group receiving standard care plus weekly speech monitoring or a control group receiving standard care plus weekly speech recordings alone. Thus, in both groups, participants will be asked to provide weekly speech samples of a few minutes each. In the intervention group, the clinician will receive a message within 48 hours providing the calculated relapse risk plus a confidence interval. The clinician will consider this risk interval and contact the participant if it overlaps with the interval given in the relapse prevention plan for a shared decision appointment. In this meeting with the participant and informal caregiver, the best course of action will be decided as specified in the personalized relapse prevention plan. Clinicians from participants in the control group will not receive messages. Relapses will be documented in both groups according to criteria defined in WP1. The primary outcome measure will be time until relapse during follow-up (12 months). Other outcomes and visit schedules are listed in the Clinical Studies Annex. At the end of follow-up, qualitative interviews with participants and clinicians will be conducted to assess acceptability and perceived trustworthiness of this AI-mediated intervention. This feedback will be used to improve user-friendliness and transparency of the monitoring system for a future iteration.

Output of the WP: This WP will provide data on efficacy, acceptability and trustworthiness of the TRUSTING AI monitoring system which will be the basis for the health economic considerations in WP5.

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**Figure 1.5.** Experimental design of the RCT. Participants speech is measured during acute psychosis (whenever possible) and again during remission. Participants are then randomized to either the control condition (standard relapse prevention plus speech recording alone) or the treatment condition (standard relapse prevention plus AI speech monitoring). Primary outcome: time until relapse during follow up of one year.

#### Health economics evaluation: assessing the cost-effectiveness of the AI monitoring system (WP5)

Based on the preliminary results of the clinical trial (WP4), we will start developing economic value frameworks for the implementation of the AI monitoring system in relevant jurisdictions as selected in WP3. These value frameworks will identify a set of dependent variables around which health economic models can be built, adapted to selected relevant countries. These analyses shall feed into the estimation of the project’s Net Present Value, supporting the exploitation activities of WP6. Data regarding levels of functioning, quality of life and use of health services from WP4 will be used to calculate health benefits and service use savings of the AI monitoring system.

Targeted sub-population: In order to maximize the health gains that are attainable through the AI monitoring system given limited resources (i.e. optimize cost-effectiveness), its implementation should focus on the clinically most relevant sub-populations (i.e., young patients, patients with severe schizophrenia). Importantly, this also increases the opportunity for TRUSTING to become reimbursed in a maximum number of national health systems or statutory health insurance systems in Europe and beyond. With this in mind, target sub-populations will be scrutinized according to their unmet medical need, and according to the challenges they present to intervention development. The risk of rapid price erosion among the TRUSTING intervention’s comparator products on the medical software market will be assessed, as a rapid drop in their prices may negate the economic efficiency of the newly developed intervention.

Evidence-based value framework development: Based on selected value drivers that can be translated into economically meaningful measures, a conceptual modelling framework will be developed. For this purpose, a systematic literature review on the clinical, humanistic, and economic burden of schizophrenia will be conducted. An up-to-date synthesis of the evidence on the disease burden in the relevant countries as identified in WP6, will be provided. Then we will explore typical health economic decision model structures with schizophrenia-specific health states, established treatment comparator(s), and relevant service user characteristics to guide the early-phase development of an economic model. Along with the value framework elements, key assumptions on treatment characteristics will be identified via targeted review of the currently available evidence. These will be translated into the definition of best case and worst acceptable case scenarios based on product features (target intervention profile) linked with economically meaningful measures.

Health economic model development and validation: Early phase health economic models will be developed on the basis of a conceptual modelling framework (see above), in a suitable, user-friendly software environment. The models will assess uncertainty in outcomes by performing scenario and sensitivity analyses. We will perform the technical and conceptual validation of the model in parallel with development. This will include the examination of internal consistency, transparency and key input parameters, technical verification of model calculations, and assurance of functionality and replicability. Besides the programming syntax, all input data will be verified with their original sources. Model validation processes will always be performed by an analyst not directly involved in the model development.

Qualitative data analysis: Data from key informant interviews and an expert workshop about context specific reimbursement criteria and processes will be analyzed using purpose-selected qualitative data analysis methods. We will identify the most appropriate methods from a list including, but not restricted to, content analysis, thematic analysis and framework analysis. Semi-structured interview and focus group guides open-ended questions but directed probes will be developed, based on the domains of the value framework developed above. This will allow for a predominantly deductive method of qualitative data analysis to be used. Themes/concepts will be derived from the value framework, while codes within these themes/concepts will be developed through free coding of the qualitative data. This approach helps to represent the variety of different approaches expressed by participants, while being structured by the main lines of the value framework developed in the project.

Output of the WP: Cost effectiveness model and net present value (NPV) estimation that can be included in value dossiers for talks with potential investors, funding agencies for public reimbursement, and other partners (WP6).

#### Pillar 3: Market readiness and project implementation Communication, Dissemination, and Exploitation Activities (WP6)

The consortium will obtain input from key stakeholders (including service user and clinician groups established in

WP3-4) and promote knowledge exchange and collaborations at EU-wide level. A full Communication, Dissemination, and Exploitation Plan will be delivered at Month 6 (see table 2.2 for dissemination strategies, means and KPIs) and updated throughout the project duration.

* Communication measures include information meetings, a project website, digital media with press releases, educational videos and factsheets, social media, publications in open-access, pre-print or peer-reviewed scientific journals, presentations at European science events (EPA, ECNP, SIRS) and attendance at events with tech displays to showcase our results. Our consortium is organizing a workshop in November 2022 where we are welcoming researchers from across the world, including researchers from the MONARCA project to learn from their experience and exchange ideas and findings. If this project is granted, we aim to organize annual workshops inviting researchers from other EU projects that started under this call and other relevant colleagues of different projects.
* Dissemination measures will address the scientific and research communities, engagement with stakeholders including industry (strategic commercial opportunities) and health authorities (opportunities to contribute to policy, regulation or programmatic initiatives).
* If convincing efficacy and trustworthiness is shown in the real-world setting as per WP4, clinical partners (Drs. Sommer and Homan) together with clinicians from the Advisory Board (Drs. Palaniyappan and Corcoran) and the EPA and GAMIAN will suggest the AI monitoring system to national and international guidelines for the treatment of schizophrenia, and will write consensus papers to explain the system’s optimal use.
* With regards to exploitation of the results, led by Norinnova (UiT’s TTO) we will develop a business plan with several commercialization routes. Depending on the maturity of the technology towards the project end, the TTO will assist in further developing it to a maturity level where it is ready for industry to take over. Activities involved in this development include fundraising, market analysis and contact as well as the management of collaboration and confidentiality agreements to ensure ownership of the technology assets is regulated correctly. Regulatory requirements for market access will be analysed and relevant documentation prepared to meet the MDR guidelines. The business strategy will integrate the reimbursement analysis from WP5.

#### Project Management and Coordination (WP7)

The final WP is not linked to a specific objective but will focus on overall coordination to ensure all project objectives are met. This entails management of the project timelines, budgets, and administrative issues. The partners will ensure that the defined deliverables and milestones are met and reported on time to the European Commission. The project’s risks will be monitored in a structured manner, and if any issues should occur, these will be dealt with in a timely and efficient manner to mitigate escalating effects and negative consequences.

#### Related research and innovation activities

Multiple national/ international R&I activities will feed their results into this project (Table 1.4).

**Table 1.4.** Overview of previous/ ongoing related research and innovation activities:

|  |  |  |
| --- | --- | --- |
| **Related projects** | **Partners** | **Knowledge/Data/Technology TRUSTING has access to** |
| HAMLETT- | UMCG | The HAMLETT cohort78 was funded by the Dutch Medical Science Foundation |
| cohort | UPF | ZonMW and started inclusion in 2017. It aims to include a total of 512 citizens who |
| (ZonMw, |  | experience a first psychotic episode. The HAMLETT study79 is designed and |
| Dutch |  | coordinated by WP1 leader Dr. Sommer. A network across the Netherlands |
| National grant) |  | consisting of 23 specialized psychosis centres collaborate to ensure inclusion and |

|  |  |  |
| --- | --- | --- |
| Expertise with SNP/NLP  analyses for quantifying subtle psychotic symptoms |  | follow-up. In 2020, the HAMLETT study was extended by a second grant, named OPHELIA80, to extend the follow-up time to ten years and provide enrichment of the phenotypical data. The total number of 512 participants is expectedly reached early 2023. During the first year after inclusion, most participants taper off their antipsychotic medication and are monitored closely for relapse. Clinical data and spontaneous speech are collected at all visits and will be used for WP1.  UMCG has several experts (Dr. Voppel, Dr de Boer, Dr. Koops, Dr Sommer) with extensive experience in quantifying signs of psychosis that can predict  relapse16,41,61,63,64. |
| DISCOURSE  in Psychosis Consortium | UMCG UPF | To access a large and crosslinguistic sample, we will collaborate with the DISCOURSE in Psychosis consortium74 a global initiative initiated by Dr. Palaniyappan, in collaboration with UMCG and UPF, to study thought, language and communication disturbances in psychosis. Currently, data collection or ethical procedures for data collection are in progress at 11 sites in 8 countries, covering 7 languages, with new sites joining as the consortium rapidly gathers momentum. Sites apply for depositing data (in formats of their choice, e.g. full audios and transcripts or only metadata) at a PsychosisBank administrated at a data management level by TalkBank, which has already set up DementiaBank and AphasiaBank on the same data sharing model. Data remain owned by sites where they are collected and access to the data is administrated through a password by  DISCOURSE. For further ethical details see ethics self-assessment. |

#### Interdisciplinary approach

**Figure 1.6.** Interdisciplinarity of TRUSTING

Our approach is a unique combination of computational linguistics, clinical prediction, AI and e-health expertise to tackle a complex and urgent clinical problem. Specific expertise from different partners is needed for each WP and feeds into the next WP (WP1: Knowledge on early detection of relapse using SNP/NLP from partner 1, WP2: Expertise on social sciences and humanities from partner 3, WP3: Expertise on developing and validating AI-based e-health systems from partner 4, WP4: Experience in conducting relapse-prevention trials from partner 2, WP5” Knowledge on health technology analyses from partner 11, WP6: Network and background from partner 9 and 10 for dissemination and communication and finally WP7: experience as EU study coordinator from partner 1). Humanities (partner 3) will provide the backbone of WP2 where the influences of different languages and migration background is studied. The current project demands excellence, experience, pre-existing data, and hands-on research activity of these disciplines to solve the scientific, technical, and clinical challenges. Our consortium has the unique ability to provide all disciplines, data and expertise needed for this task. Each partner is a leading specialist in their respective field (Figure 1.6). Beyond the expertise brought by the partners, the multidisciplinarity of the project will be complemented by a high-profile Advisory Board to provide objective and non-biased expertise and oversight throughout the project. The Advisory Board is designed to cover 5 different areas of expertise:

* Clinical expertise: Dr. Lena Palaniyappan (Mc Gill University, Canada) is a clinical psychiatrist with expertise in psychosis and computational linguistics. Dr. Cheryl Corcoran (Mount Sinai Hospital, US) is a clinical psychiatrist with expertise in computational phenotyping in psychiatry.
* AI expertise: Dr. Hugo Schnack (Utrecht University, Netherlands) is a mathematician specialized in AI paradigms and their application to speech and language data.
* Ethical expertise: Dr. Kobi Leins (King’s College London, UK) is an international lawyer with corporate, academic and policy experience in digital ethics, disarmament and human rights.
* Legal expertise: Dr. Joseph Cannataci (University of Groningen, the Netherlands) is chair in European information policy and technology law, co-director of the security, technology and e-privacy research group, and has expertise with policy, technology and security law in medical science.
* Economic expertise: Dr. David Nugent is Director of Elucidare, a technology development and investment advisory business whose activities span the entire innovation and investment cycle from invention to trade sale or IPO (<http://www.elucidare.co.uk/>). Elucidare operates in +20 technology areas, including healthcare.

#### The gender dimension

When our SLP/NLP system obtains a place in clinical practice for the monitoring of individuals with schizophrenia, the vulnerability to gender bias may cause prejudice and discriminatory decisions against females, as these are generally a minority among citizen with this disorder81. To address this challenge, robust and fair solutions have been developed to adjust our SLP/NLP methods to prevent discrimination against female users. For the development of our solutions, we will use the growing literature on debiasing approaches of crucial importance for the application of these technologies in the biomedical domain82,83. All the components of an SLP/NLP system, from the data used for training, the selection of speech-based features, and their weight in the final selection of relapse-predicting features, can potentially exhibit gender biases. In TRUSTING, we will apply effective methods to avoid discrimination against either men or women, consisting of the following:

1. The training sets as per WP1 will be well powered for both genders to allow gender-specific analyses. This means that all steps of the analyses are performed for male and female participants separately. The final set of best predicting speech-features will be compared between men and women. In case of less than 75% overlap, the rest of the project will use gender-specific analyses and thus create two sets of speech-based relapse predictors: one for men, one for women.
2. We will use a BERT model, rather than LSA or word2vec, as there may be less gender bias66.
3. For the prospective trial (WP4), we will include at least 40% female citizens, to reduce the risk for being underpowered for gender-specific analyses. This will demand an extra effort as it has historically been more difficult to include women for randomized controlled trials. We intend to provide lectures for audiences of potential participants stressing the importance of female contribution to clinical trials and reduce the demand of time and effort for the participants to improve participations, especially from female citizens. This will be achieved by recruiting from community-living as opposed to predominantly institutional/hospitalized service users, where males are over-represented.
4. In WP4 we will analyse the qualitative interviews with participants, reflecting acceptability and trustworthiness of our application, in a gender-stratified way to detect potential differences as female participants could be more hesitant to the use of AI-based health systems.

#### Open Science

The TRUSTING consortium is strongly committed to sharing the important breakthroughs of our project in line with Open Science principles, since sharing outputs early and widely brings added visibility and profile to the work and supports exploitation. All consortium partners are familiar with Open Science principles. For example, UZH (Dr. Homan) has substantial experience with sharing reproducible workflows in the context of clinical research84–86. Open Science practices including pre-registration of the main research hypotheses will be reflected in our Communication and Dissemination Plan (see Section 2.2. Measures to maximize impact). We will maximize scientific rigor, re-usage and integration of our data and resources by:

1. All sites participating in WP4 as well as UMCG will explore possibilities for ethical permissions for making their data available to researchers worldwide, subject to de-identification of these data, specifically in PsychosisBank, which will become a part of TalkBank ([www.talkbank.org](http://www.talkbank.org/)). On this site, qualified researchers will be able to apply for access to the speech data, or else meta-data about collected speech data, depending on which data have been permitted to be shared.
2. Sharing pseudo-anonymous valuable data (e.g., the trial data from WP4) upon well-motivated requests once the results of the RCT have been published.
3. Reaching out to groups with other languages to help provide validated versions of the AI monitoring system in these languages.
4. We will work with the university TTOs to establish the IP landscape for future marketing purposes to optimize access to the AI monitoring system. In WP6 we will ensure open access publication of findings and help to translate these findings for a lay audience using newsletters, vlogs, podcasts and interviews.
5. Preregistering the clinical trial (e.g., https://clinicaltrials.gov) and our main hypotheses online (i.e. [https://osf.io](https://osf.io/)).

#### Data Management Plan

A Data Management Plan (DMP) will be developed as a deliverable within the first 6 months of the project and revised throughout the project. It will provide a detailed framework that ensures data and research outputs are findable, accessible, interoperable and reusable (FAIR) and complies specifically with the applicable data protection and privacy legislation, including in particular the General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679). Dr. Koops (UMCG) has been appointed Data Manager and will drive the development of the DMP and throughout the project lifetime, supported by one person at each partner responsible for data management. To ensure that all the research outputs are FAIR, the following structures and guidelines will be employed:

* *Types:* Since the project covers the whole spectrum of medical device development, the types of data outputs are highly variable. Research outputs will comprise publications, patents, scientific and technical reports, methodologies and workflows, protocols and procedures. Non-digital data will include i.e., laboratory notebooks and documents while digital data will encompass e.g., spreadsheets, datasets, figures.
* *Findability:* All data stored is discoverable with metadata, identifiable and locatable by means of a standard identification mechanism. Digital object identifiers (DOIs) will be used for each publication, all of which will be open access, and a trusted repository will be used to increase findability as per WP7.
* *Accessibility:* In line with the IPR strategy, data not protected by patents will be made accessible via a suitable channel, such as the Discourse in Psychosis Speech databank.
* *Interoperability:* Standards, formats and vocabularies defined by the platforms for data sharing will inform interoperability between the different infrastructures and IT systems.
* *Reusability:* All generated data, tools, and techniques as well as lessons learned will be shared with minimally restrictive licences to allow wide reuse and reduce the efforts needed for integration with other data sources.
* *Curation and storage/preservation costs:* Research data are stored and backed up at all sites on secured servers to prevent data loss and ensure traceability of scientific results for at least 10 years. The storage costs will be covered by the respective consortium partners.

Given the importance of data sharing, reproducibility and replicability, the project is aimed at fully adhering to the highest standards in data management. In the light of the current replication crisis in science87, there has been a justified focus on both replicating but also reproducing study results. Reproducibility is thus a primary aim of good data management. We will ensure reproducibility by using a strict data management strategy including version control with git and fully documented workflows and data. Anonymized data and workflows will be shared publicly whenever possible, using Github and the Open Science Framework [(http://osf.io/).](http://osf.io/)) Accordingly, the current project is committed to the FAIR principles (Findable, Accessible, Interoperable, Reusable in its data management. We will adhere to these principles, except for situations where these principles conflict with privacy issues, as recorded speech can be traced back to a person.

**Management of clinical data:** During our multicenter clinical trial in WP4, personal data will be collected from participants enrolled in the trial. The collection of these data is critical for statistical purposes. All data collection and storage will be in line with the GDPR and national regulatory requirements. All clinical trials require the implementation of specific management and logistics. Clinical trial coordinating center UZH is highly experienced with the performance of clinical trials and associated data management, so the standard data management principles of the organization (fully in line with FAIR principles) will be used during the study. Clinical data will be entered into an eCRF, created using REDCAP software as provided by UZH. Data on an individual level is collected and will be kept according to data protection agencies and presented on group-level. Since we are handling sensitive personal and clinical data, data security is an important aspect to consider. UZH will be responsible for secure data storage during the clinical trial, as well as data recovery and transfer of sensitive data.

# IMPACT

* 1. **Project’s pathways towards impact**

## Expected outcomes and impacts

Table 2.1 describes how project results contribute to the Expected Outcomes set out in the work program topic.

**Table 2.1.** Unique contribution of TRUSTING towards the Expected Outcomes of the Trustworthy AI Call.

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| Outcome 1: Clinicians, medical professionals and citizens have access to and use validated AI tools for disease risk assessment. Hence, citizens are better informed and equipped for managing their own health. |

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| In line with the requirements of the call, we will **validate the performance of the AI monitoring system** in a real-world setting and compare its performance to the established practice. Our AI monitoring system will be made available as a commercial tool for mental health centers to be used by clinicians and citizens for secondary prevention. It will enable citizens to reduce or discontinue long-term preventive medication (56% of those affected by schizophrenia9), but nonetheless always be kept in the loop (regular interaction with their doctors), and to understand how AI can help them and that decisions are always made in a shared manner with them and informal  caregivers. This empowers the role of citizens, who will be better equipped for relapse prevention, and thus **better informed to manage their own health**. |
| Outcome 2: Healthcare professionals utilise robust, trustworthy and privacy-preserving AI tools that help predict the risk for progression of non-communicable diseases. Hence, citizens benefit from improved health outcomes. |
| Our monitoring system will be used for the prediction of psychotic relapse in citizens affected with schizophrenia, a **non-communicable disease** that affects 21M individuals worldwide of whom 80% have a relapsing clinical course. Relapse is the most important factor determining outcome of these citizens and an accurate and a timely predictor is urgently needed, especially now that maintenance treatment with antipsychotics is, for many citizens, no longer acceptable. Our solution will **provide clinicians with robust and trustworthy AI** to allow **citizens to**  **benefit from improved health outcomes** through early relapse identification and timely prevention strategies. |
| Outcome 3: Healthcare professionals develop recommendations/guidelines for the implementation of AI-based personalised prevention strategies. Hence, citizens benefit from measures superior to the current standard-of-care. |
| We want to empower healthcare professionals and citizens (as per WP3) and determine how to **implement the AI system** developed in this project to maximize benefits for all key stakeholders. Dissemination activities will be crucial to make a wider impact on the **development of recommendations and guidelines to use this system**. Together with GAMIAN, EPA and SRI, we will liaise with European health authorities to support the design, monitoring, review and improvement on policy and programmatic measures and initiatives. Several members from our consortium (UMCG, UZH, members of the advisory board) are part of national and international guideline committees who write and update treatment guidelines for people with psychotic disorders. These partners will translate the findings of TRUSTING into recommendations on how to use speech-based relapse prediction for monitoring of out-clinic citizens at risk for relapse. We will collaborate with the authors of the PORT and NICE  guidelines for the treatment of schizophrenia to make a recommendation on the use of this AI-monitoring tool, as these guidelines are read by a large international clinical audience. Our advisory board will help. |
| Outcome 4: Health care professionals employ quantitative indicators to identify and follow-up on individuals with high risk for the development and/or risk for the progression of chronic non-communicable diseases. |
| The quantitative nature of SLP/NLP-based predictions provides certainty estimates inherent to ML models within a predefined assessment window of prediction. This will generate a highly interpretable and quantitative prediction of the certainty estimates for psychotic relapse to occur within a month time (a percentage and confidence interval). If the RCT of WP4 shows significant longer time till relapse using the AI-monitoring tool, this will motivate  clinicians to use it. |

TRUSTING is also fully in line with the Expected Impacts of the Horizon Destination ‘Staying healthy in a rapidly changing society’. The destination focuses on major societal challenges that are part of the Commission’s political priorities, particularly mentioning mental health. TRUSTING specially aligns with the following 2 Impacts:

* *‘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’:* by using the speech recording app from home, citizens at increased risk for psychotic relapse monitor their mental health and interact with their health care providers in a shared decision-making appointment in case of potential relapse risk. In a later stage of development when false positive and false negative warnings turn out to be very rare, citizens can receive automated messages themselves, which will give them more autonomy in managing their own health.
* *‘Citizens´ trust in knowledge-based health interventions and in guidance from health authorities is strengthened, resulting in increased engagement in and adherence to effective strategies for health promotion, diseases prevention and treatment’*: creating and validating a trustworthy AI-monitoring system is at the center of this project, with service users engaged at every step of development, providing the opportunity to improve on user- friendliness and transparency in response to user feedback.

Additionally, TRUSTING will lead to the following medium/long term scientific, economic, and societal impacts:

**Scientific outcomes & impacts:** Methods such as the use of cognitive tests, neuroimaging or blood markers have been investigated vigorously in psychiatry during the past 50 years, with few, if any, implementations into clinical practice. Speech, however, is understudied as a clinical biomarker. Yet, speech is closer to the actual state of mind and hence a better reflection of a person’s ever-changing state of mind. Its structured quantification and analyses

afford new methods to understand dynamic mental states for both clinical and non-clinical researchers. Its ease of recording, being non-demanding, non-invasive and cheap, provides researchers with the means of frequent measurement and captures the transient changes in mood, thoughts and impulses central to psychiatric states.

#### Economic/technological outcomes and impacts:

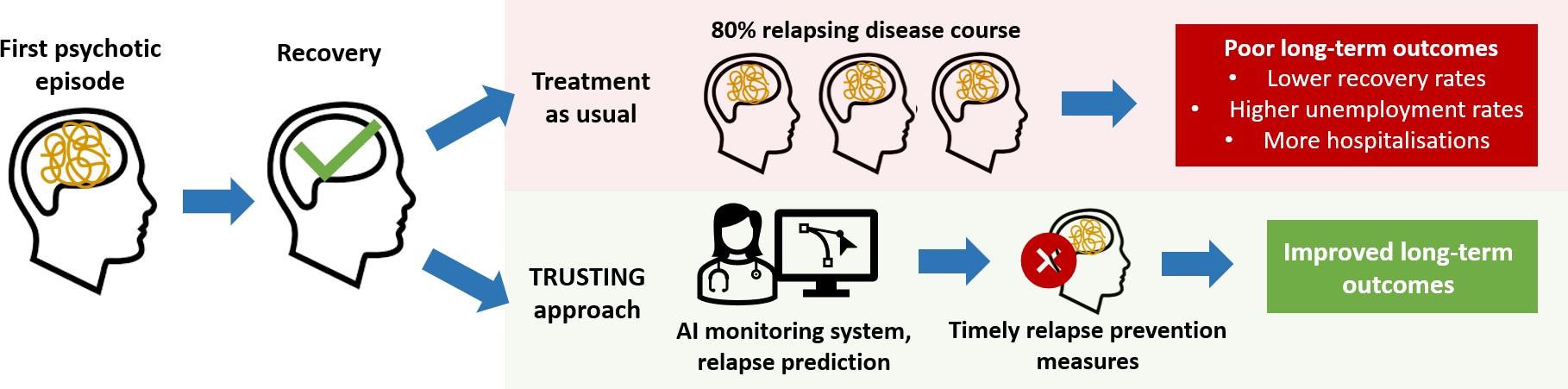
* TRUSTING will enable the development, implementation and testing of new predictive longitudinal models for monitoring mental health. It will demonstrate how a cross-disciplinary approach, incorporating ML, speech modelling and personal digital devices, can be embedded within an AI tool to monitor mental health and augment clinical decision-making to provide positive health outcomes. TRUSTING will result in novel methods, technologies and algorithms that can assess a person’s mental state in near real-time. It will be disruptive technology that enables transformation of existing status quo and opens new development paths, notably pharmaceutical, psychosocial, and other intervention developments. During the project, the commercial opportunity will be assessed and an exploitation plan will be developed, including several routes to market. While this project specifically addresses psychotic relapse, the same method of a speech-based AI monitoring system can be applied to other remitting-relapsing disorders, such as bipolar disorder, major depression, substance abuse, obsessive-compulsive disorders and anxiety disorders such as panic disorder. Thus, the project’s results can be extrapolated to numerous disorders, offering further avenues for exploitation.
* With rising healthcare costs, constrained budgets and a growth in the number and type of interventions, economic evaluations are needed to assess costs and outcomes associated with different options and support decision making with information on the value of interventions. Annual prevalence of schizophrenia ranged between 2.3% and 2.7%88. The healthcare costs associated with schizophrenia vary between persons, but are generally high (mean €29,217 per year vs. €14,903 for citizens without this disorder)88. European studies report excess costs of

€8965-€19,016 over periods of 6-12 months when a person experiences a psychotic relapse89. Reasons for these high costs are the young age of onset of schizophrenia, high disability associated with psychotic relapse and high health-care costs stemming from hospitalization, out-patient treatment and home care. The annual risk of relapse is 27% for citizens using antipsychotic medication and 64% for those who do not use medication90. Currently, approximately half of European citizens with schizophrenia are estimated to discontinue medication after initial remission91,92. In the TRUSTING project, we estimate that we can accurately predict relapse in 90% of cases (based on pilot data from the Sommer group showing 81% accuracy with just 1 SLP analysis and restricted training sample). When a warning of high relapse risk (with short confidence interval) is sent to the clinician, we expect 90% of them to respond adequately and activate the personal relapse-prevention plan. Based on a RCT from NIMH using early-warning symptoms to activate such prevention plans, we know that relapse can be prevented in 60% of cases93. We expect a similar rate of prevention for this study as it will be using comparable individualized relapse prevention plans. Based on all the above data and assumptions, the potential cost reductions would be an average of €3096 per citizen with schizophrenia per year. If we presume that 30% of the

18.7 million European citizens affected with schizophrenia would use the AI-monitoring tool, this could potentially save an annual amount of €17383 million. Another way of expressing potential impact of the proposed AI-monitoring system, is using disability-adjusted life years (DALY) to quantify the burden of diseases. DALY combines information on the impact of mortality (years of life lost because of premature death=YLL) and disability (years lived with disability=YLD). One DALY can be thought of as one lost year or lost ‘‘healthy’’ life. According to the Global Burden of Disease Study (Murray and Lopez, 1996), schizophrenia causes a high degree of disability that accounts for 1.1% of the total DALYs and 2.8% of YLDs. In the World Health Report on mental health (2001)94,95 schizophrenia was listed as the 8th leading cause of DALY worldwide in the age group. Psychotic relapse was ranked in the highest disability class, requiring daily care. Duration of relapse varies largely, with an average recovery time estimated at 9 months3. With the application of the speech-based relapse detector, we expect to prevent 49% of the relapses. Given an annual risk for relapse of 45% and a mean duration of 9 months, our application would potentially gain 0.166 DALY per citizen with schizophrenia, per year88–90,93,96. We understand the high need to demonstrate cost-effectiveness for the market transition of the project outputs and an entire work package (WP5) is dedicated to it.

#### Societal outcomes and impacts:

* Health impact: citizens with schizophrenia are an especially vulnerable group. Those with a tendency to relapse have a greater risk of harming themselves and others, smaller chance of sustaining long-term relationships, higher risk of unemployment and more functional and cognitive decline97. Accurate relapse prediction provides the time window to activate the individual prevention plan and avoid full-blown relapse to make life better and safer for citizens and their surroundings (Figure 2.1).



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**Figure 2.1.** The clinical impact of TRUSTING.

* Socioeconomic impact: Global health inequalities have been designated as one of the major challenges by the World Health Organisation98. In low- and middle-income countries, around 76-85% of people with serious mental health disorders do not obtain treatment, compared to 35-50% in high income countries99. Lack of mental health services and difficulties in accessing services could be addressed with low intensity interventions100,101, such as eHealth tools, as they offer temporal and local independence, easy accessibility, scalability and hold potential in overcoming structural healthcare barriers102. If this project is successful, it will prevent an estimated 49% of the relapses in citizens who use it. This will prevent approximately half of the hospital readmissions, enable service-users to continue their paid/volunteer work, increase the chance for long-term partner relationships and reduce the need for informal care. Using the AI-based system enables service-users to discontinue long-term medication safer, which prevents severe side-effects such as metabolic syndrome and parkinsonism. Digital mental health management reduces health inequity as travelling costs are an important reason not to obtain mental healthcare for low-income groups, such as citizens experiencing schizophrenia. TRUSTING will enable inclusion and diversity in terms of participation and access to the health system, and thereby promote health equity and justice.

#### Target groups benefitting from the TRUSTING project

TRUSTING will benefit many stakeholder groups through the impacts described above. The main group who will benefit are: citizens who have experienced at least 1 psychotic episode, often, but not necessarily diagnosed with schizophrenia. They will benefit through the implementation of relapse prevention measures, improving their long- term outcomes. Other stakeholders who will be positively affected by this project, including clinicians/ healthcare professionals (notably psychiatrists and psychiatric nurses, who will benefit by providing better healthcare), family and friends (as the need for regular monitoring by an informal caregiver is relieved), citizens who may feel threatened or compromised by a person experiencing florid psychotic relapse, the scientific community (given the novel approaches proposed and the important scientific advances we will achieve), health insurances who are given the opportunity to save costs for mental health care, and tech and e-health companies interested in commercial exploitation. Importantly, the principle of TRUSTING can also be used in other relapsing-remitting psychiatric disorders, as explained above.

## Requirements and potential barriers impacting the achievement of the expected outcomes

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| **Potential barriers** | **Mitigation strategy** |
| **Acceptance by healthcare professionals and service users** is a potential market barrier. Professionals need evidence that the system is clinically relevant from high trust sources (i.e., RCT results/ recommendations from guidelines). Barriers for service users include concerns about privacy or digital illiterateness (smart devices needed to record speech samples). User friendliness and transparency is crucial for both stakeholders, such that the system is easy to use, to interpret, and integrate into clinical workflows. | Clinical evidence will be acquired through the international RCT in this project. We will liaise with international regulatory/ health authorities to support the design, monitoring, review and improvement on policy and programmatic measures and initiatives. To achieve acceptance by healthcare professionals and service users and implementation into clinical practice we will comply with all 7 key requirements for AI to be deemed trustworthy (Table 1.1). This includes adherence to strict privacy rules and transparent information regarding data collection and anonymity. Furthermore, stakeholder co-design at all stages of this project – including the use of surveys and qualitative interviews - will ensure the development and validation of user interfaces to AI-based output that improve transparency, trustworthiness, interpretability and friendliness of use for service users and clinicians. In citizens with schizophrenia, lack of trust often prevents effective communication of symptoms, and hence adequate medical help. SNP/NLP analyses do not  require this kind of trust, and hence could be effective even if a patient does not intend to communicate anything. Nevertheless, building a |

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|  | trustworthy application for this group is a huge challenge. We think that gaining trust is only possible if we are completely transparent, fair, provide excellent data protection and only use the data for the task at hand. In TRUSTING, we take up this ultimate challenge to build an application that is trustworthy for everyone. Taking up this ultimate challenge also precludes the recording of speech from regular smartphone use (i.e., telephone calls) which can give the impression that private calls are being overheard. The use of an app that can be switched on and off for speech recording, increases trustworthiness, as does the use of a neutral, non-personal story. If our application succeeds in being judged trustworthy by this specific user group, we can be reassured that  other user groups will find it trustworthy as well. |
| **Commercialization:** Several steps need to be taken to bring the project’s results for market, including obtaining a CE-mark. The proposed AI Act will transpose ethical principles from the EU-HILEG Guidelines for Trustworthy AI into binding law. | Clinical evaluation will be in accordance with MDR guidelines, and we will anticipate and future-proof so as to comply with the proposed EU AI Act legislation. Following study completion of the project, a Quality Management System and a Technical File (audited by a Notified Body) will be established. Integration with healthcare systems and reimbursement will be prepared in WP5 and finalized once the CE-mark is obtained. The business strategy around the innovation and go-to- market plan will be well defined within the project to ensure a smooth transition and obtention of the CE mark within 1-2 years following  project completion (also see section 2.2 below). |
| **Language diversification efforts:** Europe speaks many languages and the system needs validation in different languages to be used on a large scale. Expansion to other languages requires validation of speech biomarkers in those languages. | The AI monitoring system will be validated in 6 languages, which represent a total population of 1.9 billion people (and ~5 million citizens with schizophrenia). Validation for languages of the families that are studied in TRUSTING (Germanic, Romance, Slavic and Turkic) will cover a broad spectrum of Indo-European and non-Indo-European language types that will make further validation increasingly likely. Moreover, some of the speech and language evaluations (at the semantic level) we will choose are not sensitive to cross-linguistic variation to the  same extent as morphological or phonological measures. |
| **Financial resources:** follow-up financing will be required to pursue obtention of certifications for use as medical device, market launch and commercialization. | A business strategy plan will be developed, including alternative commercialization routes as per WP5 (also see 2.2. below). We will model scenarios that allow evaluation of different options based on feasibility, risks involved, investments required, and profitability, among others. These models will help choose the optimal business model and optimize our value proposition and commercialization strategy accordingly. Along with the scientific results, these learnings will enable us to advance towards ‘investment readiness’. Led by UiT’s TTO, we will consider fund raising opportunities and manage collaboration and confidentiality agreements to ensure ownership of the technology assets is regulated correctly. In the event of formation of a  spin-off, Norinnova offers an incubator for start-ups to further assist in the early phases of a business establishment. |

* + 1. **Scale and significance of expected outcomes and impacts**

In terms of non-communicable diseases, schizophrenia and psychotic disorders affect a staggering 3% of the world population103 and has a substantial impact on individuals, their families, and society as the mean age of onset is only 20 years. Outcomes are highly variable, with unfortunately a relapsing (chronic) course for some 80% of those affected104. This means that in the European Union, around 10,752,000 people must deal with psychotic relapses. Relapse during the early years after a first psychosis is the most important determinant of clinical and functional outcome105, making the early phase after the first psychosis crucial for secondary prevention106. With current knowledge, the best way we can improve outcome is to accurately predict relapse and apply preventive interventions in time. As part of the preparation of this project, a survey was conducted among 675 members of a Dutch collaborative platform for people with mental health problems, of whom 70% responded that they would be willing to use a speech-based AI tool (if privacy concerns are met) to support their mental wellbeing. In an ideal environment, this would translate to more than 7,526,400 citizens with schizophrenia and psychotic disorders in the EU that could

be positively impacted using the AI monitoring system this project develops. Other psychiatric groups for which a similar monitoring system could be effective are citizens with bipolar disorder (prevalence 1-2%), anxiety disorders (8-12%) and substance use disorders (6-11%), together affecting around 94 million inhabitants in the EU. Importantly, our algorithm will be created and validated in collaboration with group of citizens that have an inherent paranoid tendency (as part of their vulnerability to psychosis). We take on this challenge and realize that if we can successfully build an AI based monitoring system that is deemed trustworthy by this special group of citizens, it will also be considered trustworthy by the larger community of potential users.

# Measures to maximise impact – Dissemination, exploitation and communication

The consortium will maximize the impact of the project by performing dissemination, exploitation, and communication (DEC) activities. The DEC plan will be a key standing point on the consortium’s agenda throughout the duration of the project. The consortium has designed an initial DEC plan (Table 2.2a) with clear responsibilities and key performance indicators (KPI). Dr. Elvevåg (UiT) has been appointed as the Dissemination and Communication Manager. Each project partner will nominate an internal contact point who will be responsible for liaising with the Dissemination and Communication Manager for coordination of all dissemination, communication, and reporting activities. A ‘plan for dissemination and exploitation of the project results including communication activities’ will be provided as a deliverable within the first 6 months after project start, and will be periodically updated in alignment to the project progress. Here, we present a first version of our strategy:

#### Exploitation Plan

**Exploitation Plan Development:** The Exploitation component of the project will be led by UiT with strong support from their TTO, Norinnova. Their role is to handle the commercialization process of research results from UiT and the university hospital (UNN) to ensure its realization into society. This includes management of IPR arising from research such as patent filing and maintenance, trademark registration and handling critical know-how linked to a technology. Depending on the maturity of the technology, the TTO is responsible for developing it to a maturity level where it is ready for industry to take over. Typical activities involved in such development include fundraising, market analysis and contact as well as the management of collaboration and confidentiality agreements to ensure ownership of the technology assets is regulated correctly. The transfer of the technology from TRUSTING into society will be achieved either through licensing to established industry or by the creation of a spin-off company where the TTO will negotiate terms and conditions. Initial market analysis has identified a few commercial players in this space. This includes the US based firm *Braincheck* focusing on remote cognitive assessment of patients. The tools developed in this project might be a synergetic fit with *Braincheck's* offerings and also serve as means to get access into the European market. Due to the disruptive nature of this project in terms of state of the art, creation of a spin-off company is highly likely to ensure reaching a maximum number of clinicians and patients. Determination of the best format for the users to access the tools will impact a future spin-off business model. Several software based medical technology companies offer their services in the form of downloadable apps or web services (Software as a Service). However, clinicians and hospitals in particular likely have internal regulations and safety measures that impact this choice, The consortiums partners have insights that will be leveraged to ensure that these considerations are handled in the business model that is created. In the event of formation of spin-offs, UiT’s TTO Norinnova offers an incubator for start-ups to further assist in the early phases of a business establishment until they obtain market traction. One of the focus areas of the incubator is investor readiness and introduction to appropriate private investors. The incubator holds annual demo days and has an extensive investor network, particularly in the health and medical technology segment. When the scientific results are generated, the TTO will examine the results and advise whether it is pertinent to file a ‘Disclosure of Invention’ (DOFI) and examine the consortium agreement and ownership of intellectual property (IP) of the results and evaluate whether the results are patentable. If not patentable, other ways to protect the IPR such as trademark design, trade secrets etc will be examined in order to create barriers for competing products. The TTO will also examine the market need and commercial potential for the technology and explore how the technology from TRUSTING can be commercially realized through licensing agreements to established industry or by the creation of a spin-off company. Thus, regardless of whether the knowledge is patentable, the TTO will explore avenues where TRUSTING’s assets can be developed. Naturally, the scope of the latter issue will be determined by what is in the public space, and thus they will be consulted before any publication of results from TRUSTING. We anticipate to settle on a license or spin–off strategy for commercialisation of the project towards the last quarter of projects timeline and are aware of the Horizon Results Booster program which could be a good fit in this phase

**Regulatory affairs:** Our envisioned AI tool falls under the definition of a Medical Device, and is therefore subject to the EU Medical Device Regulation (MDR) 2017/745. In order to bring our solution to the market, a CE Mark needs to be obtained, confirming that the system meets essential requirements of the MDR. The route to market for a medical device is highly dependent on its class. After discussions with regulatory experts, we conclude that we are

in a ‘grey area’ when looking at the MDR Classification Rules. An argument can be made for Class IIa, but also for Class III. The classification will impact the requirements and level of documentation needed for the solution as well as the quality of the documentation during the development. Class III devices are subjected to more stringent requirements compared to Class II, thus from a validation and documentation standpoint it would be beneficial to develop the solution with an intended use that ensures it will be regulated as a Class II device. We will continue to engage with regulatory experts from the early stages of the project to make sure that the clinical evaluation and other documentation during the project period meet the MDR requirements to ease the industry certification process in the future. The endpoint of the project from a regulatory perspective will be the compilation of risk assessments, clinical validation, and specifications, which will greatly shorten and facilitate the CE certification process.

**Reimbursement strategy:** Central to any exploitation strategy is the selection of an appropriate business model to ensure optimal market entry in key target markets. This necessitates knowledge of reimbursement pathways. Key activities to ensure this are to:

* Identify existing reimbursement codes for similar e-health tools EU and US.
* Correlate regulatory information (i.e., intended use and indications for use) with coverage and coding currently available in the EU and US.
* Ensure that benefit/added value outcome measures are included in the clinical studies. Collection of data such as healthcare resource use and quality of life data is critical to the understanding of the technology’s contribution to value added. Such data is gathered in WP4.
* Prepare a value dossier based on the results of health economic modelling (as per WP5).
* Engage with reimbursement governing authorities to help drive adoption and reimbursement.

All these aspects compiled into an Exploitation Plan and supported by strong scientific/ clinical data will put us in a strong position towards ‘investment-readiness’ following the project.

#### Communication and Dissemination Plan

The TRUSTING Consortium will maximise uptake of results and impact by performing strategic communication and dissemination activities guided by a DEC Strategy. An initial Dissemination Plan is set out in Table 2.2a below.

**Table 2.2a**: Dissemination strategies to our three target audiences, means and KPIs.

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| --- | --- |
| **Dissemination strategy** | **Dissemination means and KPIs** |
| **Scientific, research and medical community** | |
| * Expand networks; gain visibility to set the foundations for the establishment of new markets * Present results to a broad, targeted audience of researchers and academics, in particular psychiatrists, to maximise impact and future uptake of results * Establish the foundation to support clinicians in applying protocols for a clinical monitoring system * Establishment and   maintenance of connections with other relevant programmes/consortiums | ● +15 publications submitted to open-access, pre-print or peer-reviewed journals (e.g., Schizophrenia Bulletin, Lancet Psychiatry, Psychological Medicine, New England Journal of Medicine, Psychiatry Research, etc.).  ● +8 presentations at relevant conferences across all disciplines in the consortium held by major societies (e.g., EPA, Society for International Research in Schizophrenia - SIRS, GAMIAN’s booth at European College of Neuropsychopharmacology, conferences where GAMIAN are invited to speak such as World Psychiatric Association Congress, etc).   * After patenting/protection of confidential data, make data available through online repositories to allow researchers to access data across disciplines and EU national borders * Networking opportunities with other EU programmes (e.g., eMEN project – E-mental health innovation and translational implementation platform North West Europe, which has developed 7 e-mental health products, ESPERANTO   - Exchanges for SPEech ReseArch aNd TechnOlogies).   * Organization of annual workshops inviting researchers from other projects that started under this call and other relevant colleagues of different disciplines working on digital healthcare and the AI application of spoken language. Starting with the Lorentz workshop (https://[www.lorentzcenter.nl/crosslinguistic-speech-patterns-biosocial-](http://www.lorentzcenter.nl/crosslinguistic-speech-patterns-biosocial-) markers-of-psychiatric-disorders.html) in November 2022. * Guidelines, recommendations and position statements including the project findings will be published and distributed among scientific & patient organisations (e.g., European Federation of Families of Persons with Mental Illness, European Network for Users and Survivors in Psychiatry). |
| **Industry** | |

|  |  |
| --- | --- |
| * Paving the way for market-creation and future commercialisation * Proactively explore opportunities for future partnerships | * Meetings set up with potential commercialization partners (e.g. *Braincheck*), including a boost meeting with the Dutch Health Technology and Innovation Center in 2023, e-Health companies, etc. * Hosting of +6 educational webinars / events for industry   ● +6 press releases disseminated via the project website   * Attendance to showcase our results at events with tech displays. |
| **Regulatory and health authorities** | |
| * To understand the reimbursement landscape & support the design, review & improvement on policy & programmatic initiatives | * Setting-up interviews with key informants from national health systems / statutory health insurance systems of selected European and/or North American countries. * Exploration of opportunities to develop submissions to consultations, join working parties or otherwise contribute to policy, regulation or programmatic initiatives. |

#### Communication plan

The Communication Plan will communicate and educate a range of audiences about the project’s progress and results. These activities will establish the credibility of our methods with industry, mental health care users and professionals and the general public, generating exposure and visibility, and setting up acceptance for smoother implementation of the commercialisation plans. All consortium partners will contribute to the activities.

**Table 2.2b:** Communication measures including audience, channel, and timelines.

|  |  |  |  |
| --- | --- | --- | --- |
| **Target audience/s** | **Channel** | **Activity and purpose** | **Timeline** |
| All stakeholders (including in particular service users, researchers, clinicians, the general public and industry) | Citizens with schizophrenia and clinician groups | Citizen and clinician groups (user board) will also be incentivized to participate in (strategic) communication in the beginning and during the project. These user groups should advise on the content of the project’s website. Furthermore, they  are urged to actively participate in all suitable material targeted to citizens and lay audiences. | Throughout entire project |
| Website | Build and maintain a website with clear and accessible information on the project workplan, funding source, results and  future exploitation opportunities and updated at least quarterly | Built by partner 4 |
| Digital media | * A periodic newsletter will provide information on the project’s progress and results with appropriate links to public deliverables. The EPA has two periodic newsletters to share news and activities with its community of mental health professionals: EPA Minds Online (10k subscribers), and InterACT (for representatives of the 43 EPA National Psychiatric Association's members). * Provision of project information materials to be used by stakeholders as required, e.g., basic slide sets, flyers, infographics and other material on the website. * Production of lay summaries of key scientific publications. * Information sharing with national and international patient organizations via GAMIAN newsletters, blogs and interviews. | 4+ per year  \*EPA Minds is sent on a monthly basis and InterACT on a quarterly basis. |
| Social media | -Create a project Twitter account and use of the partner’s LinkedIn accounts to educate, inform and drive traffic to the project website, increasing engagement.  -Identify social media accounts (including those of other Portfolio partners) and leveraging these to extend reach. | 10  posting/year |
| Public events | Engagement with the lay community through public talks, events, and other forms of science communication to highlight the importance of ongoing research and to gain input and insight into the priorities of this community. GAMIAN’s booth at  European Patients Forum and GAMIAN’s own conferences. | During the entire project duration |

#### Intellectual Property Management Strategy

*Summary of IP management:* Partners will report on progress during project meetings and will identify and

communicate any insights generated that can be protected at an early stage. Prior knowledge is individually owned by each partner, while TRUSTING-driven findings will be jointly or solely owned by partners per their relative contribution to said findings. Details on IPR/exploitation will be outlined in the Consortium Agreement (CA) and agreed upon by all partners prior to project start. This will facilitate partner pursual of market opportunities arising from the project. The CA will manage ownership and access to key knowledge including IPR and research data.

*Access to background IP:* All partners shall retain the full rights to their own proprietary knowledge or technologies obtained before the project or developed during, but that which are independent of, the project. Access rights to pre- existing knowledge and background IP will be laid down in the CA. This will be based on, but not limited to, the following assumptions:

* Each partner is the owner and shall retain the full property of its pre-existing IP and knowhow during and after the project;
* Each partner shall grant access rights on a non-exclusive, royalty-free basis to its pre-existing knowledge required for the execution of the project and as far as this is vital for commercialization of project results;
* Each partner shall bear sole responsibility for ensuring its activities within the project do not knowingly infringe third party property rights.

*Foreseen protection measures:* The most relevant forms of IP that we will pursue are patents, as well as copyrights and trade secrets so as to ensure successful exploitation of the project results. Patentable elements of the project include those related to the selection of speech-based features to predict relapse and the algorithms used. All partners shall cooperate, where required, in relation to the preparation, filing and prosecution of patent applications and/or any other IP applications. If an IP owner is unable or unwilling to comply with this agreement, the project team shall consider how best to deal with this and may require assignment of such knowledge under fair and reasonable conditions to another partner to enable prosecution and maintenance of such knowledge. Each partner is responsible for securing ownership of such knowledge from its employees, students and other agents.

*Balancing IPR with Open Science & FAIR principles*: This strategy will have regard to the DMP that will be developed in WP7. Some deliverables will be managed at the ‘sensitive’ level to protect confidential data and preliminary results. This will be balanced by the Consortium’s commitment to share with the research community the important breakthroughs of our project in line with Open Science and FAIR principles. Before submitting a manuscript for publication, partners will seek written approval of the consortium if the study in question relates in any way to findings obtained in the context of the project.

# Summary

|  |  |  |
| --- | --- | --- |
| SPECIFIC NEED | EXPECTED RESULTS | DEC MEASURES |
| *What are the specific needs that triggered this project?* | *What do you expect to generate by the end of the project?* | *What dissemination, exploitation and communication measures will you apply?* |
| * Schizophrenia affects +21 M individuals worldwide. After the first psychotic episode, +80% individuals develop a 2nd, 3rd or a multitude of psychotic relapses. Schizophrenia contributes 13.4 million years of life lived with disability (DALY) to the burden of disease. * Over the last decade, society has witnessed a changing attitude towards antipsychotic maintenance medication among both service users and clinicians, owing to its severe side effects. * There is an urgent need to develop valid predictors of relapse in psychosis, as psychotic relapse can still be prevented using | * TRUSTING will answer this urgent need by creating and validating an AI monitoring system that leverages SLP/NLP analysis of speech. * Users can easily record speech samples weekly using their personal electronic devices for a year. The system messages are received by the clinician who integrates them into the person’s individual context and may invite him/ her and an informal caregiver for a shared decision making in which the relapse prevention plan can be activated. Human oversight controls automatic speech recognition, model accuracy and message content. * By complying with all the principles of 'trustworthy AI development' and involving clinicians and citizens with schizophrenia in the design phases, we aim to develop a system   with the highest degree of trustworthiness. | **Dissemination**   * Publications in peer-reviewed journals and presentations at conferences and events to present the project’s results to the scientific, research and medical communities. * Contributing to national and international guidelines for treatment of schizophrenia. * Meetings with potential commercialization partners and identification of value chains needed towards exploitation. * Organization of annual workshops, webinars, etc.   **Exploitation**   * Development of a business strategy consolidated into a business plan. * Analysis of CE marking routes and development of a regulatory strategy. * Development of a health economics model, analysis of the reimbursement landscape and a strategy to enter.   **Communication** |

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| intermittent medication and/or psychosocial interventions if such actions are taken in time. | * Following the project, the system will be ready to progress to TRL9. | * Leverage social media channels from project partners as well as web platforms and presentations at public events. |
| TARGET GROUPS | OUTCOMES | IMPACTS |
| *Who will use or further up-take the results of the project? Who will benefit from the results?*   * Service users: as end-users, citizens with schizophrenia represent the ultimate beneficiaries of the technologies developed in the project. * Clinicians: clinicians are a fundamental stakeholder for the adoption of the project’s results. * The scientific community/ researchers: will benefit from the data generated in the field of NLP and speech biomarkers. * European industrial players: this project will open up significant opportunities for collaboration at the industrial level. * General public: EU citizens will benefit during the project from our broad education campaign. | *What change do you expect after successful dissemination/exploitation of project results to the target group(s)?*   * Uptake by industry: validation of new technology applications will lead to follow-up partnerships   /collaborations and licensing opportunities at the industrial level; plus the potential establishment of a spin-out company for the valorization of the project’s results.   * High uptake of the scientific discoveries published: measured by relative rate of citation index of our scientific publications, n of events presented at, n of attendees at hosted events. * Integration of the AI system into treatment guidelines. * Increased public awareness of the benefits of AI and e-health tools in psychiatry: measured by numerous metrics including the number of website visits; views of and engagement with social media posts and campaigns; followers; downloads of resources including press releases, infographics, etc. | *What are the expected wider scientific, economic and societal effects of the project?* **Scientific**   * We will blaze a trail for the clinical   implementation of speech-based biomarkers, widely underutilized in the psychiatric field.  **Economic**   * The healthcare costs associated with schizophrenia vary between persons, but are generally high. Reasons for these high costs are the young age of onset of schizophrenia, high disability associated with psychotic relapse and high health- care costs stemming from hospitalization, out-patient treatment and home care. Our solution has a strong rationale for cost- saving.   **Societal**   * Improved healthcare outcomes: through early relapse identification and timely application of prevention measures, resulting in increased quality of life of affected individuals and the people close to them. |

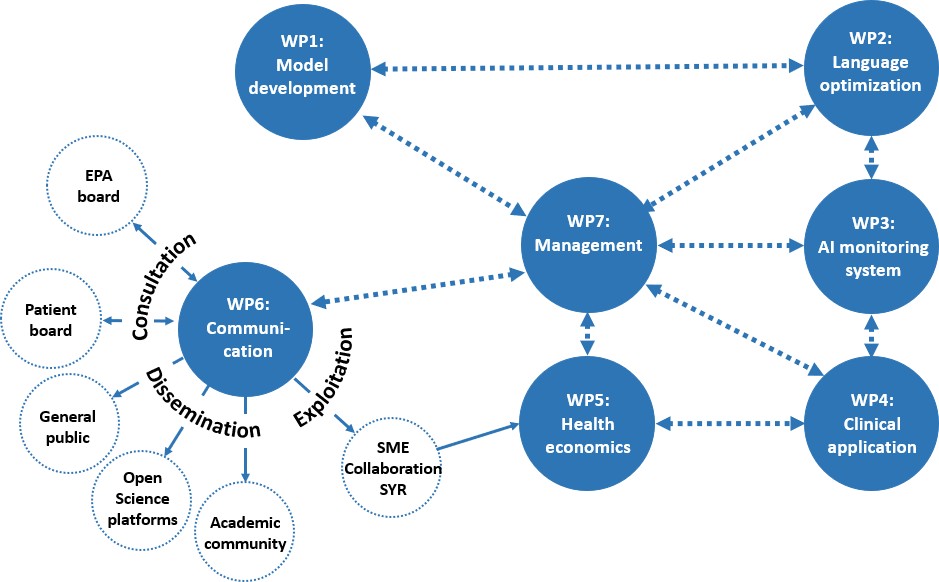
1. **QUALITY AND EFFICIENCY OF THE IMPLEMENTATION**
   1. **Work plan and resources**

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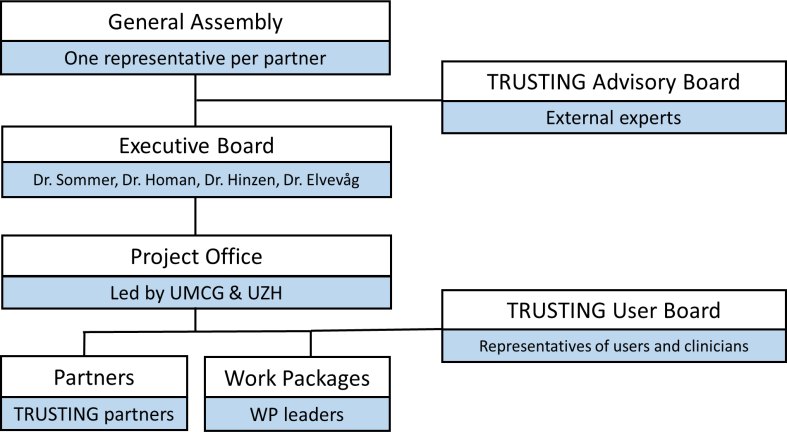
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| **WP** | **Title** | **Partners involved** | **2023** | | **2024** | | | | **2025** | | | | **2026** | | | | **2027** | | | | **2028** | | | |
| **Q3** | **Q4** | **Q1** | **Q2** | **Q3** | **Q4** | **Q1** | **Q2** | **Q3** | **Q4** | **Q1** | **Q2** | **Q3** | **Q4** | **Q1** | **Q2** | **Q3** | **Q4** | **Q1** | **Q2** | **Q3** | **Q4** |
| **WP1** | **Develop speech-based prediction model: psychotic relapse prediction with SLP/NLP** | **Lead: 1** |  | | | | | | | | | | | |  |  |  |  |  |  |  |  |  |  |
|  | 1.1 To create an accurate relapse predictor based on SLP/NLP analyses of speech | 1, 2, 3 |  | | | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1.2 To establish generalizability of the relapse predictor in an independent sample | 1 |  |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1.3 To establish test-retest reliability in people who had multiple relapses | 1, 2 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1.4 To adjust and improve accuracy of relapse prediction in both genders and socio-economic | 1, 3 |  |  |  |  |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1.5 To assess the impact of antipsychotic medication on SLP/NLP features | 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1.6 To assess accuracy of the SLP/NLP features when combined with clinical measures | 1 |  |  |  |  |  |  |  |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |
| **WP2** | **Validation of an SLP/NLP-based psychosis classifier across languages, tasks and sciodemographic** | **Lead: 2** |  | | | | | | | | | | | |  |  |  |  |  |  |  |  |  |  |
| * 1. Prepare DISCOURSE data (cross-sectional data)   2. Co-develop and replicate with WP1 of classifiers used across linguistic domains   3. Evaluate interpretability, explainability, methods-dependence, bias, subgroup sensitivity, and construct validity of classifier   4. Compare classifier performance across possible speech elicitation tasks to be used in WP3-4 | 2  1, 2 |  | | | | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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|  | 1, 2  1, 2, 3 |
|  |  |  |  |  |  | | | | | | |  |  |  |  |  |  |  |  |  |  |
| **WP3** | **Creating a trustworthy AI monitoring system based on the speech biomarker** | **Lead: 3** |  | | | | | | | | | | | | | | | | | | | | | |
| * 1. To develop & implement a remote monitoring system that administers tasks and records speech   2. To develop an e-health course   3. To develop models of speech with appropriate thresholds for personalized use   4. To test the operational functioning of the speech monitoring system in a sample of 240 patients over   a period of 3.5 years | 1,2, 3, 6, 7,10  3  1, 2, 3, 10  All partners |  | | | | | | | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| **WP4** | **Testing the efficacy of the TRUSTING AI monitoring system in a prospective clinical trial** | **Lead: 10** |  |  |  |  |  | | | | | | | | | | | | | | | | |  |
| * 1. To produce a study initiation package   2. To produce a midterm report   3. To report on the status of posting results | 1, 4, 5, 8, 9, 10, 11 ,  1, 4, 5, 8, 9, 10, 11 ,  10  1, 4, 5, 9, 10, 11 ,  1, 4, 5, 9, 10, 11 , |  |  |  |  |  | | | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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|  | 4.4 To assess efficacy of the TRUSTING AI monitoring system in reducing psychotic relapse |  |  |  |  |  | | | | | | | | | | | | | | | | | |
|  | 4.5 To evaluate trustworthiness and additional secondary outcomes of the AI monitoring system |  |  |  |  |
| **WP5** | **Health economic evaluation** | **Lead: 8** |  | | | | | | | | | | | | | | | | | | | | | |
| * 1. Exploring potential subpopulations and assessing reimbursement criteria in public financing systems   2. Development of value framework for the AI monitoring system   3. Health economic model development and adaptation to selected EU markets   4. Net Present Value estimation | 10, 3, 8  10, 3, 8  10, 3, 8  1, 2, 3, 8, 10 |  | | | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| **WP6** | **Dissemination, Communication, and Exploitation** | **Lead: 6** |  | | | | | | | | | | | | | | | | | | | | | |
| * 1. Communication and Dissemination Activities   2. Exploitation Activities   3. IP management | All partners  All partners All partners |  | | | | | | | | | | | | | | | | | | | | | |
| **WP7** | **Project Management** | **Lead: 1** |  | | | | | | | | | | | | | | | | | | | | | |
| * 1. Project coordination   2. Project and Data management   3. Financial management   4. Ethics and risk management | All partners All partners All partners  All partners |  | | | | | | | | | | | | | | | | | | | | | |

**Figure 3.1a.** Gantt chart of the TRUSTING project.

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**Figure 3.1b.** PERT chart of the TRUSTING project.

*Management structure:* the organizational structure that will be used in trusting is displayed in Figure 3.1c. To efficiently manage the consortium and the complexity of the problem, we aim for effective decision making and a financial and scientific transparent management structure. We distinguish between 4 levels of management, each with a different level of authority and responsibilities. The General Assembly (GA) is the highest decision-making body in TRUSTING.

**Figure 3.1c.** Management structure of TRUSTING.

Its responsibility is the correct implementation of

the project in accordance with the contract and the consortium agreement. The Executive Board (EB) acts as the central management team of TRUSTING, responsible for monitoring the progress of the 7 WPs towards the overall project objectives on the basis of the agreed deliverables and associated milestones, and for adhering to the budget limits. The Project Office (PO) is the day-to-day management office, located at the premises of partner 1 (UMCG) and partner 10 (UZH) , consisting of the coordinator, a project manager, a financial controller and a project secretary. At the operational level, WP Teams are responsible for an effective and efficient implementation of the work associated with a specific WP. The WP Teams consist of the leading investigators of the consortium partners who are active in that WP, together with the WP Leader. All 12 consortium members are partners. Each partner appoints one representative for the GA and one formal contact for the EB. The TRUSTING project (through the EB) will regularly consult with a TRUSTING Advisory Board (AB), consisting of external experts with domain expertise relevant to the project, clinical, technical, ethical, legal and economic matters. The AB has no formal decision power within the project. The User Board will be built with help from GAMIAN and EPA and will include individuals with lived experience and clinicians with experience in psychosis treatment.

**Table 3.1g:** ‘Subcontracting costs’ items

"Subcontracts will be awarded ensuring the best value for money or, if appropriate, the lowest price, ensuring there is no conflict of interests and that all applicable internal and/or national procurement rules have been followed."

|  |  |  |
| --- | --- | --- |
|  | **Cost (€)** | **Description of tasks** |
| **Subcontracting 3**  **UIT (portal number 3)** | 150,000 | Workpackage 3, task 3.1, building secure/sensitive data system for the AI monitoring system, providing secure data repository and analysis environment |
|  | 25.000 | Workpackage 6, task 6.2 & 6.3, services fee for the development of the Exploitation Plan (task 6.2) and help with Freedom to Operate issues (task 6.3). |
| **Total** | 175,000 |  |

**Table 3.1h:** ‘Purchase costs’ items

|  |  |  |
| --- | --- | --- |
| **UPF (portal number 2)** | **Cost (€)** | **Justification** |
|  |  |  |
| **Travel and subsistence** | 19.400 | Travel to project meetings (€3.6k), visits for joint experiments (€8.6k), travel to conferences and subsistence (€7.2k) |
| **'Other goods, works**  **and services** | 30.600 | Registration fees to conferences (€8.6k), Open access publication costs (€14k), safe storage for data (€4k), certificate in the financial statements (€4k) |
| **Total** | **50.000** |  |
| **DEU (portal number 4)** | **Cost (€)** | **Justification** |
| **Other goods/works/services** | 40.000 | Clinical trial costs (includes local admin €10k, consumables €5k, monitoring/auditing  costs €15k, travel costs for 35 participants €5k, and reimbursement for 35 participants €5k). |
| **Remaining purchase costs (<15% of pers. Costs)** | 10.000 |  |
| **Total** | **50.000** |  |
| **NIMH (portal number 5)** | **Cost (€)** | **Justification** |
| **Other goods/works/services** | 40.000 | Clinical trial costs (includes local admin €10k, consumables €5k, monitoring/auditing costs €15k, travel costs for 35 participants €5k, and  reimbursement for 35 participants €5k). |
| **Remaining purchase costs (<15% of pers. Costs)** | 10.000 |  |
| **Total** | **50.000** |  |
| **GAMIAN (portal number 6)** | **Cost (€)** | **Justification** |
| **Travel and subsistence** | 19.800 | Consortium project meetings (2 persons) (€7.2k), user group/ patient board meetings (3 persons) (€9.6k), congresses (€3k). |
| **Remaining purchase costs (<15% of pers. Costs)** | 10.000 |  |
| **Total** | **29.800** |  |
| **EPA (portal number 7)** | **Cost (€)** | **Justification** |
| **Travel and subsistence** | 28.800 | Project meetings (€10.8k), conferences (€18k). |
| **Total** | **28.800** |  |
| **RCSI (portal number 9)** | **Cost (€)** | **Justification** |
| **Other goods/works/services** | **51.000** | Clinical trial costs (includes local admin €12k, consumables €6k, monitoring/auditing costs €17k, travel costs for 35 participants €6k, and reimbursement for 35 participants €6k). (total €47k), certificate on the financial statements (€4k). |
| **Remaining purchase costs (<15% of pers. Costs)** | **10.000** |  |
| **Total** | **61.000** |  |

**Table 3.1.i: ‘Other costs categories’ items (e.g. internally invoiced goods and services)**

**No other costs categories are foreseen.**

|  |  |  |
| --- | --- | --- |
| **Participant Number/Short Name** | | |
|  | **Cost (€)** | **Justification** |
| **Internally invoiced goods**  **and services** |  |  |
|  |  |  |

**Table 3.1j: ‘In-kind contributions’ provided by third parties No other in-kind contributions from third parties are foreseen.**

|  |  |  |  |
| --- | --- | --- | --- |
| **UPF (portal number 2)** | | | |
| **Third party name** | **Category** | **Cost (€)** | **Justification** |
| **ICREA** | **Seconded Personnel** | 96.052 | ICREA (Institució Catalana de Recerca i Estudis Avançats) will provide resources to Universitat Pompeu Fabra (UPF) as a third party. This in-kind contribution concerns personnel costs and is free of charge (art.9.2 HE), ICREA is providing this seconded personnel without any retribution.  ICREA is a foundation supported by the Catalan Government and guided by a Board of Trustees which aims to recruit top scientists for the Catalan R&D system. Although employed by ICREA**, Prof. Wolfram Hinzen** is seconded at the Department of Translation and Languages Sciences and considered a member of UPF. The terms and conditions of this cooperation between ICREA and UPF are reflected in a bilateral agreement between the two parties. UPF is free to use these resources at will. Prof. Wolfram Hinzen is therefore assimilated as “own resources” of the beneficiary and will be charged to the project without being considered as a receipt. The cost will be declared by the beneficiary and it will be recorded in the accounts of the third party. These accounts will be available for auditing if  required. |
|  | **Total** | **96.052** |  |

# Capacity of beneficiaries and consortium as a whole

#### The Consortium: contribution of each partner and matching the project objectives

**Figure 3.2a.** Geographical distribution of TRUSTING.

The TRUSTING consortium consists of 12 partners with a wide geographical distribution (Fig. 3.2a) and complementary expertise in schizophrenia, linguistics, automated language analysis, AI, decision support tools, clinical trials, health technology assessment, engagement/involvement of individuals with lived experience, dissemination and communication, and project management. The objectives are directly aligned with the WPs and each partner’s complementary expertise (see Table 3.2a). For a further description of the interdisciplinary knowledge of the Consortium, please see 1.2 Methodology – Interdisciplinary approach (page 18).

**Table 3.2a:** Consortium match to project’s objectives.

|  |
| --- |
| **Objective 1. To define speech-based features sensitive for emerging relapse and assess accuracy and validity across diverse subgroups** |
| UMCG’s Dr. Sommer’s team has the expertise and experience to analyse speech using SLP and NLP software, |

|  |
| --- |
| and to adapt these tools to the Dutch language. Dr. Sommer is also an expert on female-specific psychosis research  and care, and in reducing gender bias in research. Dr. Sommer has experience in coordinating large multinational RCTs in citizens with schizophrenia. Dr. Van Vugt is an expert in longitudinal AI analyses. |
| **Objective 2. To validate speech-based features characteristic for relapse across language-tasks, languages in multiple psychosis samples, and test it in a relapse-prediction setting** |
| UPF’s Dr. Hinzen is a linguist specialized in linguistic features of psychosis. Dr. Hinzen is an expert in theoretical linguistic models that explain language disturbances in schizophrenia, and has extensive experience with linguistic  analyses in different European languages. |
| **Objective 3. To build trustworthy AI using speech-based features as the core measures that are monitored** |
| UiT’s Dr. Elvevåg has expertise and experience to build a monitoring system that meets EU’s trustworthiness criteria. Dr. Elvevåg is a pioneer in NLP research in schizophrenia, and experienced in coordinating large interdisciplinary RCTs involving eHealth and computerized assessments of language. Dr. Mikaelsen has used  mechine learning extensively to predict medical risks and develop a variety of clinical decision support tools. |
| **Objective 4. To assess efficacy of the monitoring system in a randomized controlled trial (RCT)** |
| UZH’s Dr. Homan will lead the trial with UNIGE, DEU, NIHM, SUT, and RCSI as participating centers. All  partners have demonstrated the ability to include large numbers for psychosis research. |
| **Objective 5. To achieve trust and use by clinicians and service users** |
| GAMIAN and EPA have the capacity to set-up service user and clinician groups and liaise with them the whole  project. UIT will lead AI monitoring system design integrating their feedback. |
| **Objective 6. To evaluate the cost-effectiveness of the developed AI monitoring system** |
| SRI will perform health economic assessment and modelling. SRI is committed to academic excellence and has an impressive track record of peer-reviewed publications in health economy, public health and health systems  science. |
| **Objective 7. To define the roadmap for protection and commercialization of the project’s results** |
| UiTs TTO Norinnova will lead the business strategy preparation, collaborating with all partners to handle IP  management. |

#### Expertise in social sciences and humanities, open science practices, and gender aspects

* Social sciences and humanities: UPF. PI Dr. Hinzen is an academic from the field of humanities who brings in linguistics, a key discipline for this project.
* Open science practices: UZH. PI Dr. Homan has expertise and several years of experience with sharing reproducible workflows and data, using open science platforms such as GitHub and Open Science Framework (OSF). UMCG. Dr. van Vugt also has years of experience in Open Science, and teaches the AI program’s course on open science methods in the context of both AI and social science research.
* Gender aspects: UMCG Dr. Sommer has expertise in women-specific schizophrenia care. Dr. van Vugt has been active at promoting females in the computational sciences, as evidenced from her membership in the board of Women of Mathematical Psychology.

#### Access to critical infrastructure

**Table 3.2b:** The Consortium’s access to critical infrastructure.

|  |  |
| --- | --- |
| **Partner** | **Infrastructure description** |
| UMCG | Access to high-performance computing (HPC) cluster allowing large jobs to be processed in high speed. UMCG has infrastructure for maintaining and analysing large databases, and performing data mining (e.g. in Life Lines). UMCG is the lead organisation in the Healthy Ageing Network Northern-Netherlands ([www.hannn.eu/](http://www.hannn.eu/)), which is a triple-stars reference site of the European Innovation Partnership on Active and Healthy Ageing. UMCG works with partners in technological innovation and ICT in health. That is a part of the Innovation Union strategy of the Commission that aims to enhance European competitiveness and tackle societal challenges through  R&I. |
| RBV | Post-award project management Project manager to be appointed (support on day-to-day standard project management tasks for TRUSTING) |
| UZH | Clinical Trials Center (CTC; <https://www.usz.ch/en/clinic/clinical-trials-center/>) to provide expertise and guidance throughout the clinical trial (WP4); support in planning and implementation; advice on methodological, regulatory, financial aspects; and management in  accordance w/ Good Clinical Practice. |
| UPF | Grammar & Cognition Lab: A laboratory ([www.graclab.com](http://www.graclab.com/)) based in the UPF and directed by Dr. Hinzen dedicated to language studies across major mental disorders with a rich network of |

|  |  |
| --- | --- |
|  | clinical partners in Barcelona and across Spain (5 major hospitals in Barcelona alone). Major partners worldwide include Dr. Lena Palaniyappan (Brain & Mind Institute, London Ontario). GraC is locally partnered with the Brain & Cognition Centre at the UPF ([www.upf.edu/web/cbc](http://www.upf.edu/web/cbc)) dedicated to cognitive neuroscience including shared projects on brain connectivity and language  in major mental disorders (Dr. Gustavo Deco). |
| UIT | Norwegian Center for Clinical Artificial Intelligence (Tromsø) directed by collaborator for WP4 Dr. Mikaelsen: Facilitate development and use of clinical decision support tools based on artificial intelligence. <https://www.spki.no/en>  Services for Sensitive Data (University of Oslo): Provide a secure technological infrastructure to collect, store and analyse sensitive data that can be accessed globally. <https://www.uio.no/english/services/it/research/sensitive-data/index.html> |
| UNIGE | Network of psychiatric hospitals in French-speaking Switzerland (ARIP): There is an ongoing effort to harmonize evaluation/treatment of citizens with first-episode psychosis across the whole  region. |
| DEU | Spaces for interview and recordings: Participant interview rooms in psychiatry and 2 rooms for speech recording in the neuroscience departments.  Network with other psychosis researchers in Izmir: Working closely with psychosis researchers in Katip Çelebi and Atatürk universities in İzmir which is a city with over 4 million inhabitants. Dr  Bora is the current national coordinator of schizophrenia and other psychotic disorders working group of the Psychiatric Association of Turkey (PAT) |
| NIMH | Schizophrenia spectrum enrolment network: One of NIMH flagships is aimed at establishing a national-wide multimodal database that contains data from ongoing largescale longitudinal study  focused on citizens with first-episode psychosis. |
| SUT | Access to National e-therapy centre [https://www.swinburne.edu.au/research/centres-groups-](https://www.swinburne.edu.au/research/centres-groups-clinics/centre-for-mental-health/national-etherapy-centre/) [clinics/centre-for-mental-health/national-etherapy-centre/](https://www.swinburne.edu.au/research/centres-groups-clinics/centre-for-mental-health/national-etherapy-centre/)  Access to the Clinical Trial Platforms for Mental Health via the MAGNET initiative. Australia  General Clinical Trial Network for Mental Health (GNT 2006296). The platforms include clinical assessment training, biostatistics and health economics support. |
| GAMIAN | Office space, service-user testing panel, contacts to international service users. |
| EPA | Office space, EPA website and newsletters, annual symposium for European psychiatrists. |
| SRI | Office space, computer platform for modelling, pre-existing economic models on schizophrenia. |
| RCSI | * Newcastle Hospital Mental Health Services patient population and clinical teams. * RCSI Research IT systems, RCSI Data Science Center, and RCSI medical library. |

#### Industrial/commercial involvement

* SRI: Syreon Research Institute is a Hungarian SME providing expert services in the fields of evidence synthesis, health economics, strategic pricing and corporate training for the pharmaceutical and health services sector. Led by Dr. Zoltán Kaló, Dr. Zoltán Vokó and Dr. Paul Keown, SRI scientists are experts in the interface of clinical research and health burden/economic analysis and have published widely in the area. The health economics group is supported by an economic modelling division led by Dr. Balázs Nagy with extensive experience in economic evaluation of healthcare interventions and members with a full understanding of the challenges of modelling, data management, data and statistical analysis.
* UIT TTO: Norinnova AS has for the last 25 years served as the TTO for the UiT and the University Hospital of North Norway (UNN). The TTOs role is to handle the commercialization process of research results from UiT and UNN to ensure its realization into society.
* UMCG Research BV is a full subsidiary of the UMCG offering post-award project management. UMCG Research BV as an organization has ample experience in pre- and post-award project management and a strong project management knowledge system. Project managers of the UMCG Research BV have their employment contract with the UMCG Research BV and then are seconded to different projects of the UMCG. The project manager seconded to the TRUSTING project will fulfill under the coordinator supervision the general management tasks such tracking of project progress (i.e. milestones, timelines and budget), liaison with the UMCG support office for financial, legal and administrative tasks.

#### Other countries and international organizations

The consortium includes 2 countries which are in principle not eligible for EU funding: Switzerland and Australia:

* Switzerland (UZH, UNIGE): At the time of submission, Swiss applicants are not automatically eligible for

funding since Switzerland is as of now not an Associated country in Horizon Europe. In case this situation is not resolved before signing the grant agreement, the UZH and UNIGE budget will be covered by the Swiss Secretariat for Education, Research and Innovation (SERI) (see letter attached to the end of the clinical trial Annex).

* Australia (SUT): Australian partners are not automatically eligible for funding and therefore usually have to participate at their own cost. SUT will request funding from Australian funding bodies once the project is funded. Swinburn Technology University fully supports this project and will cover additional costs that may not be covered by Australian matching grants (see letter attached to the end of the clinical trial annex). Mitigation measures are already in place in case Australian funding cannot be secured (see Risks table).

# References

1. Kassebaum NJ et al. doi:10.1016/S0140- 6736(16)31460-X

2. Hui CL et al doi:10.1017/S0033291718003070

3. Pilon D et al. doi:10.18553/JMCP.2021.27.7.904

4. Almond S et al. doi:10.1192/bjp.184.4.346

5. Ceraso A et al. doi:10.1002/14651858.CD008016.pub3. 6. Rubio JM et al. doi:10.1016/S2215-0366(20)30264-9

7. Taipale H et al. doi:10.1016/S2215-0366(22)00015-3

1. Moncrieff J et al. doi:10.1371/journal.pmed.1001861
2. Doane MJ et al. doi:10.2147/PPA.S270020

10. Palaniyappan L et al. doi:10.1038/s41537-021-00172-1

1. Lecomte T et al. doi:10.1037/abn0000447
2. Herz MI et al. doi:10.1001/archpsyc.57.3.277

13. Bighelli I et al. doi:10.1016/S2215-0366(21)00243-1

14. Hitczenko K et al. doi:10.1093/schbul/sbaa141 15. Parola A et al. doi:10.1016/j.schres.2019.11.031

16. de Boer JN et al. doi:10.1017/S0033291721002804

1. Voppel AE et al. doi:10.1016/j.psychres.2021.114130
2. Bedi G et al. doi:10.1038/npjschz.2015.30
3. Corcoran CM et al. doi:10.1002/wps.20491

20. Graham S et al. doi:10.1007/s11920-019-1094-0

21. Mota NB et al. doi:10.1371/journal.pone.0034928

22. Corcoran CM et al. doi:10.1016/j.bpsc.2020.06.004 23. Fletcher S et al. doi:10.1016/S2215-0366(20)30517-4

1. Howard R et al. doi:10.1176/appi.ajp.157.2.172
2. Fortney JC et al. PMID: [21348556](https://pubmed.ncbi.nlm.nih.gov/21348556)
3. Chandler C et al. doi: [10.18653/v1/2021.clpsych-1.20](http://dx.doi.org/10.18653/v1/2021.clpsych-1.20)
4. Chandler C et al. doi:10.1093/schbul/sbac038
5. Hitczenko K et al. doi:10.18653/v1/2021.clpsych-1.16
6. Yamagishi T et al. doi:10.1007/BF02249397
7. Marder S. doi: [10.1093/schbul/sbac092](https://doi.org/10.1093/schbul/sbac092)
8. Kaur R et al. doi:10.2174/1568026621666210521162832

32. Parks CL et al. doi:10.1007/s10278-016-9932-7

33. Chiang S et al. doi:10.1212/WNL.0000000000012570

34. Caliskan A et al. doi: 10.1126/science.aal4230 35. Iter D et al. doi: [10.18653/v1/W18-0615](http://dx.doi.org/10.18653/v1/W18-0615)

36. Parola A et al. doi: 10.1101/2022.04.03.22273354

1. Rybner A et al. doi:10.1002/aur.2721
2. Mayora O. https://joinup.ec.europa.eu/collection/ehealth/document/m onarca-monitoring-treatment-and-prediction-bipolar- disorder-episodes-monarca

39. Just S et al. doi:[10.18653/v1/W19-3015](http://dx.doi.org/10.18653/v1/W19-3015)

40. Beauchamp TL et al. ISBN: 9780190640873

41. Voppel, AE et al. doi:10.1101/2022.07.13.22277577

42. Killeen PR. doi:10.1073/pnas.1011277108

43. Jaeger HH. doi: [10.1126/science.1091277](https://doi.org/10.1126/science.1091277)

44. Verplancke T et al. doi:10.1186/1472-6947-10-4

45. Skowronski MD et al. doi:10.1016/j.neunet.2007.04.006

46. Ibrahim H et al. doi:10.1109/ACCESS.2021.3107858

47. Parola et al. doi:[10.1016/j.schres.2022.07.002](https://doi.org/10.1016/j.schres.2022.07.002) 48. Çokal D et al. doi:10.1038/s41537-018-0061-9

49. Sevilla G et al. doi:10.1371/journal.pone.0201545 50. Çokal D et al. doi:10.1016/j.schres.2022.06.024

51. Palominos C et al. doi:10.1093/schbul/sbac102 52. Chandler C et al. doi:10.18653/v1/w19-3016

53. Holmlund TB et al. doi:10.1038/s41746-020-0241-7 54. Diaz-Asper C et al. doi:10.1177/20552076211002103

55. Holmlund TB et al. doi:10.1037/pas0000647

56. Chandler C et al. doi:10.1016/j.ibmed.2020.100006

57. Chandler C et al. doi:10.1016/j.psychres.2021.113743 58. Eyben F et al. doi:10.1109/TAFFC.2015.2457417

59. Kodish-Wachs J et al. PMID: 30815110

60. Menger V et al. doi:10.1016/j.tele.2017.08.002

61. Elvevåg B et al. doi:[10.1016/j.schres.2007.03.001](https://doi.org/10.1016/j.schres.2007.03.001) 62. Devlin J et al. doi:[10.18653/v1/N19-1423](http://dx.doi.org/10.18653/v1/N19-1423)

63. Vaswani A et al. doi:[10.48550/arXiv.1706.03762](https://doi.org/10.48550/arXiv.1706.03762) 64. Wouts J et al. doi:[10.48550/arXiv.2106.01091](https://doi.org/10.48550/arXiv.2106.01091)

65. Rochester S et al. doi:[10.1016/0378-2166(83)90053-X](https://doi.org/10.1016/0378-2166(83)90053-X) 66. Foltz PW et al. [doi:10.1016/j.schres.2022.07.011](https://doi.org/10.1016/j.schres.2022.07.011)

67. Silva AM et al. doi:10.1016/j.schres.2022.06.011 68. Berisha V et al. doi:10.1038/s41746-021-00521-5

69. Hitczenko K et al. doi:[10.1093/schbul/sbab131](https://doi.org/10.1093/schbul/sbab131)

70. Morgan SE et al. doi:10.1038/s41398-021-01722-y

1. Palaniyappan L et al. doi:10.1016/j.pnpbp.2018.07.007
2. Diaz-Asper C et al. doi:10.1016/j.cortex.2022.08.005 73. Paulus JK et al. doi:10.1038/s41746-020-0304-9
3. Palaniyappan L et al. doi:10.1093/schbul/sbac058
4. Brederoo SG et al. doi:10.1016/j.jpsychires.2021.08.019

76. Gumley AI et al. doi:10.1016/S2215-0366(22)00103-1

77. Morriss R et al. doi:10.1002/14651858.CD005147.pub2

78. Begemann MJH et al. doi:10.1186/s13063-019-3822-5

1. ZonMw. https[://www.](http://www.zonmw.nl/nl/onderzoek-)zon[mw.nl/nl/onderzoek-](http://www.zonmw.nl/nl/onderzoek-) resultaten/doelmatigheidsonderzoek/programmas/project- detail/goed-gebruik-geneesmiddelen/to-continue-or-not-to- continue-a-randomized-controlled-trial-of-maintenance- treatment-versus-dis/
2. ZonMw. https[://www.](http://www.zonmw.nl/nl/onderzoek-)zon[mw.nl/nl/onderzoek-](http://www.zonmw.nl/nl/onderzoek-) resultaten/geestelijke-gezondheid- ggz/programmas/project-detail/onderzoeksprogramma- ggz/outcome-of-psychosis-heterogeneity-explained-by- long-lasting-individual-attributes-ophelia/
3. Longenecker J et al. doi:[10.1016/j.schres.2010.03.023](https://doi.org/10.1016/j.schres.2010.03.023)
4. Bolukbasi T et al. doi: [10.48550/arXiv.1607.06520](https://doi.org/10.48550/arXiv.1607.06520) 83. Cirillo D et al. doi:10.1038/s41746-020-0288-5 84. Homan P et al. doi:10.1038/s41386-019-0322-y 85. Homan P et al. doi:10.1038/s41386-019-0464-y 86. Homan P et al. doi:10.1038/s41593-018-0315-x

87. Open Science Collaboration.

doi:10.1126/science.aac4716

88. Pilon D et al. doi:10.1080/03007995.2021.1954894

89. Pennington M, McCrone P. doi:10.1007/s40273-017- 0515-3

90. Leucht S et al. doi:10.1016/S0140-6736(12)60239-6

1. Cooper RE et al. doi:10.1371/journal.pone.0218711
2. Kikkert MJ et al. doi:10.1111/eip.13138

93. Spaniel F et al. doi:10.1016/j.schres.2007.09.005 94. Saraceno B. doi:10.1017/s1121189x00005546

1. WHO-Wetern Pacific Region. https[://www.](http://www.who.int/publications/i/item/9789240049338)who[.int/publications/i/item/9789240049338](http://www.who.int/publications/i/item/9789240049338)
2. Murray CJ, Lopez AD. doi:10.1126/science.274.5288.740

97. Kane JM. doi:10.4088/JCP.12117tx1c

1. World Health Organization. ISBN: 9789241506021
2. World Health Organization. doi:

[10.1001/jama.291.21.2581](https://doi.org/10.1001/jama.291.21.2581)

100. Eaton J et aldoi:10.1016/S0140-6736(11)60891-X

101. Spanhel K et al. doi:10.1038/s41746-021-00498-1

102. Mohr DC et al. doi:10.1016/S2215-0366(14)70261-5

103. Anderson KK et al. doi:10.1017/S0033291718002933

1. Huber G et al. doi:[10.1093/schbul/6.4.592](https://doi.org/10.1093/schbul/6.4.592)
2. Birchwood M et al. PMID: 9764127

106. Harrison G et al. doi:10.1192/bjp.178.6.506

1. Alvarez-Jimenez M et al. doi:10.1016/j.schres.2012.05.007
2. Andreasen NC et al. doi:10.1176/appi.ajp.162.3.441
3. Leucht S et al. doi:10.1001/jamapsychiatry.2021.2130 110. Chopra P et al. doi:10.1097/MRR.0b013e32830150e6 111. Wistedt B et al. doi:10.1055/s-2007-1014514

112. Sonntag M et al. doi:10.1186/s12955-015-0315-4

# ETHICS SELF-ASSESSMENT

* 1. **Ethical dimension of the objectives, methodology and likely impact.**

All foreseen ethical issues are detailed below, however, if unanticipated ethical issues arise unexpectedly during this project, the Consortium will contact the EC immediately and provide detailed information on the issue and how we

intend to handle it.

2. Humans:

This project involves the use of human subjects as part of the work described in WP4 – 'Clinical application: Testing the efficacy of the TRUSTING AI monitoring system for psychosis relapse prevention in a randomized clinical trial'. This WP consists of an RCT in which 240 patients with a psychotic disorder will be recruited for weekly speech monitoring during a 12-month period. The objective of the study is to assess the efficacy of the AI monitoring system compared to usual care in reducing psychotic relapse, and to evaluate the acceptability and trustworthiness of the system compared to usual care. This represents a low, non-invasive intervention clinical trial, in which the use of the speech monitoring tool does not provide any additional risk over standard-of-care procedures. We will ensure

respect for people and for human dignity, fair distribution of research benefits and burdens and protection of the values, rights and interests of the research participants. All necessary ethical approvals and voluntary and fully informed consent of the research participants will be obtained.

4. Personal Data:

The project will involve collection and processing of sensitive primary health personal data (WP4 – 'Clinical application: Testing the efficacy of a speech monitoring system for psychosis relapse prevention in a prospective clinical trial’), as well as the processing of previously collected de-identified speech data in WP1 and 2. Certain categories of data are more ‘sensitive’ than others (e.g. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction) and these may only be processed according to specific rules. Data collection will follow a strict protocol to protect the privacy and personal data of the participants, with specific attention to combinations of data with speech data, as characteristics of speech data combined with other types of data may increase the risk of reidentification of participants. Informed consent will be obtained. All data will be handled according to strict standards as well as local national guidelines, including coding (pseudonymization) during the study. No online (cloud-based) processing of data will be done during the analysis process. Details will be provided to the European Committee on privacy/confidentiality and the procedures that will be implemented for data collection, storage, protection, retention and destruction. See box 2 below for further details.

6. Third Countries:

This project includes non-EU partners from Switzerland, Norway, Turkey and Australia, as well as the usage of de- identified speech data from non-EU partners (currently Canada and Turkey) participating in the DISCOURSE speechBank project. For the transfer of data, this study will obtain specific authorization from the national data protection authority (of the Member State from which the

data is sent). See further in box 2 below.

8. Artificial Intelligence:

The project will leverage AI to detect emerging relapse in participants. Although there are risks with clinical applications of AI, which this project will address as described in box 2 below, the recently released WHO guidelines ‘Ethics and governance of AI for health’ (June 2021: https:[//www.who.int/publications/i/](http://www.who.int/publications/i/) item/9789240029200) points out in section 6.5 that the ‘Use of AI systems to make specific, well-defined decisions may be entirely justified if there is compelling clinical evidence that the system performs the task better than a human. Leaving decisions to humans when machines can perform them more rapidly, more accurately and with greater sensitivity and specificity can mean that some patients suffer avoidable morbidity and mortality without the prospect of some offsetting benefit.’ The core design of TRUSTING is in keeping with the 'anticipatory ethics approach' (Chiang et al, doi: 10.1212/WNL.0000000000012570), encouraging a pre-emptive examination of the methodological and design choices so as to enable a careful evaluation of the ethical implications of numerous decision points in the development, calibration and implementation of algorithms.

# Compliance with ethical principles and relevant legislations.

2. Humans

Each partner involved will comply with all relevant national and EU legislations relating to the conduct of human studies. This study will follow the procedures for informed consent that are described in the Declaration of Helsinki

and the General Data Protection Regulation (GDPR). The project will comply with:

* The commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice about investigational medicinal products for human use as well as the requirements for authorization of the manufacturing or importation of such products (OJ L 91, 9.4.2005, p. 13).
* The EU Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
* The guidelines on Good Clinical Practice (GCP) from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

4. Personal Data

The project will comply with ethical principles and applicable international, EU and national law on personal data and in accordance with the General Data Protection Regulation (GDPR) (EU) 2016/679. For data used in this project in WP2 from the DISCOURSE consortium, all sites participating in DISCOURSE can opt for applying locally for ethical permissions for either sharing their speech data themselves, or else only meta-data about them, on a PsychosisBank, which will form part of TalkBank (https://talkbank.org/), on the model of existing data-sharing platforms on this site such as DementiaBank or AphasiaBank. Data governance: all applications to use data will go to the DISCOURSE steering committee, who will approve the intended use. Users need to agree to a code of conduct, which in particular prohibits non-research use of data. Access to data will be password protected. Data ownership remains with the participating sites. TalkBank is in charge of data storage mechanisms. All participants consenting to their speech data being deposited will retain the right to remove them at any point in the future. The general strategy for sharing data within the DISCOURSE consortium is outlined here: https://doi.org/10.1093/schbul/sbac058.

6. Third Countries

For the research activities carried out outside the EU, the consortium will ensure that:

1. the activities are accepted and comply with the legal obligations of the third country,
2. the research is compatible with EU and international law,
3. it is shown that the research could have been legally conducted in (at least) one of the EU Member States.

This will be done by submitting the approval of the European ethics committee (e.g. the ethics committee of the institution hosting the researcher(s) that conduct the activity). Getting such approval is mandatory when there is no competent structure in the third country. In this case, the consortium must moreover implement other safeguards (e.g. appoint an independent ethics adviser from the third country or an ethics advisory board).

8. Artificial Intelligence:

With regards to AI specifically, besides all applicable regulations stated above, this project will address the Ethics Guidelines for Trustworthy Artificial Intelligence presented by the European Commission’s High-Level Expert Group (EU-HLEG) on AI in 2019 (Table 1.1 on pages 4 & 5 of the main project). A European legal regulation (the AI Act) has been proposed, which will transpose these ethical principles from the EU-HLEG Guidelines for Trustworthy AI into binding law. As such, this project anticipates and will futureproof so as to comply with upcoming EU AI legislation. In the application of NLP methods, there is always a risk of inadvertently identifying race, gender, minority, and education differences in speech with the use of the high-dimensional or black box approaches in machine learning, and thus we will strive toward transparent methods that nurture fairness and minimize bias by a continual screening of the error rates (which can point to bias) (Paulus, JK et al. doi: 10.1038/s41746-020-0304-9). Furthermore, usage of our AI monitoring system will be evaluated in terms of (ethical) professional responsibility and legal liability. In particular, we will evaluate to what extent physicians feel free to overrule recommendations from the system, and what the liability risks are if they chose not to follow the AI recommendations. Or alternatively, who is responsible if the algorithms are found to be incorrect. Our project tackles many of these problems according to the EU-HLEG guidelines, primarily by incorporating our unique human-in-the-loop methodology. Moreover, in November 2022 a Lorentz Workshop in Leiden is initiated by UCMG, incorporating

legal, privacy and ethical issues relevant to the use of SLP/NLP in psychiatry.

# CLINICAL STUDIES.

* 1. **Description of the clinical study**

## Title, acronym, unique identifier (e.g. EudraCT Number5, or identifier from ISCRTN6, ClinicalTrials.gov7 if available) of the clinical study

The study is not yet registered but will be registered at ClinicalTrials.gov before starting enrolment. It will be called “A TRUSTworthy speech-based AI monitorING system for the prediction of relapse in individuals with schizophrenia”. Acronym: TRUSTING.

## Study rationale

Please provide the overall rationale for conducting the proposed study.

After the first psychotic episode most citizens with schizophrenia (approximately 80%) will develop a second, third and in many cases a multitude of psychotic relapses, with complete or incomplete recovery in between1. Individuals with a relapsing course have greater suicide risk2, smaller chance of sustaining long-term relationships3, higher risks of unemployment and increased functional and cognitive decline4 compared to those who do not relapse. In addition, relapse may contribute to treatment resistance5. Relapse during the early years after the first psychosis is the most important determinant of clinical and functional outcome of schizophrenia6. Maintenance treatment with antipsychotics largely decreases the risk for relapse7, but many service users prefer to reduce or stop their medications as side-effects can be bothersome, especially with long-term use8. This has made intermittent treatment with antipsychotic medication (i.e., use only when relapse is imminent/manifest) just as common as maintenance treatment9,10. To accommodate this social change, it is imperative to improve clinical and functional outcome by accurately predicting relapse as early as possible, and to create a window of opportunity to apply preventive interventions, which may differ per individual and per situation. The purpose of WP4 and this clinical study is to apply a trustworthy monitoring system of relapse risk through detailed and automated analysis of participants’ speech profiles with artificial intelligence (AI). The aim is to prevent relapse in citizens at high risk for psychotic relapse by providing accurate and timely prediction of relapse. To this end, a randomized clinical trial (RCT) will be conducted, for which citizens with schizophrenia will be recruited and followed up through a period of 12 months, a time window where a psychotic relapse is likely to occur, particularly if people discontinue antipsychotic treatment11. Prior to randomization, and whenever possible, speech will be recorded already during a psychotic episode (psychosis speech profile); and then once again during remission (remission speech profile). Participant, informal caregiver and clinician together will work out a personalized relapse prevention plan, which can be activated if relapse is considered imminent. Participants will be randomized either to a control condition (treatment as usual plus weekly speech recordings) or to a treatment condition (treatment as usual plus weekly AI speech monitoring and relapse prediction). Thus, in both conditions we will collect weekly speech samples but they will only be acted upon in the treatment condition: here we will use spoken language processing (SLP) and natural language processing (NLP) to detect subtle reflections of psychosis in participants’ speech and use this to calculate the risk of emerging psychotic relapse. To do this, participants will be asked to provide a speech sample online on a weekly basis (speech elicitation task; e.g. recall of a short story). Using an AI speech monitoring system, developed and shaped in the previous work packages (WP1-3), and taking into account the similarity with the previously recorded speech profiles during psychosis and remission, a relapse risk will be computed (expressed in percentages) together with a confidence interval and sent to the clinician within 48 hours. The clinician will then decide together with the service user and following the personalized relapse plan the best course of action (shared decision making). Most importantly, this whole decision cycle (from speech recording to shared decision making) will involve human oversight, a European Commission key requirement of trustworthy AI: we will allow human intervention at three crucial steps during each decision cycle:

(1) the first human-in-the-loop will check sound quality and automated transcript of the audio recording; (2) the

second human-in-the-loop will check the model output; (3) the third human-in-the-loop, the clinician, uses the calculated relapse risk as basis for shared decision making together with the service user. The primary outcome is time until relapse during a follow-up period of one year, secondary outcomes include acceptability and trustworthiness. Our hypothesis is that time until relapse can be significantly prolonged when extending standard care with our novel AI speech monitoring system compared to standard care with speech recordings alone, and that this intervention is well accepted and perceived as trustworthy by both service-users and clinicians.

#### Extent and evaluation of current knowledge directly linked to the scientific question(s) to be answered by the clinical study.

An assumption we make in this trial is that psychosis is reflected by the individual’s speech, and that SLP/NLP can quantify the amount of psychotic deviation in speech. There is extensive literature demonstrating the efficacy of SLP/NLP to identify subtle signs of psychosis. A recent meta-analysis by Argolo et al.12 included 28 studies using speech-based measures that identified the presence of psychosis or conversion from ultra-high-risk state to

psychosis13 . Accuracy of these studies ranged from 70% to 100%. While building on this prior work, the research question of the current study goes beyond it in important ways: i) by focusing on the re-occurrence of psychosis; ii) by testing the clinical impact of SLP/NLP in a truly prospective way. We not only aim to predict if a participant will relapse, but also when this will happen. Our pilot data (provided in part 1.2 of the main application) confirmed that it is possible to predict psychotic relapse using SLP with high accuracy (81%). Unlike these pilot data, our TRUSTING SLP/NLP analyses will combine speech-based characteristics of different linguistic domains (semantic,

i.e. BERT models, syntactic, i.e. graph-analysis, and acoustic), which further increases the accuracy as compared to a single domain 14. We assume that the clinician will take appropriate actions when provided with a high relapse risk and a short confidence interval calculated from the participant’s current speech profile. Thus, bringing together artificial and human intelligence. The importance of such human interaction when applying digital technology in relapse prevention has recently been shown in a large US multi-site trial, where relapse was reduced when combining digitally enhanced relapse prevention with a human health technology coach 15. In addition, early warning signs have been shown to reduce relapse risk in general RCTs, 16 further highlighting the potential of intervening early when risk for relapse is increasing.

#### Outcomes (efficacy, safety) of completed and number of ongoing clinical studies utilising the same intervention in the same indication (including review of public registers)

This RCT will evaluate the efficacy of SLP/NLP in prolonging time to relapse and thus improve outcome. No previous study investigated SLLP/NLP interventions prospectively while several other studies investigated the efficacy of training participants to recognize early warning signs (such as disturbed mood, subtle psychotic signs, social isolation, sleeping problems). The systematic detection of early warning signs shows similarities to the current study, as SLP/NLP also detects subtle signs of re-emerging psychosis in speech, but is not quite the same, as SLP/NLP can quantify the relapse risk objectively. A 2013 Cochrane review (focused on the efficacy of interventions targeting recognition of early warning signs of psychotic relapse) included 15 RCTs16 Significant effects of training to recognize early warning signs were found for the risk of relapse (n=1502; RR 0.53, 95% CI 0.36-0.79) and the risk for rehospitalisation (n=1457; RR 0.48, 95% CI 0.35-0.66). No safety measures were reported. We expect effects of similar size for the intervention in the proposed TRUSTING trial. Since the meta-analysis by Morriss et al. 16, several new studies have been initiated, which we summarize here:

Steare et al.17 reported on a small feasibility trial using an app (without SLP/NLP analyses) for self-management and relapse prevention in psychotic participants. They reported on inclusion and retention rate, but not yet on efficacy and safety. The EMPOWER study18 is comparable to the current study in that it also provides online warnings for emerging relapse, albeit not on the basis of SLP/NLP. Results are not yet known as the study is ongoing. We also identified a study (ClinicalTrials.gov Identifier: NCT01952041) that uses a smartphone app to prevent relapse. It is not detailed what the smartphone app detects. The main outcome, time to relapse, was not significantly lower in the smart phone app condition (Hazard Ratio 0.78 CI 0.42-1.44). Safety outcomes were not reported. Another study employing e-health to prevent relapse, led by TRUSTING partner 5, NIMH (ClinicalTrials.gov Identifier: NCT01885923) is still ongoing. Dr. Homan from UZH (TRUSTING partner 10 ) was the lead author on a recent and large multi-centre study in the US with over 400 participants that applied digitally enhanced relapse prevention and found a reduction of almost 5 days of rehospitalization during a 6-months follow up 15.

#### Level of evidence related to the mechanism of action of the intervention in the planned clinical study population

To the best of our knowledge, SLP/NLP has not been used for the prediction of psychotic relapse before. However, several studies have used these methods to predict conversion to the first psychotic episode in individuals at ultra- high-risk for psychosis (reviewed by Corcoran et al. 19with high accuracy (83% and cross-validated accuracy of 79%). We assume that predicting psychosis after remission taps into a similar process, and expect comparable accuracy for relapse prediction by SLP/NLP. Indeed, pilot results described in paragraph 1.2 show accuracy of 81% using SLP only. As the TRUSTING project will involve the optimization of psychosis prediction through validating and combining a variety of different language features (semantic, syntactic, and acoustic) we may find even higher accuracy.

## Objective(s) of the clinical study

Please differentiate between primary and secondary objective(s)

*Primary outcome* Time until a psychotic relapse. Relapse is defined as a clinical deterioration of psychosis needing hospital admission, as this is the most commonly used definition 20.

*Secondary outcomes:*

* WHO-DAS-II disability scale 21
* Social and Occupational Functioning Assessment Scale (SOFAS) 22
* Number and duration of psychiatric admissions
* Rates of self-harm (including suicide, suicide attempts and aggressive incidents) assessed with the Social Dysfunction & Aggression Scale (SDAS) 23
* Quality of life assessed with the EuroQoL (EQ-5D-5L) 24
* Evaluation of acceptability and perceived trustworthiness: To evaluate how the speech-based monitoring intervention is perceived by end users (i.e., service users and clinicians) we will assess trustworthiness of the procedure (using the General Trust Scale, GTS) 25 at every visit. In addition, after the last visit, assessors will be unblinded and have a qualitative interview with the participants and clinical team to assess acceptability and trustworthiness of the intervention.

## Characteristics of the study population (size, age group, sex distribution, inclusion and exclusion criteria; all items with justification!)

*Inclusion criteria:*

* The target population is citizens in remission from a psychosis, as defined by the criteria of Andreasen et al. 26. Diagnosis can consist of schizophrenia, (codes 295.xx). We opted for this population as it is arguably the most difficult population for gaining trust, given their tendency to paranoid thinking.
* The age range will be 18-65. It is important to keep the age limit broad, as women commonly experience a first psychosis at middle or even older age 27. A tight age limit will unintentionally exclude many women and we intend to include at least 40% women to allow sex-specific analyses. Citizens above the age of 65 may not have hands-on experience in using smart device apps, which is needed for this trial.
* Participants need to be able and willing to provide informed consent and participate in the trial as per Helsinki convention, and able to speak and understand any of the languages that have been validated in TRUSTING WP2 (English, German, Dutch, French, Czech or Turkish) as the AI-monitoring system will be validated only for these 6 languages (as per WP2).
* Participants need to be able to have access to a smartphone or computer and be capable of using an online app for speech-based monitoring.

*Exclusion criteria:*

* Pregnancy or lactating, severe comorbid speech disorders (aphasia or severe stuttering) that prevent adequate speech recording. Individuals who are not able or willing to understand the purpose and details if the trial cannot be included. Citizens with psychiatric or somatic comorbidity, drug- or alcohol abuse will be allowed to participate, so that the sample will reflect the general population of citizens with psychosis and the study’s outcomes will be generalizable. Drop-out criteria are kept as few as possible. Language and migration background will be assessed for sensitivity analyses, including place of birth of the participant, languages learned, age and place (i.e., at home/school/work) of acquisition, frequency of use, and information regarding the birthplace and languages of the parents. All speech data will be included as long as we have information regarding relapse or no relapse in the month following the speech recording. When this information is missing, the speech recording cannot be used. So even if a participant has only a few recordings, these recordings will be included in the models as long as we know whether it was followed by a relapse or not. The number of times the app is used to provide a speech sample is recorded and used as a covariate. Only participants who cannot be traced anymore, have died or withdrawn their informed consent will be considered to have dropped out. Participants who can be traced on a later stage or who change their mind after leaving the study are then welcome to be followed-up again.

#### Details on sample size and power calculation.

Sample size is based on the ability to find a significant reduction in relapse between the two conditions. We used the meta-analysis by Morriss et al. 16 to estimate the reduction of relapse when participants are given a warning based on recognition of early warning signs. The duration of our intervention (12 months) is comparable to the studies meta- analysed by Morriss et al. 16. While most participants studied in the RCTs included in the Morriss meta-analyses were medicated, participants in this RCT are expected to be sometimes medication free, as maintenance treatment is not the rule anymore. This will increase the number of relapses we expect to document during the 12 months period of this trial and hence improve the power. In the HAMLETT cohort, where half of the participants discontinue their medication after remission, we found an annual relapse risk of 43% (unpublished results). We expect a similar relapse risk in the current trial. The power.prop.test was used (p1 = 0.432, p2 = 0.229, significance level = 0.05, power = 0.80). Two-sample comparison of proportions power calculation yielded a minimum of n=83 per group to obtain a power of 0.8. To be robust against a maximal drop-out rate of 33%, we will aim for 120 inclusions per group, hence 240 randomized participants.

## Design of the clinical study (controlled / uncontrolled; randomised; open / blinded; parallel group / cross over / other; please justify the appropriateness of the selected design)

TRUSTING’s WP4 will be a randomized clinical trial, single blinded (raters only), with parallel groups and comparison of standard relapse prevention plus AI relapse prediction (treatment condition) against standard relapse prevention plus speech recordings alone (control condition). Thus, speech will be recorded in both conditions. Randomization will allow us to eliminate selection bias, balance arms with respect to known and unknown prognostic variables, and provide the basis for our statistical analysis framework (with the null hypothesis of equality of treatments). Thus, using a randomized controlled parallel group trial will allow us to obtain an unbiased estimate of the treatment effect, avoiding confounding.

## Type of intervention (medicinal product / advanced therapy medicinal product / medical device / in vitro diagnostic medical device / surgical or other invasive procedure / other medical intervention, including, e.g., counselling)

The intervention is a weekly online assessment of speech, to detect subtle characteristics of psychotic speech. These recordings are made through an app that maximizes accessibility for individuals (via smartphone or computer) on the day and time the participant finds suitable. Participants will be asked to listen to a short amusing story and are then asked to provide a short summary of that story. Speech is recorded and analysed remotely with human oversight as described earlier by Dr. Elvevåg’s group 28,29 and detailed in WP3 and below. Within 48 hours after the speech sample has been recorded, a message is sent to the clinician by email providing the calculated relapse risk (0-100%) and a 95% confidence interval. Clinicians are instructed to evaluate this information considering their professional expertise and knowledge about the current situation of the particular participant, and discuss with the participant and informal caregiver in case action may be required. Together they will then reach a decision through shared decision- making regarding the best course of action (which can be stress-reduction, medication change, more frequent consultation etc.).

## Description and timing of study procedures

Please provide an overview, preferably in a tabular format, about the schedule of study procedures. Please give a simple statement on how long individual patients or healthy volunteers participate in the clinical study.

*Recruitment of participants* Seven centers will provide information about this trial to their employees and service users. Eligible service-users at these medical centers will be identified through electronic medical records and approached by local personnel to be invited for the study. Individuals who appear to fulfil inclusion criteria are invited for an information appointment together with their informal caregiver. If the service user is interested, they are given written information and an appointment for an informed consent procedure is made. The recruitment phase lasts 30 months.

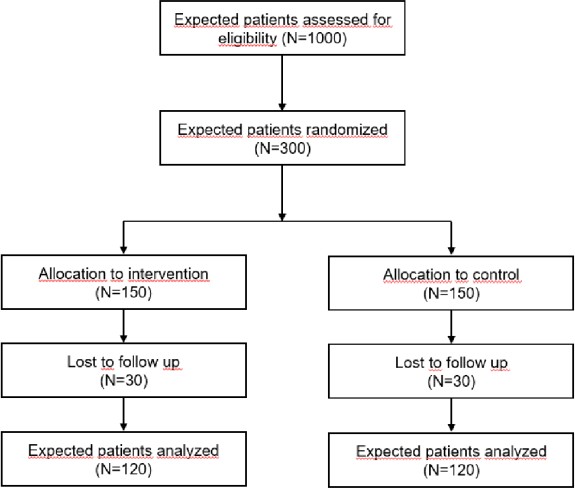


Figure 1. Study flow chart and expected numbers of participants

*Overall study flow*

Participants will be recruited over 2.5 years (30 months) and will be randomly assigned to the intervention condition (treatment as usual plus speech-based relapse prediction) or the control condition (treatment as usual plus speech- recording alone). Follow up time will be 12 months (Figure 1). Random allocation will be stratified for sex and center.

TRUSTING AI monitoring will include 4 components:

* + - * The construction of an individualized relapse prevention plan by the participant, informal caregiver and clinician, including an individual range of relapse risk (within which a clinician will contact the participant for a shared decision appointment, see below) and how to act in case of expected relapse. Many citizens with schizophrenia may already have such a prevention plan, in which case an update will suffice.
      * Education, motivation and empowerment of the participant and informal caregiver in the use of the speech recording app.
      * Weekly app-based speech recordings, analyzed by the AI speech monitoring system to compute a psychosis relapse risk.
      * Alerts sent to clinician within 48 hours after speech recordings detailing the predicted relapse risk and a confidence interval. The clinician will consider this risk interval and contact the participant if it overlaps with the interval given in the relapse prevention plan for a shared decision appointment. In this meeting with the participant and informal caregiver, the best course of action will be decided as specified in the personalized relapse prevention plan. For some participants, this may be to reduce stress levels, or improve sleep, for others it may be to increase treatment frequency/ intensity or re-institute/raise dose of antipsychotic medication.

*Visits* Research assistants are trained in the systematic assessment of outcomes and will interview the participants at baseline, 6 and 12 months. Assessors (but not participants) are blind to treatment allocation. When unintentionally losing the blind during such an interview (as participants may mention their clinical team is receiving messages) the rater will be replaced by another trained rater who is still blind. The table below lists all visits and the outcome measures that will be obtained in each visit.

*Reimbursement* To keep participants motivated to provide the high number of speech samples required for this trial, they will receive 20 euros for each visit and 2 euro for each time they had their speech recorded by the app, adding up to a maximal amount of 104 euro for the speech recordings.

**Screening Consent Baseline 6 months 12 months Qualitative**

**interview**

Inclusion exclusion criteria

Signing of Informed consent

WHO-DASII SOFAS, QoL SDAS EQ-5D- 5L GTS

Language & migration background

Relapse WHO- DASII SOFAS,

QoL Hospital days SDAS EQ- 5D-5L GTS

Relapse WHO- DASII SOFAS,

QoL Hospital days SDAS EQ- 5D-5L GTS

Acceptability and trustworthiness of the AI intervention

Table 1. visit schedule Involving the participants and a family member or other informal caregiver

If the participant has an involved family member, partner or roommate, he/she is invited to join the education and empowerment session. Informal caregivers can provide an important incentive to stay motivated throughout the trial. They can also be involved in the shared decision making regarding the activation of the relapse prevention plan.

# Preparedness status

## Development of the clinical study protocol

Please describe how the below aspects have been or will be addressed in developing the clinical study protocol (if applicable):

#### Scientific advice from regulatory and health technology assessment bodies

The study documents will be prepared by partner nr. 10 , UZH’s Dr. Homan, who will first prepare the central European application for ethical examination for clinical trials that employ a medical device, like the current study. Once the study protocol is accepted, it will be shared with all European centers and translations will be prepared and checked in all languages for the participant documents (information letter, questionnaires, informed consent). Local authorities will decide if all European centers are allowed to perform this study. For centers outside the EU (Switzerland, Turkey, Australia), national and local ethical reviews will be performed. Health technology assessments will be performed using outcome data from this RCT by partner 8 , Syreon Research Institute (SRI).

#### Clinical efficacy, safety, and methodological guidelines (including guidelines on statistics)

We will ensure that all participating researchers are trained in Good Clinical Practice before the trial starts. An initial monitoring visit will certify all approval documents are present and all procedures are followed before the centers start recruiting participants. Privacy and legal issues regarding the use of speech recordings are described in WP3

28,29.

*Legal considerations*

1. This study will be conducted internationally such that data are generated across several countries, cultures and languages. This raises countless (several that are hitherto unknown) legislative challenges because of the different laws that govern data collection, storage and transfer in these different countries. Indeed, developing online assessment tools for multiple countries simultaneously presents different regulatory challenges. Therefore, TRUSTING will have complete control over the source code and data flow, and that data will be sent immediately (in an encrypted format) when a device is online (and if offline, then encrypt and queue the data in temporary storage until the device is back online). Further, we will ensure that the data is only available for analysis within a secure zone dedicated to the project. Also, since the participants themselves are classified as vulnerable (as they are mentally ill) and potentially going to get very sick (i.e., relapse), we will use natural non-revealing descriptions of the application in for example app stores to avoid categorizing users (e.g., not listing an application as: “This is an application for patients with mental illness”). These fundamental features will help towards ensuring confidentiality, integrity and regulatory compliance. Therefore, this project will ensure that it is in all possible ways future-proofed to deal with the full range of legal issues.
2. The legal issues for longitudinal assessment are linked to the right to privacy, unequivocally established in Article 12 of the Human Rights Declaration (UN General Assembly, 1948) 30 . Since the data collection and processing will span periods where opinions may change, participants may wish to withdraw their consent for participation and thus retract their data. This may be especially an issue in patients with serious mental illness whose mental states may by the very nature of their illness fluctuate. Also, the nature of the data collected and analysis performed may be opaque to participants, challenging the notion that consents are conducted with true knowledge of the scope of the contract that is agreed upon. These issues can be addressed by designing and implementing rigorous privacy policies and data declassification pathways and thus comply with the strictest legal standards.
3. The continual strengthening of individuals’ right to control over their own data, including the right to have their private data deleted (the “right to be forgotten”; European Union, 2014, 2016)31 represents a legal challenge in this project. Drawing from solutions in biobank research, this challenge will be solved within the IT design of WP3 itself such that a ‘dynamic consent’ procedure will be employed 32–34. This is an interactive personalized interface where participants will be able to engage with the relevant members of the TRUSTING consortium and alter their consent choices in real time 34. Tracking and controlling the information flow is a mature topic in computer science, and fine-grained control of information flow is possible by attaching policy labels to files (e.g., Johansen et al., 2015) 35 which identify a state in a per-user privacy robot (a so-called Privaton) that grants or denies access based on the stated purpose of processing. These privacy labels can be attached to data when created and made inseparable from that data, even when uploaded to a remote storage infrastructure. While existing institutional infrastructure are protected using traditional security mechanisms such as encryption, firewalls, and multifactor authentication, the systems in TRUSTING will be designed to enable individual control over one’s own data such that a technology that can potentially be experienced as invasive to privacy can actually instead result in personal empowerment.
4. The sensitivity of data can suddenly escalate because of the sheer volume and unique possibilities of combining data such that there will always be a possibility that previously trivial data can suddenly turn into highly sensitive information. Thus, this project will always default to a higher classification in order to be proactive. For statistical analyses, we will follow the CONSORT guidelines for clinical trials 36.

#### Involvement of citizens / patients, carers in drawing up the clinical study protocol

In preparation of this application, we performed a survey among potential users to investigate their preferences and acceptability of an SLP/NLP tool 37. We used the answers of the 675 respondents as a basis for designing this trial. The RCT will also be co-designed by service users who have experienced psychosis and clinicians who treat citizens with psychosis. We will set up a panel of individuals with lived experience in collaboration with GAMIAN (partner

6 ) and EPA (partner 7 ). This panel will be headed by the co-design program coordinator. Procedures of visits, outcomes, speech recordings, payments and messages will be decided upon in dialogue with this panel. An initial meeting will be held to try out technology that can be used for speech recordings. Based on this meeting, we will select the most user-friendly speech recording method. In a second panel meeting, we will go through the proposed speech elicitation task (e.g. story recall), fine-tuned and potentially extended in previous work packages (WP1-WP3) and will confirm with the User Board that it is suitable for speech recordings. Outcome measures of the RCT may be adjusted or extended on the initiative of this panel.

## Regulatory intelligence to ensure timely regulatory approval and ethics clearance of the clinical study in all jurisdictions where its implementation is planned.

Please provide information on the following regulatory and ethics aspects:

#### How the consortium will ensure access to regulatory expertise necessary to get advice on, and management of,

**regulatory affairs activities in all concerned jurisdictions?**

As per June 2021 there is a central European application for ethical examination for clinical trials that employ a medical device, like the current RCT (Medical Device Regulation, nr 536/2014). Once the study protocol has obtained EU approval, it will be shared with all European centers and translations will be prepared and checked in all languages for the participant documents (information letter, questionnaires, informed consent). Local authorities will decide if all European centers are allowed to perform this study. For centers outside the EU (Switzerland, Turkey, Australia), national and local ethical reviews will be performed. Regulatory affairs regarding the recording of speech are described in WP3.

The goal of WP 3 is to create and operate a technical, legal and ethical IT infrastructure that enables the collection, processing and analysis of speech data across multiple continents, countries and languages. At the core is the data management platform in WP 3 that will provide a secure infrastructure for confidential data storage, collaborator networking, and authentication of participant identity is essential for the proposed multinational collaboration. Concern about privacy issues is a major topic for potential end users of the proposed online service.37 While there are mature frameworks for such data management already available, a tailored solution for the current application in psychiatry is critical. An effective infrastructure must be compliant under several different legal frameworks. A particular challenge with outpatient and longitudinal procedures is data integrity, namely that we can verify the participant identity over the entire course of the study. We will ensure the participant is the participant we assume it is by employing a combination of voice ID and/or strong authentication procedures that follow those that are the cultural norm of the respective countries. Crucially, at all stages of this pipeline the data will be collected, processed and stored in a secure manner that conforms with all relevant national and international legislation, and in an ethical manner ensuring the highest level of privacy protection. This necessitates consideration of at least three core components, namely technical, legal and ethical issues. Given that these three issues are evolving, WP3 will consult with relevant experts in industry to ensure that the technical solution is - at all times during the lifetime of the project

- both state of the art, future-proofed and conforms to the highest level of security possible, consult with international lawyers who are expert on the latest in information technology law and data privacy issues, as well as with ethical experts who work in the challenges of ensuring that applications of clinical AI are trustworthy.

#### How the consortium will ensure access to ethics expertise necessary to get advice on current proceedings and documentation requirements of all concerned ethics committees?

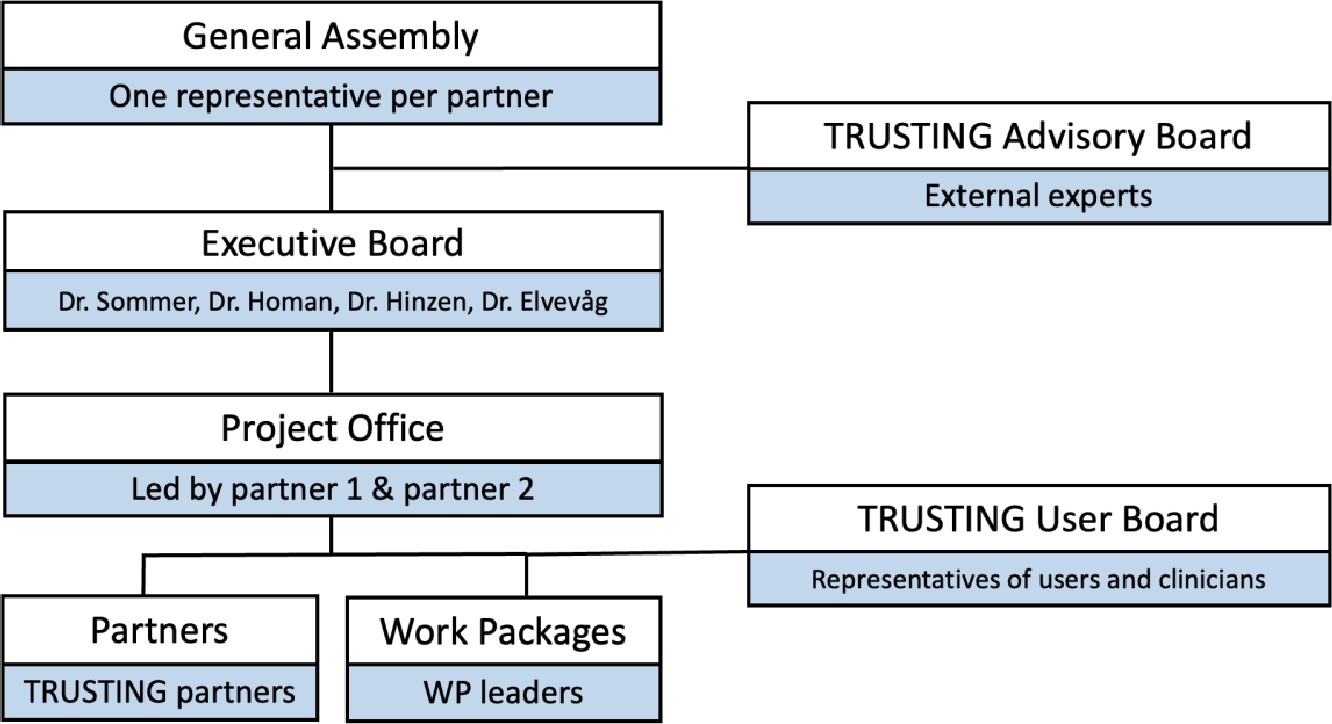
All participating centers have a local ethical board that can be asked for ethical review of the study documents and advise on a central EU submission. Coordinating partner 10 (UZH) has an ethical expertise center (https://[www.ethik.uzh.ch/en/ethikkommission.html)](http://www.ethik.uzh.ch/en/ethikkommission.html)) that will be involved in preparing the study.

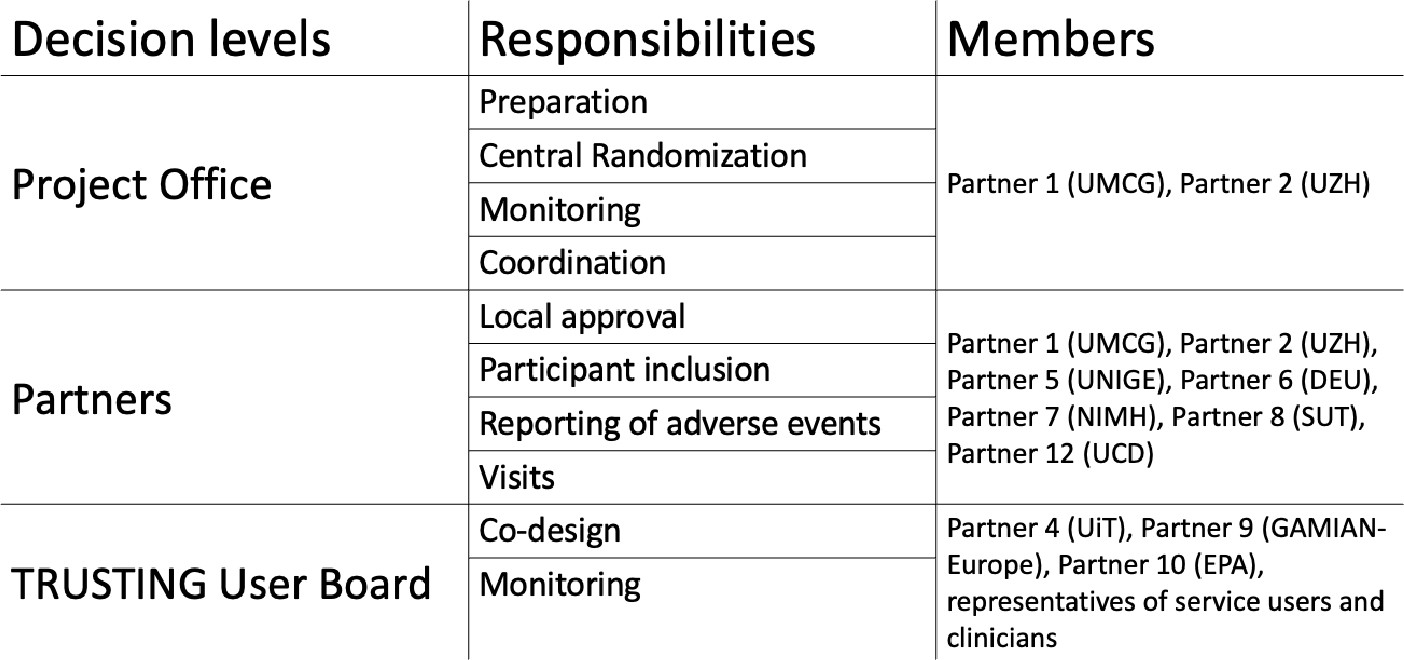
## How the scientific and operational governance of the clinical study will be ensured?

#### Please give details about the sponsor(s) (name, type of entity, seat or country of residence).

Partner 10 (UZH) will act as sponsor for the clinical trial (University of Zurich, Rämistrasse 71, 8006 Zurich, Switzerland).

**Please describe the composition, the role and the functioning of the planned board(s), governing bodies.** Figure 2 shows the management structure for TRUSTING as per the main document. For the clinical trial, the Project Office, Partners and the User Board will be most relevant. The Project Office (led by partner 1 (UMCG) and partner 10 (UZH) ) will coordinate the trial, managing all partners participating in the trial. An additional TRUSTING User Board will provide input and guidance.





**Figure 2.** TRUSTING Management structure and responsibilities for the clinical trial Project Office

The Project Office is the day-to-day management office, located at the premises of partner 1 (UMCG) and partner 10 (UZH) , consisting of the coordinator, a project manager, a financial controller and a project secretary. The Project Office will work closely together with the UZH Clinical Trials Center (CTC; https://[www.usz.ch/en/clinic/clinical-trials-center/)](http://www.usz.ch/en/clinic/clinical-trials-center/)) in Zurich, for expertise and guidance throughout the clinical trial; support in planning and implementation; advice on methodological, regulatory and financial aspects; and clinical trial management in accordance with Good Clinical Practice. When necessary, the Project Office can be expanded with a legal expert and/or ethicist to support the coordinator. The financial controller will assist the project manager in monitoring the budget and financial reporting to the European Commission and is available to the trial partners for financial or budgetary questions during the implementation of TRUSTING. The legal advisor can be appointed to address arising legal issues (e.g. intellectual property rights etc) considering the activities of TRUSTING. If appropriate and necessary the Project Office can consult third parties (e.g. a patent office) for which a financial estimate is reserved in the budget. The Executive Board decides whether or not a third party is to be consulted. The main responsibilities of the Project Office include the activities allocated to WP7 (Project management) and WP4

(Clinical Trial). Partners

At the partner level, each trial beneficiary (partners 1 (UMCG), 4 (DEU), 5 (NIMH), 9 (RCSI), 10 (UZH), 11 (UNIGE), 12 (SUT)) appoints one formal contact. This partner contact is the first spokesperson for their institute vis-à-vis the Project Office on issues related to participant recruitment, conduct of studies, ethical issues and financial performance in relation to the partner budget input.

User Board

The RCT will be co-designed by service users who have experienced psychosis and clinicians who treat citizens with psychosis. We will set up a TRUSTING User Board of individuals with lived experience and clinicians in collaboration with partner 6 (GAMIAN-Europe) and partner 7 (EPA). Procedures of visits, outcomes, speech recordings and messages will be confirmed upon in dialogue with the User Board. An initial meeting will be held to try out the prototype developed in WP3. Based on this meeting, we will select the most user-friendly speech recording method. In a second board meeting, we will go through the translated stories and select the best ones to be used for speech recordings. Outcome measures of the RCT may be adjusted or extended on the initiative of the User Board.

# Operational feasibility

## 5.3.a. Please describe how the availability of the intervention(s) (including comparators) is secured throughout the entire implementation phase (give details on manufacturing, packaging/ labelling operations, storage, logistical, import/export issues, etc.)

WP3 will create an AI monitoring system for relapse prediction, based on SLP/NLP analyses. This infrastructure will be capable of recording the speech of participants by means of programs designed with progressive web apps (PWAs) to prompt for speech on personal smart devices (e.g., cell phones or iPads), transfer it automatically to a secure data repository and analysis environment (Services for Sensitive Data (TSD) at the University of Oslo in Norway), perform analyses with human oversight and generate feedback (predicted relapse risk plus confidence interval) for clinicians. This task also includes extensive legislative and technical work to ensure compliance with prevailing data protection regulations across five countries and six languages.

However, for the TRUSTING monitoring system to be adopted it must be considered useful and acceptable by the users, namely patients. Therefore, prior to developing the online interface and core infrastructure, we will assess user needs in a survey format in all the different countries in which this is to be implemented. Already, a survey by Iris Summers’ group 37 in the Netherlands (alone) among 675 participants found that they were open to using an AI monitoring system, but their willingness to use it is strongly related to how, among other things, privacy-sensitive data is handled and how this is communicated with potential users. And so this current user needs assessment will build on this and examine these same issues in all participating countries and languages. Indeed, for the purpose of designing a specialized system for use in an RCT, a broad range of user groups such as patients, their families and clinicians will be surveyed. The resulting information from this will inform and constrain the subsequent development of the TRUSTING system. Our usability engineering focus will be that the tasks and resulting software should be easy and pleasant to use such that it is acceptable to the participants (Nielsen, 1993), and that the data collection will be efficient and sufficiently constrained in how the tasks could be taken such that the data is comparable with in-person testing, and critically that the system is considered cross-culturally acceptable and appropriate. Previous research (by others and our team; e.g. Holmlund et al.29 has shown that participants generally prefer shorter testing sessions despite the best efforts to make these as short as is scientifically meaningful. This latter issue points to a limitation of frequent and self-administered assessment tasks where there is no external reward (i.e., an encouraging experimenter physically present) and thus necessitates reward incentives such as money (via micro- transactions), principles of gamification such as rewarding weekly “streaks" of responses, and - where appropriate - useful insights into participants’ own health (via structured feedback about their own responses and performance). Such reward mechanisms require the infrastructure development to handle transactions and information flow in a compliant manner (which the current system can provide), and in return increases adherence to protocols and a more robust way to acquire behavioral data.

The actual design of the platform and interface for patients’ online interaction will be created according to best practices of usability engineering, with the added challenge of giving patients an enjoyable experience and nurturing retention which is critical to the success of the tool and the RCT. By using progressive web applications we will design a cross-platform interface accessible through both a web interface and a mobile application that administers a series of language-based interaction tasks (based upon our team’s previous work as well as the findings in the current project, notably from WPs1 and 2). Concretely, first, a user-needs assessment will establish participants’ behaviour regarding online systems notably their tolerance (i.e., for task duration). Second, informed by the user-needs

assessment, the system to collect speech data will be built using progressive web applications. Third, a pilot study will be conducted in a sample of healthy people in all the participating countries and languages (40 participants from each country). Fourth, the configuration of the analysis environment will be refined. Fifth, where possible, the pipeline from task administration to data recording and analysis that generates a clinically actionable inference will be fully automated, specifically the generation of the index regarding risk of relapse. WP3 will run alongside the trial and ensure durable availability of the monitoring system.

Details on data infrastructure that will be employed throughout WP3 to conduct the RCT in WP4:

The Services for Sensitive Data (TSD) at the University of Oslo in Norway is the country’s most secure data infrastructure to store, view, and process data by logging on using two-factor authentication. Each project is allocated its own virtual machine, a dedicated emulation of a suitable computer system hosted on servers running on university premises, connected to a network storage system with secure backups. The service is designed to protect and ensure privacy of the respondents in compliance with EU laws and regulations (elaborated in detail below in the following 9 points).

1. Introduction - TSD (Services for sensitive data) will be the secure backend to the speech app or web interface that will be developed with progressive web appliances (PWA), and all data traffic between the app and TSD will be done using the application programming interface (API). The TSD system was developed at the University Centre for IT (USIT) at the University of Oslo (UiO) in Norway and launched in 2014. The Research Infrastructure TSD is set up to comply with EU’s GDPR regarding policies for research on sensitive data. TSD is a centralised on-site cloud technology based-service. Storage, virtual machines, databases, private physical servers and High-Performance Computing is provided within this secure environment. Every project has its own set of virtual machines (VMs) inside TSD as a virtual workspace. Users are required to access and work on their data via virtual workspaces, and there are technical and administrative restrictions regarding downloading data to local facilities.
2. System description - Sensitive data are kept within a virtual workspace including separated storage volumes, and users access it via remote connection protocols. A firewall guards the system by allowing only authenticated and authorized access. All research projects reside within their own segmented network, either a VLAN or a micro- segmented network region. This gives the system several layers of security and it gives strict separation between TSD projects.
3. TSD login - TSD offers various login functions to enable secure GUI access to the project VMs inside TSD such as 2-factor login as the primary login protocol. The symmetric secret used to generate one-time codes for Multifactor Authentication is generated by TSD, and distributed to users as a QR code. (Smartphones utilize this QR code using apps such as Google Authenticator or FreeOTP).
4. Gateways / jumphosts - There are two network gateway servers (aka jumphosts). All incoming traffic is routed by, and inspected by, the firewall servers. Each project is separated from the other by automatically generated firewall rules set by the jumphosts. This ensures that a user from a given project can only access components and storage resources leased by that project.
5. Giving access to projects and users - All users in TSD are registered to the project they are a member of and given a combination of a one-time code and a password to access the system. Authentication occurs via password and one- time code.
6. Backup - Backup is based on Commvault that resides within TSD, but with the data (dedicated disk and shared tape) placed in a different building. All data that is written to tape is encrypted, and the encryption is done inside TSD before data is written to the Commvault system
7. Monitoring and antivirus - Monitoring of the system uses special agents to check the status of machines, disks and processes, and is designed to prevent transportation of project data hidden in logfiles or reports.
8. Digital dynamic consent system - TSD has developed a system based on eSignatures that enable digital consent and the possibility to change them. Importantly, this ensures that all citizens will be able to have the ‘right to be forgotten’.
9. Risk evaluation - TSD has been through a thorough evaluation by the chief of IT-Security at the University of Oslo. The security assessment of TSD is a continuous process and the risk evaluation is updated when a significant change has to be made in the infrastructure. TSD has also been under penetration testing by an internationally recognized IT security expert. The penetration testing attempted i) an illicit login without valid user credentials and

ii) and illicit access to data of a given project operated by a licit user of another project. None of the targeted attacks were successful.

*Please describe how the study population will be recruited. Please give details on the recruitment strategy, monitoring of progress and potential mitigation measures*

Seven specialized psychosis units will collaborate to include a total of 240 participants over a 30 months period. We expect each team to include a mean of 16 participants per year. Given that psychosis teams treat an annual number of 100-300 citizens and the majority of these citizens will match our inclusion criteria, less than 10% of potential participants need to participate in order to fulfil inclusion norms. Each trial partner has a PI (a TRUSTING partner and member of the general assembly) to promote and implement the study. Each site also has a dedicated includer (i.e. a team member, for instance a research nurse) located in the center with the task to facilitate inclusion) to assist clinicians in selecting and inviting potential participants. Progress will be monitored by the WP4 project board during bi-weekly virtual meetings with the PIs and dedicated includers.

How many clinical sites will contribute to the recruitment of the study population in which countries? Are these clinical sites part of an established clinical trial network? Please also describe the selection criteria of the clinical sites.

Seven centers experienced with the conduct of clinical trials and with a keen research interest in NLP, will collaborate to include 240 participants over the course of 30 months. We expect an inclusion rate of 16 participants per year per center, which is highly feasible given the ten, - to twentyfold higher number of citizens treated for psychosis in each center. Centers have been selected on the basis of their experience with clinical trials in citizens with psychosis. Another selection criteria was the diversity in languages, as we aim to include at least five European languages and Turkish, as this is the language of an important minority in many European countries. These partners are all members of the Discourse in Psychosis Consortium and have been working together on studies regarding language in psychosis. A list of participating centers, their PI and country is provided below.

#### Spokesperson/P.I. Beneficiary organisation name

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Will recruitment of the study population be of competitive nature between the clinical sites? (Please describe how underperformance of individual clinical sites in recruitment will be managed.)

Recruitment will not be competitive, as from each language a minimum of 40 inclusion is needed. Yet, if inclusion of at least 10 participants is not met in the first year, finance of that center and further inclusion for the trial may be stopped.

What evidence supports the ability of the individual clinical sites to recruit the required number of study participants within the planned timeline (e.g. documented performance in previous clinical studies of similar complexity targeting very similar study population)?

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Please describe what additional supply (e.g. an electronic device for remote data capture, a specific instrument for administering the investigational product, etc.) is necessary to carry out the required study procedures and how this supply will be made available to the clinical sites.

Access to electronic Case Report Form (eCRF): All centers will have access to the eCRF, created in REDCAP and stored centrally at the Project Office, for which a standard computer and internet access is needed. The TRUSTING Project Office will build the eCRF and provide coded and password protected access to all centers. Use of the intervention: Participants will need to have access to a smartphone (either Android or iPhone) or personal computer to use the app for speech recording. Please see WP3 for details.

Please provide plans on data management aspects (data standards, type of data capture, verification of data, central data collection, cleaning, analysis, reporting, security)

The successive steps for data collection and management and the responsible for that part are provided in the table below. The sponsor (partner 10 , UZH) will hire at least one independent clinical research associate for monitoring the centers.

|  |  |
| --- | --- |
| **Data Flow** | **Responsibility** |
| Screening and consenting   * Informed consent is performed and stored locally * Data will be recorded from the participant during visits * Data is entered in the eCRF locally and stored centrally | **Participating center** |
| Enrolment and de-identification   * Participants who will be enrolled in the study will receive a unique pseudonymous identifier, an opaque unguessable ID generated by the Project Office via the centralized eCRF. No information that can reveal the   identity of the participant will be stored in the eCRF, thus only de-identified data | **Project Office, Participating center** |

|  |  |
| --- | --- |
| * The confidential list matching participants’ real information to their pseudonymous IDs will be stored centrally by the Project Office and kept separately from all other study documents |  |
| Randomization   * Randomization will be centralized at the Project Office * The Project Office will have generated a randomization sequence through block randomization, ensuring equal treatment allocation within each block * Block size will be masked to participating centers so that allocation sequence remains unpredictable and selection bias can be avoided | **Project Office** |
| Source Data   * Relevant documents such as the informed consent form and inclusion criteria will be stored locally at each center * All study documents (such as scoring forms) completed during the visits are stored locally, using the pseudonymous participant ID | **Participating center** |
| Data entry   * Entering the data into the eCRF via the internet can be done by authorized study personnel using a secure internet connection * Data including adverse events are entered locally via eCRF and stored centrally at the Project Office | **Participating center** |
| Serious adverse events   * In case of a serious adverse event the participating center will file a comprehensive report according to the directions and definitions in the study protocol | **Participating center** |
| Data validation   * Automatic data validation of the data entered into the eCRFs will continuously take place through the data validations and quality checks * Manual data validation by comparing source data to the data entered in the eCRF will be performed during monitoring visits * A “Query” Workflow for clarification will ensure a high quality of data * Discrepancies and questions resulting from source data verification and review of the eCRFs are entered into the eCRF as a query * Queries will remain open until being addressed by the data entry staff * If a proposed resolution on the discrepancy does not adequately resolve the issue, the discrepancy will be reissued and will remain open * The Project Office will periodically run open query reports containing the number of outstanding discrepancies. All queries have to be resolved before database lock | **Project Office** |

|  |  |
| --- | --- |
| Data cleaning   * Answer queries * Check and correct data as necessary | **Participating center** |
| Protocol deviation   * Document deviations and violations of protocol as ”Protocol Deviation” will be indicated as corresponding type of queries | **Project Office** |
| Database Closure   * Before eCRFs will be locked by the data manager the following quality checks will be performed:  1. Source data verification has been completed 2. All Queries have been solved and closed 3. All eCRFs are signed 4. A final review of data listings is performed and no discrepancies are found 5. All medical coding activities have occurred 6. SAE reconciliation has been completed 7. Data Collection tools have been deactivated/removed for the data collection 8. Set all users to read-only  * Finally, closure of the database is performed | **Project Office** |
| Database Reopening   * If errors are found after database lock, the sponsor will decide if the database has to be re-opened * A “Database re-opening Request Form” has to be completed * When all changes have been made and documented, a “Database Re-Locking Approval Form” will be signed | **Project Office** |
| Export   * After the database closing data will be exported and provided to the biostatistician as encrypted zip-File | **Project Office** |
| Archiving   * At the end of the study final exports and reports will document that all queries haven been closed * Access to the database will be set to read-only * An archive of the data including audit trail will be created * The final exports and final reports will be stored on the dedicated SharePoint for the Sponsor * The Sponsor will collect confirmation receipts from the participating centers and provide a confirmation receipt | **Project Office** |

Please give details on how reporting obligations (regarding study initiation, safety of study participants, ethical concerns, quality issues, integrity of data, study results) to regulatory bodies and ethics committees will be met.

*Communication*

To guarantee an optimal result, all parties involved will be in contact on a regular basis. To accomplish this, different types of meetings will be organised:

* Investigator meetings at the start of the study, after 6, 12 and 18 months during execution of the trial
* To ensure everyone involved is adequately trained in all aspects of the study protocol, project team meetings will be held every 2 weeks (online) with partners and Project Office to discuss the status of the study and actions needed to ensure proper and timely execution of the trial
* Monitoring meetings at least once a year (to be decided by Project Office), to ensure all personnel in all participating centers is adequately trained in all aspects of the study protocol and monitoring requirements specified in the monitoring manual.
* Study management team meetings (every 6 months) between PIs, User Board and Project Office to discuss the status of the study and actions needed

*Safety reporting*

This study will be performed according to the Declaration of Helsinki (59th WMA general assembly; October 2008) and the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP). The definitions of adverse events and serious adverse events described in these guidelines will be used for the present study. In accordance with section 10, subsection 1, of the WMO, the investigator will inform the participants and the reviewing accredited Ethical Review Board (ERB) if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research project. The study will be suspended pending further review by the accredited ERB. The sponsor will take care that all beneficiaries are kept informed.

*Adverse events*

Adverse events (AEs) are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to the investigational intervention. All AE reported by the participant or observed by the investigator or his staff will be recorded. A serious adverse event (SAE) is any untoward medical occurrence or effect that: results in death; is life threatening (at the time of the event); requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect. Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the participant or may require an intervention to prevent one of the outcomes listed above. Importantly, the sponsor will report any SAEs through the web portal to the accredited ERB and Competent Authority that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions. Any SAE that results in death or is life threatening will be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. In case additional information is required, this will be provided through an update report within the next 8 days (within 15 days in total). Hospitalisation due to exacerbation of psychosis-related symptoms is a very common occurrence in citizens with schizophrenia. Although this is regarded as being an SAE, these hospitalisations are part of the usual illness course and are therefore not reported to the authorities immediately. Rather, they will be reported once a year as part of the Annual Safety Report. Immediate reporting will not have any added value for the authorities in evaluating participant’s safety and will result in over-reporting. Adverse reactions are all untoward and unintended responses to an investigational intervention.

Please list all items of the sponsor’s responsibilities (e.g. monitoring clinical sites, meeting regulatory obligations, data management, etc.) that will be supported by entities that are not part of the sponsor’s organisation. Please describe how the sponsor will ensure oversight of these activities.

These responsibilities, all provided by the Project Office, include study management, monitoring, data management, quality assurance and communication; they are described below:

*Study management*

The Project Office will conduct study management, thus supporting the organization and conduct of the trial and has the primary responsibility for implementation of study project plan, communication plan, and management strategy. Study management also involves line management for all other staff, including recruitment, training, performance reviews, coaching and development.

*Data management*

Data Management will entail the development of a high-quality IT infrastructure for the TRUSTING data collection, controlling and reporting. All IT functions will be integrated and accessible through an internet web portal under a common e-corporate identity. Major functions will be the development of content and document management, data capturing and workflow support. Web-based case report forms will be developed in REDCAP. The forms will be integrated into the web content management system. Only a standard web browser will be needed for online data entry. Data management also supports the logistic processes in the participant-related actions on site by implementing electronic workflow. Horizontal IT-services cover administration of users and access control and the technical security- and privacy framework. A firewall protects the communication functions of the web- and application server

from the outside Internet. A second firewall protects the application server (data analysis, database access, etc.) towards the database server. Furthermore, it is impossible for outsiders to obtain a direct connection from the internet to the database and all communications, which transmit sensitive data, as these will be encrypted. The database will facilitate easy collection of data, monitoring and management of the study directly and closing of the database rapidly for further analysis and publication purposes, but without compromising confidentiality and integrity of the data and according to GCP standards for electronic data entry, exports and collection and the applicable data protection laws of all countries involved.

*Quality assurance*

Quality Assurance will ensure compliance with standard operating procedures (SOPs), study specific SOPs, ICH- GCP and local regulations. The Project Office will maintain oversight of training for study staff, audit the study on a regular basis and advise on all aspects of study conduct.

*Monitoring*

Monitoring will be performed by a qualified and properly trained clinical research associate (hired by partner 10 , UZH) in all 7 centers. It is anticipated that each site will be visited approximately once per year, at time intervals determined by the independent monitors depending on recruitment rates and particular problems at centers. The procedures to follow will be described in the monitoring manual that will be available before the start of trial. The procedures, including reporting, will be performed according to ICH-GCP guidelines and SOP’s. The local PI is responsible for the country and/or site specific ethical and regulatory approval procedures. This process will be supported and monitored by the clinical research associate to guarantee a timely start of recruitment. The initiation visits will be the responsibility of the Sponsor. It is possible that monitoring visits will be performed virtually (i.e. online), given potential travel limitations. Each clinical site will be monitored to ensure the trial site staff conduct, record, and report the trial according to the protocol, ICH-GCP guidelines and any country specific regulatory guidelines. During these visits Source Data Verification (SDV) will take place. Monitoring visits provide an opportunity for training, for discussion of trial issues and for the establishment of a good working relationship between the monitor and the PI and dedicated includers.

What are the plans for major study milestones and what evidence supports its feasibility?

Please describe a realistic plan (based on prior experience) detailing the time necessary for (i) compiling the required regulatory and ethics submission package, (ii) receipt of regulatory and ethics approval, (iii) initiation of clinical site(s), (iv) completion of recruitment of the study population, (v) final assessment of all study participants, (vi) analysis and reporting of the study results.

The RCT will start in month 24 of the project. We expect to need 12 months for all centers to receive full ethical approval of all documents and have had the initiation monitor visit to allow them to start. Centers that have received full approval and have been monitored can start, so that during the first year a cumulative number of centers will start including for the study.

1. **Milestone 1:** All centers have ethical approval at 24 months a. We will recruit for a maximum of 30 months and in that time will include 240 participants. After the first year of inclusion, we expect to have 96 participants.
2. **Milestone 2:** Inclusion at 50% at 40 months a. By the second year we will include the second half of the participants
3. **Milestone 3:** Inclusion at 100% at 54 months a. The last year of WP4 will be dedicated to follow-up of included participants, data completion and cleaning and finally data lock.
4. **Milestone 4:** Follow-up finished at 66 months

References

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Grant Agreement number: 101080251 — TRUSTING — HORIZON-HLTH-2022-STAYHLTH-01-two-stage

## ESTIMATED BUDGET FOR THE ACTION

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**ANNEX 2**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Estimated eligible1 costs (per budget category)** | | | | | | | | | | **Estimated EU contribution2** | | | |
| **Direct costs** | | | | | | | | **Indirect costs** | **Total costs** | **EU contribution to eligible costs** | | | **Maximum grant amount6** |
| **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** |
| * 1. Employees (or equivalent)   2. Natural persons under direct contract   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 - UMCG** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **1.1 - RBV** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **2 - UPF** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **3 - UiT** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **4 - DEU** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **5 - NIMH** | 288 365.00 | 0.00 | 0.00 | 0.00 | 10 000.00 | 0.00 | 40 000.00 | 0.00 | 84 591.25 | 422 956.25 | 100 | 422 956.25 | 422 956.25 | 422 956.25 |
| **6 - GAMIAN** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **7 - EPA** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **8 - SRI** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **9 - RCSI** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |
| **10 - UZH** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **11 - UNIGE** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **12 - SUT** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Σ consortium** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** | **VYMAZÁNO** |

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) 71151) 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](https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/how-to-participate/reference-documents%3BprogramCode%3DHORIZON)).

**HE and Euratom Research Infrastructure actions**2

Type: unit costs

Units3: 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:

average annual total trans-national access costs to the installation (over past two years4) average annual total quantity of trans-national access to the installation (over past two years5)

For virtual access:

total virtual access costs to the installation (over the last year6)

total quantity of virtual access to the installation (over the last year7)

**Euratom staff mobility costs**8

#### Monthly living allowance

Type: unit costs

1 Commission [Decision](https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/common/guidance/unit-cost-decision-sme-owners-natural-persons_en.pdf) 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](https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/common/guidance/unit-cost-decision-research-infrastructures_horizon-euratom_en.pdf) 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](https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/euratom/guidance/unit-cost-decision-staff-mobility_euratom_en.pdf) 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 202110 EU-Member States11

|  |  |
| --- | --- |
| **Country / Place** | **Coefficient (%)** |
| Bulgaria | **VYMAZÁNO** |
| Czech Rep. | **VYMAZÁNO** |
| Denmark | **VYMAZÁNO** |
| Germany | **VYMAZÁNO** |
| Bonn | **VYMAZÁNO** |
| Karlsruhe | **VYMAZÁNO** |
| Munich | **VYMAZÁNO** |
| Estonia | **VYMAZÁNO** |
| Ireland | **VYMAZÁNO** |
| Greece | **VYMAZÁNO** |
| Spain | **VYMAZÁNO** |
| France | **VYMAZÁNO** |
| Croatia | **VYMAZÁNO** |
| Italy | **VYMAZÁNO** |
| Varese | **VYMAZÁNO** |
| Cyprus | **VYMAZÁNO** |
| Latvia | **VYMAZÁNO** |
| Lithuania | **VYMAZÁNO** |
| Hungary | **VYMAZÁNO** |
| Malta | **VYMAZÁNO** |
| Netherlands | **VYMAZÁNO** |
| Austria | **VYMAZÁNO** |
| Poland | **VYMAZÁNO** |
| Portugal | **VYMAZÁNO** |
| Romania | **VYMAZÁNO** |
| Slovenia | **VYMAZÁNO** |

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 | **VYMAZÁNO** |
| Finland | **VYMAZÁNO** |
| Sweden | **VYMAZÁNO** |

Third countries

|  |  |
| --- | --- |
| **Country/place** | **Coefficient (%)** |
| China | **VYMAZÁNO** |
| India | **VYMAZÁNO** |
| Japan | **VYMAZÁNO** |
| Russia | **VYMAZÁNO** |
| South Korea | **VYMAZÁNO** |
| Switzerland | **VYMAZÁNO** |
| Ukraine | **VYMAZÁNO** |
| United Kingdom | **VYMAZÁNO** |
| United States | **VYMAZÁNO** |

**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 children12**}**

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.)

**ANNEX 3**

**ACCESSION FORM FOR BENEFICIARIES**

**UNIVERSIDAD POMPEU FABRA (UPF)**, PIC 999867077, established in PLACA DE LA MERCE, 10-12, BARCELONA 08002, Spain,

## hereby agrees

**to become beneficiary**

**in Agreement No 101080251 — TRUSTING** (‘the Agreement’)

**between** ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG) **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

**VYMAZÁNO**

**ANNEX 3**

**ACCESSION FORM FOR BENEFICIARIES**

**UNIVERSITETET I TROMSOE - NORGES ARKTISKE UNIVERSITET (UiT)**, PIC 999874643, established in HANSINE HANSENS VEG 14, TROMSO 9019, Norway,

## hereby agrees

**to become beneficiary**

**in Agreement No 101080251 — TRUSTING** (‘the Agreement’)

**between** ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG) **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

**VYMAZÁNO**

**ANNEX 3**

**ACCESSION FORM FOR BENEFICIARIES**

**IZMIR DE DOKUZ EYLUL UNIVERSITESI\*DOKUZ EYLUL UNIVERSITY OF IZMIR UNIVERSITE DOKUZ EYLUL D'IZMIR FACULTY OF LAW DEU HUKUK FAKULTESI DEKANLIG (DEU)**, PIC 999871636, established in CUMHURIYET BULVARI 144, ALSANCAK

### IZMIR 35210, Turkiye,

**hereby agrees**

**to become beneficiary**

**in Agreement No 101080251 — TRUSTING** (‘the Agreement’)

**between** ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG) **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

**VYMAZÁNO**

**ANNEX 3**

**ACCESSION FORM FOR BENEFICIARIES**

**NARODNI USTAV DUSEVNIHO ZDRAVI (NIMH)**, PIC 999462684, established in TOPOLOVA 748, KLECANY 250 67, Czechia,

## hereby agrees

**to become beneficiary**

**in Agreement No 101080251 — TRUSTING** (‘the Agreement’)

**between** ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG) **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

**VYMAZÁNO**

**ANNEX 3**

**ACCESSION FORM FOR BENEFICIARIES**

**GLOBAL ALLIANCE OF MENTAL ILLNESS ADVOCACY NETWORKS EUROPE AISBL (GAMIAN)**, PIC 951109251, established in RUE DU TRONE 60, BRUXELLES 1050, Belgium,

## hereby agrees

**to become beneficiary**

**in Agreement No 101080251 — TRUSTING** (‘the Agreement’)

**between** ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG) **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

**VYMAZÁNO**

**ANNEX 3**

**ACCESSION FORM FOR BENEFICIARIES**

**ASSOCIATION EUROPEENNE DE PSYCHIATRIE (EPA)**, PIC 918282705, established in AVENUE DE LA LIBERTE 15, STRASBOURG 67000, France,

## hereby agrees

**to become beneficiary**

**in Agreement No 101080251 — TRUSTING** (‘the Agreement’)

**between** ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG) **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

**VYMAZÁNO**

**ANNEX 3**

**ACCESSION FORM FOR BENEFICIARIES**

**SYREON KUTATO INTEZET KORLATOLT FELELOSSEGU TARSASAG (SRI)**, PIC

### 952715183, established in MEXIKOI UT 65/A, BUDAPEST 1142, Hungary,

**hereby agrees**

**to become beneficiary**

**in Agreement No 101080251 — TRUSTING** (‘the Agreement’)

**between** ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG) **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

**VYMAZÁNO**

**ANNEX 3**

**ACCESSION FORM FOR BENEFICIARIES**

**ROYAL COLLEGE OF SURGEONS IN IRELAND (RCSI)**, PIC 999867368, established in ST STEPHEN'S GREEN 123, DUBLIN 2, Ireland,

## hereby agrees

**to become beneficiary**

**in Agreement No 101080251 — TRUSTING** (‘the Agreement’)

**between** ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG) **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

**VYMAZÁNO**

 Associated with document Ref. Ares(2023)2437294 - 04/04/2023

**ANNEX 4 HORIZON EUROPE MGA — MULTI + MONO**

**FINANCIAL STATEMENT FOR [PARTICIPANT NAME] FOR REPORTING PERIOD [NUMBER]**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Eligible1 costs (per budget category)** | | | | | | | | | | | | | | | | | **2**  **EU contribution** | | | |
| **Direct costs** | | | | | | | | | | | | | | | **Indirect costs** | **Total costs** | **EU contribution to eligible costs** | | | **Total requested EU contribution** |
| **A. Personnel costs** | | | **B. Subcontracting costs** | **C. Purchase costs** | | | **D. Other cost categories** | | | | | | | | **E. Indirect cost 2**  **s** | **Funding rate 3**  **%** | **Maximum EU contribution4** | **Requested EU contribution** |
| * 1. Employees (or equivalent)   2. Natural persons under direct contract   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) | 5  Unit costs | Actual costs | Actual costs | Actual costs | Actual costs | *[* Actual costs*]* | Unit costs (usual accounting practices) | 5  *[* Unit costs *]* | 5  *[* Unit costs *]* | *[* Actual costs*]* | 5  *[* Unit costs *]* | *[* Actual costs*]* | *[* Actual costs*]* | 6  Flat-rate costs |
|  | 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 *[* + | f = a+b+c+d+e | U | g = f\*U% | h | m |
| ~~d5~~*~~][+ d6]~~ [* +d7*] ~~[+ d8~~]* ) |
| **XX – [short name beneficiary/affiliated entity]** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

|  |
| --- |
| **Revenues** |
| **Income generated by the action** |
|  |
| n |
|  |

**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).

 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.

**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 2015/4441 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 Integrity2.

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 Researchers3, 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 traceability5 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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