

Call: HORIZON-HLTH-2023-DISEASE-03

(Tackling diseases (Single stage - 2023))

Topic: HORIZON-HLTH-2023-DISEASE-03-07**Type of Action: HORIZON-RIA****Proposal number: 101137181****Proposal acronym: DEFINE****Type of Model Grant Agreement: HORIZON Action Grant Budget-Based****Table of contents**

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Administrative forms

Proposal ID 101137181

Acronym DEFINE

1 - General information

Fields marked * are mandatory to fill.

Topic	HORIZON-HLTH-2023-DISEASE-03-07	Type of Action	HORIZON-RIA
Call	HORIZON-HLTH-2023-DISEASE-03	Type of Model Grant Agreement	HORIZON-AG
Acronym	DEFINE		
Proposal title	Decreasing Fatigue After Infections – Complex mechanisms, innovative diagnostic tools and targeted preventive measures of fatigue following COVID-19 and other infections		
	Note that for technical reasons, the following characters are not accepted in the Proposal Title and will be removed: < > " &		
Duration in months	60		
Fixed keyword 1	Infectious diseases		
Fixed keyword 2	Clinical trials		
Fixed keyword 3	Neurosciences (including psychophysiology)		
Fixed keyword 4	Immunology		
Fixed keyword 5	Clinical management		
Free keywords	<i>Fatigue, Post-infective fatigue syndrome, Post-COVID-19 condition, Long COVID</i>		

Abstract *

Post-infective fatigue syndrome (PIFS) is a common yet poorly understood sequel to many infectious diseases including COVID-19, resulting in extensive patient suffering and societal burdens. Tools to diagnose, treat and prevent PIFS are urgently needed to manage the current cases of PIFS and to be prepared for future pandemics.

The Decreasing Fatigue After Infection (DEFINE) consortium will address PIFS by formulating a case definition; identifying risk factors; determining potential causal mechanisms; designing a tool for early identification and a preventative intervention; and setting up a product portfolio of countermeasures.

DEFINE will exploit existing data from post-infective cohorts and population-based cohorts (24,000 and 500,000 datasets), and recruit prospective data from about 850 patients for experimental studies as well as a multi-center randomised controlled trial. We will perform risk factor analyses by applying artificial intelligence and machine learning (AI/ML); analyse brain network dynamics; assess (epi)genetic-endocrine-immunological disease markers; design an algorithm for individual risk prediction; and design and test a preventative, transdiagnostic intervention delivered through a web-based app supported by a therapeutic chatbot and a healthcare provider. Outputs will be made available on a new PIFS platform while adhering to ethical/legal standards, safeguarding patient contribution and ensuring widespread dissemination.

Our consortium is highly multidisciplinary, bringing together world-leading researchers on PIFS as well as experts in digital health innovations, AI/ML, big data analyses, functional brain imaging, qualitative research and health economics.

DEFINE will close large knowledge gaps in an under-researched field; reduce suffering and strain on family and social networks; reduce sick leave, improve productivity and increase the resilience of the healthcare system.

Remaining characters

66

Administrative forms

Proposal ID 101137181

Acronym DEFINE

Has this proposal (or a very similar one) been submitted in the past 2 years in response to a call for proposals under any EU programme, including the current call?

☐ Yes ☒ No

Please give the proposal reference or contract number.

Previously submitted proposals should be with either 6 or 9 digits.

Administrative forms

Proposal ID 101137181

Acronym DEFINE

Declarations

Field(s) marked * are mandatory to fill.

- 1) We declare to have the explicit consent of all applicants on their participation and on the content of this proposal. * ☒
- 2) We confirm that the information contained in this proposal is correct and complete and that none of the project activities have started before the proposal was submitted (unless explicitly authorised in the call conditions). * ☒
- 3) We declare:
 - to be fully compliant with the eligibility criteria set out in the call ☒
 - not to be subject to any exclusion grounds under the [EU Financial Regulation 2018/1046](#)
 - to have the financial and operational capacity to carry out the proposed project. *
- 4) We acknowledge that all communication will be made through the Funding & Tenders Portal electronic exchange system and that access and use of this system is subject to the [Funding & Tenders Portal Terms and Conditions](#). * ☒
- 5) We have read, understood and accepted the [Funding & Tenders Portal Terms & Conditions](#) and [Privacy Statement](#) that set out the conditions of use of the Portal and the scope, purposes, retention periods, etc. for the processing of personal data of all data subjects whose data we communicate for the purpose of the application, evaluation, award and subsequent management of our grant, prizes and contracts (including financial transactions and audits). * ☒
- 6) We declare that the proposal complies with ethical principles (including the highest standards of research integrity as set out in the [ALLEA European Code of Conduct for Research Integrity](#), as well as applicable international and national law, including the Charter of Fundamental Rights of the European Union and the European Convention on Human Rights and its Supplementary Protocols. [Appropriate procedures, policies and structures](#) are in place to foster responsible research practices, to prevent questionable research practices and research misconduct, and to handle allegations of breaches of the principles and standards in the Code of Conduct. * ☒
- 7) We declare that the proposal has an exclusive focus on civil applications (activities intended to be used in military application or aiming to serve military purposes cannot be funded). If the project involves dual-use items in the sense of [Regulation 2021/821](#), or other items for which authorisation is required, we confirm that we will comply with the applicable regulatory framework (e.g. obtain export/import licences before these items are used). * ☒
- 8) We confirm that the activities proposed do not
 - aim at human cloning for reproductive purposes;
 - intend to modify the genetic heritage of human beings which could make such changes heritable (with the exception of research relating to cancer treatment of the gonads, which may be financed), or
 - 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. ☒
 - lead to the destruction of human embryos (for example, for obtaining stem cells)
 These activities are excluded from funding. *
- 9) We confirm that for activities carried out outside the Union, the same activities would have been allowed in at least one EU Member State. * ☒

The coordinator is only responsible for the information relating to their own organisation. Each applicant remains responsible for the information declared for their organisation. If the proposal is retained for EU funding, they will all be required to sign a declaration of honour.

False statements or incorrect information may lead to administrative sanctions under the EU Financial Regulation.

Administrative forms

Proposal ID 101137181

Acronym DEFINE

2 - Participants

List of participating organisations

#	Participating Organisation Legal Name	Country	Role	Action
1	AKERSHUS UNIVERSITETSSYKEHUS HF	Norway	Coordinator	
2	HUS-YHTYMA	Finland	Partner	
3	ACADEMISCH MEDISCH CENTRUM BIJ DE UNIVERSITEIT VAN	Netherlands	Partner	
4	UNIVERSITETET I OSLO	Norway	Partner	
5	NORTHWESTERN UNIVERSITY CORPORATION	United States	Partner	
6	ASSISTANCE PUBLIQUE HOPITAUX DE PARIS	France	Partner	
7	RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU	Netherlands	Partner	
8	UNIVERSITY OF NEW SOUTH WALES	Australia	Associated	
9	UNIVERSITY COLLEGE LONDON	United Kingdom	Partner	
10	FONDAZIONE HUMAN TECHNOPOLE	IT	Partner	
11	NUROMEDIA GMBH	Germany	Partner	
12	CHINO SRL	Italy	Partner	
13	ACCELOPMENT SCHWEIZ AG	Switzerland	Associated	

Administrative forms

Organisation data

PIC	Legal name
965672346	AKERSHUS UNIVERSITETSSYKEHUS HF

Short name: AHUS

Address

Street	SYKEHUSVEIEN 25
Town	LORENSKOG
Postcode	1478
Country	Norway

Webpage

Specific Legal Statuses

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is unknown (small- and medium-sized enterprise) for the call.

SME self-declared status	unknown
SME self-assessment	unknown
SME validation	unknown

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	Dept. of Paediatrics and Adolescent Medicine	☐ not applicable
	☒ Same as proposing organisation's address	
Street	SYKEHUSVEIEN 25	
Town	LORENSKOG	
Postcode	1478	
Country	Norway	

Department 2

Department name	Health Services Research Unit	☐ not applicable
	☒ Same as proposing organisation's address	
Street	SYKEHUSVEIEN 25	
Town	LORENSKOG	
Postcode	1478	
Country	Norway	

Links with other participants

Type of link	Participant
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Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☐ Woman	☒ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e@medisin.uio.no				
Position in org.	5.1.2e				
Department	Dept. of Paediatrics and Adolescent Medicine			☐ Same as organisation name	
	☒ Same as proposing organisation's address				
Street	SYKEHUSVEIEN 25				
Town	LORENSKOG	Post code	1478		
Country	Norway				
Website	https://www.ahus.no/				
Phone	+47 5.1.2e	Phone 2	+XXX XXXXXXXXXX		

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e@accelopment.com	+XXX XXXXXXXXXX
		5.1.2e@accelopment.com	+XXX XXXXXXXXXX
		5.1.2e@ous-hf.no	+XXX XXXXXXXXXX
		5.1.2e@gmail.com	+XXX XXXXXXXXXX
		5.1.2e@ahus.no	+XXX XXXXXXXXXX
		5.1.2e@ahus.no	+XXX XXXXXXXXXX
		5.1.2e@ahus.no	+XXX XXXXXXXXXX

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e 5.1.2e 5.1.2e 5.1.2e									Orcid ID
									Orcid ID
									Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	Selvakumar J, Havdal LB, Brodwall E, Lund-Berven L, Stiansen-Sonerud T, Leegaard TM, Tjade T, Zetterberg H, Blennow K, Cvejic E, Sandler C, Lloyd A, Wyller VBB. Prevalence and predictors of long COVID in adolescents and young adults. 2023. Preprint: https://doi.org/10.21203/rs.3.rs-2021203/v1 . A main publication from the LoTECA cohort of COVID-19 in adolescent and young adults, applying methodologies that will be analogous in the assessment of risk factors in the present project.
Publication	Sommen S, Havdal LB, Selvakumar J, Einvik G, Lund-Johansen F, Michelsen AE, Mollnes TE, Legaard TM, Tjade T, Stiansen-Sonerud T, Wyller VBB, Berven, LL. Inflammatory markers and pulmonary function in adolescents and young adults 6 months after mild COVID-19. <i>Front Immunol</i> 2023; 13: 1081718. A publication from the LoTECA cohort of COVID-19 in adolescent and young adults, applying methodologies that are relevant for the suggested functional assays on PBMC in the present project.
Publication	Kristensen MS, Stabursvik J, O'Leary EC, Pedersen M, Asprusten TT, Leegaard TM, Osnes LT, Tjade T, Skovlund E, Godang K, Wyller VBB. Clinical symptoms and markers of disease mechanisms in adolescent chronic fatigue following Epstein-Barr virus infection: A cross-sectional study. <i>Brain Behav Immun</i> 2019; 80: 551-63. A publication from the CEBA cohort of EBV-infection in adolescents, applying methodologies relevant to the present project.
Publication	Pedersen M, Asprusten TT, Godang K, Leegaard M, Osnes LT, Skovlund E, Tjade T, Øie MG, Wyller VB. Predictors of chronic fatigue in adolescents six months after acute Epstein-Barr virus infection: a prospective cohort study. <i>Brain Behav Immun</i> 2019; 75: 94-100. A main publication from the CEBA cohort of EBV-infection in adolescents, applying methodologies relevant to the present project.
Publication	Havdal LB, Lund-Berven L, Selvakumar J, Stiansen-Sonerud T, Leegaard TM, Tjade T, Zetterberg H, Blennow K, Wyller VBB. Neurological involvement in COVID-19 among non-hospitalised adolescents and young adults. <i>Front Neurol</i> 2022; 13: 915712. A publication from the LoTECA cohort of COVID-19 in adolescent and young adults, applying methodologies that are relevant to the present project.

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
COFFI: Collaborative on Fatigue Following Infection	An ongoing collaborative on post-infective cohort studies to investigate the development of fatigue and other long-term sequels across COVID-19 and other infections. Prof. Wyller chairs the collaborative since 2019. www.coffi-collaborative.com .
MINIRICO	Mental Intervention and Nicotinamide Riboside supplementation in Long COVID. An ongoing study on the efficacy and safety of a mental intervention program vs. usual care and nicotinamide riboside (NR) vs. placebo for improving health-related quality of life in long covid: A 2 x 2 factorial randomized controlled trial.
SIPCOV	Short-time behavioural intervention in post-Covid syndrome. An ongoing study of a short-time behavioural intervention in Long COVID vs. care as usual: A pragmatic randomised controlled trial.
LoTECA	Long-term effects of COVID-19 in adolescents. A completed observational cohort study on the long-term effects of COVID-19 in adolescents and young adults; the data are included in the COFFI collaborative.
CEBA	Chronic fatigue following Epstein-Barr virus infection in adolescents. A completed observational cohort study on the development of fatigue and other long-term symptoms in adolescents following acute EBV infection; the data are included in the COFFI collaborative.

Administrative forms

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
<i>COFFI Joint Data Center</i>	<i>A dedicated data storage centre for COFFI data sharing; adheres to the GDPR regulation and has received institutional approbation.</i>
<i>EpiGen laboratory, AHUS</i>	<i>A state-of-the-art molecular research laboratory.</i>
<i>Population based cohort studies</i>	<i>Large population-based cohort studies in Norway are managed by the Norwegian University of Science and Technology and the Norwegian Institute of Public Health; a long-standing collaboration with both these institutions has been established.</i>

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
999483830	HUS-YHTYMA

Short name: HUS

Address

Street	STENBACKINKATU 9
Town	HELSINKI
Postcode	00029
Country	Finland
Webpage	www.hus.fi

Specific Legal Statutes

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is unknown (small- and medium-sized enterprise) for the call.

SME self-declared status	unknown
SME self-assessment	unknown
SME validation	unknown

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	Clinic for the Long term effects of Covid-19	☐ not applicable
	☐ Same as proposing organisation's address	
Street	Paciuksenkatu 21	
Town	Helsinki	
Postcode	00009	
Country	Finland	

Department 2

Department name	Clinic for Functional Disorders	☐ not applicable
	☐ Same as proposing organisation's address	
Street	Maistraatinpolku 2	
Town	Helsinki	
Postcode	00009	
Country	Finland	

Links with other participants

Type of link	Participant
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Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☒ Woman ☐ Man ☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e
E-Mail*	5.1.2e @hus.fi		
Position in org.	5.1.2e		
Department	Clinic for the Long term effects of Covid-19		☐ Same as organisation name
	☐ Same as proposing organisation's address		
Street	Paciuksenkatu 21		
Town	Helsinki	Post code	00009
Country	Finland		
Website	www.hus.fi		
Phone	+358 5.1.2e	Phone 2	+358 5.1.2e

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e @hus.fi	+XXX XXXXXXXXXX
		5.1.2e @hus.fi	+XXX XXXXXXXXXX

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e					5.1.2e	5.1.2e		5.1.2e	Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☒
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☒
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	<i>Factors Contributing to Medication Adherence in Patients with a Chronic Condition: A Scoping Review of Qualitative Research.</i> Kvarnström K, Westerholm A, Airaksinen M, Liira H. <i>Pharmaceutics</i> . 2021 Jul 20;13(7):1100. doi: 10.3390/pharmaceutics13071100.PMID: 34371791
Publication	<i>Education and training for preventing sharps injuries and splash exposures in healthcare workers.</i> Cheetham S, Ngo HT, Liira J, Liira H. <i>Cochrane Database Syst Rev</i> . 2021 Apr 14;4(4):CD012060. doi: 10.1002/14651858.CD012060.pub2.PMID: 33871067
Publication	<i>A randomized controlled trial protocol for persistent physical symptoms associated with indoor environment or chronic fatigue: Effectiveness of video-based functional case conceptualization and web-program for improving quality of life.</i> Selinheimo S, Keinonen K, Vuokko A, Liesto S, Sainio M, Lappalainen R, Paunio T. <i>Front Psychol</i> . 2023 Jan 6;13:923532. doi: 10.3389/fpsyg.2022.923532. eCollection 2022.PMID: 36687807
Publication	<i>ICF-linking and psychometric properties of upper extremity mobility outcome measures in spinal cord injury - a scoping review.</i> Poutanen J, Savolainen S, Shulga A, Arokoski J, Hiekkala S. <i>J Spinal Cord Med</i> . 2023 Jan 9:1-13. doi: 10.1080/10790268.2022.2161867. Online ahead of print.PMID: 36622355

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
AICCELERATE	AICCELERATE is an H2020 project that runs until 2024. The project is developing an AI-powered smart hospital care pathway engine. Project is led by HUS. The Smart Health Care Pathway Engine will be tested in three different pilots during the project. https://aiccelerate.eu/
LONG COVID	Long Covid is a HUS Helsinki University Hospital-led consortium to examine the mechanisms behind the long-term effects of a COVID-19 infection. The objective is also to create a Decision support system for prediction and management of Long Covid Syndrome (LCS). https://longcovidproject.eu/
Clinics for Long Covid and Functional Disorders	Long Covid policlinic and Functional disorders policlinic: HUS founded a new multidisciplinary Long Covid policlinic in June 2021. Earlier in June 2019, HUS founded a multidisciplinary policlinic for functional disorders. Both policlinics are research hubs increasing scientific knowledge on how to manage these patients groups.
MeiVac	Meilahti Infectious Diseases and Vaccine Research Center, MeiVac: MeiVac has been acting as a research center also for COVID. It has enabled centralized recruitment and collection of blood and other samples from COVID vaccinees and COVID patients and negative controls. I has also handled the follow-up samplings and background and frequent questionnaires to allow prospective follow-up of patients with /without long COVID.

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
HUS research infrastructure	HUS is a significant provider of research in specialist medical care, medical science and drug development. HUS conducts approximately two thousand different medical and healthcare research projects on an ongoing basis.
IT department	HUS has an IT department, which builds and ensures technical capability, and safe platforms for data management.

Administrative forms

Biobank Helsinki	<i>Since the Biobank Act in 2013, there are 11 Biobanks in Finland regulated by Finnish Medicines Agency. Biobank Helsinki enables the collection and multiple usage of patient specimens collected. Most specimens in this study entity will be collected there with standardised procedures.</i>
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Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
998732274	ACADEMISCH MEDISCH CENTRUM BIJ DE UNIVERSITEIT VAN AMSTERDAM

Short name: AUMC

Address

Street	MEIBERGDREEF 15
Town	AMSTERDAM
Postcode	1105AZ
Country	Netherlands
Webpage	www.amc.nl

Specific Legal Statutes

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	yes
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	24/01/2022 - no
SME self-assessment	unknown
SME validation	30/10/2008 - no

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	Department of Medical Psychology	☐ not applicable
	☒ Same as proposing organisation's address	
Street	MEIBERGDREEF 15	
Town	AMSTERDAM	
Postcode	1105AZ	
Country	Netherlands	

Links with other participants

Type of link	Participant
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Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☐ Woman	☒ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e @amsterdamumc.nl				
Position in org.	5.1.2e				
Department	Department of Medical Psychology			☐ Same as organisation name	
	☒ Same as proposing organisation's address				
Street	MEIBERGDREEF 15				
Town	AMSTERDAM	Post code	1105AZ		
Country	Netherlands				
Website	Please enter website				
Phone	+31	5.1.2e	Phone 2	+31	5.1.2e

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e @amsterdamumc.nl	+XXX XXXXXXXXX

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e					5.1.2e	5.1.2e			Researcher ID
									Orcid ID
									Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☒
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other	☒
If yes, please specify: (Maximum number of characters allowed: 50)	

Conduction of a clinical trial

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	doi: 10.1093/cid/cix013 Effectiveness of Long-term Doxycycline Treatment and Cognitive-Behavioral Therapy on Fatigue Severity in Patients with Q Fever Fatigue Syndrome (Qure Study): A Randomized Controlled Trial. Clin Infect Dis. 2017 Apr 15;64(8):998-1005. This was the first controlled study showing that post-infectious fatigue could be effectively treated with a cognitive behavioural intervention.
Publication	doi: 10.1186/s13063-021-05569-y A randomised controlled trial testing the efficacy of Fit after COVID, a cognitive behavioural therapy targeting severe post-infectious fatigue following COVID-19 (ReCOVer): study protocol. Trials. 2021 Dec 2;22(1):867. This will be the first controlled study testing the efficacy of a cognitive behavioural intervention for post-infectious fatigue following COVID-19.
Publication	doi: 10.1016/S2213-8587(17)30098-0 Web-based cognitive behavioural therapy blended with face-to-face sessions for chronic fatigue in type 1 diabetes: a multicentre randomised controlled trial. Lancet Diabetes Endocrinol. 2017 Jun;5(6):448-456. This was the first controlled study showing that chronic fatigue in Diabetes Type I could be effectively treated with a web-based behavioural intervention.
Publication	doi: 10.1038/s41598-021-00337-z. Fatigue in patients with chronic disease: results from the population-based Lifelines Cohort Study. Sci Rep. 2021 Oct 25;11(1):20977. A study in 23 long term medical conditions showing that fatigue is mainly associated with transdiagnostic (behavioural) factors that are potential targets for behavioural interventions.
Publication	doi: 10.1016/j.brat.2022.104243. The relation between cognitive-behavioural responses to symptoms in patients with long term medical conditions and the outcome of cognitive behavioural therapy for fatigue - A secondary analysis of four RCTs. Behav Res Ther. 2023 Feb;161:104243. The same behavioural responses to fatigue moderate and mediate treatment outcome across conditions, supporting a transdiagnostic approach to fatigue.

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
ReCoVer	A Randomised Controlled Trial testing the efficacy of Cognitive Behavioural Therapy for preventing chronic post-infectious fatigue among patients diagnosed with COVID-19. The project (2020-2023) is funded by the Netherlands Organization for Health Research and Development (ZonMw: project number 10430012010025, research program COVID-19). PI: H. Knoop.
VIS	Project (2020-2023) Long-term mental health trajectories in recovered Covid-19 patients: exploring the interplay of psychosocial and biological factors affecting health-related quality of life with project number 10430032010010 of the research programme COVID-19 which is financed by the Netherlands Organisation for Health Research and Development (ZonMw). PI: P. Nieuwkerk and H.Knoop
OPTIMISTIC	OPTIMISTIC (FP7, 2012-2017): An Observational Prolonged Trial In Myotonic dystrophy type 1 to Improve Quality of Life- Standards, a Target Identification Collaboration. It aimed at improving clinical practice and standards of care for patients with DM1 internationally. WP leader: H.Knoop developed a behavioural intervention aimed at fatigue and disability and conducted an international, multi-centre randomized controlled trial.
TIMELY	TIMELY - A patient-centered early risk prediction, prevention, and intervention platform to support the continuum of care in coronary artery disease (CAD) using eHealth and artificial intelligence funded by the EU (H2020). In this project artificial intelligence is used to develop a web-based low intensity behavioural intervention for patients with CAD. Workpackage leader:

Administrative forms

<i>Tireless</i>	<i>TIRELESS – Making cognitive behavioral therapy for cancer-related fatigue fit for implementation in patients with advanced cancer receiving palliative systemic treatment. Tireless (2023-2026) is supported by the Dutch cancer society and aimed at the development of an evidence based low intensity intervention for severely fatigued patients during the palliative phase of cancer treatment.</i>
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Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
<i>Minddistrict</i>	<i>A commercial software tool used to deliver webbased behavioural interventions and apps. The platform is available in different languages and in multiple EU member states.</i>
<i>Clinical Research Unit (CRU)</i>	<i>The CRU of the Amsterdam UMC supports several aspects of conducting a clinical trial: 1) data management; 2) organization, administration and monitoring of study; 3) methodological and statistical support.</i>

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
999975814	UNIVERSITETET I OSLO

Short name: UiO

Address

Street	PROBLEMVEIEN 5-7
Town	OSLO
Postcode	0313
Country	Norway
Webpage	www.uio.no

Specific Legal Statutes

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	yes
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	31/08/2022 - no
SME self-assessment	unknown
SME validation	20/05/2008 - no

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	Department of Psychology	☐ not applicable
	☐ Same as proposing organisation's address	
Street	Forskingsveien 3A	
Town	Oslo	
Postcode	0373	
Country	Norway	

Links with other participants

Type of link	Participant
--------------	-------------

Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☐ Woman	☒ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e@psykologi.uio.no				
Position in org.	5.1.2e				
Department	Department of Psychology			☐ Same as organisation name	
	☐ Same as proposing organisation's address				
Street	Forskningsveien 3A				
Town	Oslo	Post code	0373		
Country	Norway				
Website	https://www.sv.uio.no/psi/english/people/aca/larstweng/				
Phone	+47 5.1.2e	Phone 2	+47 5.1.2e		

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e@psykologi.uio.no	5.1.2e
		5.1.2e@psykologi.uio.no	

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e 5.1.2e 5.1.2e									Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☒
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	<i>Alnæs D, Kaufmann T, Marquand A, Smith S, Westlye LT. Patterns of socio-cognitive stratification and perinatal risk in the child brain. Proceeding of the National Academy of Sciences (PNAS), 2020 June 2, 117 (22) 12419-12427. https://doi.org/10.1073/pnas.2001517117</i> <i>Relevance: Demonstration of environmental impact on the developing brain using brain imaging and multivariate tools</i>
Publication	<i>de Lange AMG, Kaufmann T, van der Meer D, Maglanoc LA, Alnæs D, Moberget T, Douaud G, Andreassen OA, Westlye LT. Population-based neuroimaging reveals traces of childbirth in the maternal brain. Proceeding of the National Academy of Sciences (PNAS), 2019, 116 (44) 22341-22346. https://doi.org/10.1073/pnas.1910666116</i> <i>Relevance: Demonstration of beneficial effects of parity and childbirths on the maternal ageing brain, proof of principle of the hypothesis of sensitive phases in the brain.</i>
Publication	<i>Kaufmann T, van der Meer D, Doan NT, ..., Westlye LT. Common brain disorders are associated with heritable patterns of apparent ageing of the brain, Nature Neuroscience, 2019, 22, 1617–1623. http://dx.doi.org/10.1038/s41593-019-0471-7</i> <i>Relevance: Big-data and machine learning analysis of brain MRI demonstrate common and distinct patterns of brain ageing across mental and neurological disorders</i>
Publication	<i>Maglanoc LA, Kaufmann T, van der Meer D, Marquand AF, Wolfers T, Jonassen R, Hilland E, Andreassen OA, Landrø NI, Westlye LT. Brain connectome mapping of complex traits and their polygenic architecture using machine learning. Biol Psychiatry. 2020 ; 87(8):717-726. https://doi.org/10.1016/j.biopsych.2019.10.011</i> <i>Relevance: Machine learning on brain MRI measures to predict relevant demographic and clinical traits and their polygenic architecture</i>
Publication	<i>Kaufmann T, Alnæs D, Doan NT, Brandt CL, Andreassen OA, Westlye LT. Delayed stabilization and individualization in connectome development are related to psychiatric disorders. Nature Neuroscience. 2017 Apr;20(4):513-515. https://doi.org/10.1038/nn.4511</i> <i>Relevance: Advanced network modelling of fMRI shows increasing brain stability during adolescence and relevance for mental illness</i>

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
environMENTAL	<i>Reducing the impact of major environmental challenges on mental health. Addresses the relevance of the complex interplay between genes and environment on mental health in the population using novel tools for brain imaging, statistical genetics and environmental profiling (satellite imaging, geospatial coding), with a particular focus on challenges related to the Covid-19 pandemic. Strong focus on the joint benefits of scientific discoveries and development of novel interventions.</i>
MULTIMENT	<i>Research Council of Norway – FRIPRO: Large-scale Interdisciplinary Researcher Project MULTIMENT: Polygenic and psychosocial interplay in brain development across mental disorders. Collaborative and interdisciplinary project addressing the complex dynamics between adolescent brain development, environmental exposures and experiences, and genetics with a particular focus on the early and prodromal phases of mental disorders.</i>

Administrative forms

MoBaBrain	Research Council of Norway – FRIPPRO. Parsing the developmental and genetic architecture of risk and resilience in the adolescent brain. National project aiming to characterize factors that harm and protect the developing brain during childhood and adolescence, with a particular focus on population-based mental health. Will use unique Norwegian population and health registries, including the Norwegian Mother, Father and Child study.
BRAINMINT	ERC Starting Grant. Brains and minds in transition: The dark side of neuroplasticity during sensitive life phases. Aiming to identify general mechanisms of brain plasticity which modulate the risk of developing mental disorders by studying and comparing the brain, psychological and biological changes occurring during two sensitive life phases: adolescence and pregnancy (maternal).
MATERNALBRAIN	Research Council of Norway. Women's Health programme. From synapses to symptoms in maternal mental health during pregnancy and postpartum. Aiming to characterize and identify predictive factors for maternal mental disorders including postpartum depression and anxiety by studying the dynamic changes in the maternal brain, cognition, immune responses and mental health before, during and after pregnancy.

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
NORMENT2050	NORMENT2050 provides access to a large harmonized database of clinical and population-based data, including brain imaging, genetics and clinical information, with possibilities for linkage with the Norwegian population and health registries.
Regional Core Facility MRI Neuroimaging	Hosts the state-of-the-art 3T MRI GE Premier scanner which will be used for the current project. Provides access to excellent technological and computational facilities and routines for the identification and handling of incidental clinical findings.
CTNC	This UiO-based Core Facility provides access to cutting-edge research infrastructure and lab facilities for cognitive and neuronal phenotyping using behavioral and cognitive experimental setups and tools for the continuous recording of brain activity (e.g. EEG), autonomous responses and eye-tracking
TSD	Secure platform for storage, analysis and sharing of sensitive data, hosted by UiO. TSD provides a platform for researchers at UiO and other public research institutions.

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
999627778	NORTHWESTERN UNIVERSITY CORPORATION

Short name: NUFSoM

Address

Street	CLARK STREET 633
Town	EVANSTON
Postcode	60208
Country	United States
Webpage	www.northwestern.edu

Specific Legal Statutes

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	yes
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is unknown (small- and medium-sized enterprise) for the call.

SME self-declared status	unknown
SME self-assessment	unknown
SME validation	unknown

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	Feinberg School of Medicine	☐ not applicable
	☐ Same as proposing organisation's address	
Street	420 E. Superior St.	
Town	Chicago	
Postcode	IL 60611	
Country	United States	

Department 2

Department name	Lurie Children's Hospital, Division of Infectious Diseases	☐ not applicable
	☐ Same as proposing organisation's address	
Street	225 E Chicago Avenue, Box # 20	
Town	Chicago, IL	
Postcode	60611	
Country	United States	

Links with other participants

Type of link	Participant
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Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☐ Woman	☒ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e @luriechildrens.org				
Position in org.	5.1.2e				
Department	Feinberg School of Medicine			☐ Same as organisation name	
	☐ Same as proposing organisation's address				
Street	420 E. Superior St.				
Town	Chicago	Post code	IL 60611		
Country	United States				
Website	https://www.feinberg.northwestern.edu/faculty-profiles/az/profile				
Phone	312	5.1.2e	Phone 2	+XXX XXXXXXXXXX	

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e @luriechildrens.org	5.1.2e

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e						5.1.2e			Orcid ID
									Orcid ID
									Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	doi: 10.1093/cid/ciaa1886 - Clin Infect Dis - Risks for developing ME/CFS in college students following infectious mononucleosis. This paper followed college students beginning when they were well to identify baseline risk factors for the development of ME/CFS following mono.
Publication	doi:10.1016/j.peds.2019.01.035 - J Pediatr - A validated scale for assessing the severity of acute infectious mononucleosis. In this paper we validated a severity of mononucleosis scale and showed that more severe mono was a risk for meeting > 1 set of criteria for ME/CFS (what we have termed severe ME/CFS).
Publication	doi: 10.1080/21641846.2021.1994222 - Fatigue: Biomedicine, Health & Behavior - Saliva fatigue biomarker index as a marker for severe ME/CFS in a community based sample. In this paper we showed that the FBI was associated with the diagnosis of severe ME/CFS in a sample of children and adolescents.
Publication	doi: 10.1039/d2mo00124a - b.1.24 Omics - Pre-illness data reveals differences in multiple metabolites and metabolic pathways in those who do and do not recover from mono. We showed differences at baseline (when well) between college students who did and did not develop ME/CFS 6 months following mono in pathways essential for proliferating cells particularly during a pro-inflammatory response and were able to classify patients correctly about 95% of the time based on a profile of 8 metabolites.
Publication	doi: 10.1080/21641846.2022.2150487 - Fatigue: Biomedicine, Health & Behavior - Establishing a consensus on ME/CFS exclusionary criteria. In this paper, we established a consensus on ME/CFS exclusionary criteria, which will be similar to what will be required for coming up with a universal and accepted definition for long covid as well.

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
R01 NS111105	NIH/NINDS - Maintenance and Incidence of ME/CFS Following Mono The major goal of this study is to follow up those with Mono and ME/CFS who had been former college youth.
3R01 NS111105-02S1	NIH/NINDS - Maintenance and Incidence of ME/CFS following mono - Supplement. The major goal of this study is to use our same cohort of over 4500 healthy college students to study risk factors for development of non-recovery from covid-19.
R01 AI105781	NIH/NIAID - A prospective study of CFS following infectious mononucleosis in college students. This major aim of this study was to uncover pre-illness risk factors for the development of ME/CFS following IM in college students. This study has led to 6 major publications to date, including sme that were listed above.
R01 HD072208	NIH/NICHHD - Pediatric CFS in a community-based sample. The major aim of this study was to estimate the prevalence of ME/CFS in a community-based pediatric sample. Our major finding from this study, which yielded an incidence of 0.75%, with a higher incidence in Black and Latino/a youth, has been published (doi:10.1007/s10566-019-09543-3).

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
Special Infectious Diseases laboratory (SIDL)	The SIDL contains 6 ultralow freezers for storing samples. The SIDL staff is trained bi-annually in all aspects of both domestic and international shipping. Both electronic shipment and preparation and tracking software are available to manage and track specimen movement.

Administrative forms

Metabolomics Core Facility (MCF)	<i>The MCF provides metabolomics services including identification, semi-quantification and quantification of primary and secondary metabolites from biological samples. Major equipment includes a Thermo-Ultimate-3000 Ultra Performance Liquid Chromatography System and a Q-Exactive Mass Spectrometer.</i>
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Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
999645432	ASSISTANCE PUBLIQUE HOPITAUX DE PARIS

Short name: APHP

Address

Street	55 BOULEVARD DIDEROT
Town	PARIS
Postcode	75012
Country	France
Webpage	www.aphp.fr

Specific Legal Statutes

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is unknown (small- and medium-sized enterprise) for the call.

SME self-declared status	unknown
SME self-assessment	unknown
SME validation	unknown

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	Internal medicine, Hopital européen Georges Pompidou	☐ not applicable
	☐ Same as proposing organisation's address	
Street	20 rue Leblanc	
Town	Paris	
Postcode	75015	
Country	France	

Department 2

Department name	Psychiatry, Hotel Dieu	☐ not applicable
	☐ Same as proposing organisation's address	
Street	1 place du parvis de Notre Dame	
Town	Paris	
Postcode	75004	
Country	France	

Links with other participants

Type of link	Participant
--------------	-------------

Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☒ Woman	☐ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e@aphp.fr				
Position in org.	5.1.2e				
Department	Internal medicine		☐ Same as organisation name		
	☐ Same as proposing organisation's address				
Street	20 rue Leblanc				
Town	Paris	Post code	75015		
Country	France				
Website	Please enter website				
Phone	+33 5.1.2e	Phone 2	+33 5.1.2e		

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e@aphp.fr	+XXX XXXXXXXXXX

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e5.1.2e						5.1.2e			Orcid ID
									Orcid ID
									Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other	☐
If yes, please specify: (Maximum number of characters allowed: 50)	

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	<i>Lemogne C, Gouraud C, Pitron V, Ranque B. Why the hypothesis of psychological mechanisms in long COVID is worth considering. J Psychosom Res. 2023 Feb;165:111135. doi: 10.1016/j.jpsychores.2022.111135.</i>
Publication	<i>Kachaner A, Lemogne C, Dave J, Ranque B, de Broucker T, Meppiel E. Somatic symptom disorder in patients with post-COVID-19 neurological symptoms: a preliminary report from the somatic study (Somatic Symptom Disorder Triggered by COVID-19). J Neurol Neurosurg Psychiatry. 2022 Aug 25;jnnp-2021-327899.</i>
Publication	<i>Bottemanne H, Gouraud C, Hulot JS, Blanchard A, Ranque B, Lahlou-Laforêt K, Limosin F, Günther S, Lebeaux D, Lemogne C. Do Anxiety and Depression Predict Persistent Physical Symptoms After a Severe COVID-19 Episode? A Prospective Study. Front Psychiatry. 2021 Nov 10;12:757685. doi: 10.3389/fpsy.2021.757685.</i>
Publication	<i>Matta J, Wiernik E, Robineau O, [...], Ranque B, [...], Lemogne C. Association of Self-reported COVID-19 Infection and SARS-CoV-2 Serology Test Results With Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic. JAMA Intern Med. 2022 Jan 1;182(1):19.</i>
Publication	<i>Gouraud C, Ranque B, Ouazanna C, Pitron V, Xiang K, Karmochkine M, Lemogne C [Psychiatric assessment as part of a multidisciplinary program for patients with persistent symptoms after infection SARS-CoV-2: Presentation and first results]. Congrès Français de Psychiatrie, Lille, décembre 2022. Oral Communication.</i>

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
CASPER COVID	<i>A multidisciplinary day-hospital evaluation for patients with long COVID opened in July 2021 in Hotel Dieu Hospital, Paris. Patients are self-referred or referred by their general practitioners. Along the day of hospitalization, patients undergo consultations with an internist or infectious disease specialist, a psychiatrist, and an adapted physical activity specialist. They are given a personalized care protocol and reassessed at 3 months.</i>
ECHAP COVID	<i>Controlled randomized trial: assessment and comparison of multi-disciplinary hospital management (adapted physical activity, CBT, cognitive mediation) versus waiting list for symptoms persistent after an acute episode of COVID-19. The main outcome is the quality of life at 6 months. The trial is ongoing.</i>
EMPATY	<i>Stepped wedge controlled randomized trial to assess the efficacy of educating general practitioners on SSD diagnosis and care to improve the quality of life of their patients with persistent symptoms attributed to COVID-19. The RCT aims to recruit 720 patients with long COVID in 12 months. The trial is ongoing.</i>
COVILEV	<i>Epidemiological study of quality of life, clinical evolution and use of care for long COVID, in a cohort of general practitioners and in the general population in metropolitan France, led by the "réseau sentinelle" and Santé Publique France. The trial has passed the ethical agreement and will start soon.</i>

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
<i>Disposition d'appui à la coordination "COVID long"</i>	<i>"Long COVID" support cells funded by the regional health agency (ARS) in 2021, whose role is to coordinate the management of patients with post-COVID persistent symptoms by providing advice and referral to other professionals if necessary.</i>

Administrative forms

<i>Réseau Sentinelles</i>	<i>"Réseau Sentinelles" a research and health monitoring network in primary care in metropolitan France. Created in November 1984, it was developed under the joint supervision of the National Institute of Health and Medical Research (Inserm) and Sorbonne University. It involves more than 500 GPs.</i>
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Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
999991431	RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU

Short name: RIVM

Address

Street	Antonie Van Leeuwenhoeklaan 9
Town	BILTHOVEN
Postcode	3721 MA
Country	Netherlands
Webpage	www.rivm.nl

Specific Legal Statutes

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	13/01/2022 - yes
SME self-assessment	unknown
SME validation	25/03/2010 - no

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	Centre for Infectious Disease Control	☐ not applicable
	☒ Same as proposing organisation's address	
Street	Antonie Van Leeuwenhoeklaan 9	
Town	BILTHOVEN	
Postcode	3721 MA	
Country	Netherlands	

Links with other participants

Type of link	Participant
--------------	-------------

Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☐ Woman	☒ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e @rivm.nl				
Position in org.	5.1.2e				
Department	Centre for Infectious Disease Control			☐ Same as organisation name	
	☒ Same as proposing organisation's address				
Street	Antonie Van Leeuwenhoeklaan 9				
Town	BILTHOVEN	Post code	3721 MA		
Country	Netherlands				
Website	Please enter website				
Phone	+31	5.1.2e	Phone 2	+316	5.1.2e

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e @rivm.nl	5.1.2e
5.1.2e		5.1.2e @rivm.nl	
5.1.2e		5.1.2e @rivm.nl	

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e	5.1.2e		5.1.2e			5.1.2e			
	5.1.2e		5.1.2e			5.1.2e			
	5.1.2e		5.1.2e			5.1.2e			

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other	☐
If yes, please specify: (Maximum number of characters allowed: 50)	

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	Baarsma, M. E., F. R. van de Schoor, S. A. Gauw, H. D. Vrijmoeth, J. Ursinus, N. Goudriaan, C. D. Pops, H. J. Ter ^{5.1.2e} M. M. Leeflang, K. Kremer, C. C. van den Wijngaard, B. J. Kullberg, L. A. Joosten, and J. W. Hovius. "Diagnostic Parameters of Cellular Tests for Lyme Borreliosis in Europe (Victory Study): A Case-Control Study." <i>Lancet Infect Dis</i> 22, no. 9 (Sep 2022): 1388-96. https://dx.doi.org/10.1016/S1473-3099(22)00205-5 .
Publication	Mutubuki, E. N., T. van der Maaden, K. Y. Leung, A. Wong, A. D. Tulen, S. de Bruijn, L. Haverman, H. Knoop, E. Franz, A. J. van Hoek, and C. C. van den Wijngaard. "Prevalence and Determinants of Persistent Symptoms after Infection with Sars-Cov-2: Protocol for an Observational Cohort Study (Longcovid-Study)." <i>BMJ Open</i> 12, no. 7 (Jul 1 2022): e062439. https://dx.doi.org/10.1136/bmjopen-2022-062439 .
Publication	Ursinus, J., H. D. Vrijmoeth, M. G. Harms, A. D. Tulen, H. Knoop, S. A. Gauw, T. P. Zomer, A. Wong, I. H. M. Friesema, Y. M. Vermeeren, L. A. B. Joosten, J. W. Hovius, B. J. Kullberg, and C. C. van den Wijngaard. "Prevalence of Persistent Symptoms after Treatment for Lyme Borreliosis: A Prospective Observational Cohort Study." <i>Lancet Reg Health Eur</i> 6 (Jul 2021): 100142. https://dx.doi.org/10.1016/j.lanepe.2021.100142 .
Publication	van der Maaden, T., E. N. Mutubuki, S. de Bruijn, K. Y. Leung, H. Knoop, J. Slootweg, A. D. Tulen, A. Wong, A. J. van Hoek, E. Franz, and C. C. van den Wijngaard. "Prevalence and Severity of Symptoms 3 Months after Infection with Sars-Cov-2 Compared to Test-Negative and Population Controls in the Netherlands." <i>J Infect Dis</i> (Dec 7 2022). https://dx.doi.org/10.1093/infdis/jiac474 .
Publication	Harms, M. G., A. Hofhuis, H. Sprong, S. C. Bennema, J. A. Ferreira, M. Fonville, A. Docters ^{5.1.2e} W. J. J. Assendelft, Hcpm Van Weert, W. Van Pelt, and C. C. Van den Wijngaard. "A Single Dose of Doxycycline after an Ixodes Ricinus Tick Bite to Prevent Lyme Borreliosis: An Open-Label Randomized Controlled Trial." <i>J Infect</i> 82, no. 1 (Jan 2021): 98-104. https://dx.doi.org/10.1016/j.jinf.2020.06.032 .

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
InfectieRadar study	InfectieRadar (www.infectieradar.nl) is an ongoing observational cohort study, where participants weekly administer their symptoms of acute infections. Participants also can report a positive COVID test (self-tests supplied by the researchers), and can subsequently be invited for additional medical scientific studies including the currently proposed intervention study.
TekenRadar study	An ongoing observational cohort study (www.tekenradar.nl) to the long-term follow up of tick bites and Lyme disease. Participants can report after a tick bite or physician diagnosed Lyme disease, and are followed-up for long-term symptoms. They can also be subsequently invited for additional medical scientific studies including the currently proposed intervention study.
RIVM LongCovid study	The RIVM LongCovid study (LongCOVID-onderzoek (rivm.nl)) is an ongoing observational cohort study to the prevalence of longCovid-like symptoms after COVID-19. Participants can report after a positive COVID test, and are followed-up for long-term symptoms. They can also be subsequently invited for additional medical scientific studies similar as Infectieradar and Tekenradar.
LymeProspect study	A completed prospective observational cohort study to the prevalence of persistent symptoms after treatment for Lyme borreliosis. Participants with acute Lyme disease were largely recruited online through www.tekenradar.nl .
TTPP: Tick Test and Prophylaxis Proof study	A completed open-label randomized controlled trial to prophylactic treatment after a tick bite to prevent Lyme disease. Tick bite participants were recruited online through www.tekenradar.nl .

Administrative forms

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
<i>www.tekenradar.nl</i>	<i>Online platform for recruitment and inclusion of participants with tick bites and physician-diagnosed Lyme disease, and long-term follow-up for long-term symptoms including post-infectious fatigue.</i>
<i>Infectieradar</i>	<i>Online platform for weekly reporting acute symptoms in a population cohort. After reporting an acute COVID-19 diagnosed by study-supplied self-tests, a follow-up is started to screen for long-term symptoms including post-infectious fatigue.</i>
<i>LongCOVID-onderzoek (rivm.nl)</i>	<i>Online platform for inclusion of participants with acute COVID-19, and long-term follow-up for long-term symptoms including post-infectious fatigue. Participants can be invited for additional medical scientific studies, similar as Tekenradar and Infectieradar.</i>
<i>CASE-based software for online recruitment</i>	<i>The CASE-based software allows selection of patients with specific characteristics during follow-up, to be able to specifically invite participants for subsequent medical studies for which they fulfill the inclusion criteria.</i>

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC 998090910	Legal name UNIVERSITY OF NEW SOUTH WALES
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Short name: UNSW

Address

Street	ANZAC PARADE
Town	SYDNEY
Postcode	2052
Country	Australia
Webpage	http://www.unsw.edu.au

Specific Legal Statutes

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	yes
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	01/07/1990 - no
SME self-assessment	unknown
SME validation	unknown

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	Kirby Institute	☐ not applicable
	☐ Same as proposing organisation's address	
Street	Level 5, Wallace Wurth building, High st	
Town	Kensington	
Postcode	NSW 2052	
Country	Australia	

Department 2

Department name	UNSW Fatigue Clinic and Research Program	☐ not applicable
	☐ Same as proposing organisation's address	
Street	32 Botany Street	
Town	Randwick	
Postcode	NSW 2031	
Country	Australia	

Links with other participants

Type of link	Participant
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Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
									Orcid ID
									Orcid ID
									Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other	☐
If yes, please specify: (Maximum number of characters allowed: 50)	

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	<i>Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, International Chronic Fatigue Syndrome Study Group including Lloyd A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med. 1994 Dec 15;121(12):953-9. doi: 10.7326/0003-4819-121-12-199412150-00009. Citations 4,191.</i>
Publication	<i>Wilson A, Hickie I, Hadzi-Pavlovic D, Wakefield D, Parker G, Straus SE, Dale J, McCluskey D, Hinds G, Brickman A, Goldenberg D, Demitrack M, Blakely T, Wessely S, Sharpe M, Lloyd A. What is chronic fatigue syndrome? Heterogeneity within an international multicentre study. Aust N Z J Psychiatry. 2001 Aug;35(4):520-7. doi: 10.1046/j.1440-1614.2001.00888. FWCI 2.3 Citations 102.</i>
Publication	<i>Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, Reeves WC, Lloyd A; Dubbo Infection Outcomes Study Group. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: Prospective cohort study. BMJ. 2006 Sep 16;333(7568):575. doi: 10.1136/bmj.38933.585764.AE. FWCI 15.78, Citations 493.</i>
Publication	<i>Vollmer-Conna U, Piraino BF, Cameron B, Davenport T, Hickie I, Wakefield D, Lloyd AR; Dubbo Infection Outcomes Study Group. Cytokine polymorphisms have a synergistic effect on severity of the acute sickness response to infection. Clin Infect Dis. 2008 Dec 1;47(11):1418-25. doi:10.1086/592967. FWCI 1.63, Citations 74.</i>
Publication	<i>Sandler CX, Wyller VBB, Moss-Morris R, Buchwald D, Crawley E, Hautvast J, Katz BZ, Knoop H, Little P, Taylor R, Wensaas KA, Lloyd AR. Long COVID and post-infective fatigue syndrome: A review. Open Forum Infect Dis. 2021 Sep 9;8(10):ofab440. doi: 10.1093/ofid/ofab440 FWCI 4.11, Citations 45.</i>

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
<i>Dubbo Infection Outcomes Study (DIOS)</i>	<i>Prospective cohort following subjects with acute infective illnesses (Epstein Barr virus, Ross River virus, Q fever) over at least 12 months from the onset of illness.</i>
<i>FolCan (Follow-up after Cancer) study</i>	<i>Prospective cohort following women being treated from early-stage breast cancer to measure the occurrence of post-cancer fatigue (PCF).</i>
<i>Coronavirus Outbreak Samples in NSW (COSIN)</i>	<i>Prospective cohort following patients infected with SARS-CoV-2 from several major hospitals in NSW.</i>
<i>COFFI: Collaborative on Fatigue Following Infection</i>	<i>International consortium of investigators and their prospective cohorts following individuals from the onset of acute infection for post-infective fatigue and related outcomes.</i>
<i>InC3</i>	<i>This highly successful international consortium studying outcomes of acute hepatitis C infection amongst high risk injecting drug users (Professor Lloyd was an investigator) provided a model for the more recent COFFI consortium including in governance structures, data and specimen sharing policies, publication policies, and administrative procedures.</i>

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
<i>Viral and Immunology Systems Program (VISP)</i>	<i>VISP is a collaborative team of clinicians and scientists encompassing the disciplines of clinical infectious diseases and epidemiology, and laboratory-based biomedical researchers. VISP is located within the Kirby Institute at University of NSW, Sydney.</i>
<i>VISP biomedical laboratory facilities</i>	<i>The laboratory has accredited biosafety level 2 and 3 laboratory facilities for conducting experiments in virology, immunology, and genetics with stored clinical specimens (e.g., serum, plasma, peripheral blood mononuclear cells, etc).</i>

Administrative forms

<i>UNSW Fatigue Clinic and Research Program</i>	<i>The UNSW Fatigue Clinic is an integrated tertiary referral clinical service and research facility for medically-unexplained fatigue states, including chronic fatigue syndrome (CFS), post-cancer fatigue (PCF), and post-infective fatigue syndrome (PIFS).</i>
<i>Kirby Biobank</i>	<i>The biobank for the Kirby Institute included extensive -80°C freezers, and vapour phase nitrogen storage vessels with centralised alarms, and associated inventory systems for sophisticated specimen search and retrieval.</i>
<i>Kirby IT systems</i>	<i>As the Kirby Institute has a strong focus on epidemiology and clinical trial activities, as well as state-of-the art high throughput biomedical research technologies (including advanced imaging and various -omics platforms) it has comprehensive IT systems for databasing with cloud-based back-up.</i>
<i>Ramaciotti Centre for Genomics</i>	<i>This centre is a genomics research and resource centre based at the University of NSW, with capabilities to deliver data, and analysis. It is Australia's largest genomics facility (accredited ISO/IEC 17025). It is comprehensively equipped with the latest next-generation sequencing technologies.</i>

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
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 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
999975620	UNIVERSITY COLLEGE LONDON

Short name: UCL

Address

Street	GOWER STREET
Town	LONDON
Postcode	WC1E 6BT
Country	United Kingdom
Webpage	http://www.ucl.ac.uk

Specific Legal Statutes

Legal person	yes
Public body	yes
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	yes
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	01/02/2022 - no
SME self-assessment	unknown
SME validation	30/05/2008 - no

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	UCL Institute of Education	☐ not applicable
	☐ Same as proposing organisation's address	
Street	20 Bedford Way	
Town	London	
Postcode	WC1H 0AL	
Country	United Kingdom	

Links with other participants

Type of link	Participant
--------------	-------------

Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☐ Woman	☒ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e@ucl.ac.uk				
Position in org.	5.1.2e				
Department	UCL Institute of Education			☐ Same as organisation name	
	☐ Same as proposing organisation's address				
Street	20 Bedford Way				
Town	London	Post code	WC1H 0AL		
Country	United Kingdom				
Website	https://iris.ucl.ac.uk/iris/browse/profile?upi=JDCAR32				
Phone	+44 5.1.2e	Phone 2	+XXX XXXXXXXXXX		

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e@ucl.ac.uk	5.1.2e
		5.1.2e@ucl.ac.uk	

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e					5.1.2e			0000-0001-7550-1676	Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☒
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	Fang, C., Baz, S., Carpentieri, J. D., & Sheard, L. (2023). <i>Understanding and supporting the long-term effects of COVID-19: A report from the Qualitative Long COVID Research Network in the United Kingdom (Convalescence long COVID Study briefing report)</i> . UCL.
Publication	Baz, SA, Fang, C, Carpentieri, JD, Sheard, L. 'I don't know what to do or where to go'. Experiences of accessing healthcare support from the perspectives of people living with Long Covid and healthcare professionals: a qualitative study in Bradford, UK. <i>Health Expectations</i> . 2023; 26: 542- 554.
Publication	Carpentieri, J., Wielgoszewska, B., Church, D., Goodman, A. (2020). <i>In their own words: five generations of Britons describe their experiences of the coronavirus pandemic. Initial findings from the COVID-19 Survey in Five National Longitudinal Studies</i> . London: Centre for Longitudinal Studies. https://cls.ucl.ac.uk/wp-content/uploads/2020/11/In-their-own-words-Initial-findings-from-COVID-19-survey.pdf
Publication	Carpentieri, J.D., Amarin, J., & Mallows, D. (2020). <i>Methodological credibility, theoretical relevance and policy impact in the evaluation of adult basic skills programs: the case of the New Opportunities Initiative in Portugal</i> . <i>Adult Literacy Education: The International Journal of Literacy, Language, and Numeracy</i> .
Publication	Carpentieri, J., Cara, O., Popov, J. and Litster, J. (2018). <i>Guidance and Orientation for Adult Learners (GOAL): Six-country evaluation report</i> . Brussels: European Commission.

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
Convalescence	Coronavirus post-acute long-term effects: constructing an evidence base: Longitudinal Qualitative Study. The longitudinal qualitative study aims to understand individuals' experiences of and perspectives on long COVID. In-depth interviews are being undertaken with 40 geographically dispersed participants across the five cohort studies hosted at UCL (spanning ages 20 to 75 years across the whole of the UK), and 40 participants from Born in Bradford.
UCL Covid-19 survey	The UCL Centre for Longitudinal Studies conducted three online surveys of participants in five nationally representative cohort studies. The Covid-19 study was designed to help researchers understand the economic, health and social consequences of the coronavirus outbreak, to give a unique insight into how people's experiences during the pandemic vary depending on their earlier lives, and to be able to track the impact into the future.
Guidance and Orientation for Adult Learners (GOAL)	The "Guidance and Orientation for Adult Learners" Project (GOAL) was a collaboration between six partner countries: Belgium (Flanders), the Czech Republic, Iceland, Lithuania, the Netherlands, and Slovenia. The hypothesis underpinning GOAL was that an independent one-stop guidance service putting the specific needs of low-educated adults at its centre could help to increase the participation of this target group in adult education.
Scotland in miniature	This mixed methods research study investigated older people's experiences of physical decline related to chronic and acute conditions. The research focused in particular on using successful adaptations to maintain psychological well-being despite physical decline.
Literacy cubed	This collaboration between three partner countries – Romania, Slovakia and Montenegro – explored the processes and impacts of a family literacy intervention targeted at highly disadvantaged Roma families. Carpentieri was the PI on the three-country mixed methods evaluation of this project.

Administrative forms

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
<i>Centre for Longitudinal Studies</i>	<i>The Centre for Longitudinal Studies at UCL is home to four national longitudinal cohort studies, which follow the lives of tens of thousands of people.</i>

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
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- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
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 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
895748732	FONDAZIONE HUMAN TECHNOPOLE

Short name: FHT

Address

Street	VIALE LEVI MONTALCINI RITA 1
Town	MILANO
Postcode	20157
Country	Italy
Webpage	https://www.humantechnopole.it

Specific Legal Statutes

Legal person	yes
Public body	no
Non-profit	yes
International organisation	no
Secondary or Higher education establishment	no
Research organisation	yes

SME Data

Based on the below details from the Participant Registry the organisation is unknown (small- and medium-sized enterprise) for the call.

SME self-declared status	unknown
SME self-assessment	unknown
SME validation	unknown

Administrative forms

Departments carrying out the proposed work

Department 1

Department name	Health Data Science Centre	☐ not applicable
	☒ Same as proposing organisation's address	
Street	VIALE LEVI MONTALCINI RITA 1	
Town	MILANO	
Postcode	20157	
Country	Italy	

Links with other participants

Type of link	Participant
--------------	-------------

Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☐ Woman	☒ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e @fht.org				
Position in org.	5.1.2e				
Department	Health Data Science Centre			☐ Same as organisation name	
	☒ Same as proposing organisation's address				
Street	VIALE LEVI MONTALCINI RITA 1				
Town	MILANO	Post code	20157		
Country	Italy				
Website	https://humantechnopole.it/en/research-centres/health-data-scienc				
Phone	+39	5.1.2e	Phone 2	+39	5.1.2e

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e @fht.org	+XXX XXXXXXXXX
		5.1.2e @fht.org	+XXX XXXXXXXXX

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e	5.1.2e		5.1.2e		5.1.2e@fht.org	5.1.2e			Orcid ID
	5.1.2e				5.1.2e@fht.org				Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	WHO CVD Risk Chart Working Group. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. <i>Lancet Glob Health</i> . 2019 Oct;7(10):e1332-e1345. https://doi.org/10.1016/S2214-109X(19)30318-3
Publication	SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. <i>Eur Heart J</i> . 2021 Jul 1;42(25):2439-2454 https://doi.org/10.1093/eurheartj/ehab309
Publication	Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling analyses. <i>PLoS Med</i> . 2021 Jan 14;18(1):e1003498 https://doi.org/10.1371/journal.pmed.1003498
Publication	Mild-to-Moderate Kidney Dysfunction and Cardiovascular Disease: Observational and Mendelian Randomization Analyses. <i>Circulation</i> . 2022 Nov 15;146(20):1507-1517. https://doi.org/10.1161/CIRCULATIONAHA.122.060700
Publication	Including measures of chronic kidney disease to improve cardiovascular risk prediction by SCORE2 and SCORE2-OP <i>Eur J Prev Cardiol</i> . 2023 Jan 11;30(1):8-16. https://doi.org/10.1093/eurjpc/zwac176

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
European Society of Cardiology (ESC) - SCORE 2	Development, validation, and illustration of an updated prediction model (SCORE2) to estimate 10-year fatal and non-fatal cardiovascular disease (CVD) risk in individuals in Europe without previous CVD or diabetes aged 40–69 years.
WHO "Risk Chart Working Group	Development, calibration and validation of new risk prediction models for cardiovascular disease risk in 21 global regions.
European Society of Cardiology	Developing European guidelines for the prevention of cardiovascular diseases.
RADprecise	Personalized radiotherapy (ERA-permed research projects on personalized medicine - Smart combination of pre-clinical and clinical research with data and ICT solutions) Incorporating cellular response to irradiation and genomic predisposition in personalized treatment planning to minimize late radiation toxicity in prostate cancer patients.
ONCO Data Platform	Evaluation of effects (outcomes and costs) of early innovative oncological treatments using Real World Data: an application to lung and ovarian cancer.

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
FHT Data Centre	The Data Centre offers computing resources and technical support for research activities at FHT. It includes HPC clusters, VDI clusters (24TB of RAM, 1536 cores, 19TB of NVMe read-cache, 140TB of vSAN all-flash, 72 GPUs with a total of 3.5TB of GPU memory), high-performance storage (9 PB).

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
968574392	NUROMEDIA GMBH

Short name: NURO

Address

Street	SCHAAFENSTRASSE 25
Town	KOLN
Postcode	50676
Country	Germany
Webpage	www.nuromedia.com

Specific Legal Statutes

Legal person	yes
Public body	no
Non-profit	no
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	31/12/2018 - yes
SME self-assessment	31/12/2018 - yes
SME validation	08/03/2006 - yes

Administrative forms

Departments carrying out the proposed work

No department involved

Department name	<i>Name of the department/institute carrying out the work.</i>	☒ not applicable
	☐ Same as proposing organisation's address	
Street	<i>Please enter street name and number.</i>	
Town	<i>Please enter the name of the town.</i>	
Postcode	<i>Area code.</i>	
Country	<i>Please select a country</i>	

Links with other participants

Type of link	Participant
--------------	-------------

Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☐ Woman	☒ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e@dec.nuromedia.com				
Position in org.	5.1.2e				
Department	NUROMEDIA GMBH		☒ Same as organisation name		
	☒ Same as proposing organisation's address				
Street	SCHAAFENSTRASSE 25				
Town	KOLN	Post code	50676		
Country	Germany				
Website	https://www.nuromedia.com				
Phone	+49	5.1.2e	Phone 2	+XXX XXXXXXXXXX	

Other contact persons

First Name	Last Name	E-mail	Phone
5.1.2e		5.1.2e@nuromedia.com	+XXX XXXXXXXXXX
		5.1.2e@nuromedia.com	+XXX XXXXXXXXXX
		5.1.2e@nuromedia.com	+XXX XXXXXXXXXX

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e5.1.2e									

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☐
Technology developer	☒
Testing/validation of approaches and ideas	☒
Prototyping and demonstration	☒
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	<i>DIGITAL HEALTH NEWS is the first European digital health news portal and one of the most visited sites on the Internet for digital health decision-makers, professionals and stakeholders looking for the latest digital health breaking news.</i>
Service	<i>Digital Health Technology We learn from our project partners / customers and they learn from us, we build together, we innovate together, we work together towards creating impact on healthcare delivery</i>
Software	<i>At DigitalTwin Technology, we need to continuously strengthen our commitment to make ourselves more inclusive and to contribute to make our world more just. Where every great idea can be heard and where everybody belongs.</i> <i>Website: https://www.digitaltwin.technology</i>

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
LongCovid	<i>LongCOVID project (HORIZON) aims to develop tools and knowledge to support physicians in accurately managing Long COVID syndrome (LCS) Nuromedia is developing a LongCOVID data portal to collect the data for LCS research, develop novel methods for harmonizing and accessing integrated data for distributed data analyses, develop Static and Interactive graphic user interface infographics for patients, clinicians, and researchers, and develop an AI-informed LC prediction support tool.</i>
ParkinsonAKTIV	<i>The Parkinson AKTIV project brings together various professional stakeholders in the care of the Parkinson disease and builds standardised communication tools for improving the therapy outcomes.</i>
AICCELERATE	<i>AICCELERATE (H2020) aims at developing AI-based solutions that optimise hospital processes and improve the quality of patient care. Consequently, a tool will be developed - Smart Hospital Care Pathway Engine. This cloud-based tool collects information from different sources and generates outputs using AI, Machine Learning, 3D Modelling, etc. The main goal is to improve decision-making regarding hospital management and patient care.</i>
ReliVR	<i>The ReliVR research project is developing digital therapy modules for patients with severe depression in order to be able to better meet their psychotherapeutic needs. For this purpose, various VR-based modules (ReliVR-VR), as well as a desktop version (ReliVR-Online), are implemented, taking into account the needs of patients and therapists.</i>
DIGI-B-CUBE	<i>The DIGI-B-CUBE project (H2020) aims to unlock the cross-sectoral collaborative potential of SMEs by combining Artificial Intelligence (AI), Cognitive Computing Digital Technologies (CCDT) with the Bioimaging-Biosensing-Biobanking (B-CUBE) industries to deliver market sensitive disruptive technologies and generating innovative solutions that enhance patient-centred diagnostic work-flows, delivered through the improved algorithms for Medical Diagnostics' efficiency and accuracy.</i>

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
LongCOVID DataPortal	<i>Data Portal with related data visualisation tools developed in the frames of the LongCOVID Project</i> <i>Website: https://dataportal.longcovidproject.eu</i>

Administrative forms

<i>Nurogames</i>	<i>Nurogames develops gaming and serious games solutions for consumers and for the industry. Nurogames covers the entire value chain of game development - from the initial idea to the final product - for all major mobile, web, PC, console, VR, AR and XR platforms with a track record of more than 14 yea</i>
<i>ReliVR Platform</i>	<i>ReliVR platform (web-based end-user interfaces enhanced with virtual reality (VR) scenarios) developed in the frames of the ReliVR project</i>

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☒ Yes ☐ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
928335591	CHINO SRL

Short name: CHINO

Address

Street	VIA SEGANTINI 28
Town	ROVERETO
Postcode	38068
Country	Italy
Webpage	https://www.chino.io

Specific Legal Statutes

Legal person	yes
Public body	no
Non-profit	no
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	31/12/2016 - yes
SME self-assessment	31/12/2016 - yes
SME validation	unknown

Administrative forms

Departments carrying out the proposed work

No department involved

Department name	<i>Name of the department/institute carrying out the work.</i>	☒ not applicable
	☐ Same as proposing organisation's address	
Street	<i>Please enter street name and number.</i>	
Town	<i>Please enter the name of the town.</i>	
Postcode	<i>Area code.</i>	
Country	<i>Please select a country</i>	

Links with other participants

Type of link	Participant
--------------	-------------

Administrative forms

Main contact person

This will be the person the EU services will contact concerning this proposal (e.g. for additional information, invitation to hearings, sending of evaluation results, convocation to start grant preparation). The data in blue is read-only. Details (name, first name and e-mail) of Main Contact persons should be edited in the step "Participants" of the submission wizard.

Title	5.1.2e	Gender	☐ Woman	☒ Man	☐ Non Binary
First name*	5.1.2e	Last name*	5.1.2e		
E-Mail*	5.1.2e @chino.io				
Position in org.	5.1.2e				
Department	CHINO SRL			☒	Same as organisation name
	☒ Same as proposing organisation's address				
Street	VIA SEGANTINI 28				
Town	ROVERETO	Post code	38068		
Country	Italy				
Website	Please enter website				
Phone	+XXX XXXXXXXXX	Phone 2	+XXX XXXXXXXXX		

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e									Orcid ID
									Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☒
Co-definition of research and market needs	☒
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☒
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☐
Contributions from the social sciences or/and the humanities	☐
Other	☐
If yes, please specify: (Maximum number of characters allowed: 50)	

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Service	<i>Chino.io Toolkit is a modular development platform designed to solve the complex problem of compliant processing and sharing of sensitive health data. This includes secure storage, data encryption, pseudonymisation, consent management and audit logs. The Chino.io Toolkit has been developed with the support of SME Instrument Phase 2 grant (now called EIC Accelerator)</i>

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
<i>AICCELERATE Project</i>	<i>AICCELERATE is an H2020 project that runs until 2024. The project is developing an AI-powered smart hospital care pathway engine. The aim is to use AI to deliver better patient care and clinical outcomes/ Chino leads all the ethics and data protection aspects of this project. This has given us significant experience in AI ethics within the healthcare space. We will be able to apply this knowledge to the work being proposed in the project.</i>
<i>LongCovid Project</i>	<i>LongCovid is Horizon Europe project started in 2022. LongCovid aims at developing tools and knowledge to support physicians in accurately managing Long COVID syndrome (LCS) which has a significant impact on sufferers as well as their surroundings. Chino is part of the consortia dealing with all ethics, privacy, data protection, data security and other compliance related aspects. We will be able to apply this knowledge to the work being proposed in this project.</i>
<i>Chino.io Toolkit</i>	<i>Chino.io Toolkit was developed using funding from the EIC SME Instrument Phase 2. It provides a platform for the secure processing of health data, including modules for storage, pseudonymisation, audit logging, consent management, and user management. While developing the platform, we gained significant experience in the cybersecurity and data protection challenges inherent in processing and sharing sensitive health data. This experience will help steer the data security aspects of the project.</i>
<i>RES-Q Plus Project</i>	<i>RES-Q Plus is Horizon Europe project that is built on the success of RES-Q (Registry of Stroke Care Quality) - currently, used by many EU countries and 74 worldwide - to improve stroke care quality by collecting and analyzing hospital discharge reports. RES-Q Plus will revolutionize these improvements by capturing the whole patient pathway. Chino is part of the consortia dealing with all ethics, privacy, data protection, data security and other compliance related aspects..</i>
<i>C3ISP Project</i>	<i>C3ISP was an H2020 project where Chino Srl collaborated with large companies and research centres such as BT, HPE, SAP and CNR building a collaborative and confidential information sharing, analysis and protection framework as a service for cybersecurity companies.</i>

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
<i>Chino.io Toolkit</i>	<i>The Chino.io toolkit provides a platform for the secure processing of health data, including modules for storage, pseudonymisation, audit logging, consent management, and user management.</i>

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☐ Yes ☒ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

PIC	Legal name
998454369	ACCELOPMENT SCHWEIZ AG

Short name: accelCH

Address

Street	SEEFELDSTRASSE 198
Town	ZURICH
Postcode	8008
Country	Switzerland
Webpage	www.accelopment.com

Specific Legal Statutes

Legal person	yes
Public body	no
Non-profit	no
International organisation	no
Secondary or Higher education establishment	no
Research organisation	no

SME Data

Based on the below details from the Participant Registry the organisation is an SME (small- and medium-sized enterprise) for the call.

SME self-declared status	31/12/2019 - yes
SME self-assessment	31/12/2019 - yes
SME validation	24/07/2008 - yes

Administrative forms

Departments carrying out the proposed work

No department involved

Department name	<i>Name of the department/institute carrying out the work.</i>	☒ not applicable
	☐ Same as proposing organisation's address	
Street	<i>Please enter street name and number.</i>	
Town	<i>Please enter the name of the town.</i>	
Postcode	<i>Area code.</i>	
Country	<i>Please select a country</i>	

Links with other participants

Type of link	Participant
--------------	-------------

Administrative forms

Researchers involved in the proposal

Title	First Name	Last Name	Gender	Nationality	E-mail	Career Stage	Role of researcher (in the project)	Reference Identifier	Type of identifier
5.1.2e					5.1.2e				
									Orcid ID

Administrative forms

Role of participating organisation in the project

Project management	☒
Communication, dissemination and engagement	☒
Provision of research and technology infrastructure	☐
Co-definition of research and market needs	☐
Civil society representative	☐
Policy maker or regulator, incl. standardisation body	☐
Research performer	☐
Technology developer	☐
Testing/validation of approaches and ideas	☐
Prototyping and demonstration	☐
IPR management incl. technology transfer	☐
Public procurer of results	☐
Private buyer of results	☐
Finance provider (public or private)	☐
Education and training	☒
Contributions from the social sciences or/and the humanities	☐
Other If yes, please specify: (Maximum number of characters allowed: 50)	☐

Administrative forms

List of up to 5 publications, widely-used datasets, software, goods, services, or any other achievements relevant to the call content.

Type of achievement	Short description (Max 500 characters)
Publication	<i>Cavallaro, M. & Lepori, B. (2021). Institutional barriers to participation in EU framework programs: contrasting the Swiss and UK cases. Scientometrics, 126, 1311-1328. doi.org/10.1007/s11192-020-03810-0 - This study compares the effect of EU funding restrictions following Switzerland's 2014 reclassification as a 'third country' and the uncertainties resulting from the 2016 Brexit vote in the UK.</i>
Publication	<i>Neville, K., et al. (2013), Supporting Cross Border Emergency Management Decision-Making. ECIS 2013 Research in Progress, 33. aisel.aisnet.org/ecis2013_rip/33 - Research about decision support tools in managing emergencies. The findings of the study provided a rich foundation for research on the design of incident/emergency management decision support tools. Mueller, J. is co-author.</i>
Publication	<i>Kaar, J. (2011), The Impact of Participation in Publicly Funded R&D Projects on Firm Competitiveness. Olten, Diplomica. One of the findings is that once companies are familiar with the processes and have acquired experience in funded projects, they tend to work together overtime with the same universities and other partners in several projects.</i>

List of up to 5 most relevant previous projects or activities, connected to the subject of this proposal.

Name of Project or Activity	Short description (Max 500 characters)
MyPath	<i>www.mypath-cancercare.eu - GA no. 101057514, HORIZON-HLTH, 2022-2027 - This project will develop technology-enhanced and evidence-based patient-centred care pathways to be merged with tumour-centred treatments across supportive, palliative, survivorship, and end-of-life care. Successfully achieving the milestones will reduce the physical, emotional, and ultimately economic burden linked to cancer. accelCH supports the project management and communication, dissemination, and exploitation.</i>
COVend	<i>www.covend-project.eu - GA no. 101045956, HORIZON-HLTH, 2021-2025 - By advancing a promising therapeutic candidate, FX06, through a multi-centre phase II/III clinical trial, COVend aims to deliver a new effective therapy against SARS-CoV-2 to prevent disease progression from mild or moderate stages to a severe stage. accelCH supports the project management and communication, dissemination, and exploitation.</i>
GENEGUT	<i>GA no. 101057491, HORIZON-HLTH, 2022-2026 - GENEGUT will transform treatment of ileal Crohn's disease by developing a first-in-class oral RNA-based therapy, tackling inflammation locally in the intestinal tissue, while avoiding systemic side effects. accelCH supports the project management and communication, dissemination, and exploitation.</i>
CORENET	<i>GA no. 101046294, HORIZON-EIC-PATHFINDEROPEN, 2022-2026 - Producing microfluidic chip devices that perform high-level computing with molecules, synthesising and analysing a pattern of output molecules in situ. This molecule-based computing power enables sustainable AI and speaks the language of living systems. Application areas include implantable devices and brain-machine interfaces, among others. accelCH supports the project management and communication, dissemination, and exploitation.</i>
AI-MIND	<i>www.ai-mind.eu - GA no. 964220, H2020-SC1, 2021-2026 - Developing an AI-based solution that is able to provide a fast and accurate (>95%) prediction for the individual dementia risk. The tool can be easily integrated into existing clinical practices. By offering a globally accessible, cheap and precise tool for dementia prediction, AI-Mind will improve the health care system and boost innovation. accelCH supports the project management and communication, dissemination, and exploitation.</i>

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work.

Name of infrastructure of equipment	Short description (Max 300 characters)
-------------------------------------	--

Administrative forms

<i>accelCLOUD</i>	<i>A secure and central online storage for project files will be provided by accelopment. This Document Management System will allow for notifications on changed files, version control and will be regularly backed up. All files are hosted within the EU.</i>
<i>accelCOCKPIT®</i>	<i>Extensive project management tool for administration, monitoring finances and reporting, tracking of deliverables, finances and tasks, risk management, and more.</i>
<i>Communication tools</i>	<i>An extensive set of tools for communication, dissemination and exploitation, including stakeholder mapping, SWOT and PESTEL and IPR monitoring will be used to facilitate and support the outreach activities of the project and its consortium members.</i>

Administrative forms

Gender Equality Plan

Does the organization have a Gender Equality Plan (GEP) covering the elements listed below?

☐ Yes ☒ No

Minimum process-related requirements (building blocks) for a GEP

- **Publication:** formal document published on the institution's website and signed by the top management
- **Dedicated resources:** commitment of human resources and gender expertise to implement it.
- **Data collection and monitoring:** sex/gender disaggregated data on personnel (and students for establishments concerned) and annual reporting based on indicators.
- **Training:** Awareness raising/trainings on gender equality and unconscious gender biases for staff and decision-makers.
- **Content-wise, recommended areas to be covered and addressed via concrete measures and targets are:**
 - o work-life balance and organisational culture;
 - o gender balance in leadership and decision-making;
 - o gender equality in recruitment and career progression;
 - o integration of the gender dimension into research and teaching content;
 - o measures against gender-based violence including sexual harassment.

Administrative forms

Proposal ID 101137181
Acronym DEFINE

3 - Budget

No.	Name of beneficiary	Country	Role	Personnel costs/€	Subcontracting costs/€	Purchase costs - Travel and subsistence /€	Purchase costs - Equipment/€	Purchase costs - Other goods, works and services/€	Internally invoiced goods and services/€ (Unit costs - usual accounting practices)	Indirect costs/€	Total eligible costs	Funding rate	Maximum EU contribution to eligible costs	Requested EU contribution to eligible costs/€	Max grant amount	Income generated by the action	Financial contributions	Own resources	Total estimated income
1	Akershus Universitetssykehus HF	NO	Coordinator	S 1.1 c								100	S 1.1 c			0.00	0.00	0.00	1 970 625.00
2	Hus-ythyma	FI	Partner									100				0.00	0.00	0.00	675 000.00
3	Academisch Medisch Centrum Bil	NL	Partner									100				0.00	0.00	0.00	1 237 303.75
4	Universitetet i Oslo	NO	Partner									100				0.00	0.00	0.00	928 875.00
5	Northwestern University Corporation	US	Partner									100				0.00	0.00	0.00	385 881.25
6	Autorance Publique Hôpital de Rijnswinkel	FR	Partner									100				0.00	0.00	0.00	200 750.00
7	Voor Volksgezondh	NL	Partner									100				0.00	0.00	0.00	268 625.00
8	University Of New South Wales	AU	Associated									100				0.00	310 000.00	0.00	310 000.00
9	University College London	UK	Partner									100				0.00	0.00	0.00	185 365.00
10	Fondazione Human Technology	IT	Partner									100				0.00	0.00	0.00	327 500.00

Administrative forms

Proposal ID 101137181
Acronym DEFINE

11	Nurcomedia GmbH	DE	Partner	5.1.1c							100	5.1.1c				0.00	0.00	0.00	387 600.00
12	Chino Srl	IT	Partner								100					0.00	0.00	0.00	327 500.00
13	Accellapment Schweiz Ag	CH	Associated								100					0.00	433 500.00	0.00	433 500.00
TOTAL				4 573 563	367 000	205 707	9 000	394 150	50 000	1 295 605.00	6 895 025.00		6 895 025.00	6 895 025.00	6 895 025.00	0.00	743 500.00	0.00	7 638 525.00

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4 - Ethics & security

Ethics Issues Table

1. Human Embryonic Stem Cells and Human Embryos		Page
Does this activity involve Human Embryonic Stem Cells (hESCs)?	☐ Yes ☒ No	
Does this activity involve the use of human embryos?	☐ Yes ☒ No	
2. Humans		Page
Does this activity involve human participants?	☒ Yes ☐ No	14
Are they volunteers for non medical studies (e.g. social or human sciences research)?	☐ Yes ☒ No	
Are they healthy volunteers for medical studies?	☒ Yes ☐ No	14
Are they patients for medical studies?	☒ Yes ☐ No	14
Are they potentially vulnerable individuals or groups?	☒ Yes ☐ No	14
Are they children/minors?	☒ Yes ☐ No	14
Are they other persons unable to give informed consent?	☐ Yes ☒ No	
Does this activity involve interventions (physical also including imaging technology, behavioural treatments, etc.) on the study participants?	☒ Yes ☐ No	14
Does it involve invasive techniques?	☐ Yes ☒ No	
Does it involve collection of biological samples?	☒ Yes ☐ No	14
Does this activity involve conducting a clinical study as defined by the Clinical Trial Regulation (EU 536/2014) ? (using pharmaceuticals, biologicals, radiopharmaceuticals, or advanced therapy medicinal products)	☐ Yes ☒ No	
3. Human Cells / Tissues (not covered by section 1)		Page
Does this activity involve the use of human cells or tissues?	☒ Yes ☐ No	14
Are they human embryonic or foetal cells or tissues?	☐ Yes ☒ No	
Are they available commercially?	☐ Yes ☒ No	
Are they obtained within this project?	☒ Yes ☐ No	14
Are they obtained from another project, laboratory or institution?	☒ Yes ☐ No	14
Are they obtained from biobank?	☒ Yes ☐ No	14
4. Personal Data		Page
Does this activity involve processing of personal data?	☒ Yes ☐ No	18
Does it involve the processing of special categories of personal data (e.g.: genetic, biometric and health data, sexual lifestyle, ethnicity, political opinion, religious or philosophical beliefs)?	☒ Yes ☐ No	12
Does it involve processing of genetic, biometric or health data?	☒ Yes ☐ No	12
Does it involve profiling, systematic monitoring of individuals, or processing of large scale of special categories of data or intrusive methods of data processing (such as, surveillance, geolocation tracking etc.)?	☒ Yes ☐ No	12

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Does this activity involve further processing of previously collected personal data (including use of preexisting data sets or sources, merging existing data sets)?	☒ Yes ☐ No	11
Is it planned to export personal data from the EU to non-EU countries? Specify the type of personal data and countries involved	☒ Yes ☐ No	11
Health data, demographic data and questionnaire responses within already conducted post-infective cohort studies; to be exported from the Netherlands and France (both EU) to Norway (non-EU) as part of the COFFI Joint Data Centre.		
Is it planned to import personal data from non-EU countries into the EU or from a non-EU country to another non-EU country? Specify the type of personal data and countries involved	☒ Yes ☐ No	11
1: Health data, demographic data and questionnaire responses within already conducted post-infective cohort studies; to be imported from Australia, the US and the UK (all non-EU) to Norway (non-EU) as part of the COFFI Joint Data Centre. 2: Health data, demographic data and questionnaire responses related to a randomised controlled trial of a preventative intervention; to be imported from Australia and Norway (non-EU) to the Netherlands (EU).		
Does this activity involve the processing of personal data related to criminal convictions or offences?	☐ Yes ☒ No	
5. Animals		Page
Does this activity involve animals?	☐ Yes ☒ No	
6. Non-EU Countries		Page
Will some of the activities be carried out in non-EU countries?	☒ Yes ☐ No	45
Norway, Australia, the United States, the United Kingdom, Switzerland		
In case non-EU countries are involved, do the activities undertaken in these countries raise potential ethics issues?	☒ Yes ☐ No	45
Norway		
It is planned to use local resources (e.g. animal and/or human tissue samples, genetic material, live animals, human remains, materials of historical value, endangered fauna or flora samples, etc.)?	☒ Yes ☐ No	12
Is it planned to import any material (other than data) from non-EU countries into the EU or from a non-EU country to another non-EU country? For data imports, see section 4.	☐ Yes ☒ No	
Is it planned to export any material (other than data) from the EU to non-EU countries? For data exports, see section 4.	☐ Yes ☒ No	
Does this activity involve low and/or lower middle income countries , (if yes, detail the benefit-sharing actions planned in the self-assessment)	☐ Yes ☒ No	

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Could the situation in the country put the individuals taking part in the activity at risk?	☐ Yes ☒ No	
7. Environment, Health and Safety		Page
Does this activity involve the use of substances or processes that may cause harm to the environment, to animals or plants.(during the implementation of the activity or further to the use of the results, as a possible impact) ?	☐ Yes ☒ No	
Does this activity deal with endangered fauna and/or flora / protected areas?	☐ Yes ☒ No	
Does this activity involve the use of substances or processes that may cause harm to humans, including those performing the activity.(during the implementation of the activity or further to the use of the results, as a possible impact) ?	☒ Yes ☐ No	12
8. Artificial Intelligence		Page
Does this activity involve the development, deployment and/or use of Artificial Intelligence? (if yes, detail in the self-assessment whether that could raise ethical concerns related to human rights and values and detail how this will be addressed).	☒ Yes ☐ No	12,17
9. Other Ethics Issues		Page
Are there any other ethics issues that should be taken into consideration?	☐ Yes ☒ No	
I confirm that I have taken into account all ethics issues above and that, if any ethics issues apply, I will complete the ethics self-assessment as described in the guidelines How to Complete your Ethics Self-Assessment		☒

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Ethics Self-Assessment

Ethical dimension of the objectives, methodology and likely impact

DEFINE will consider ethics and trustworthiness across the project and across all WPs. Ethics and trustworthiness are vital aspects of any AI model, especially when used for healthcare. Recently, the EU has stated that they want to become a world leader in this field. To this end, they have published the Ethics Guidelines for Trustworthy AI. DEFINE will incorporate EU Ethics Guidelines when creating the AI model. According to the guidelines, an AI model must be lawful, ethical, and robust. This means the model must adhere to all relevant legislation (especially relating to data protection and privacy). It must be ethical, respecting human autonomy, preventing harm, giving fair results and being explainable. It is also imperative that the model is robust, secure, free from bias and capable of proving the repeatability of its results. The guidelines also provide a draft checklist that can be used to assess the compliance of any model. DEFINE will follow these guidelines. The project consortium will adopt the EC's Ethics Guidelines for Trustworthy AI [EC2019]. A detailed checklist based on these 7 principles will be delivered. The consortium will appoint a patient advisory board and coordinate their work by passing on feedback to relevant WPs. During the project, it will be ensured that all the AI models developed are ethical, robust, trustworthy and explainable. A framework for data security and privacy will be constructed through interactions with hospital security specialists and local ethics committees.

During the project, all personal data will be handled according to GDPR and national legislation. Each hospital partner will secure necessary approvals from their local ethical committees and hospital administration. Patient recruitment will be based on informed consent, which is freely given, informed and specific, and patients will be able to revoke it and exit the study at any point. GDPR compliance, data security, access and privacy management are considered fundamental aspects of DEFINE.

The overall approach will implement privacy-by-design by allowing to compute the training of algorithms at the secure PIFS platform developed by DEFINE consortium, without sharing sensitive patient data outside of it, thus minimising any risk of privacy breach. The PIFS platform will adhere to the principles of the GDPR and FAIR.

Data security and data protection require good audit trails, which will be ensured by DEFINE partner Chino. This includes tracking who accessed what data, when and why. Full, immutable, legally valid audit trails will help secure the data and form the basis for interactions with ethics committees and security specialists in hospitals. Although the data will not be shared from the source environment, as enabled by federated learning, data will still be pseudonymised (or anonymised where possible) and all network communications will be encrypted through appropriate SSL/TLS protocols. Combined with the encryption, this offers the strongest possible level of protection for special data such as health data. The core data storage module integrates both these techniques by default (achieving the GDPR requirement of "data protection by design and default"). A data management plan will be developed in the first phase of the DEFINE project and cover all steps of the active project time as well as the post-project data management plan. The application of the methodologies explained above will guarantee secure management of the data along the project, in respect of the primary governing ethical principle of "primum non nocere" – first, do no harm.

Remaining characters

1380

Compliance with ethical principles and relevant legislations

The clinical study involves sensitive patient data. Security policy will follow the Clinical Trials Regulation 536/2014/EU and the new General Data Protection Regulation 2016/679/EU (GDPR). Details for procedures on data collection, storage, protection measures as well as transfer and destruction will be documented according to national and EU legislation concerning data privacy and use. Data safety planning, details on data safety procedures and compliance will be followed. The screening information, Case Report Forms (CRFs) and other sensitive data will be stored according to data privacy laws. All data is handled according to the security policy. Overall, we will comply with obligations and requirements in accordance with EU regulations and Directive (1982/2006/2014/2016 EC), General Data Protection Regulation 2016/679 (GDPR) and the ePrivacy Directive (2002/58/EC), and respective current national legislation of every participating country. Ethical principles adhered to in this proposal are for example: the Declaration of Helsinki published by the World Medical Association (2008).

All principles of the Helsinki Declaration and the requirements of GDPR are fulfilled. All efforts are made to bother the patients as little as possible with the examinations. Some of the patients include vulnerable patient populations. Their special needs will be attended to the best possible.

Remaining characters

3602

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Security issues table

1. EU Classified Information (EUCI) ²		Page
Does this activity involve information and/or materials requiring protection against unauthorised disclosure (EUCI)?	☐ Yes ☒ No	
Does this activity involve non-EU countries which need to have access to EUCI?	☐ Yes ☒ No	
2. Misuse		Page
Does this activity have the potential for misuse of results?	☐ Yes ☒ No	
3. Other Security Issues		Page
Does this activity involve information and/or materials subject to national security restrictions? If yes, please specify: (Maximum number of characters allowed: 1000)	☐ Yes ☒ No	
Are there any other security issues that should be taken into consideration? If yes, please specify: (Maximum number of characters allowed: 1000)	☐ Yes ☒ No	

Security self-assessment

Not applicable.

Remaining characters

4985

²According to the Commission Decision (EU, Euratom) 2015/444 of 13 March 2015 on the security rules for protecting EU classified information, "European Union classified information (EUCI) means any information or material designated by an EU security classification, the unauthorised disclosure of which could cause varying degrees of prejudice to the interests of the European Union or of one or more of the Member States".

³Classified background information is information that is already classified by a country and/or international organisation and/or the EU and is going to be used by the project. In this case, the project must have in advance the authorisation from the originator of the classified information, which is the entity (EU institution, EU Member State, third state or international organisation) under whose authority the classified information has been generated.

⁴EU classified foreground information is information (documents/deliverables/materials) planned to be generated by the project and that needs to be protected from unauthorised disclosure. The originator of the EUCI generated by the project is the European Commission.

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5 - Other questions

Essential information to be provided for proposals including clinical Trials / studies / investigations

Clinical study means, for the purpose of this document, any systematic prospective or retrospective collection and analysis of health data obtained from individual patients or healthy persons in order to address scientific questions related to the understanding, prevention, diagnosis, monitoring or treatment of a disease, mental illness, or physical condition. It includes but it is not limited to clinical studies as defined by [Regulation 536/2014](#) (on medicinal products), clinical investigation and clinical evaluation as defined by [Regulation 2017/745](#) (on medical devices), performance study and performance evaluation as defined by [Regulation 2017/746](#) (on in vitro diagnostic medical devices).

Are clinical studies / trials / investigations included in the work plan of this project?

☒ Yes

☐ No

Please upload the dedicated annex 'Essential information for clinical studies / trials / investigations' (a Word template is provided under 'download templates' in the up-load section for Part B and Annexes).

This document should include the relevant information of each clinical study / trial / investigation included in the work plan of this project.

Please give a short title, an acronym or a unique identifier to each clinical study / trial / investigation,
to be used as a reference/ identifier in the other parts of the proposal.

FINE



**Decreasing Fatigue After Infections –
Complex mechanisms, innovative diagnostic tools and targeted preventive measures
of fatigue following COVID-19 and other infections**

Call: HORIZON-HLTH-2023-DISEASE-03-07 —
Relationship between infections and non-communicable diseases
#@APP-FORM-HERIAIA@#

List of participants

#	Organisation	Short name	Ctry	Core expertise
P01 HOS	Akershus University Hospital Dept. of Pediatrics and Adolescent Medicine 5.1.2e Health Services Research Unit 5.1.2e 5.1.2e	AHUS AHUS-HS	 NO	5.1.2e
P02 HOS	Helsinki University Hospital Clinic for the Long-term effects of COVID-19 5.1.2e	HUS	 FI	
P03 HOS	Amsterdam University Medical Centers Department of Medical Psychology 5.1.2e	AUMC	 NL	
P04 UNI	University of Oslo Department of Psychology 5.1.2e	UiO	 NO	
P05 UNI	Northwestern University Feinberg School of Medicine 5.1.2e	NUFSOM	 US	
P06 HOS	Assistance Publique – Hôpitaux de Paris 5.1.2e	APHP	 FR	
P07 PUB	National Institute for Public Health and the Environment Centre for Infectious Disease Control 5.1.2e 5.1.2e	RIVM	 NL	
P08 UNI	University of New South Wales The Kirby Institute 5.1.2e	UNSW	 AU	
P09 UNI	University College London Institute of Education 5.1.2e	UCL	 UK	
P10 RES	Fondazione Human Technopole Health Data Science Centre 5.1.2e 5.1.2e	FHT	 IT	
P11 SME	Nuromedia GmbH 5.1.2e	NURO	 DE	
P12 SME	Chino SRL 5.1.2e	CHINO	 IT	
P13 SME	accelopment Schweiz AG 5.1.2e	accelCH	 CH	

Call: HORIZON-HLTH-2023-DISEASE-03-07 — Relationship between infections and non-communicable diseases

Supporting bodies and networks

#	Name	Short name	Role
S01	Collaborative on Fatigue Following Infection	COFFI	Provision of data from 17 prospective cohort studies (Sample size: 24,413)
S02	The Norwegian Institute of Public Health	NIPH	Provision of population-based cohorts
S03	The Norwegian University for Science and Technology	NTNU	Provision of population-based cohorts
S04	Oslo University Hospital	OUS	Provision of brain imaging infrastructure
S05	US Centers for Disease Control and Prevention	CDC	Support for the case definition
S06	US Institute of Neurological Disorders and Stroke	NINDS	Support for the case definition
S07	US Institute for Allergy and Infectious Diseases	NIAID	Support for the case definition
S08	World Health Organisation	WHO	Support for the case definition
S09	Réseau Sentinelle	SENTINELLE	Support for dissemination among General Practitioners
S10	ORCHESTRA: Connecting European Cohorts to Increase Common and Effective Response to SARS-CoV-2 Pandemic	ORCHESTRA	Intent of collaboration, e.g. on predictive modelling.

Scientific Advisory Board

#	Name and institution	Expertise
SAB1	5.1.2e Radboud University Medical Centre, NL	Infectious diseases, post-infective syndromes, translational and clinical research
SAB2	5.1.2e King's College, London, UK	Health psychology, persistent fatigue, clinical trials
SAB3	5.1.2e University of Michigan, US	Chronic pain, rheumatology, translational and clinical research

Patient Advisory Board

#	Name, Ctry	Infection/Condition
PAB1	5.1.2e	Post-COVID-19 condition
PAB2		Post-viral fatigue after Epstein-Barr virus infection
PAB3		Post-viral fatigue after Epstein-Barr virus infection
PAB4		Post-COVID-19 condition
PAB5		Post-COVID-19 condition

List of main abbreviations

AI	Artificial Intelligence
CBT	Cognitive Behavioural Therapy
COFFI	Collaborative on Fatigue Following Infection
FAIR	Findable, Accessible, Interoperable, Reusable data
fMRI	functional Magnetic Resonance Imaging
GDPR	General Data Protection Regulation
JDC	Joint Data Center
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
ML	Machine Learning
PIFS	Post-Infective Fatigue Syndrome
RCT	Randomised Controlled Trial

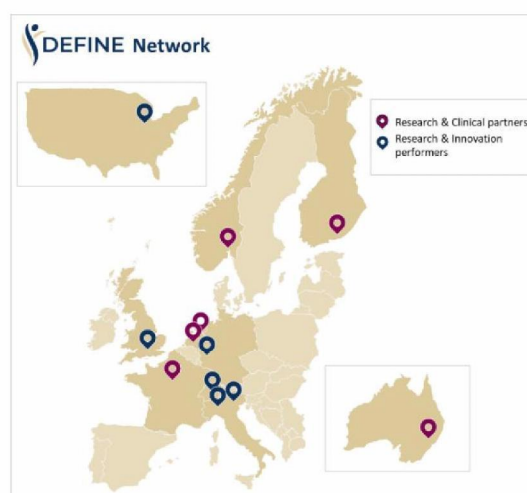


Figure 1: Map of the DEFINE consortium

1 Excellence #@REL-EVA-RE@#

5.1.2e

Fatigue is a common and disabling, yet poorly understood, sequel to COVID-19 and many other infections, resulting in extensive patient suffering and profound societal burdens. DEFINE (Decreasing Fatigue After Infection) will provide scientific evidence of fatigue mechanisms as well as cutting-edge clinical tools to diagnose and prevent prolonged fatigue after infections, thus improving current healthcare and preparing for the next pandemic.

5.1.2e

Post-infective fatigue syndrome (PIFS), a highly prevalent non-communicable disorder: Fatigue is a common phenomenon among healthy individuals with a prevalence of an estimated 10 % in the general population. It is a feature across a wide range of physical and mental conditions, including acute infections, and a major reason for consultations in primary care.¹ While most cases of infection-associated fatigue resolve within the febrile phase, a substantial number of individuals experience persistent fatigue long after the acute infection, evolving into an illness in its own right.² Persistent PIFS is commonly accompanied by other taxing symptoms, e.g. cognitive disturbances/“brain fog”, exertional intolerance, musculo-skeletal pain, dizziness, and sleep and mood disturbances. Much of what is currently termed *post-COVID-19 condition* or *long COVID* is considered one variant of PIFS, affecting millions of people worldwide as a “pandemic within the pandemic” with huge societal consequences.³ PIFS is also triggered by several other acute infections, such as “kissing disease” or infectious mononucleosis (caused by a virus), Lyme diseases (caused by a bacterium) and certain gut infections (caused by various parasites or bacteria).⁴ Across multiple prospective cohort studies,⁵ about 10–15 % of the included patients suffer from PIFS with significant disability at 6 months follow-up, making it *one of the most common non-communicable disorders that is precipitated by an infection*.

A high burden for society, the economy and healthcare: PIFS commonly affects adolescents and young adults, with profound negative implications for academic development, family dynamics, working ability and social networks, leading some to express that they are bereaved of their future.⁶ This condition affects females three times more commonly than males, and thus is a major threat to women’s health and gender equality.⁷ The costs related to sick leave, diminished work ability and related insurance reimbursements are immense. For instance, in the US, some researchers have estimated that post-COVID-19 conditions alone are keeping as many as four million people out of work, corresponding to 1.8% of the US labour force.⁸ Furthermore, PIFS is putting a strain on limited healthcare resources. In many countries, the post-COVID-19 condition pandemic threatens to overload healthcare capacities, potentially developing into a further public health catastrophe.

A common but heavily under-researched condition: Tools to diagnose, treat and prevent PIFS are urgently needed, both to manage the current prevalent post-infective conditions and to be prepared for future pandemics. This requires an advanced understanding of the underlying mechanisms; surprisingly, however, scientific knowledge on the condition is limited. As shown by a recent scoping study mandated by the European Commission (EC), fatigue is an under-researched field, and the societal attention and resource allocation is disproportionally low as compared to other fields with similar wide-ranging health implications.⁹ Correspondingly, there exists no practical tools for healthcare workers to identify patients at risk of developing PIFS and provide personalised countermeasures.

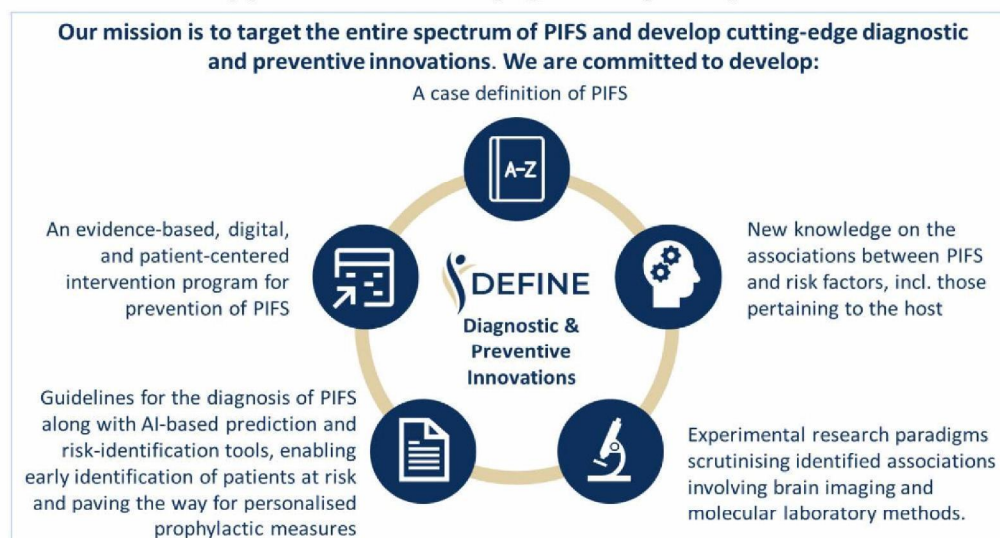


Figure 2: DEFINE mission and contributions

A dedicated interdisciplinary and multistakeholder network: This project brings together world-leading researchers on PIFS in Europe and beyond, supported by experts in digital health innovations, artificial intelligence (AI) and machine learning (ML), big data analyses, brain imaging, qualitative research and health economics. It is an initiative of the Collaborative on Fatigue Following Infection ([COFFI](#)), which was established prior to the COVID-19 pandemic by investigators from across the globe, with the aim of sharing data and specimens to underpin collaborative investigation on PIFS. COFFI provides access to 17 prospective cohorts encompassing more than 24,000 patients, along with a board of [PIFS patient representatives](#) and a scientific advisory board of distinguished researchers to co-design interventions and tools to diagnose, prevent and treat PIFS. Links between the COFFI and EU-funded projects, such as [Long Covid](#), [AICCELERATE](#) and [ORCHESTRA](#), ensures continuity of European research efforts.

1.1 Objectives and ambition #@PRJ-OBJ-PO@#

The overarching aim of the DEFINE project is to elucidate *illness mechanisms*, develop *diagnostic tools* and design a *preventive intervention* of PIFS for many people who have suffered from a variety of infectious diseases. DEFINE will address the different needs of people and patients, healthcare providers and other stakeholder groups.

1.1.1 Specific objectives

To achieve the main goal of delivering effective solutions that can reduce a major burden on the health and quality of life of millions of people in Europe and beyond, we have defined seven specific, measurable, achievable, relevant and time-bound (S.M.A.R.T.) objectives:

1. **Formulate a validated, reliable and applicable case definition of PIFS** (WP1) by surveying the scientific literature, establishing an iterative process involving researchers, clinicians, patients and other stakeholders, and using the COFFI Joint Data Center (JDC) for validation studies. The successful definition of operationalised criteria (such as cut-offs for fatigue severity) and recommended guidelines (such as validated questionnaires and structured interviews to assess fatigue and related symptoms) will be delivered by month (M)24.
2. **Identify risk factors associated with the development of PIFS** (WP2) by harmonising clinical data across all COFFI cohorts within the COFFI JDC and performing prediction analyses (encompassing ML-techniques) within the COFFI JDC as well as several large-population-based cohorts, resulting in a multivariable model of risk factors for PIFS development. This risk factor model will be expressed in mathematical or probabilistic terms, e.g. regression coefficients with confidence intervals, and be delivered by M36.
3. **Determine potential causal mechanisms for the development and opportunities for alleviation of PIFS** (WP3) by analysing existing brain imaging data from the COFFI cohorts; performing experiments directed at assessing and manipulating fatigue states during functional brain imaging; obtaining longitudinal brain imaging data from participants in the clinical trial of WP4; and performing laboratory assays to determine the interactions between (epi)genetic, neuroendocrinological and immunological markers. The case-control studies will recruit 100 individuals (patients and matched healthy or recovered controls).
4. **Design a feasible and effective transdiagnostic preventive intervention for PIFS** (WP4) by systematically reviewing the scientific literature; designing a preventive intervention (i.e. 12 weeks to 6 months after the acute infection for at-risk patients) delivered through a web-based app supported by a therapeutic chatbot and a healthcare provider; developing manuals and digital learning tools for healthcare professionals providing the intervention; and assessing the effectiveness and cost-utility of the intervention in a multi-centre randomised controlled trial (RCT) with 750 patients at risk recruited in five countries.

The web-based app intervention programme will be finalised and delivered before M15, containing generic as well as infection- and context-specific elements, along with a digital learning programme for healthcare providers empowering them to deliver the intervention.

A report on the effectiveness, cost-utility and eventual side effects of the intervention programme across five countries will be completed by the end of the project.

5. **Set up an innovative, patient-centred and applicable product portfolio, counteracting PIFS for all players in healthcare** (WP5) by collating practical outputs from previous WPs; surveying needs and requirements from end users with a particular focus on primary healthcare providers; developing and testing an AI-based tool for individual risk prediction; and developing a digital *PIFS platform* featuring an iterative development strategy and safeguarding further technical support and refinement.

The web-based PIFS platform will be compatible with commonly used electronic health records containing diagnostic and therapeutic tools for counteracting PIFS, and will be delivered by M60. A PIFS secure data exchange hub will be developed to maintain PIFS platform data management and integration, adhering to the principles of findable, accessible, interoperable and reusable (FAIR) and General Data Protection Regulation (GDPR).

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6. **Assess legal, ethical and socio-economic aspects of DEFINE (WP6)** by evaluating consortium activities and products against ethical standards, safeguarding that data management adheres to the GDPR standards and the FAIR principles and comparing the societal and economic burden of PIFS with the beneficial effects entailed by a wide exploitation of the DEFINE product portfolio.
7. **Communicate the DEFINE project to different audiences and disseminate the project results to different users and stakeholder groups according to Open Science principles (WP7)** by pursuing a multi-channel and multi-media approach as well as a training- and exploitation-oriented strategy involving patients, healthcare providers, policymakers and the scientific community in the entire research and development process. Each activity planned has specific key performance indicators (KPIs), as shown in Section 2.2.

Relevance to the call HORIZON-HLTH-2023-DISEASE-03-07

Scope of the call	DEFINE contribution
Elucidate causative links between infections and NCDs onsets, and the impact of infections on the exacerbation of existing NCDs or vice versa, in children or adults.	We will investigate potential causal mechanisms and contributing factors between acute infections (including COVID-19) and the onset of PIFS in adolescents and adults (WPs 2 and 3).
Integration of the analysis of genetics, immune status, immune or inflammatory responses, microbiome, lifestyle and/or other relevant factors to get information for prevention, early diagnosis, risk factors and to better understand causative links as well as the progression of those NCDs.	We will elucidate biological, psychological, behavioural and environmental risk factors for development of PIFS by applying both traditional multivariable modelling and ML techniques on prospective infectious cohort data and large population-based cohort data. We will conduct experiments, using functional brain imaging and laboratory assessment of (epi)genetic, neuroendocrinological and immunological interactions, to identify objective early markers for risk and disease, uncover potential causal mechanisms and inform strategies for prevention and treatment (WPs 2, 3 and 4).
Address any infection including those with pandemic potential (viral, bacterial or fungal) with NCDs of major importance.	PIFS is a major consequence of several infectious diseases, including those with epidemic and pandemic potential, with a case rate of 10–15%. COFFI enables us to address PIFS across a wide range of viral (COVID-19, infectious mononucleosis), bacterial (Q-fever, Lyme disease) and parasitic infections (Giardiasis) (WPs 1–4).
Special attention to vulnerable individuals, such as those with known existing preconditions.	We will study the role of physical and mental co-morbidities in the analyses of PIFS predictors and design the preventive intervention to fit adolescents (a vulnerable age group) and adults (WPs 2 and 4).
Proposals could include patient follow-up to identify conditions that may appear only after a patient has recovered from the infectious disease.	The definition of PIFS requires a persistence of fatigue and other symptoms (e.g. brain fog and post-exertional malaise) for at least 6 months after the infection. We benefit from access to 17 existing prospective cohort studies through COFFI, including more than 24,000 individuals with follow-up data up to 24 months (WPs 1–4).
In case of clinical evaluation: sound feasibility assessment, provide details of the methodology, including an appropriate patient selection and realistic recruitment plans, justified by available publications or preliminary results.	The COFFI JDC of prospective cohort studies ($n \sim 24,000$) as well as six population-based cohorts ($n \sim 500,000$) will be available for the project. <i>De novo</i> recruitment of patients for experimental research ($n \sim 100$) and a clinical trial ($n=750$) is feasible within the multicentre infrastructure. Further details on the feasibility and methodology can be found in Section 1.2.1 and the Clinical Study document (WPs 3, 4).
Encouragement to incorporate AI tools for data analysis and assessment or prediction of the risk of developing a disease and/or disease progression or severity.	We will create an AI-based tool to be used by physicians and other healthcare providers to predict patients' risk of developing PIFS after acute infections. AI/ML techniques will be incorporated into the study of predictors and potential causal mechanisms (WPs 2 and 5).
Projects that focus on COVID-19 and post COVID-19 conditions are strongly encouraged to collaborate and build links with relevant EU-funded projects and pay special attention and link to the European COVID-19 data sharing platform .	The consortium is tightly linked to EU-funded projects, incl. Long Covid and AICCELERATE . We will collaborate with ORCHESTRA , e.g. testing predictive models from COFFI JDC in their database. Generated data will be shared on the European COVID-19 data platform in adherence with the GDPR regulations, FAIR principles and Open Science principles (WPs 1–5, 7).

1.1.2 Ambition

The overall ambition of DEFINE is to *understand* the mechanisms underlying PIFS, correctly *identify* individuals suffering from or at risk of developing PIFS and *counteract* PIFS by an effective preventive intervention. In other words, the ultimate goal is to *decrease fatigue after infections*, to the benefit of individual patients, the healthcare system and society at large. At present, about one out of seven patients develop PIFS after certain acute infections. A realistic aim for DEFINE as a whole is to reduce this number by 50%.

The research and innovation advancements to be performed within the project are summarised in the table below.

Table 1: Overview of the various research and innovation advances proposed within the project.

Current state	State at the end of the project
1. New database for cohort studies of PIFS	
Technology Readiness Level (TRL)3: A COFFI JDC adhering to the GDPR has been formally established at AHUS, ready to store data on the servers of the Services for Sensitive Data .	TRL9: Data harmonised across cohorts and used for risk factor modelling of PIFS, utilising both traditional and machine learning methods. A standardised import and harmonisation protocol will be in place to ensure the continuous addition and integration of future cohorts into the database and predictive models.
2. New case definition of PIFS	
TRL1: Case definition of PIFS suggested in a few scientific publications; no operationalised criteria, no universal agreement, no formal testing of validity, reliability and applicability.	TRL8: Case definition of PIFS with operationalised criteria and clinical guidelines tested for validity, reliability and applicability across the cohorts of the COFFI JDC and agreed upon by panel of key stakeholders. Integrated in the PIFS platform and ready to be used along the entire healthcare value chain.
3. New app-based intervention to prevent PIFS after acute infections	
TRL3: Core elements of the intervention are based upon cognitive behavioural theory and have been tested in RCTs of patients with PIFS after COVID-19 and Q-fever.	TRL8: Web-based app, including a therapeutic chatbot and supported by a therapist if needed, developed and efficacy tested in a multicentre (five countries) RCT, accompanied by an educational programme. Integrated into the PIFS platform and ready to be used in primary care.
4. New prediction tool for early identification of individuals at risk of PIFS	
TRL1: No general prediction tool for early identification of PIFS has previously been developed.	TRL8: An AI-based algorithm developed across the cohorts of the COFFI JDC as well as large population-based cohorts, and further refined and validated using real-world clinical data. Integrated in the PIFS platform and ready to be used along the entire healthcare value chain.
5. New knowledge on (epi)genetic, neuroendocrine and immunological interaction in PIFS	
TRL2: Studies suggest slightly enhanced systemic inflammation in PIFS, possibly caused by epi(genetic), neuroendocrine and immunological interactions.	TRL4: Molecular laboratory experiments using viable white blood cells from PIFS patients and recovered or healthy controls as well as within a nested RCT have delineated the (epi)genetic, neuroendocrine and immunological interactions in PIFS.
6. New knowledge on functional brain alterations in PIFS	
TRL2: Studies suggest functional brain alterations in PIFS patients.	TRL6: Experiments exploiting functional brain imaging (fMRI) have delineated the brain network dynamics of fatigue states and their alleviation across PIFS patients and recovered or healthy controls as well as within a nested RCT.
7. New open data repository for PIFS research	
TRL2: No open data repository for PIFS research exists.	TRL8: An open data repository containing anonymous data generated through the DEFINE project, adhering to the GDPR regulation and the FAIR principles, available for researchers globally in line with recent Open Science strategies.

1.1.2.1 Health ambition: better quality of life

Patients with PIFS suffer devastating persistent fatigue featuring a prominent post-exertional exacerbation after minor activity, combined with several other symptoms, including musculo-skeletal pain, cognitive difficulties (“brain fog”), shortness of breath, dizziness, and non-refreshing sleep.¹⁰ These symptoms often result in severe disability and poor quality of life; a great majority of PIFS patients are unable to attend work or school, and some are bedridden. Their suffering increases if their healthcare providers convey a somewhat brutal, but still partly true, reality: “We do not know what this is, and we do not know what to do about it”.

The diagram illustrates a patient's experience with Persistent Infectious Fatigue Syndrome (PIFS). It starts with a fever (5.1.2e) and transitions to persistent fatigue (5.1.2e). Two scenarios are compared:

- No intervention:** The fever passes, but the patient is left extraordinarily fatigued along with recurrent sore throat, tender lymph nodes, and difficulties in concentrating. She contacts her GP, who says she will just have to rest, wait and see – as there is no established treatment. The fatigue and related symptoms are debilitating; she misses her exams and entry to university.
- Our solution:** The GP conducts a clinical assessment and laboratory investigations to ensure there is no other condition causing the ongoing symptoms, and then uses an online tool to predict Aisha's risk of developing persistent fatigue after infectious mononucleosis. The GP informs her that she is in a moderate to high-risk category and suitable for early intervention. With appropriate care and support, Aisha can complete her exams and get on with her life.

The reality is that PIFS is an under-researched field:

- The disease mechanisms are poorly understood. It is clear that PIFS represents a *continuation* of many of the common symptoms of acute infection, but without persistence of the pathogen. Previous studies have identified risk factors that are generic across very different precipitating infectious diseases, including features linked to severity of the acute infection, such as markers of host immune responses, subjective symptom severity and functional impairments.¹¹ In addition, prior emotional distress as well as female sex have been associated with increased risk of PIFS development across several studies, pointing to the need for a biopsychosocial perspective on the illness.¹²
- The therapeutic options are limited. However, several randomised controlled intervention trials have shown beneficial effects of cognitive behavioural therapy (CBT) in persistent fatigue states generally¹³ as well as in PIFS.¹⁴

The ambition of DEFINE is to go substantially *beyond* the state-of-the-art, which will ultimately result in better quality of life for patients and a reduced burden on society. We will:

- Exploit the unique COFFI JDC to identify the *risk factors for PIFS development* (WP2). The COFFI JDC consists of pooled clinical data from 17 COFFI prospective cohorts, making it by far the largest database of its kind in the world.
- The risk factor analyses, combined with experimental studies on potential causalities, will inform the development of an *early intervention to prevent PIFS after acute infections* (WP4). The intervention will be tailored to patients' needs and will be conveniently delivered as an app with a therapeutic chatbot and a supporting therapist. It will build upon previous knowledge of the effectiveness of CBT and related approaches and will serve as a *preventive* measure.
- The intervention programme will be *intimately adjusted to patients' needs and preferences* by establishing an iterative developmental process informed by large patient surveys as well as by including patients' representatives recruited from the COFFI Consumer Advisory Committee (CAC) at all stages (WP5).

Patient contribution: The DEFINE consortium is committed to facilitating patients' active participation at all stages of the research process. The COFFI CAC, whose members are involved in the DEFINE Patient Advisory Board (PAB), plays a key role in this regard in compliance with the governance documents of COFFI. The present proposal has been informed and inspired by a [CAC-led workshop](#) (8 Feb. 2023) on COFFI's future research agenda and priorities and has also been critically and independently reviewed by three CAC members.

The PAB will be directly involved in further planning and execution of the different WPs, most notably in WP4, when PAB members will contribute to the planned content of the different modules within the intervention programme and will be on the trial steering committee. The PAB will also substantially contribute to WPs 1 and 5. In addition, patients' opinions will be charted through large-scale surveys.

1.1.2.2 Healthcare ambition: empowering healthcare providers

Healthcare providers for PIFS patients may feel helpless and puzzled when exposed to suffering, which may seem difficult to explain and difficult to alleviate. To a large extent, health professionals are devoid of practical tools to manage the clinical challenges of PIFS; unfortunately, this may sometimes result in a tendency to dismiss or avoid these patients. Furthermore, PIFS does not “belong” to a specific medical speciality; hence, the great majority of patients are managed in primary care, often resulting in a discrepancy between their substantial functional disabilities and the limited resources available.

Again, the current state-of-the-art is that PIFS is an under-researched field. In addition to the lack of knowledge on disease mechanisms and treatment, as mentioned above, the field is characterised by the following:

- The diagnosis is disputed. There is no universal PIFS case definition, and the definitions that do exist have not been validated and lack operationalised criteria.¹⁵ No diagnostic biomarker has been identified.
- Scarce tools exist to identify individuals at risk. Despite PIFS being one of the most common non-communicable conditions following acute infection, at present, nothing exists to guide primary care providers to those patients who should be prioritised for preventive intervention.

The ambition of DEFINE is to empower healthcare providers in their encounters with PIFS sufferers. We will:

- Use the COFFI JDC and affiliated expertise to formulate a *valid, reliable and applicable case definition of PIFS* (WP1). The case definition will be accompanied by operationalised criteria and clinical guidelines, enabling healthcare providers to make the correct diagnosis.
- Develop an *AI-based prediction tool* for the identification of individuals with acute infections who are at risk of developing PIFS (WP2 and 5). This will enable healthcare providers to offer *personalised clinical management*.
- Develop an *educational programme to accompany the preventive intervention*, enabling healthcare providers to deliver correct and tailored prophylactic treatment (WP4).
- Ensure that all end-products are *adjusted to healthcare providers' needs and preferences*, with a particular focus on primary care. This will be accomplished by establishing an iterative developmental process, informed by large patient surveys, as well as by including clinicians (especially primary care doctors) at all stages (WP5).

1.1.2.3 Science ambition: closing the knowledge gaps

The relative lack of large and well-informed research initiatives to study PIFS obviously creates a scientific challenge. The key problem is the poor understanding of the underlying aetiology and pathophysiology, which in turn hampers the development of diagnostic, therapeutic and preventive measures.

The current scientific understanding regarding PIFS is that it is triggered by acute infection, with ongoing symptoms caused by a complex blend of genetic or epigenetic¹⁶ and psychosocial¹⁷ vulnerabilities, in concert with autonomic¹⁸, neuroendocrineological¹⁹ and immunological²⁰ alterations. Generally, previous research findings have been hypothetically explained by two alternative yet not mutually exclusive models (Figure 3):

- The first model (A) proposes *altered immunity* to be the underlying mechanism²¹ supported by reports of low-grade systemic inflammation,²² possibly linked to autonomic or neuroendocrine dysfunction²³, auto-antibodies²⁴ and human leukocyte antigen (HLA) allele associations²⁵ as well as the precedent set by post-infectious autoimmune encephalitis.²⁶
- The second model (B) considers *functional brain alterations* to be the central pathophysiological element,²⁷ supported by functional brain imaging studies,²⁸ clinical trial outcomes²⁹ and fundamental neurobiological concepts.³⁰

5.1.2e

Our solution: The DEFINE product portfolio provides Lena with the tools she needs to help her patients. The *educational program* gives her a deeper understanding of the likely mechanisms underpinning her patients' condition, and the *prediction tool* lets her focus her attention on those patients at greater risk for developing prolonged PIFS. The *preventive intervention* enables her to provide care for patients instead of watching them deteriorate.

5.1.2e

Our solution: By performing neurocognitive testing and functional MRI scans on Jorge and comparing them with those of his partner, we can map differences in cognitive performance and associated neural activity between those who are ill and those who have recovered. The patterns that emerge from scans of hundreds of patients can lead us to identify disease mechanisms, which in turn can guide the development of targeted treatment for people like Jorge.

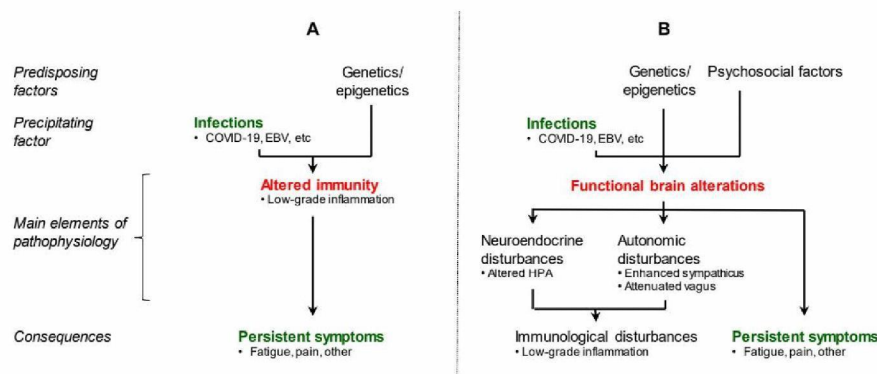


Figure 3: Models summarising the competing scientific understanding of PIFS, with immune alterations (A) and functional brain alterations (B) as potential underlying mechanisms.

Our ambition is to close the most pertinent knowledge gaps in the scientific understanding of PIFS. We will:

- Use the COFFI JDC as well as several large population-based cohorts, to *determine predictors of PIFS* (WP2). The exploitation of population-based cohorts (the largest amounts to ~ 250,000 participants) enables identification of predictors preceding the acute infection, such as *genetic variants*, *personality traits* and *adverse life events* and allows *big data* analyses. This approach has never been used in previous PIFS research. The *application of AI/ML technology*—also novel to the field—will enable the modelling of potential causal relationships.
- Design experiments that further *address potential causal factors* (WP3). Informed by the prediction analyses, we will focus on: a) *functional brain imaging studies* addressing the potential causal associations between dynamic brain network configurations, cognitive functions, and the subjective experiences and apperceptions of the symptoms; and b) *molecular and cellular immunological studies* addressing the potential causal associations between (epi)genetic markers, autonomic or neuroendocrine alterations and immunological aberrations.
- Establish robust links to other EU-funded projects (Long COVID, ACCELERATE and ORCHESTRA), ensuring continuity of European research efforts as well as pivotal players on the global health scene, such as the World Health Organisation (WHO), the US Center for Disease Control and Prevention (CDC) and the US National Institutes of Health (NIH).

1.1.2.4 Societal ambition: minimising PIFS-induced healthcare and economic burden

PIFS after COVID-19 and other infections is a huge public health problem, causing significant strain on many levels.³¹ Caregivers suffer from a lack of understanding from others for the condition, emotional distress from having a disabled family member and a loss of income and increase of expenditures.³² Healthcare services on all levels of the value chain are affected, with one report estimating a \$528 billion increased expenditure in the USA from long COVID alone.³³ It is a major cause of sick leave as well as permanent disability reimbursement among young people, hampers academic and career development and reduces the total work force.³⁴ In other words, PIFS is immensely *costly*, in both the human and financial sense of the word.

Given the lack of appropriate countermeasures, the current state-of-the-art is that very little can be done to reduce these costs. In particular, no means exist to identify individuals at risk of developing PIFS or any evidence-based interventions to prevent the development of the condition.

The ambition of DEFINE is to substantially reduce the societal costs related to PIFS, as follows:

- Develop an evidence-based, innovative *product portfolio* encompassing prediction and preventive intervention tools that can easily be applied in the primary care setting, thus alleviating the strain on secondary and tertiary health services (WP5).
- Effectively *disseminate the product portfolio* for exploitation by all players along the healthcare value chain as well as relevant patient groups (WPs 5 and 7).
- Oversee that the product portfolio does not conflict with other societal goods, particularly ethical standards and legal requirements (WP6).

#\$PRJ-OBJ-PO\$#

1.2 Methodology ##CON-MET-CM@# ##COM-PLC-CP@#

PIFS may be precipitated by a wide range of pathogens (Figure 4). Phenotypically, PIFS manifests as an abnormal prolongation of the *acute sickness response*, which is a stereotyped collection of physiological, behavioural and psychological manifestations including fatigue, musculoskeletal pain, fever and cognitive impairment as well as sleep and mood disturbances.³⁵ Another characteristic feature of the acute sickness response is that relatively minor physical or cognitive activity triggers a prolonged symptom exacerbation.³⁶

Viral		Bacterial	
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	Coronavirus disease 2019 (COVID-19)	Coxiella burnetii	Q-fever
Epstein-Barr Virus (EBV)	Infectious mononucleosis ("kissing disease")	Borrelia spp.	Lyme disease
Ross River virus (RRV)	Ross River fever	Campylobacter jejuni	Gastroenteritis
Chikungunya virus (CHIKV)	Chikungunya	Parasitic	
Dengue virus	Dengue fever		
Ebola viruses	Ebola virus disease		
		Giardia lamblia	Giardiasis

Figure 4: Infectious agents (left columns) and diseases (right columns) with well-established links to PIFS

When fatigue persists for 6 months or more, it is normally termed “chronic”, although the researchers behind this proposal prefer the term “persistent”, as recovery is consistently possible during the prolonged illness course.³⁷ When thorough clinical assessments and investigations do not reveal alternative explanations for persistent fatigue at 6 months post-infection, a diagnosis of PIFS may be considered.³⁸

DEFINE will exploit a multitude of methods, ranging from molecular and cellular immunological assays, functional brain imaging, AI/ML algorithms in *big data* population-based cohorts, qualitative approaches to understand patient’s experiences and priorities and a multi-centre RCT. In WP1, an expert panel of researchers, clinicians and patients will develop an international case definition of PIFS. The case definition will be validated and refined using the COFFI cohorts as a testing dataset before being put into use in the remaining WPs. WP2 utilises both traditional multivariable regression and machine learning techniques to identify risk factors and determine the best prediction model for PIFS. In parallel, WP3 will conduct experimental studies to cast light on the potential causal mechanisms leading to PIFS, aiming to identify links in the causal chain that can be targeted by preventive interventions. The knowledge gained about risk factors in WP2 and potential causal mechanisms in WP3 will be used in WP4 to design and test a preventive intervention in an RCT.

In WP5, the knowledge from WPs 1–4 will be used to design a secure *PIFS platform* for patients and healthcare providers, consisting of diagnostic guidelines for PIFS, an AI-based tool to predict patients at risk of developing PIFS after acute infections and an app-based intervention programme and accompanying educational tools to prevent the development of PIFS. The PIFS platform can easily be revised as new data become available, emphasising the flexibility and interactivity among our WPs.

Legal and economic analyses will be undertaken in WP6, efficient communication and dissemination are safeguarded in WP7 and WP8 is dedicated towards goal-directed management and coordination.

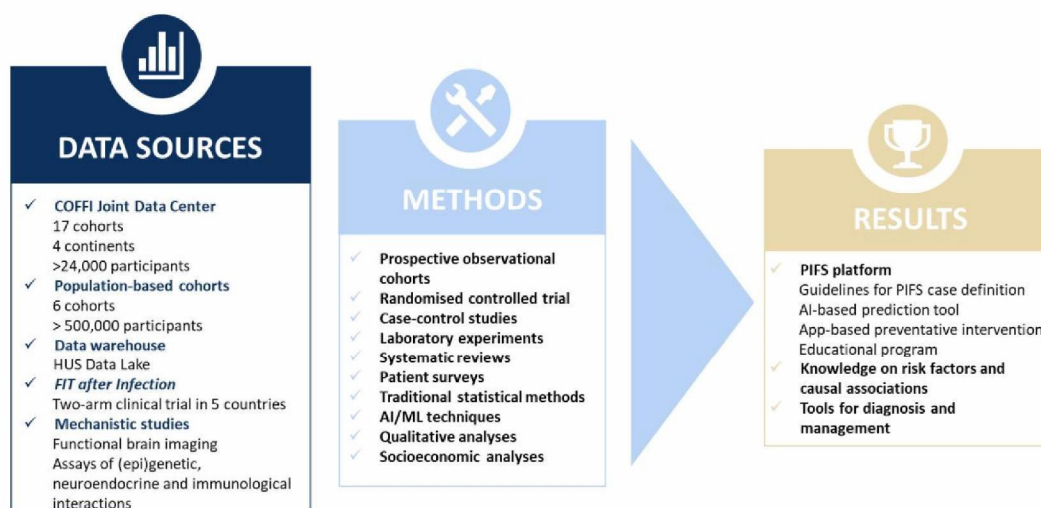


Figure 5: DEFINE methodology overview

1.2.1 Overall methodology

1.2.1.1 Development and validation of an operationalised case definition for PIFS (WP1)

Case definitions for the diagnosis of PIFS rely upon the patients' symptom reports and a description of disability, accompanied by careful clinical and laboratory assessments to exclude other potential explanatory conditions. However, validity has not been established and operationalised criteria are lacking. As individual symptoms are both subjective and common in primary care, there is a fundamental diagnostic challenge. Several well validated questionnaires³⁹ and one structured interview schedule⁴⁰ exist to characterise fatigue states, including after infection. The DEFINE project will develop an operationalised and validated case definition for PIFS. In addition, the PIFS context offers an opportunity to study a homogenous subpopulation of the broader and more heterogeneous chronic fatigue syndrome (CFS).⁴¹ Within the CFS field, case definitions have been a matter of controversy, and more than 20 different ones have been published.⁴²

A panel of clinical researchers across the disciplines of epidemiology, public health, infectious diseases, paediatrics and psychiatry will be convened, including the COFFI members listed as part of this WP (see Section 3.1) as well as international experts on CFS disease classification, such as Dr Leonard Jason of DePaul University. On behalf of COFFI, Dr Andrew Lloyd and Dr Ben Katz are currently organising an international working group to develop a consensus case definition for PIFS after COVID-19, with representatives from the US National Institute of Neurological Disorders and Stroke (NINDS), the US National Institute of Allergy and Infectious Diseases (NIAID), the US Centers for Disease Control and Prevention (CDC), the Australian National Health and Medical Research Council (NHMRC) and the World Health Organisation (WHO). We will use the experience generated by this endeavour as well as many of its members in our quest for a useful, international and universal definition of PIFS that would also be applicable to the next infectious agent that leaves post-infectious sequelae in its wake.

The DEFINE panel will systematically survey the literature using standardised methodologies⁴³ regarding definitions of post-infective or post-infectious fatigue (PIFS), post-viral fatigue syndrome (PVFS), myalgic encephalomyelitis (ME) or CFS and the post-COVID-19 condition. As no objective diagnostic tests exist for these clinical syndromes, the review will focus on literature using tools that have proved useful in separating PIFS patients from individuals who have recovered uneventfully or healthy individuals as well as structured interviews to define the key symptom domains and the disability associated with PIFS.⁴⁴

After an evidence-based case definition of PIFS is developed, it will be tested on various well-defined patients and controls already classified as having, for example, ME or CFS following infectious mononucleosis, COVID-19, Q-fever, etc. This will also include consideration of between-cohort validation (generalisability) and within-patient reliability (test re-test), consistent with the previous demonstration of the temporal stability of the PIFS diagnosis in one of the cohorts. Since the COFFI cohorts have used rigorous approaches to define patients versus controls (e.g. using standardised, validated questionnaires, such as the Chalder fatigue scale⁴⁵ or the DePaul Symptom questionnaire⁴⁶), we assume that at least 85 % of our previously categorised PIFS patients and controls will be correctly classified using our new definition. If this is the case, WP1 will be completed before month 24. If this is not the case, the panel will re-examine the case definition and the basis of misclassified patients to refine the diagnostic criteria for PIFS and re-examine the cohorts again for the accuracy of the new definition. We expect 24 months to be sufficient time for this project so that the case definition may be shared with other DEFINE partners who will rely on it for their WP.

1.2.1.2 Determining and modelling risk factors (WP2)

A COFFI JDC has been formally established at AHUS. The JDC fully adheres to the EU GDPR (EU regulation 2016/679). Deidentified data within the JDC are stored on a designated server with the [Services for Sensitive Data](#) at UiO, which complies with the highest security standards for sensitive data. Data import from COFFI cohorts to the JDC is well underway.

All COFFI cohorts employ validated, multidimensional questionnaires (such as the Chalder fatigue questionnaire⁴⁷) to assess fatigue at inclusion and follow-up. Likewise, all cohorts have made use of validated (albeit different) instruments to obtain supplementary data, such as other symptoms (pain, post-exertional malaise, "brain fog", anxiety or depression), functional abilities or quality of life, demographics and clinical characteristics (medications, co-morbidities, etc.). Symptom data from the different COFFI cohorts will be harmonised using principal component analyses (PCAs) to describe the broad symptom domains or "endophenotypes" of the acute and post-infective phases, as described previously.⁴⁸ The PCA scores will be validated against independent measures of functional impairment (e.g. hospitalised, confined to bed or unable to work or study) to ensure that the measures reflect the severity of the illness. Missing data will be replaced by multiple imputation techniques.

For preliminary analyses, a caseness assessment based upon the most used diagnostic definition of PIFS will be applied.⁴⁹ However, as soon as an updated, validated case definition of PIFS with operationalised criteria is established (cf. WP1), this will be used for caseness assessment at the 6-month follow-up across the entire JDC. A

distinction will be made between “certain” and “less certain” classifications, based upon the extent of a detailed assessment of other conditions (e.g. medical or psychiatric comorbidity) that may explain symptoms.⁵⁰

The scientific literature on PIFS will be scrutinised to identify potential predictors of PIFS caseness at 6 months post infection, such as specific infectious agents, background or constitutional factors (sex, age, obesity, ethnicity and chronic co-morbidities), genetic markers, biomarkers (immunological, neuroendocrinological or autonomic), cognitive functions, baseline clinical symptoms, psychological traits and social or behavioural markers. Collinearity between predictor variables will be assessed by correlation analyses, and dimensionality reduction by PCA will eventually be considered. Bivariate analyses between the outcome variable (PIFS caseness) and each hypothesised predictor variable will be performed by generalised linear modelling using a modified Poisson approach (log-link and robust error variances). Variables for multivariable modelling will be selected using techniques for penalised regression (LASSO and elastic net). A total number of more than 24,000 individuals in the JDC yields a power of approximately 80 % to detect a predictor with a relative risk (RR) of 1.15 ($\alpha = 0.05$). Sensitivity analyses with imputation of missing data points and exclusion of uncertain cases, respectively, will be carried out.

Thereafter, hypothesis-driven prediction modelling will be carried out in six separate population-based cohorts, primarily focusing on potential pre-exposure risk factors, such as genetic markers, personality factors and life events. Caseness assessment (PIFS vs non-PIFS, that is, prompt recovery after infection) will be performed as described for the JDC above; linkages with health registries (e.g. the Norwegian Patient Registry, the Norwegian Surveillance System for Communicable Diseases (MSIS) and the Norwegian Prescription Database) will be used to verify a diagnosis of preceding acute infection and consider alternative causes of persistent fatigue. Prediction analyses will be carried out as outlined above (Poisson approach with log-link and robust error variances).

The hypothesis-driven predictor analyses will be supplemented with a data-driven approach applying machine learning algorithms on the JDC as well as the population-based cohorts, aiming at defining a fatigue score based on a comprehensive fingerprint of the patient, possibly represented in a lower-dimensional embedding space. As input, the ML algorithm will use the patients' data, together with the PIFS caseness classification and calculate how to best map each patient representation to its specific scoring class. This task, complemented by methods of “model explainability”, will be used to identify which variables are most salient in discerning between PIFS and non-PIFS cases. Furthermore, methods of causal inference, such as graphical probabilistic models and Pearl's structural causal models, will be exploited.⁵¹ The results from this data-driven approach will be fed back to standard prediction modelling approaches and used to refine the final multivariable model. Some pilot analyses have already been performed on one of the COFFI cohorts (the LoTECA cohort on young people with COVID-19),⁵² demonstrating its feasibility (Figure 6).

Finally, dependent on the previous findings, we will consider applying both hypothesis-driven and data-driven approaches to explore predictors of spontaneous recovery from PIFS, i.e. conversion from PIFS-caseness at 6 months follow-up to non-PIFS-caseness at later follow-ups.

1.2.1.3 Assessments of functional brain alterations and (epi)genetic, neuroendocrinological, and immunological interactions in PIFS (WP3)

Persistent fatigue is frequently ‘uncoupled’ from well-defined pathophysiological mechanisms; that is, there is a mismatch between the subjective experience of overwhelming exhaustion and the objective findings at standard clinical examination. This lack of correspondence constitutes a fundamental challenge for scientific investigations.

Complex human traits, including cognitive, emotional, motivational, and motor functions, are supported by the fine-tuned synchronisation of neuronal activity across large-scale brain networks.⁵³ Together with the clinical heterogeneity and relevance across a range of neurological and post-infectious conditions, this brain network model suggests that a one-to-one mapping between complex traits, such as fatigue and brain regions or networks, does not exist. This is also supported by previous functional neuroimaging studies investigating fatigue in different patient groups.⁵⁴ The brain networks involved in fatigue are likely part of a more general network serving to guard bodily and mental homeostasis, which complies with the evolutionary understanding of fatigue as a signal of potential energy deficits.⁵⁵ Therefore, the experience of fatigue typically evokes a stress response; that is, automated bodily defence mechanisms that include immunological, hormonal, cognitive, and behavioural adjustments.⁵⁶

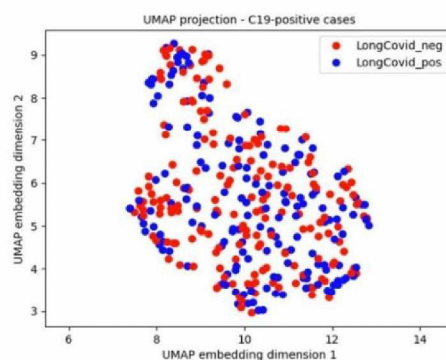


Figure 6: Uniform manifold approximation and projection (UMAP) dimension reduction technique applied as a pilot analysis on 27 immune markers in the LoTECA dataset (Selvakumar 2023). This example of applied ML techniques demonstrated that the selected mix of immune markers did not distinguish between patients with the post COVID-19 condition (blue dots) and patients without this condition (red dots) at 6 months follow-up.

By exploiting hemodynamic response functions, functional magnetic resonance imaging (fMRI) allows for a detailed assessment of brain activation and large-scale brain network dynamics in the living human brain. fMRI studies have shown that the brain can be conceptualised as reflecting a hierarchical network structure comprising various brain nodes (regions) and their connections (edges)⁵⁷. The general functional brain network organisation of the functional connectome has been shown to persist across a range of mental states, including sleep, rest, and during cognitive effort, and is assumed to reflect a backbone upon which the brain is enabled to modulate the activity and between-node synchronisation in response to specific tasks and demands.⁵⁸

Mental phenomena, such as sustained attention and cognitive effort, are associated with distinct and dynamic modulations, both of the activity within specific brain network nodes and their connections with other regions,⁵⁹ and there is increasing evidence that clinical conditions, such as fatigue, may be mediated by functional brain network aberrations, which can be assessed using fMRI. Mental states (e.g. cognitive effort and fatigue) and their corresponding brain network dynamics can be manipulated and measured using experimental cognitive paradigms in combination with fMRI. By manipulating the cognitive effort required to successfully perform a task while simultaneously assessing the corresponding brain activity using fMRI, we can map the functional brain network dynamics associated with the objective and subjective experience of cognitive effort and mental fatigue. Importantly, this will enable a detailed characterisation of the hierarchical and coordinated brain responses associated with sustained effort and increasing levels of fatigue, as well as the brain network dynamics associated with its alleviation, such as during periods of rest and successful task engagement. DEFINE partners have previously used advanced brain imaging and computational approaches to delineate the brain and cognitive phenotypes of fatigue among neurological patients,⁶⁰ and the current efforts will enable further generalisation and clinical implementation in PIFS patients. This delineation of brain networks and cognitive control functions involved in the complex mental experience of fatigue will provide a new understanding of the functional brain underpinnings of PIFS and inform interventions.

DEFINE will take advantage of this functional brain network conceptualisation of complex human traits to obtain a novel characterisation of the brain network modulations supporting cognitive effort and fatigue both among individuals with PIFS and healthy or recovered controls. We will employ an optimised version of the Multiple Object Tracking (MOT) task,⁶¹ which allows for the experimental manipulation of cognitive effort while obtaining functional brain readouts using fMRI. DEFINE partners have already successfully obtained preliminary MOT-fMRI data from >120 patients enrolled in the LoTECA study (included in the COFFI consortium), demonstrating feasibility and sensitivity (see Figure 6). Building on these promising preliminary results, DEFINE will leverage fMRI recording during MOT performance to i) obtain a novel characterisation of PIFS case-control differences in the brain networks involved in cognitive effort and fatigue, ii) test the associations between brain network dynamics and key clinical characteristics among PIFS patients, and iii) test the utility of fMRI-based brain network dynamics as an individualised brain readout to predict and monitor response to a novel intervention aimed to prevent PIFS development after acute infections (see below, WP4).

Enhanced innate immunity responses has been reasonably consistently reported in PIFS and other chronic fatigue conditions.⁶² Recently, unpublished results from the AHUS research group showed significant alterations in whole blood gene transcripts across post-COVID-19 condition sufferers and recovered controls from the LoTECA project (Figure 7).

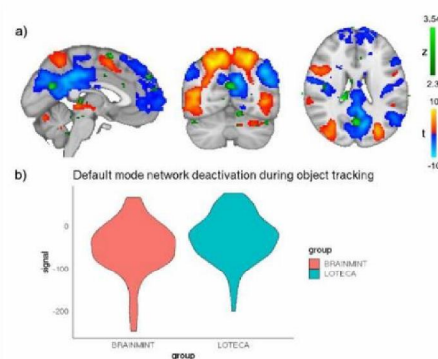


Figure 6: Preliminary fMRI analysis of young adults performing a multiple objects tracking (MOT) paradigm. a) Activation (red) and deactivation (blue) in LoTECA participants at 6 months follow-up after acute COVID-19 during tracking of multiple objects. Green indicates group difference in deactivation between LoTECA participants and age-matched healthy controls from the BRAINMINT project. b) Group difference in precuneus deactivation during tracking of objects

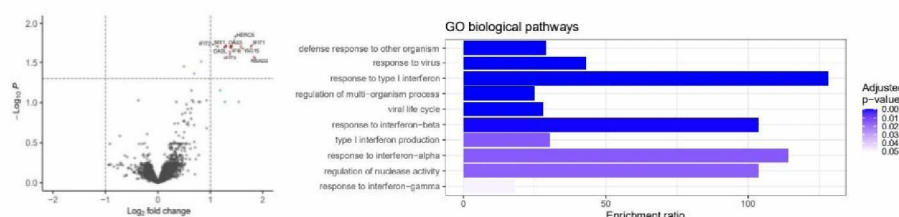


Figure 7: (Left) Gene expression results: Cross-sectional comparison of post-COVID-19 condition patients and recovered SARS-CoV-2 positive controls, showing differential expression of genes related to innate immunity (upper right corner). (Right) Gene Ontology analyses of differentially expressed genes among post-COVID-19 condition patients and recovered SARS-CoV-2 positive controls, confirming innate immunity involvement.

Several lines of evidence suggest that enhanced innate immunity responses in patients suffering from PIFS and other chronic fatigue conditions may be caused by altered autonomic and/or neuroendocrine activity.⁶³ For instance, inflammatory proteins and gene transcripts are statistically associated with attenuated parasympathetic (vagal) and enhanced sympathetic nervous activity⁶⁴ in these patients groups, and treatment with the sympathetic inhibitor and parasympathetic stimulator *clonidine* has been shown to lower inflammatory activity⁶⁵. Recently, pilot experiments at AHUS from the LoTECA project featuring cytometry by time of flight (CyTOF) suggested a similar alteration of neuroendocrine-immunological interactions among patients with the post-COVID-19 condition (Figure 8).

Genetic and epigenetic factors may further impact these complex regulatory relationships. For instance, a single-nucleotide polymorphism (SNP) in the glucocorticoid receptor gene (*NR3C1*) is related to an increased risk of persistent fatigue,⁶⁶ and hypomethylation of the same genetic locus may account for altered HPA axis dynamics, as observed in some chronically fatigued patients.⁶⁷ Previous (unpublished) pilot experiments from the AHUS research group on adolescents with ME/CFS found significant differences in the interferon regulatory factor (IRF) 7 promoter methylation level between persistent fatigue sufferers and controls ($p = 0.004$, hypermethylation in the fatigue group). IRF7 is a multifunctional transcription factor that controls type I interferon (IFN) responses, which are important in both innate and adaptive immunity.⁶⁸ Interestingly, altered IFN signalling is also implicated in the recent gene expression analyses from post-COVID-19 condition sufferers in LoTECA (cf. Figure 8).

In the present project, these relationships will be further scrutinised using viable peripheral blood mononuclear cells (PBMC) isolated from COFFI cohorts, from PIFS patients and healthy/recovered controls recruited *de novo*, and from a subsample of patients included in the RCT of WP4 (cf. below). PBMC (and cell subpopulation) cultures will be co-cultured with cortisol and catecholamines. Readouts will be a) multiplex analyses of conditioned media to compare the secretion of pro- and anti-inflammatory cytokines/chemokines and IFNs; b) single-cell RNA seq of selected genes related to innate and adaptive immunity; and c) alterations in cell properties and differentiation trajectories as assessed by CyTOF.

Next, we will perform genotyping and epigenotyping of candidate genes involved in pathways assumed to be affected (e.g. *NR3C1*, *IRF7*, *TNF*, *IL1B*, *COMT*, *IRF7*, *SLC6A4*) and assess responses of PBMC (and cell subpopulation) cultures to inflammation-enhancing stimuli and neuroendocrine signalling (such as catecholamines and cortisol) across different genotypes or epigenotypes. Readouts will be at both the mRNA, protein and cell physiology levels.

1.2.1.4 A primary care intervention ('Fit after Infection') to prevent PIFS (WP4)

PIFS often has a chronic course in both adults and adolescents and is associated with substantial functional impairment. The natural history is generally regarded as one of slow resolution over months to years, with the case rate being 10–15 % at six months and falling to 5–10 % at 12 months.⁶⁹ The ongoing symptoms after acute infection are believed to trigger behavioural factors, such as reduced physical activity or disrupted sleep-wake patterns, which act to perpetuate the illness according to the cognitive behavioural model of PIFS.⁷⁰ These cognitive behavioural perpetuating factors can be addressed in cognitive behavioural therapy (CBT)⁷¹. Previous research into PIFS following Q-fever⁷² and a recent study of PIFS after COVID-19⁷³ have shown that CBT specifically designed for PIFS can lead to a significant reduction in fatigue severity. The effect size in the more recent COVID-19 study is moderate, with a substantial proportion of patients showing clinically relevant improvement in both fatigue and disability compared to the control conditions. Most patients in the post-Q-fever and COVID-19 studies met the criteria of PIFS, with symptom duration substantially longer than the criterion of six months. We hypothesise that timely offering a low-intensity behavioural intervention for fatigue (i.e. 12 weeks up to six months after the acute infection) will significantly reduce the proportion of patients who progress to PIFS and foster patients' work ability and physical and social functioning, as well as reduce other somatic symptoms, such as pain and sleep disturbance alongside fatigue. It is assumed that this result can be achieved irrespective of the triggering acute infection with a low-intensity digital intervention requiring less time from healthcare providers than intensive and time-consuming face-to-face CBT. Previous studies, both in COVID-19 and other medical conditions, have shown that internet-based behavioural intervention can reduce fatigue with less involvement of a therapist.⁷⁴ The proposed intervention will be based on previous evidence-based interventions for PIFS and further improved based on qualitative studies and a systematic review of all evidence-based interventions for PIFS, as well as the knowledge obtained in WP1–3.

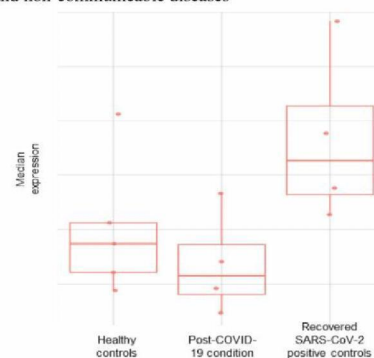


Figure 8: Expression of Granzyme B (a proinflammatory mediator) in natural killer (NK)-cell cultures from healthy controls (n=5), post-COVID-19 condition patients (n=5) and recovered SARS-CoV-2 positive controls (n=5) following stimulation with cortisol. Cell cultures were obtained from the LoTECA study; expression levels were assessed by CyTOF methodology. The expression levels are lower among post-COVID-19 condition sufferers, suggesting attenuated cortisol effect in this group; i.e. an alteration of the neuroendocrine-immunological interaction.

Study design: The proposed study is a pragmatic 2-arm RCT in which patients who have recovered from an acute infection, but suffer from ongoing severe and debilitating fatigue, will be randomised to either *Fit after Infection* or an active control condition in a 1:1 ratio. Both interventions will have a duration of a maximum of four months. Assessments will take place before randomisation (T0), at 4.5 months (T1) and at a follow-up six months after T1 (T2). Recruitment will occur in five countries among consecutive patients visiting outpatient clinics of participating hospitals, from referrals of general practitioners, prospective cohorts of patients with an infection, associated microbiological laboratories, and self-referrals. Allocation of participants to either *Fit after Infection* or the active control condition will be stratified based on (1) age (12–18, ≥ 18 years), (2) type of infectious disease (COVID-19, Lyme, EBV, other), and (3) time since symptom onset and randomisation (≤ 18 weeks, > 18 weeks).



Figure 9: DEFINE clinical study process

Patient eligibility criteria:

Patients are eligible for entry in the study if they:

1. were diagnosed with an acute infectious disease. The way the infection is diagnosed will differ depending on the health care system of participating countries and recruitment strategy applied:
 - a) Diagnosed by a GP or other physician with a symptomatic infectious disease, confirmed by lab findings, e.g. symptomatic COVID-19 confirmed by a positive PCR or rapid antigen test (RAT) for SARS-CoV-2 (*Finland, France, Netherlands, Norway, Australia*);
 - b) Specific antibody responses towards Epstein-Barr Virus (EBV) antigens including viral capsid antigen (VCA) IgM and IgG, and EBV nuclear antigen (EBNA) IgG assayed in serum samples; qualitative detection of heterophile antibodies will be performed if results from the three specific tests are inconclusive. A serological pattern confirming recent acute EBV infection is required for inclusion (VCA IgM positive, VCA IgG negative, EBNA IgG negative, heterophile antibodies positive; or VCA IgM positive, VCA IgG positive, EBNA IgG negative) (*Norway, Australia*);
 - c) Recruitment via a national website for patients following a tick bite (www.tekenradar.nl) or following a positive COVID-19 (RAT) (www.infectieradar.nl). Patients who meet the criteria for a clinical diagnosis of Lyme disease confirmed by contacting the patient's GP and online uploading a picture of the skin manifestation, and patients uploading a picture of a positive RAT test for COVID-19 (*Netherlands*);
 - d) Diagnosed by a GP or other physician with a symptomatic acute infectious disease without objective confirmation but with a definite onset of documented fever ($>38^{\circ}\text{C}$) and associated symptoms of the acute sickness response leading to functional impairments in the acute phase of the illness (absence of work or school and/or substantial reduction of other usual daily activities) (*Netherlands, Finland, France, Australia*).

Recruitment of participants with strategies a), b), and c) are defined as 'definite' infectious disease onset, and strategy d) as 'likely' infectious disease onset.

2. are between 3 to 6 months after onset of the symptomatic infectious disease. Three months is chosen because there is substantial spontaneous recovery of post-infective fatigue in the first few months after the onset of symptoms⁷⁵.
3. experiencing severe fatigue (≥ 35 for adults and ≥ 40 for adolescents on the fatigue subscale of the Checklist Individual Strength [CIS-fatigue]⁷⁶. The severe fatigue must have started with the onset of the fever and associated symptoms of the acute infectious disease, without a symptom free interval thereafter.
4. report physical and/or social disability (≤ 65 on the SF-36 physical functioning subscale⁷⁷) and/or a score of ≥ 10 on the Work and Social Adjustment Scale [WSAS]⁷⁸ or [WSAS-Y]⁷⁹ or school absence ($<75\%$ attendance in the last 2 weeks prior to assessment) in the case of adolescents;
5. are 12 years of age or older;
6. have sufficient command of the language of the country they reside;
7. have access to and can use a smart phone, tablet or computer with internet access.

Patients will be excluded if they:

1. have a known physical, mental or social condition that can explain their fatigue. In *Norway and Australia*, patients will be thoroughly assessed for alternative conditions that may explain persistent fatigue, following a previously established algorithm involving clinical and laboratory examination.⁸⁰ In the *Netherlands, Finland and France*, this will be assessed using questionnaire data as well as data from GPs health records;
2. are pregnant;
3. report a current demanding life event that makes it impossible for the patient to follow the treatment.

The intervention: *Fit after Infection* consists of a web-based app with a therapeutic chatbot combined with consultations with a healthcare provider trained to deliver the low-intensity intervention. The web-based app consists of modules based on existing evidence-based (cognitive) behavioural interventions for PIFS. Eight modules will be available and aimed at 1) psychoeducation, 2) goal setting (e.g. resumption of school or work), 3) regulation of the sleep-wake pattern, 4) graded activity, 5) changing fatigue-related beliefs, 6) managing pain, 7) social support, and 8) realising goals. The contents of these modules will be modified according to the findings from the systematic review of existing evidence of the treatment of PIFS and the knowledge obtained through WP1–3. In addition, the intervention will be personalised based on a baseline assessment before the start of treatment in which questionnaires and short-intake relevant modules will be selected. Two versions will be made available: One suitable for adolescents between 12 and 18 years and one for adults (>18 years).

The active control condition consists of a web-based app offering relaxation training and a second module containing more general advice on a healthy lifestyle.

In both interventions, all patients have a short initial session with a trained healthcare provider, either face-to-face or via video consultation. Follow-up video consultations will be available if the patient needs more guidance than the app offers to prevent attrition and optimise treatment results. The treatment lasts four months and will end with a second short clinical evaluation via video consultation.

Outcomes: Assessments will take place before randomisation (T0), after *Fit after Infection* or the active control condition (T1) and six months after T1 (T2).

PIFS caseness is the primary outcome, defined as 1) scoring ≥ 35 (for adults) or ≥ 40 (adolescents) on the CIS-fatigue, 2) fatigued for longer than six months, and 3) scoring ≤ 65 on the physical functioning subscale or ≥ 10 on the WSAS (adults) or WSAS-Y (adolescents).

It is hypothesised that timely offering *Fit after Infection*, that is, between three months to six months after an acute infection, will reduce the proportion of patients who progress to established PIFS and foster patients' work ability or school attendance and physical and social functioning, as well as will give relief to concentration problems and other persistent physical symptoms both at T1 and T2.

Power calculations: The primary outcome of this study is PIFS caseness, defined as being severely fatigued for six months or more and reporting substantial functional impairment. Previous cohort studies using validated questionnaires to assess fatigue following infectious disease found that prevalence rates of severe fatigue decline steeply the first three months after the onset of symptoms. Hence, in the present study, we estimate that the prevalence of severe and disabling fatigue will decrease with one third from 12 weeks up to 6 months without treatment, and with a declining recovering rate in this period⁸¹. This would imply that a maximal of one third (i.e. $\approx 33.3\%$) of severely fatigued patients would show spontaneous recovery if all were recruited at 3 months (12 weeks) post-infection, i.e. lower limit of the recruitment window. If we assume a placebo effect in the active control condition leading to a further 12 % decrease of caseness, about 55 % of patients in the active control condition group would still meet criteria for caseness at the primary endpoint⁸². If the effect of the experimental intervention is twice as large as the expected placebo effect (i.e. 24 %), a total of 43 % of patients would meet criteria for caseness in the intervention group at the primary endpoint. Including 750 patients (150 patients from each country), and assuming a drop-out rate of 20 %, the study has a power of 84 % to detect a difference in caseness of 12 % (55–43 %) between the intervention group and the control group using a two-sided alpha of .05 and with a two-group χ^2 test.

Statistical analysis: In an intention-to-treat analysis, the difference in the proportion of patients being cases at T1 (the primary endpoint) between the *Fit after Infection* and active control condition will be tested with a logistic regression analysis. This analysis will be repeated for the proportion of patients being cases at T2.

Longitudinal mixed linear models on secondary outcomes will be performed on an intention-to-treat basis. We will evaluate the between-group difference (*Fit after Infection* vs active control condition) in mean scores on each of the secondary outcomes during follow-up (T1 and T2), with the baseline score of the particular outcome (T0) included as a covariate. If statistically significant between-group differences in the secondary outcomes are found, we will conduct post hoc tests to assess the between-group difference at the separate follow-up measurements (T1 and T2).

We will explore the extent to which the presence of somatic co-morbidity, time since acute infection, type of infection, diagnosis (definitive vs likely), age (adult vs adolescents), and sex impact primary and secondary outcomes and whether this impact differs between *Fit after Infection* and the active control condition using logistic regression and mixed linear models. In all analyses, two-sided p -values < 0.05 are considered to indicate statistical significance.

Experimental sub-study: Patients in Norway (AHUS clinical site, $n = 150$) will undergo functional brain imaging and laboratory assays involving viable PBMC (cf. methodological description of WP3 above). We will explore whether the intervention impacts brain network dynamics and/or neuroendocrine-immunological interactions.

Qualitative approach: Qualitative research conducted in Norway, Finland, and the Netherlands (the qualitative focus countries) will provide insights into study members' experiences of and perspectives on the *Fit after Infection*

(*FiF*) intervention. In doing so, the qualitative research will support and inform (1) the training of healthcare staff who will deliver the intervention, (2) patient recruitment, and (3) the intervention. Semi-structured interviews will be conducted with:

- 12–15 healthcare staff per focus country (36–45 total) to support and continually improve the staff training and subject recruitment processes.
- 12–15 fatigue patients per focus country (36–45 total) to support patient recruitment, such as by exploring patient attitudes towards using a chatbot counselling tool.
- 20–25 intervention subjects per focus country (60–75 total) and 10–12 control group members per focus country (30–36 total). Subjects will engage in semi-structured interviews at T1 (after the intervention or control and T2 (six months later). The key outcome will be an in-depth understanding of participants' experiences of and perspectives on the intervention and its impacts on their lives in the subsequent six months. Analysis of these experiences and perspectives will provide insights into the mechanisms, processes, pathways, and contexts associated with intervention outcomes.⁸³

Interviews will be transcribed in the national language and analysed using reflexive thematic analysis.⁸⁴ Analysis will be written in English. The thematic analysis process will be iterative, with country-specific analyses being complemented in an ongoing fashion with cross-country analyses.⁸⁵ Analysis will be longitudinal to capture change over time and will focus on two time points: T1 (immediately after intervention or control) and T2 (six months later). Throughout the data collection and analysis process, the qualitative research team will work closely with the project's quantitative researchers to facilitate integrated mixed-methods analysis of the processes, mechanisms, experiences, pathways, and perspectives underlying intervention outcomes.

HTA assessment: AHUS-HS will perform a health economic evaluation of the intervention tested in the RCT, using data gathered from all five sites. The evaluation will be conducted as a cost-utility analysis combining costs and quality-adjusted life years (QALYs). QALYs will be calculated based on Short-form six dimensions (SF-6D),⁸⁶ which will be calculated from measurements of RAND-36 during the trial. The analyses will take a societal perspective, thereby capturing both resource use consumed in the health services and potential production gains from the increased ability to work.

1.2.1.5 Development and configuration of a digital product portfolio counteracting PIFS (WP5)

Outputs from WP1–4, such as reports, scientific papers, and digital tools or algorithms, will be stored at a designated server area within the [Services for Sensitive Data](#). The leader of each WP is responsible for continuously updating this 'project outcome catalogue', whereas the coordinating partner is responsible for selecting outputs that can be further developed into innovative, tailored, and applicable products. The main foreseen products are a) Clinical guidelines to be used by health personnel for PIFS diagnosis according to a validated and operationalised case definition (from WP1), b) An AI-based prediction tool to be used by health personnel for early identification of patients at risk of developing PIFS after acute infection (from WP2), c) A web-based app to be used by at-risk patients for the prevention of PIFS development and a treatment manual for healthcare providers (from WP4 – 'Fit after Infection'), and d) An educational programme for healthcare personnel on the delivery of the preventive intervention (from WP4).

To further develop the AI-based prediction tool (from WP2), studies using real-world data from the HUS data warehouse ('HUS Data Lake') are warranted. In these studies, HUS will bring the experience and the AI/ML algorithms from its existing EU-funded projects (AICCELERATE and Long Covid). Raw clinical real-world data will be collected from the data warehouse and pre-processed. Thereafter, the feasibility of the predictive algorithm on data from infectious disease patients will be assessed, demonstrating the scalability of the developed model. Finally, the prediction tool will be implemented in an electronic health record system. Natural language processing (NLP) methodology will be used to extract useful information from clinical notes, and the algorithm will be taught to identify patients that fulfil the case definition of PIFS defined in WP1. Both primary and secondary healthcare data will be involved to ensure that the application in different environments does not unsatisfactorily affect the performance regarding the scope and quality of the outputs.

The PIFS platform, which brings together the four outcomes mentioned above, will be developed by NURO following a structured and iterative process with a continuous focus on the end-user needs and requirements, including easy integration with commonly used electronic health records platforms. The design methodology will follow three steps:

1. We will implement active guidance with the elaboration and collection of all the project's wide use cases, preferably in a similar data format and data structure. A use case template will be provided to all project partners. The use cases will be used to specify the context of the use of the system and any related modules by utilising storyboarding, schematic and minimalistic prototypes, and mock-ups in conjunction with user interviews to gather insightful user feedback on different proposed concepts.
2. We will evaluate heuristically and via cognitive walkthroughs with small multidisciplinary end-user (healthcare professionals and patients) groups the proposed prototypes to review and specify the main elements of the main

functionalities, interfaces, and the required communication frameworks all aligned to the healthcare standards (HL7 FHIR) and appropriate security (TLS) and data privacy (GDPR, 2002/58/EC) measures.

3. We will specify and design the PIFS platform's systems and/or modules data architecture, which will serve as the main background for the development and implementation of the back end. The PIFS platform's back end will be enhanced with active communication and data exchange interfaces in line with the RESTful (representational state transfer) API design model (RADM) and a method for its use. The front end will be developed with an easy-to-use, understandable, and familiar interface through the web browser and/or apps and desktop own data synchronisation applications.

The PIFS platform will be enhanced with the PIFS Secure Data Exchange Hub (PIFS SDEH) that will maintain the data management and data integration, adhering to the principles of FAIR (Findability, Accessibility, Interoperability, and Reuse of digital assets) and GDPR. We will emphasise an extensible, iterative, and modular approach to implement a secure, privacy conform and a project-wide data management strategy embedded into a sustainable PIFS SDEH architecture design. This will be elaborated on top of the end-users' requirements and needs, all highlighted, structured, and presented in the related project WPs.

The PIFS SDEH architecture will be based on open message communication and data exchange standards, and to assure practical interoperability, our main choice is the HL7 FHIR. Additionally, the PIFS SDEH will provide a powerful web interface for configuring, managing, and monitoring all data management functionalities for the administrator and/or other securely connected systems with active usage of the REST API.

Close to the advanced back-end interfaces and secure REST API communication, the PIFS SDEH will provide a web, front-end interface, which will allow the end-users to share, access, or store their data, files and folders, initiate and control data sharing, monitor who is doing what with their files, and search, comment, edit, view, and download files.

The PIFS SDEH will provide advanced control over data access and data sharing to the administrators and data 'owners' or data 'consumers'. The front end will be developed with an easy-to-use, understandable, and familiar interface through the web browser and/or apps and desktop own data synchronisation applications. In addition, its architecture will include advanced data analytics functionalities and interfaces enhanced with explainable AI models, which will be required for meta-analysis and/or to generate risk scores and other outcomes of interest.

The PIFS SDEH REST API will allow secure integration of the data sources in almost any AI/ML scenario. Almost all the core functionalities can be used by external code that calls the PIFS SDEH REST API.

To guide the product development according to end-users' needs and requirements, the Scientific and Patient Advisory Boards will be consulted throughout the WP.

1.2.1.6 Ethics, legal, and socioeconomic aspects (WP6)

The project will involve collecting and sharing large amounts of data with different levels of sensitivity and confidentiality (e.g. reported cases, trials, and examples to include). To ensure compliance with the latest EU Ethics and Data Protection regulations and recommendations, the project will conduct tasks in WP2 aiming at providing guidance across all WPs and to all partners.

The consortium will adopt the EC's Ethics Guidelines, and it will construct a framework for data security and privacy through interactions with data providers and their security specialists and ethics committees. We will carry out data mapping and legal basis analysis for data sharing and seek eventual approvals from providers' local ethical committees. The participation of the patients will be based on explicit consent. This is freely given, and patients can revoke it and exit the study at any point. Patient data used for analysis will be accessed for research purposes, and the participants have already allowed the use of their data in this manner. Ethical permits will be obtained by clinicians and extended to methods and techniques used in other WPs. Data pseudonymisation and anonymisation will be applied to reduce risks and prevent unauthorised access to sensitive data used for research and data analysis. Information enabling pseudonymisation will be stored for a limited duration, as requested by local regulatory requirements. We will ensure that all personal data is processed to not unduly prejudice the rights and freedoms of the participants.

We will perform a general assessment of the socio-economic impact of PIFS, using Norwegian population-based cohorts as an example (in particular, HUNT and MoBa; cf. Paragraph 1.2.2.2 below). These two cohorts gather data on participants in the general population and are combined with Norwegian registries that follow all hospital events, visits to general practitioners, and the need for social services. The analysis will gather data on health service resource use and social benefits for participants in the HUNT and MoBa cohorts. Participants will be followed from participation until the end of 2023, regardless of PIFS diagnosis. Analyses will compare resource implications for PIFS with other participants without PIFS after infection over the period from 2010 to 2023. We will present aggregated and disaggregated data to facilitate other countries adapting the analyses to their jurisdictions.

1.2.2 Relevant national or international research and innovation activities

The DEFINE consortium members all have extensive experience in collaborative projects at national, European, and international levels. Outcomes from these initiatives will contribute to the project's objectives.

1.2.2.1 The Collaborative on Fatigue Following Infection (COFFI)

The Collaborative on Fatigue Following Infection (COFFI) is an international scientific collaborative of post-infective cohort studies formally established in 2019 and led by Prof Wyller, AHUS, who is also the coordinator of DEFINE. The overarching aim of COFFI is to investigate factors influencing the development of long-term symptoms (in particular, fatigue) following certain infectious diseases (such as infectious mononucleosis (IM)). The pooling of resources, data, and biological samples from post-infective cohort studies worldwide is a prerequisite for achieving this aim, and a COFFI Joint Data Center (JDC) hosted by AHUS has been established. In addition, COFFI aims to promote knowledge exchange between researchers in the field of persistent post-infective symptoms and related areas and to undertake an advocacy role regarding research priorities and healthcare services.

Currently, 17 post-infective prospective cohort studies (of which six include COVID-19 patients) are included in COFFI, summing up to more than 24,000 individuals. In all cohorts, the acute infection was confirmed via laboratory diagnosis, participants were followed for at least six months, and fatigue was assessed with a validated, multi-item questionnaire. The COFFI collaborative comprises a multidisciplinary team of investigators, including infectious disease specialists, epidemiologists, clinical researchers, psychologists, and laboratory-based immunology and virology researchers. In addition, COFFI has a [Consumer Advisory Committee](#) (CAC) that meets regularly to consider new collaborative research proposals and advice on research plans and a [Scientific Advisory Board](#) (SAB) of distinguished PIFS researchers that also meets regularly to guide the consortium's research priorities.

COFFI is at the centre of the DEFINE project: Five of the consortium partners (AHUS, UNSW, AUMC, NUFSoM, and RIVM) are also key members of COFFI. The CAC has been formative in setting the DEFINE agenda and will be used throughout the project period to provide the patient/consumer perspective at all stages of the research process. The SAB will play a crucial role in overseeing the quality and applicability of the final product portfolio generated by DEFINE (WP5). The JDC encompasses rich datasets from 17 prospective cohort studies (about 24,000 individuals) across eight different infections and will be used for the main analyses in WP1 and WP2 (cf. table below).

Table 2: COFFI cohorts included in the COFFI JDC

COFFI cohorts within the Joint Data Centre	Sample size	Infectious agent(s)	Infectious disease
Patient-reported outcomes and thromboembolism after COVID-19 without hospitalisation , NO	458	SARS-CoV-2	COVID-19
Long term effects of COVID-19 in adolescents , NO	516	SARS-CoV-2	COVID-19
ReCOVer - internet-based Cognitive Behavioural Therapy [iCBT] for severe fatigue after COVID-19 , NL	114	SARS-CoV-2	COVID-19
RECoVERED study - Evolution of COVID-19 symptoms during the first 12 months after illness onset , NL	349	SARS-CoV-2	COVID-19
Prevalence and determinants of persistent symptoms after infection with SARS-CoV-2 , NL	15,000	SARS-CoV-2	COVID-19
The Post-hospitalisation COVID-19 study , UK	2,235	SARS-CoV-2	COVID-19
The CHIKGene cohort study on Reunion Island , FR	609	CHIKV	Chikungunya
Chronic Fatigue after Acute EBV Infection in Adolescents , NO	270	EBV	IM
Prospective Study of the Natural History of IM Caused by EBV , US	150	EBV	IM
Prospective Study CFS following IM , US	301	EBV	IM
Auckland IM and Campylobacter gastroenteritis cohorts , UK	246	EBV, <i>Campylobacter jejuni</i>	IM, Campylobacter gastroenteritis
Dubbo Infection Outcomes Study , AU	495	EBV, <i>C. burnetii</i> , RRV	IM, Q-fever, Ross River fever
Dutch Q fever study , NL	336	<i>C. burnetii</i>	Q-fever
Treatment of Q-fever fatigue syndrome with CBT vs doxycycline vs placebo , NL	155	<i>Coxiella burnetii</i>	Q-fever
Askøy Campylobacter Outbreak Study , NO	749	<i>Campylobacter jejuni</i>	Campylobacter gastroenteritis
LymeProspect study , NL	1,178	<i>Borrelia ssp.</i>	Lyme disease
Bergen Giardiasis cohort , NO	1,252	<i>Giardia lamblia</i>	Giardiasis
TOTAL	24,413		

1.2.2.2 Population-based cohorts

Six population-based cohorts linked with national health registries are available for DEFINE (cf. table below). Taken together, these cohorts contain more than 500,000 individuals across all age groups, the longest observational period is 39 years, and very rich datasets (including genomic data) are available. The datasets contain rich real-time information about symptoms, testing, and diagnoses related to COVID-19 during the pandemic.

In DEFINE, the population-based cohorts will be used for prediction analyses and risk factor identification in WP2, featuring both conventional hypotheses-driven methods and data-driven machine learning approaches. The outcomes of these analyses will inform the AI-based prediction tool further developed and refined in WP5. In addition, these cohorts will be exploited for the socioeconomic analyses in WP6.

Table 3: Population-based cohorts to be used in DEFINE

Cohort	Sample size	Description
MoBa NIPH, NO 1998-ongoing	284,926 (95,243 mothers; 75,210 fathers; 114,473 children)	A large birth cohort study with rich longitudinal phenotypic data from before and during the COVID-19 pandemic, incl. measures of prior psychological distress and adverse life events. Includes DNA and plasma samples, quality-controlled genome-wide genotype data.
HUNT NTNU, NO 1984-ongoing	~250,000	One of the largest health studies ever performed; encompasses questionnaire data, clinical measurements, and biological specimens (incl. DNA) from a county's inhabitants since 1984.
YoungAdult NIPH, NO 2020-ongoing	12,000 (8,000 women and 4,000 men), aged 18–30 y.o.	Monitoring the consequences of the COVID-19 pandemic, including vaccination effects; encompasses questionnaire data as well as biological specimens.
NorSen NIPH, NO 2020-ongoing	4,800 seniors (65–80 y.o.)	Monitoring of immune responses to COVID-19 and vaccination in seniors; encompasses questionnaire data as well as biological specimens.
CFS following IM in College Students NUFSOM, US 2014-2019	4,501 college students	Designed to study the natural history of infectious mononucleosis in young people; encompasses clinical data, questionnaire results, and biological specimens before, during, and after infectious mononucleosis.
NorFlu NIPH, NO 2009-2010	4,500 mothers and children	Monitoring of the consequences of the influenza A H1N1 pandemic infection and vaccination from pregnancy onwards; also contains data from the COVID-19 pandemic. Historic blood samples, including PBMCs, are available on more than 2,600 mother-child pairs.

1.2.2.3 Other relevant EU and national initiatives

In addition, we will build upon existing knowledge developed in recent EU and national projects.

Table 4: Examples of projects which outcomes will be leveraged in DEFINE

Project name	Partner	Description	Knowledge that will be leveraged
MINIRICO Clinical trial, NO 2023-2025	AHUS	Efficacy and safety of a mental intervention programme vs usual care and nicotinamide riboside vs placebo.	Experiences and results from the trial will inform the design of the intervention in WP4.
Long Covid Horizon Europe 2022-2026	HUS, NURO, CHINO	AI-based decision-support for prediction and management of Long COVID Syndrome.	Outcomes will inform the development of similar AI-based prediction tool for PIFS in WP5.
TIMELY Horizon 2020 2021-2024	AUMC	AI-based, risk prediction, prevention, and intervention platform to support care in coronary artery disease.	User interface (suitable for iOS and Android mobile devices) to support conversational pipelines for the chatbot in WP4.
AICCELERATE Horizon 2020 2021-2024	HUS, NURO, CHINO	Use of AI to improve patient outcomes within healthcare.	Expertise in AI and healthcare interventions.
CONVALESCENCE NHIR-UKRI, UK 2021-2023	UCL	Longitudinal qualitative study of Long COVID patients' experiences and management of Long COVID.	Experiences of fatigue and fatigue-related symptoms; experiences of healthcare systems in addressing these. Relevant to the qualitative part of WP4.
BRAINMINT ERC StG Horizon 2020 2019-2024	UiO	Use of advanced brain imaging to describe dynamic changes in brain and cognition and their relevance for complex traits during sensitive life phases, including adolescence.	Methods development, data sharing, access to 3T MRI scanner, and harmonised protocols. Opportunities to generalise findings across a population-based sample and large training sets.

1.2.3 Interdisciplinary approach

As stated in Section 1.1.2.3, the state-of-the-art scientific understanding of PIFS regards the illness as resulting from a complex blend of genetic or epigenetic and psychosocial vulnerabilities in concert with autonomic, hormonal, and immunological alterations. Moreover, as fatigue is essentially a personal experience that cannot be measured directly, insight into subjective perceptions and their associated interpretations, attributions, emotions, linguistic expressions, and behavioural consequences are pivotal. Furthermore, given the fundamental societal consequences of PIFS related to families, social networks, and the economy, a sociological and socioeconomic understanding is warranted.

Therefore, the DEFINE consortium is highly multidisciplinary in its composition, enjoying contributions from experts in clinical medicine, including paediatrics (mainly WPs 1, 4), clinical and experimental psychology (WPs 3, 4), neurobiology and brain imaging (WP3), epidemiology, including genetic epidemiology (WP2), molecular neuroendocrinology and immunology (WP3), digital health (WP5), artificial intelligence/machine learning (WPs 2, 5), big data analyses (WP2), qualitative research (WP4), health economics (WP4), socioeconomics (WP6), and legal and ethical aspects (WP6). In other words, PIFS will be investigated from a biopsychosocial perspective,⁸⁷ where insights from several biomedical disciplines are integrated with perspectives from the humanities and social sciences. In the coordination and management of DEFINE, this multidisciplinary ambition will promote real integration via internal conferences, workshops, and seminars. This will avoid the pitfall of research in separate fields being pursued in parallel without substantial interaction and collaboration.

1.2.4 Gender dimensions

PIFS and other chronic fatigue states are more common among females than males; several studies report a ratio of about 3:1.⁸⁸ Furthermore, the female sex is a well-established risk factor for the development of persistent symptoms, including fatigue following COVID-19 and other established triggers of PIFS.⁸⁹ Thus, PIFS is typically a ‘women’s disease’, with strong impact on women’s health, but with a disproportionately low attention scientifically and clinically; when compared with diseases typical for males, American researchers found that the disparity between funding and disease burden was double for diseases typical for females.⁹⁰ This gap is even wider for chronic fatigue states, with the conditions receiving a mere 7% of the funding commensurate with disease burden.⁹¹

The underlying reasons for sex differences are largely unknown. Hence, sex differences will receive strong attention:

- In WP1, we will ensure that the finalised PIFS case definition is equally valid among males and females.
- In WP2, the female sex will be thoroughly investigated as a potential risk factor for PIFS development; in addition, we will determine whether the female sex is a potential mediator of other risk factors and scrutinise potential interaction effects between the female sex and other risk factors.
- In WP3, the impact of the female sex will be investigated in experimental models of causality, determining, for instance, the extent to which sex differences impact the brain’s response to stimuli.⁹² In laboratory molecular assays, the effects of female sex hormones (estradiol, progesterone) and their receptors will be directly addressed.
- In WP4, we will determine intervention effects separately across females and males and determine whether sex exerts any mediating effects.
- In WP5, we will conduct analyses stratified by sex to scrutinise whether prediction models should be similar in females and males.

1.2.5 Open science practices

We will follow *five principles of open science*, adhering to the eight ambitions stated in the [EU’s Open Science policy](#). We intend to maximise the impact of our project results by sharing them as widely and as openly as possible.

1. **Open methodology:** We will follow an open methodology approach to research by not only sharing the research results from work packages but also the methods and data openly via the EU’s open research platform. With this, we will make our research comprehensible and reproducible for external researchers.
2. **Open-source:** The AI tools developed in WPs 2 & 5 will build on existing open-source software and be made freely available by our ICT/AI partners FHT and NURO, for possible modification and redistribution via the open-source platform GitHub. The source code in the health economic evaluation will also be shared via GitHub.
3. **Open data:** DEFINE will participate in the EU Open Research Data scheme adhering to the EC’s rules to facilitate *open research data*, and a Data Management Plan (D8.3) will be set up by M6. In the plan, the consortium will clearly define the rules for data management to be followed by all beneficiaries. Care will be taken to apply the Findable, Accessible, Interoperable, Reusable (FAIR) principles to the data collected within the project.
4. **Open access and review:** This approach includes adhering to the EC open access rules and guaranteeing free access to all peer-reviewed publications by either paying (gold) or placing them in an accessible repository (green). All publications will also be shared on the project website to facilitate access.
5. **Open educational resources:** Training material will be developed to inform and train end users (patients and health care providers) on how to use the project outcomes. The developed training material as well as the clinical

guidelines will be made open, to facilitate clinical sites in the adoption, implementation and uptake of the project outcomes on European and international levels.

When new platforms, tool or channels are launched by the EU to support their open science ambitions, the DEFINE consortium will evaluate and define best practices to implement these actions within the project, where relevant.

1.2.6 Research data management and management of other research outputs

All DEFINE beneficiaries are committed to actively managing their data throughout the entire research lifecycle. It is the obligation of each partner to ensure the reliability, discoverability, and usability of data, all of which is the essence of research. The collection of existing and new data will thus comply with obligations and requirements outlined in ethics and data protection regulations such as General Data Protection Regulation 2016/679 (GDPR) and the ePrivacy Directive (2002/58/EC). The consortium foresees the use and collection of the following data:

- **Existing data:** Prospective observational data from COFFI, incl. demographics, clinical investigations, laboratory tests, genetic markers, organ function tests, patient-reported outcomes (PROs), social/behavioural markers (WPs 1 and 2); big data from population-based cohort studies, incl. demographics, genetic markers, patient-reported outcomes (PROs), social/behavioural markers (WPs 2 and 6); ‘real-world’-data from existing data warehouse at HUS (‘HUS Data Lake’) (WP5).
- **Data generated in DEFINE:** Systematic reviews of scientific literature (e.g., meta-analyses) (WPs 1, 4); case definitions, operationalised criteria, guidelines (WP1); surveys/workshops/focus groups on experts’, clinicians’ and patients’ opinions (WPs 1, 5); risk factor models (WP2); functional and structural brain imaging data (WP3); (epi)genetic, transcriptomic, proteomic and cell physiology data (WP3); preventive intervention description, associated manuals and educational programs (WP4); data from clinical trial, incl. demographics, clinical investigations, laboratory tests, PROs, social/behavioural markers, beneficial/adverse effects, compliance (WP4).

The Guidelines for Data Management in Horizon Europe and the European Clinical Research Infrastructure Network (ECRIN) [certification standards](#) related to IT and data management will be applied.

FAIR principles: All digital research data generated in the project will follow the FAIR principles:

Findable



We will assign a unique and persistent Digital Object Identifier (DOI) to the items in the repository, thus making them easily findable; the consortium plans to make the Long COVID-related metadata available in the [European COVID-19 data sharing platform](#); for other conditions, trusted repositories such as [ZENODO](#) will also be considered.

Accessible



DEFINE (meta)data will be retrievable by its identifier; all beneficiaries will ensure open access to the deposited data as soon as possible, following the principle ‘as open as possible as closed as necessary’; if open access is not provided to the data needed to validate scientific conclusions, the respective beneficiary will provide the access – digital or physical – needed for validation purposes.

Interoperable



DEFINE (meta)data will use a formal, accessible, shared, and broadly applicable language for knowledge representation, and will include qualified references to other (meta)data. Interoperability resources such as [FAIRsharing](#) will be applied.

Reusable



The conditions under which the data can be used will be made transparent through easy-to-use copyright licenses, such as Creative Commons (Creative Commons Attribution International Public License, CC BY) or Creative Commons Public Domain Dedication (CC 0).

Data management: To implement the data policy, we will set up a **Data Management Plan**. The DMP be set up before the project start, and the final deliverables will be submitted in the first six months of the project, which will be openly accessible, and updated during the project. For the DMP, we will follow the structure of the template provided by the EC, which entails the following main components: 1) Data summary, 2) FAIR Data, 3) Allocation of resources, 4) Data security, 5) Ethical aspects, and 6) Other procedures for data management.

Data storage and transfer concept: At the project level, each research partner will store its data according to the respective institution’s data management rules. Results will be shared in the form of Deliverables, meeting minutes and other documentation on a cloud-based system provided by accelCH (see WP8).

Clinical data: CHINO will assist in setting up a secure portal, give access, and assist partners to populate clinical, lifestyle and omics data and images of patients. The reciprocal transfer of information between the partners and the electronic health record systems will be in accordance with the GDPR requirements and adapted to the confidentiality and regulatory issues at each site. To facilitate the data exchange, data and metadata will be stored and transferred in a format compatible with MS Office. Additionally, other formats may include csv, pdf, txt, dxf, dwg, tiff and GDSII-compatible formats. The data will be collected without any explicit personal identifying information. The portal will be maintained, and regular backups will be taken. #SCON-MET-CM\$# #SCOM-PL-CP\$# #REL-EVA-RE\$#

2 Impact #@IMP-ACT-IA@#

Non-communicable diseases (NCDs) pose a major health, societal and economic burden. NCDs are, for example, responsible for up to 80 % of EU healthcare costs.⁹³ PIFS, which is a highly prevalent NCD, has a profound impact on daily functioning, including work ability and quality of life, and therefore economic implications due to increased absenteeism and healthcare consumption. More recently, the post-COVID-19 condition or ‘*Long COVID*’ – where a majority of cases are considered a variant of PIFS – affects millions of people worldwide as a ‘pandemic within the pandemic’ with huge societal consequences, for example, keeping about four million people out of work in the US.

Hence the objectives of **Horizon Europe’s Destination 3 in the Health Work Programme** to focus research and innovation efforts on 1) better understanding diseases and their drivers; 2) better methodologies and diagnostics enabling timely and accurate diagnosis, the identification of personalised treatment options; 3) the development and validation of effective intervention; 4) innovative health technologies tested in clinical practice; 5) scientific evidence for policy-making at an EU and global levels. The DEFINE consortium is committed to contributing to these objectives along with the following impact areas of Horizon Europe’s Strategic Plan 2021-2024:

- Good health and high-quality accessible healthcare
- A resilient EU prepared for emerging threats
- High-quality digital services for all

2.1 Project’s pathways towards impact

The impact of DEFINE unfolds in the short, medium and long term, as the project results obtained within the five years of the project are used to achieve the **expected outcomes** of both the call topic and Destination 3. This process of transforming the project results into the desired expected outcomes towards the realisation of our long-term vision results will be described across the **three main impact dimensions of Horizon Europe’s Key Impact Pathways**: Impacts on scientific knowledge (Section 2.1.1.2), the overall economy and technology landscape (Section 2.1.1.3), and society (Section 2.1.1.4). The foreseen impact within and beyond the project is summarised in the Table below:

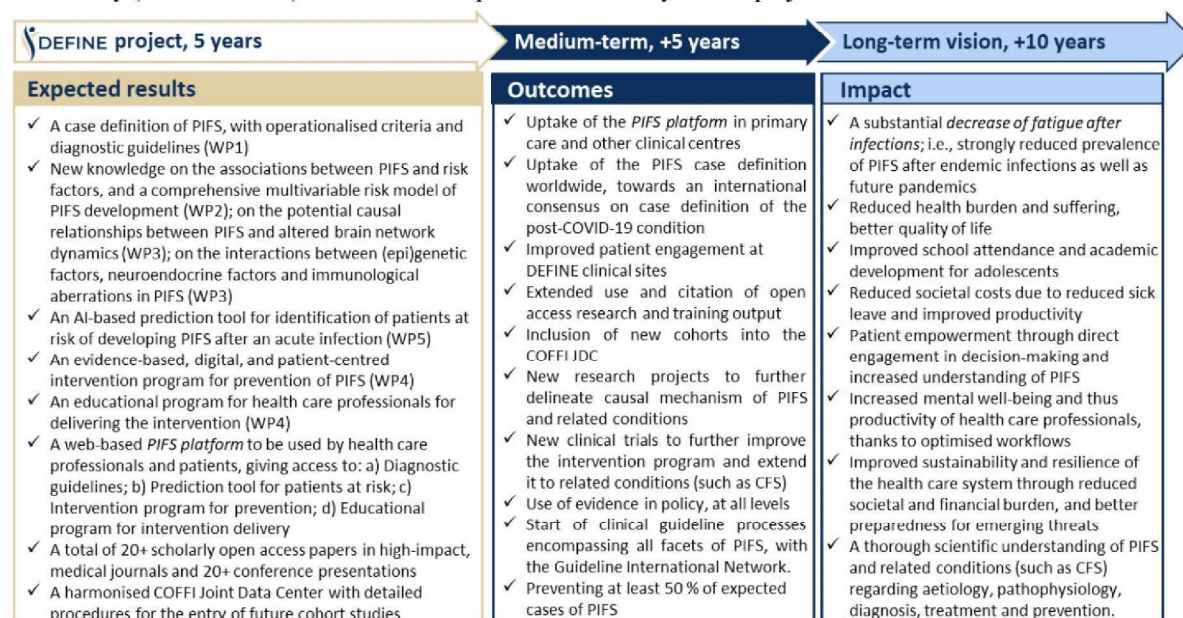


Figure 10: Foreseen outcomes and impact in the short-, medium- and long-term

2.1.1 Contribution of project results to outcomes and wider impact in the work programme

2.1.1.1 Expected Impacts of the call and destination

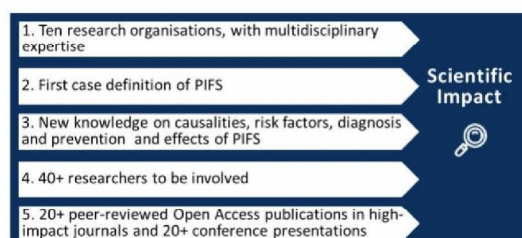
To achieve the highest impact possible, DEFINE contributes to several of the expected impacts of the Horizon Europe health **work programme’s destination 3**: “Tackling diseases and reducing disease burden”, and fully addresses the expected outcomes (EO) of the call topic **HORIZON-HLTH-2023-DISEASE-03-07: “Relationship between infections and non-communicable diseases”**.

Table 5: DEFINE contribution to the expected outcomes of the call HORIZON-HLTH-2023-DISEASE-03-07

Expected outcome of the call	DEFINE contribution
All players along the health care value chain are provided with new knowledge for a better understanding of the links between infectious diseases (IDs) and non-communicable diseases (NCDs) and comorbidities, incl. knowledge on host risk factors that impact the development of disease progression for NCDs and/or IDs	We will determine risk factors and potential causal links for the development and perpetuation of PIFS after COVID-19 and other infections. The examined risk factors/causal links will include genetic and epigenetic markers, neuroendocrinological and immunological aberrations, functional brain alterations, psychological, behavioural, and social/environmental factors.
Researchers and clinicians are provided with a robust evidence base that will contribute to the development of new or improved tools to diagnose and prevent the development and aggravation of NCDs as well as early treatment and management of patients suffering from co-morbidities following an infectious disease.	We will develop a validated, reliable and applicable case definition of PIFS after acute infections, accompanied by operationalised criteria and a diagnostic guideline. Furthermore, we will develop and assess the efficacy of an app-based intervention program for patients accompanied by an educational program for health care providers aiming to prevent PIFS development after acute infection.
Healthcare practitioners have access to knowledge to guide them on preventive measures, on early identification of diseases onset and of those patients at risk of developing severe disease progression, and on the optimal treatment of patients.	We will develop an AI-based prediction tool for early identification of individuals at risk of developing PIFS after acute infections, along with a web-based portal presenting the final product portfolio of DEFINE: a) The clinical guidelines for diagnosis of PIFS; b) The AI-based tool for early identification of patients at risk; c) The app-based intervention program for preventing PIFS; d) The educational program for the intervention.

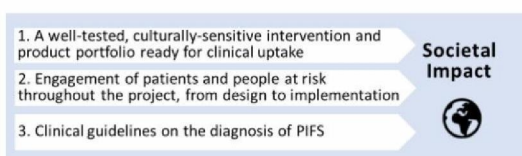
2.1.1.2 Scientific impact

DEFINE will generate a scientific impact by creating **high-quality new knowledge and enabling its diffusion, strengthening human capital in R&I, and promoting open science**. New knowledge in the areas of clinical medicine, clinical and experimental psychology, neurobiology, epidemiology, genetics, neuroendocrinology and immunology, along with social sciences and humanities applied to clinical contexts. With our focus, we intend to address significant knowledge gaps in PIFS and fatigue research, which is considered by a European Commission study as a high-burden but under-researched area.⁹⁴



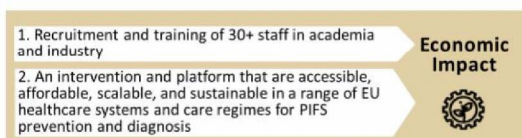
2.1.1.3 Societal impact

In DEFINE, we will contribute to EU and global policy goals by **reducing disease-related burden in society for patient, people at risk, families, and healthcare providers**. Early involvement in the co-design of the PIFS case definition, the intervention program and the PIFS platform, fosters the probability of user and patient acceptability along with its uptake in clinical settings. We hereby contribute to **the UN's Sustainable Development Goals (SDGs)**, specifically, SDG 3, which “ensures healthy lives and promote(s) well-being for all at all ages”, and **SDG Target 3.4** “to promote mental health and well-being” among patients with NCDs, by 2030.



2.1.1.4 Economic/technological impact

The DEFINE consortium will make the solution affordable to the healthcare systems in Europe and worldwide. To ensure the uptake of the PIFS platform and intervention program, their **cost-effectiveness and impact on the healthcare system and clinical workflows** will be thoroughly studied in WP6, while an Innovation Manager will oversee the innovation process within the project duration and prepare a **post-project roadmap for exploitation roadmap (D7.7)**. #SPRJ-OBJ-PO\$#



2.1.2 Requirements and potential barriers

To identify the possible obstacles and barriers to achieving the expected impacts of DEFINE, we have performed an analysis of the technology environment and identified appropriate mitigation measures (see Table 6).

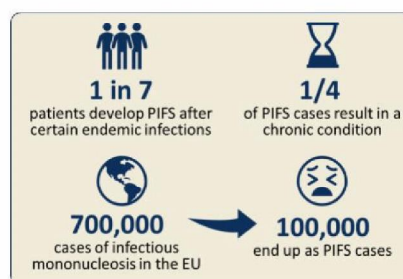
Table 6: Environment analysis and mitigation measures

	Potential barriers and obstacles	Mitigation measures
Politico-Legal	- Scientific controversies and public polemics over the understanding of PIFS, preventing appropriate political actions - Privacy legislation barriers	- Broad inclusion of researchers/stakeholders with different expertise and views in the consortium as well as in various expert groups (WPs 1 & 5); provision of high-quality research that will settle disagreements (WPs 2,3,4) - Detailed plan for dissemination to policymakers and general public outreach (WP7) - Assessment of potential barriers and mitigation measures prior to and during the project (WP6)
Economic	Reluctance of health care providers to invest as cost-effectiveness not clear	Assessments of economic impact on health care and society via health economic models (WP4)
Social-Ethical	- Reluctance of clinicians to integrate the <i>PIFS</i> portal into their clinical practice - Reluctance of patients to use the intervention program in the PIFS portal - Concerns on the use of personal health data - Low levels of digital literacy	- High user-friendliness and usability, following various iteration processes with patients and end-users (WP5) - Maximum transparency with regard to data collection and use (WP6)
Technological	Emergence of competing technologies	Market assessment and technology monitoring in the Roadmap for Exploitation (WP7, D7.7)

These potential obstacles will be addressed in the analysis of ethical, social, legal, and economical aspects (WPs 4 & 6), and monitored already during the project, through risk assessments (WP8). Pro-active communication, dissemination and exploitation measures will further help to overcome foreseen and unforeseen barriers.

2.1.3 Scale and significance of the project's contributions to the expected outcomes and impacts

The ultimate goal of DEFINE is to *decrease fatigue after infections*. At present, about 1 out of 7 patients develop PIFS after certain endemic infections such as infectious mononucleosis, as well epi-/pandemic infections such as COVID-19. A realistic aim for DEFINE is to reduce this number by at least 50 %. Infectious mononucleosis alone has a yearly incidence of about 0,7 % in adolescents and young adults resulting in an estimated number of 700,000 infected individuals across the European Union in this age group, of whom 100,000 will end up as PIFS cases with substantial long-term disability and poor quality of life. A reduction of 50 % implies a total of 50,000 persons spared from the immense burden of PIFS, and a correspondingly reduced strain on the families and health care providers, increased productivity, and reduced sick-leave costs. If, as an estimate, 1/4 of the PIFS cases after infectious mononucleosis end up as a permanent condition, the significance of DEFINE implies that *12,500 young people within the EU are rescued from life-long suffering and disability each year*. In the case of future pandemics similar to COVID-19, the scale and significance will be substantially higher.



2.2 Measures to maximise impact – Dissemination, exploitation and communication

#@COM-DIS-VIS-CDV@#

Measures to maximise impact will be delivered via WP7, led by accelCH, with extensive experience in EU projects, with the involvement of all partners. Support and feedback on the planned measures, and their long-term impact for commercial and non-commercial exploitation, will be received from a dedicated Innovation Manager at CHINO. The primary goals in WP7 are to raise awareness about the project and its objectives, to provide information on the DEFINE project and its potential impact through outreach activities, to disseminate the research results generated in the scientific WPs, and to pave the way for exploitation of the DEFINE innovations.

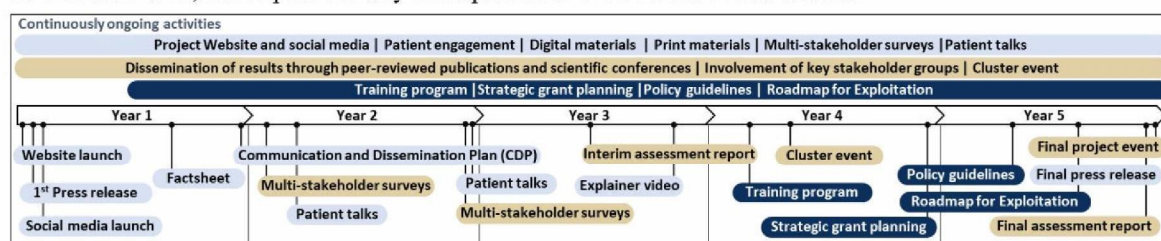


Figure 11: Dissemination, exploitation and communication timeline

2.2.1 Plan for the dissemination and exploitation including communication activities

All partners will contribute to dissemination, exploitation and communication through the following **joint strategies**:

- **Stakeholder involvement:** Dissemination and exploitation activities have been defined and adapted specifically for the target and interest group(s) they are addressing as their main audience. The proposed target-group orientation allows us to define and implement measures geared toward the specific needs of different audiences (see Figure 12). The project will collect feedback from interested and influential stakeholders and disseminate its results and achievements to them to maximise project impact.
- **Open Science (OA) Policy:** We will follow the [EU's Open Science policy](#) (see section 1.2.6) to maximise the impact of its project results by disseminating and exploiting research results as widely and as openly as possible.
- **Cross-channel and multimedia approach** to impart information and knowledge: to ensure the widest possible outreach to all stakeholders, the consortium will use different channels and different media to provide information about the project and to disseminate research and innovation results.
- **Using the extended network:** All partners have existing channels and measures, which the project will use to implement and multiply measures. DEFINE will notably benefit from the well-established networks of COFFI and its links with several EU-funded projects, such as [Long Covid](#), [AICCELERATE](#) and [ORCHESTRA](#).

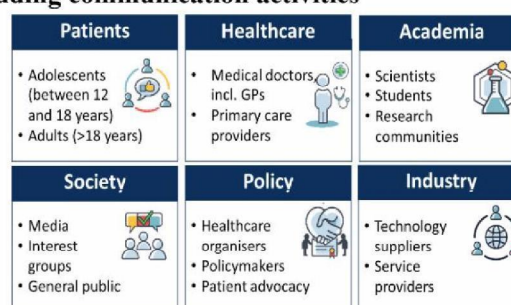


Figure 12: DEFINE target groups

By following the above-mentioned strategies, we will create awareness among the widest possible audience about DEFINE activities, results and outcomes for society. An initial **plan for dissemination, exploitation and communication**, are shown below, and a detailed communication and dissemination plan (D7.2), including a refined strategy, planned activities as outlined in WP7, and their expected impacts, will be set up at the start of the project. A roadmap for exploitation to facilitate the uptake of results will be developed in the final project year (D7.7). WP7 will be jointly implemented by all consortium members, guided by accelCH.

Activity lead	Description Target group	Impact KPI
Dissemination activities		
 Publications, conferences and special sessions <i>UNSW</i>	- Publish open access in peer-reviewed journals, e.g., <i>Brain Behaviour and Immunity</i>, <i>Nature Neuroscience</i>, <i>the Lancet</i>, <i>BMC Medicine</i>. - Present results at international conferences, e.g., IACFS/ME, WONCA Europe, ECCMID, and International Fatigue Congress. - Contribute to the EC's Knowledge Centre on Health Promotion and Disease Prevention, and European COVID-19 Data Platform by sharing relevant project outcomes via their platform. <i>Scientific community</i>	Peer scrutiny and validation, knowledge transfer, networking, and feedback on results <i>Min. 20 publications. Min. 20 conference presentations</i>
 eLearning <i>AUMC</i>	- The PIFS portal (WP5) will be made available in several languages, to facilitate clinical sites in the uptake of the project outcomes. - Training of local medical staff through webinars, which will be available online to reach a broader audience, also beyond the project. <i>Clinicians, medical staff and hospital management</i>	Training and transfer of knowledge. <i>200 downloads of material</i>
 Cluster event <i>accelCH</i>	- accelCH will organise a DEFINE cluster event, where several EU-funded projects funded under HORIZON-HLTH-2023-DISEASE-03-07 and other relevant calls, can present their results and outcomes. - Networking sessions to exchange knowledge, and foster synergies <i>Scientific community, clinicians, industry</i>	Knowledge sharing, stimulating future research <i>50 participants at event</i>
 Final project event <i>accelCH</i>	- Present final results at a key EU event, such as the EU Health Summit - Present the developed best practice guidelines - Invite members from the established networks, incl. members from the European Commission, EU member states <i>Patients, medical staff, healthcare professionals and policy-makers</i>	Knowledge sharing, validation and feedback from experts <i>60-80 participants</i>
Exploitation activities		
 Strategic grant planning <i>accelCH</i>	Strategic grant planning (SGP) conducted by accelCH in the fourth year to identify future funding opportunities for results and sub-results - Identify where further research is required to address unresolved issues to support improved care of PIFS across Europe <i>DEFINE partners and related communities</i>	Pre-selecting relevant calls, follow-up projects / <i>min 1 SGP</i>

Call: HORIZON-HLTH-2023-DISEASE-03-07 — Relationship between infections and non-communicable diseases

 Policy guidelines <i>AUMC</i>	• Guidelines, reports and recommendations for policymakers developed by AUMC on the integration of PIFS preventive treatment and diagnostics into standard of care and best practice factsheets. • Materials developed will be made freely available through the project website, presented at events and disseminated by AUMC. • Published results will be presented during the final project event. <i>Policymakers, relevant authorities, healthcare providers</i>	Inform healthcare professionals about new guidelines; brief policymakers; contribute to healthcare standards <i>to be defined in D7.7</i>
 Roadmap for exploitation <i>AHUS</i>	• The RfE (D7.7) outlines a plan for future commercial and non-commercial use of DEFINE results. • Develop strategies to overcome barriers (PESTLE, SWOT analysis) • Define the project scope, an implementation strategy, details on processes of a short- and long-term monitoring, evaluation plan. • IP and innovation management of all partners will be monitored by AHUS and supported by their local technology transfer offices. <i>Industry, potential collaborators, hospitals and planners</i>	Clear definition of strategies, measures and time plan for exploitation <i>to be defined in D7.7</i>
Communication activities		
 Project website, social media <i>accelCH</i>	• Constantly updated information on achievements, results and events. • Dedicated sections for healthcare professionals and patients, contacts and possibilities to interact with project members. • Links to social media for sharing relevant information. <i>All target groups</i>	Awareness raising, spreading knowledge on project results and events <i>300 users per month</i>
 Patient engagement <i>AHUS</i>	• Patient talks (workshops) offered by our Patient Advisory Board, involving voices of those with lived experience of PIFS, providing patients with the opportunity to hear experiences from a first-person perspective and gain insight into the challenges faced by those living with PIFS. These workshops will also be joined by experts and clinicians to contribute discussions with their professional feedback. • Patient-centred website section, as an information source for patients consisting of a permanently updated list of FAQs as well as a glossary translated into the languages of the countries participating in the clinical trial. This website page will also provide interested citizens with the possibility to contact the consortium through a contact form. <i>Patients, patient associations, healthcare providers, clinicians</i>	Informing patients and relevant audiences on procedures and objectives of DEFINE <i>3 workshops, 20 participants at each event</i>
 Digital and print materials <i>accelCH</i>	• Audience-specific print and online materials to show healthcare providers how DEFINE will benefit their work, incl. posters, flyers and roll-ups for use in hospitals and project-specific templates and factsheets. • Personas, use cases, visualised with audio-visual material, e.g., videos or infographics providing an overview of the benefits of the project. • Press releases and regular newsletters for key stakeholders, in collaboration with partners' PR departments. <i>General public, media, healthcare providers, patients, industry</i>	Information transfer, raising awareness and presenting the benefits <i>100 downloads of individual materials</i>

2.2.2 Strategy for management and intellectual property

The multi-disciplinary and cross-sectoral nature of DEFINE requires a **new approach to intellectual property (IP) strategy**, for two reasons. First, in medical sciences, traditional IP rights concepts still prevail, with patents being the most common form of IP protection. However, computing and IT build on knowledge-sharing to decrease development time, and enable community-supported development and code review as well as platform adoption. Second, considering the different interests of the partners, the quest for publications and the needs of academic partners to secure IPRs for their institutions, the DEFINE IP strategy will be fully adapted to this new setting. We will, hence, follow a **hybrid approach**, allowing partners to simultaneously support an **open science philosophy** at the industry partners while maintaining an **active IP programme** supported by the Technology Transfer Offices at universities.

IP management: To maximise the exploitation of new IP, an appointed **Innovation Manager**, Jovan Stevovic (CHINO), will oversee the IP and project innovation process, guiding all consortium members, in collaboration with their local **IP management support infrastructure**, towards a sustainable pathway for exploitation. They will coordinate a set of exploitation measures ranging from the development of a **roadmap for exploitation** (D7.7) to the identification of **patent filing** opportunities and the creation of **business models**.

IP rights: To facilitate the implementation of such a hybrid IP strategy, the consortium has agreed on the following:

- **Confidentiality:** All information provided by a partner to other partners within the project is confidential unless it was already known to the partner before the negotiations started, or the information provided is public property, or it is explicitly specified otherwise by the originator of the information.
- **Existing IP (Background):** All partners are the exclusive owners of any tools, data and information held prior to this project, as well as of copyrights or other intellectual property rights pertaining to such information. Several project partners will bring in backgrounds that will be used in the project, e.g., the Sensitive Data Services used to host the COFFI JDC, developed and hosted by the UiO; AUMC's preventive intervention developed from an existing CBT program; IP related to imaging analyses (UiO).
- **Access rights:** All partners will grant access to their background and foreground knowledge to other partners and their affiliates on a royalty-free basis unless otherwise agreed, if needed by the requesting partner for performing its tasks. Partners have agreed to use the information provided only for the purposes of conducting the project. Disclosure of confidential information to a third party requires the explicit consent of the originator.
- **IP Protection (Foreground/Results):** As a general rule, solely generated IPs will be owned by the generating partner, and jointly generated IPs will be jointly owned by the partners involved in its creation. In such cases, a separate Joint Ownership and Management Agreement will be signed by the partners concerned. The owning partner(s) will decide on a protection strategy for the newly generated knowledge (Foreground IP).
- **Dissemination (Publication rules):** Partners are required to give prior notice of any planned publication, 30 days before the dissemination or publication of project results, to all other members of the consortium. A separate extraordinary meeting may be convened. In case of objections, all reasonable measures will be taken to resolve these. Valid reasons for objection will be detailed in the Consortium Agreement and are likely to include a beneficiary's legitimate academic or commercial interest being compromised by the publication, or protection of foreground or background IPR being adversely affected and confidential information of another beneficiary being disclosed. Objections will be handled by the Coordinator according to the conflict resolution process.

Exploitation of expected outcomes: The expected project results will be used for commercial and non-commercial purposes. In WP7, we will develop a *Roadmap for Exploitation* (RfE, D7.7, M54) that will include a plan for the commercial and non-commercial use of project results, as well as a series of exploitation tools such as an updated stakeholder map, PESTEL and SWOT analyses. The Scientific Advisory Board and the Patient Advisory Board will be asked for advice on the RfE and the proposed rollout plan. This will help facilitate the use of the project results as outlined in Table 7. The management of the IP in DEFINE will be described and agreed upon in an IP management plan prior to the project start. The plan will be overseen and monitored continuously throughout the entire project period.

Table 7: Expected outcomes from the DEFINE Research and Innovation Action

Expected outcome (partner)	IP strategy	Measure
Harmonised dataset for cohort studies of PIFS (AHUS)	Open for researchers	Standardised import and harmonisation protocol to ensure the integration of future cohorts
Knowledge on risk factors and potential causal mechanisms (AHUS, UiO, FHT)	Passive protection	Open access peer-reviewed publications, further research
The PIFS platform (AHUS, NURO), incl. • Clinical guidelines (NUFSOM, UNSW) • AI-based prediction tool for early identification of patients at risk (AHUS, HUS) • "Fit after infection", an app to be used by at-risk patients for PIFS prevention (AUMC, HUS, AHUS, NUFSOM, APHP) • Training programme for healthcare professionals (AUMC)	Copyright on contents	Provided for free to non-profit research institutions, hospitals and GPs. The platform will be maintained by researchers at AHUS, and hosting costs will be covered by COFFI.
Health-economic models (AHUS-HS)	Passive protection	Open access peer-reviewed publications, further research

#§COM-DIS-VIS-CDV§#

2.3 Summary

Specific needs	Expected results	D & E & C measures
- PIFS-related burden continues exerting physical, emotional, and financial strains on a significant number of patients, families, and the health care system. - Despite its high prevalence, PIFS is an under-researched medical condition.	- A case definition of PIFS - New knowledge on risk factors and potential causal mechanisms of PIFS - An AI-based prediction tool to identify patients at risk after infection - A digital and patient-centred intervention programme for prevention of PIFS, with educational resources for clinicians - A web-based PIFS platform for clinicians and patients - A harmonised COFFI Joint Data Center, ready to integrate further cohort studies	Dissemination towards health care and the scientific community: Open access research output, training toolkit, scientific and policy events, clinical guidelines. Exploitation: IP management, digital demonstrations, policy recommendations, identification of funding opportunities, Roadmap for Exploitation. Communication towards citizens: Patient engagement, website and social media, print and digital material, press releases and media coverage, audio-visual and video.
Target groups	Outcomes	Impacts
- Patients, adolescent & adults - Healthcare professionals, in particular GPs and other primary care providers - Researchers and students in clinical medicine, IT and SSH - Policymakers, patient groups	Raised awareness in society for the DEFINE project. Uptake of open research outcomes in scientific community.	Scientific: New knowledge in various disciplines resulting from the case definition process, clinical studies, and the analysis of socio-economic aspects. Economic: Increased efficiency and sustainability of health care systems due to new knowledge and optimised workflows. Societal: Patient empowerment and improved quality of life; reduced PIFS-related burden; increased satisfaction of patients, relatives, and caregivers.

#\$IMP-ACT-IA\$#

3 Quality and efficiency of the implementation #@@QUA-LIT-QL@# #@@WRK-PLA-WP@#

The DEFINE project consists of eight closely aligned and fully integrated work packages (WPs), which are underpinned and supported by a thorough coordination and network organisation (WP8).

A valid, reliable and applicable case definition of PIFS will be developed in **WP1** and form the basis for the understanding of PIFS across the other WPs. In **WP2**, a multivariable risk factor model for PIFS (applying the case definition from WP1) will be elaborated based on existing patient cohorts and population-based cohort data. In **WP3**, we will determine potentially causal mechanisms for the development of PIFS through experimental studies exploiting functional brain imaging as well as molecular analyses of (epi)genetic, neuroendocrinological and immunological interactions. **WP4** entails the development of an app-based intervention program supported by a therapist (“Fit after infection”) informed by the previous WPs and aimed to prevent PIFS after acute infection; the program will be thoroughly assessed in a multicentre RCT across five countries. The outcomes of WPs 1 to 4 will feed into **WP5**, which consists of the iterative development of a digital and user-centred product portfolio enabling informed decision-support for GPs and other health care professionals, as well as the preventive “Fit after infection” program to be used by patients at risk of developing PIFS. Also, in this WP, the multivariable risk factor model from WP2 will be configured into an AI-based tool for early identification of patients at risk.

Ethical, legal, and socio-economic aspects related to the whole process will be identified and necessary adaptations will be conducted in **WP6**. Throughout the project, we will ensure proper dissemination of results to expert and non-expert audiences, such as researchers, clinicians, GPs, patients, and policymakers (**WP7**).

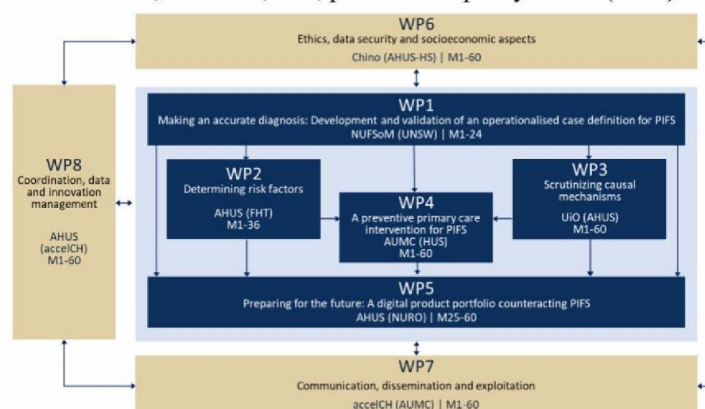


Figure 13: DEFINE PERT scheme

Table 8: List of work packages (Table 3.1a)

Table 8: List of work packages (Table 3.1a)

Work Package		Lead Participant		Resources	Duration	
No.	Title	No.	Short name	PMs	Start	End
1	Case definition of PIFS	05	NUFSoSM	40	1	24
2	Identification and modelling of risk factors	01	AHUS	94	1	36
3	Assessments of causal mechanisms	04	UiO	146	1	60
4	Preventive primary care intervention for PIFS	03	AUMC	269	1	60
5	A product portfolio counteracting PIFS	01	AHUS	96	25	60
6	Ethics, data protection and socioeconomic aspects	11	CHINO	54	1	60
7	Communication, dissemination and exploitation	13	accelCH	40	1	60
8	Coordination, data and innovation management	01	AHUS	47	1	60
Total person-months				786		

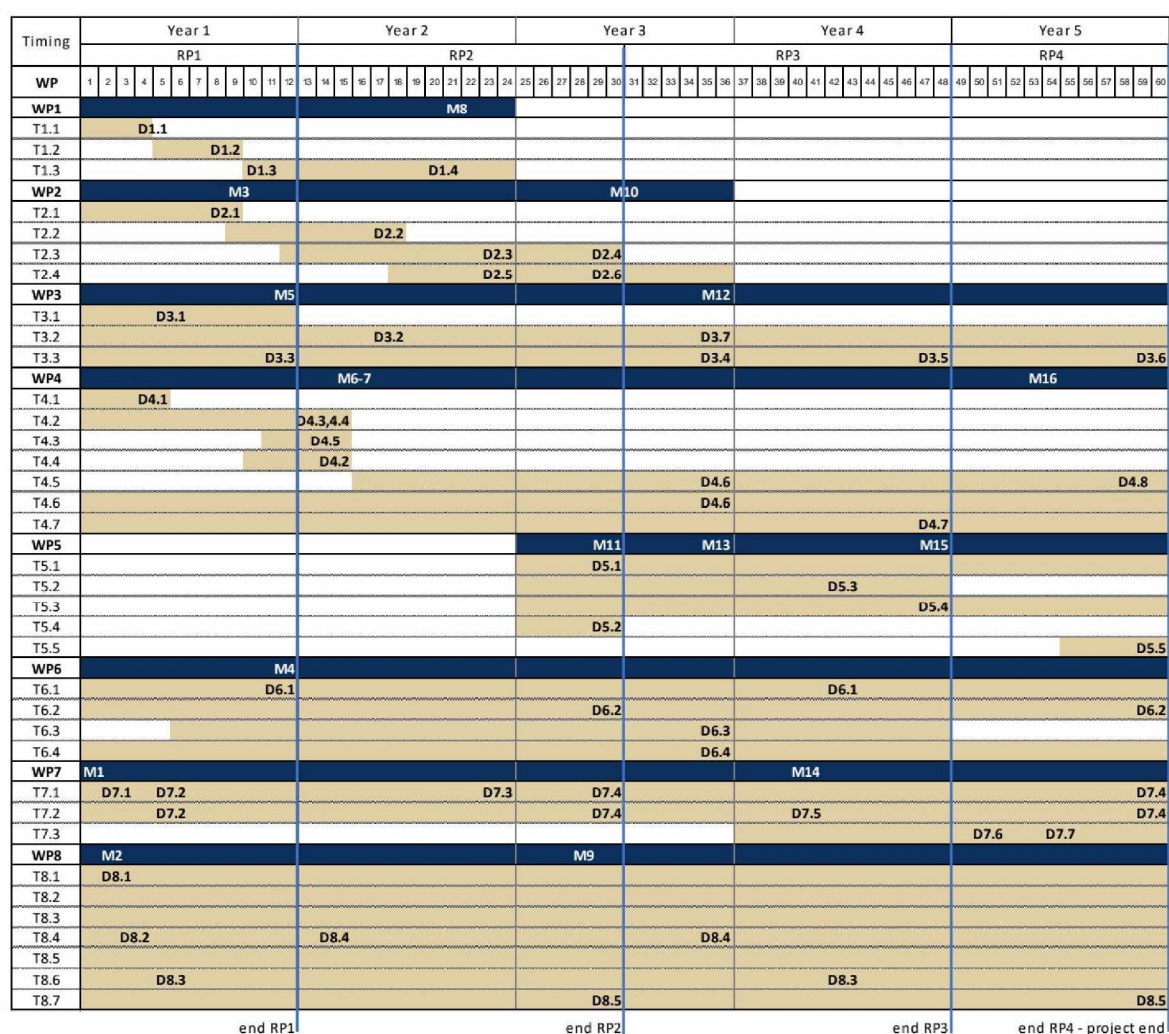


Figure 14: DEFINE workplan

Table 9: Work package descriptions (Table 3.1b)

Table 9: Work package descriptions (Table 3.1b)			
WP number	1	Lead / Deputy	5.1.2e
WP title	Making an accurate diagnosis: Development and validation of an operationalised case definition for PIFS		
Start date – End date of the WP		M1-M24	
Objectives: The main goal of WP1 is to formulate a valid, reliable and applicable case definition of PIFS for adults and adolescents, with operationalised criteria and guidelines for separating patients from controls. We will:			
• Perform a systematic literature review of existing PIFS case definition and associated research, especially research that is able to clearly separate cases from controls. • Convene a broad working group of key stakeholders including i) researchers, clinicians, epidemiologists, public health experts, relevant adult and paediatric specialist disciplines (e.g. infectious diseases, neurology, psychiatry, respiratory medicine), ii) patients and other stakeholders to arrive at a case definition and provide operational guidelines including recommended questionnaires, structured interview schedules, and case assessment protocols (e.g., including meaningful cut-offs for severity and frequency that have utility in distinguishing cases from control subjects). NUFSoM and UNSW are already involved in a similar project for the post-COVID-19 condition, in collaboration with WHO, NINDS, NIAID, CDC, and NHMRC Australia. • Determine the validity, reliability and applicability of the case definition of PIFS within the COFFI Joint Data Centre (JDC), and eventually modify the definition and associated operational guidelines according to the results such that the new case definition of PIFS identifies those with significant disability attributable to the condition.			
Description of work			
Task 1.1: Systematically review the literature regarding case definitions of PIFS, PVF (post-viral fatigue), ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) and the post-COVID-19 condition (lead: NUFSoM; participants: UNSW, AHUS, AUMC) (M1-4)			
• Systematically review the literature on case definitions of PIFS • Systematically review the literature on case definitions of the post-COVID-19 condition (and related conditions) • Systematically review the literature on case definitions of ME/CFS			
Task 1.2: Systematically review the literature regarding structured clinical interviews and validated questionnaires to characterise subjects with PIFS/PVFS/ME/CFS/long COVID in comparison to control subjects (lead: NUFSoM; part.: UNSW, AHUS, AUMC) (M5-9)			
• Systematically review the literature on studies defining the key symptom domains and disability associated with PIFS, as well as separating patients defined as having PIFS/PVFS from recovered and/or uninfected controls • Survey the literature on studies defining the key symptom domains and disability associated with PIFS after COVID, as well as separating patients defined as having PIFS from recovered and/or uninfected controls • Survey the literature on studies defining the key symptom domains and disability associated with ME/CFS, as well as separating patients defined as having ME/CFS from controls			
Task 1.3: Formulate and demonstrate the utility of an evidence-based case definition of PIFS (lead: NUFSoM; part.: UNSW, AHUS, AUMC) (M10-24)			
• Data from Tasks 1.1 and 1.2 will be reviewed and synthesised by an expert panel of researchers and patient representatives to develop an evidence-based, broadly applicable case definition of PIFS • The panel will assess the validity, reliability and applicability of the new, proposed case definition of PIFS in all COFFI JDC cohorts. It will use the new case definition on established COFFI cohorts that used validated questionnaires and applied protocolised clinical assessment (physical & mental health history and examination) and exclusionary criteria/investigations to confirm that patients previously rigorously classified with CFS or other similar disorders meet the new case definition of PIFS and that controls from those cohorts do not. • If necessary the process (steps 1-3 of Task 1.3) will be repeated until a definition of PIFS is developed that can be retrofitted to cover nearly all of the previously defined cases in the previous, well-studied COFFI JDC cohorts. NUFSoM, AHUS, UNSW, and AUMC are affiliated with several COFFI cohorts and will thus play a major role in evaluating how well the proposed definition works and in helping decide, in consultation with the expert panel, if any, and if so, how many iterations of steps 1-3 of Task 1.3 are needed.			

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WP number	2	Lead / Deputy	5.1.2e
WP title	Determining risk factors: Links between PIFS, acute infection markers, and host characteristics		
Start date – End date of the WP		M1-M36	
Objectives: The main goal of WP2 is to identify and advance knowledge on risk factors associated with the development of PIFS in adults and adolescents long after (i.e., at least 6 months) exposure to infection. More specifically, we will:			
• Harmonise clinical data from all COFFI cohorts (n=17) into a Joint Data Center (JDC) hosted by AHUS. • Apply the case definition of PIFS (WP1) on all JDC cohorts and population-based cohorts, and carry out prediction analyses resulting in multivariate models of risk factors across different infections • Further refine the multivariate risk model as well as identify potential causal relationships and amendable factors through the use of AI/ML techniques.			
Description of work			
Task 2.1: Harmonisation of clinical data across all COFFI cohorts (lead: AHUS; part.: FHT, CHINO) (M1-9)			
• AHUS and CHINO will refine the formal/legal and practical framework for data sharing into the JDC, building upon the existing digital infrastructure and privacy approbations obtained for COFFI. • AHUS and CHINO will assist COFFI collaborators that are still lacking formal data-sharing approval from their institutions in gaining this. • AHUS will assist all COFFI collaborators in importing de-identified data into the JDC. • AHUS and FHT will perform modification of all COFFI original data in order to obtain a de-identified, harmonised and merged dataset. Missing data will be replaced by multiple imputation techniques.			
Task 2.2: Identification of risk factors in post-infective cohorts (lead: AHUS; part.: FHT, UNSW) (M9-18)			
• AHUS will apply the case definition of PIFS (from WP1) on the merged dataset in JDC. • AHUS and UNSW will define an <i>a priori</i> list of potential predictors identified in previous studies. • AHUS and FHT will carry out bivariate and multivariate regression analyses with PIFS caseness as dependent variables (modified Poisson regression with log-link). • AHUS will explore potential predictors of recovery (i.e. conversion from PIFS caseness to non-PIFS caseness) in cohorts with long-time follow-up data.			
Task 2.3: Identification of risk factors in large population-based cohorts (leader: AHUS; participants: FHT, UNSW) (M12-30)			
• AHUS will apply the case definition of PIFS (from WP1) to the population-based cohorts. • AHUS will verify the diagnosis of PIFS through linkage with health registries. • AHUS and UNSW will define an <i>a priori</i> list of potential predictors, informed by Task 2.2. • AHUS and FHT will carry out bivariate and multivariate regression analyses with PIFS caseness as dependent variables. • AHUS will use the findings to refine the multivariate risk model determined in Task 2.2. • AHUS will explore potential predictors of recovery (i.e. conversion from PIFS caseness to non-PIFS caseness)			
Task 2.4: Modelling of causalities through AI/machine learning (leader: FHT; part.: AHUS) (M18-36)			
• FHT will apply machine-learning techniques (data-driven approach, no <i>a priori</i> assumptions) on the JDC and the population-based cohorts for the identification of risk factors for PIFS, taking advantage of the already applied case definition from WP1 in task 2.2 and task 2.3. • FHT will apply statistical and machine-learning techniques for modelling causal relationships, primarily focusing on potential amendable factors. • FHT and AHUS will use the findings to further refine the multivariate risk model determined in Task 2.3. This model will importantly inform WPs 3, 4 and 5.			

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WP number	3	Lead / Deputy	5.1.2e
WP title	Scrutinising causal mechanisms: Assessments of functional brain alterations and (epi)genetic, neuroendocrinological and immunological interactions in PIFS		
Start date – End date of the WP	M1-M60		
Objectives: The main goal of WP3 is to determine brain network underpinnings and neuroendocrine-immunological interactions as potential causal mechanisms for the development and alleviation of PIFS symptoms in adults and adolescents, informed by the finding from the risk-factor analyses of WP2 and applying the case definition of WP1. More specifically, we will:			
- Analyse and compare brain imaging data across patients with PIFS and healthy/recovered controls from selected COFFI cohorts as well as individuals recruited <i>de novo</i>, using harmonised experimental and functional imaging protocols (fMRI). - Design and perform experimental paradigms directed at assessing and manipulating fatigue states in PIFS patients and healthy/recovered controls recruited <i>de novo</i>, with brain network dynamics using functional brain imaging as the main read-out. - Design and perform laboratory assays across patients with PIFS and healthy/recovered controls, directed at identifying interactions between (epi)genetic (e.g., cortisol receptor gene methylation), neuroendocrinological (e.g., hair cortisol levels) and immunological (e.g. markers of inflammation) factors, using stored peripheral blood mononuclear cells (PBMC) from selected COFFI cohorts as well as individuals recruited <i>de novo</i>. - Perform functional brain imaging and neuroendocrine-immunological interaction analyses on a subset of patients (n=150) included in the clinical trial of WP4.			
Description of work			
Task 3.1: Common platform and harmonisation of brain MRI data across COFFI cohorts (lead: UiO; part.: NUFSOM, AHUS) (M1-12)			
- UiO, NUFSOM and AHUS will obtain approvals for sharing and common storage of brain MRI data. - UiO will provide a high-performance computing (HPC) platform for storage and harmonised analyses of brain MRI data. - UiO will develop and apply a harmonised processing pipeline for structural and functional MRI data and provide standardised readouts (e.g. brain morphometry, brain network connectivity etc) for further analyses and sharing with the other WPs.			
Task 3.2: Experimental causal mapping of the phenotypes and corresponding brain network configurations of fatigue states (lead: UiO; part.: NUFSOM, AHUS) (M1-60)			
- UiO, NUFSOM and AHUS will design and pilot experimental paradigms for provoking and manipulating the fatigue state and optimise the paradigms for simultaneous recordings of brain activity using functional MRI. - UiO and AHUS will apply the experimental paradigms and brain recordings (fMRI) in PIFS patients and healthy/recovered controls recruited <i>de novo</i>. - UiO and AHUS will conduct fMRI in the Norwegian subset of patients (n=150) included in the clinical trial of WP4. - UiO will develop and apply analysis pipelines for functional MRI data to obtain robust imaging-based markers of the brain network dynamics underlying fatigue states, which is key for mechanistic models and discoveries, as well as monitoring of treatment responses.			
Task 3.3: Assessment of immunological, (epi)genetic and neuroendocrinological interactions in PBMCs (lead: AHUS) (M1-60)			
- AHUS will design in-vitro laboratory experiments on peripheral blood mononuclear cells (PBMC) isolated from PIFS patients and healthy/recovered controls within the COFFI cohorts as well as recruited <i>de novo</i>. - AHUS will carry out the designed experiments focusing on the interaction of (epi)genetic, neuroendocrinological and immunological markers. The main read-out of these experiments is altered PBMC function as determined by transcriptomic, proteomic and/or cell physiology assays. - AHUS will carry out analogous laboratory assays in the Norwegian subset of patients (n=150) included in the clinical trial of WP4.			

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WP number	4	Lead / Deputy	5.1.2e
WP title	Impeding PIFS development: A preventive primary care intervention (“FIT after infection”) for severely fatigued patients after acute infection		
Start date – End date of the WP		M1-M60	
Objectives: The main goal of WP4 is to design and test an easily accessible web-based primary care intervention named <i>Fit after infection</i> that can be applied to individuals (adults and adolescents) experiencing severe fatigue following an acute infection with the aim of preventing PIFS. More specifically, we will:			
• Determine the evidence base for a preventive intervention against PIFS early after infection, including a systematic review of existing preventive measures and interventions for persistent fatigue states. • Develop in collaboration with patient representatives a low-intensity intervention consisting of psycho-education and behavioural interventions aimed at preventing PIFS using digital tools (web-based app with a therapeutic chatbot) supported by trained health care professionals, if needed. • Develop a training program for general practitioners and other health care professionals for effective delivery of the intervention. The training program will be informed by qualitative research on the perception of healthcare providers of PIFS and the extent to which it is amenable to a behavioural intervention. • Develop different strategies for the recruitment of patients depending on the cultural context and the health care system of the participating countries. The strategies will among others be based on qualitative research with respect to the doctor-patient relationship in PIFS – and the particular challenges related to this relationship and how they can be addressed during consultations. • Determine the efficacy of the intervention in a RCT comparing the proposed intervention with an active control condition (i.e., web-based relaxation training and general advice promoting a healthy lifestyle). The primary outcome is caseness, i.e., meeting the case definition of PIFS at post-intervention assessment. The RCT will be evaluated with a mixed methods design, incl. qualitative research to understand the contexts and mechanisms by which outcomes are achieved and how outcomes are perceived by patients. • Determine by a qualitative approach the experiences of patients and healthcare staff involved in <i>Fit after infection</i> through semi-structured interviews. • Determine the cost-utility of the intervention based on RCT data. • Explore the effects of the intervention on brain network dynamics and neuroendocrine-immunological interactions (cf. WP3).			
Description of work			
Task 4.1: Determine the evidence base for a preventive intervention (lead: HUS; part.: AUMC) (M1-5)			
• Systematic review of the literature on (preventive) behavioural interventions for PIFS. As only a limited number of studies should be available, we will extend our review to interventions in other persistent fatigue states. • The review will focus on digital or web-based interventions for patients with fatigue or other persisting symptoms after infection as compared to treatment as usual or other interventions. • We will observe recovery, symptoms, quality of life and functional ability as outcomes. • The emphasis in the review is on the effectiveness of these interventions. However, we will also thoroughly evaluate the content of the interventions, as well as feedback from users and health professionals. • Based on the literature, evidence-based strategies to prevent PIFS or reduce persistent fatigue will be described.			
Task 4.2: Development of <i>Fit after infection</i> (lead: AUMC; part.: HUS, AHUS) (M1-15)			
• Design of the core transdiagnostic intervention for PIFS consisting of a) a web-based app with a therapeutic chatbot included, and b) a web-based manual for health care providers on how to deliver the low-intensity intervention. The web-based app consists of modules which will be based on two existing evidence-based cognitive-behavioural interventions for PIFS following Q-fever and COVID-19 respectively. Eight modules will be available aimed at 1) psycho-education; 2) goal setting (e.g. resumption of school or work); 3) regulation of the sleep-wake pattern; 4) graded activity; 5) changing fatigue-related beliefs; 6) managing pain; 7) optimisation of social support; 8) realising goals. The intervention will be personalised based on a baseline assessment before the start of treatment. Based on questionnaires and a short intake interview, relevant modules will be selected. Two versions will be made available, one suitable for adolescents between 12 and 18 years, and one for adults (>18 years). The intervention has a stepped-care approach: for each perpetuating factor the intervention starts with psycho-education, followed by behavioural interventions supported by a therapeutic chatbot. If this does not suffice the patient will have a video-consultation with a healthcare provider. The intervention will be developed together with patient representatives. • Design of additional transdiagnostic intervention strategies or modification of existing strategies based on the output from WP2 and 3, the review of the literature, and the results of ongoing studies among the partners aimed at reduction of Long Covid symptoms/PIFS following COVID-19 with a behavioural intervention (see also task 4.1).			

- Development, using artificial intelligence techniques of a therapeutic chatbot which will aid patients in the implementation of the interventions. The chatbot can give advice or give comments on homework assignments on the basis of scenarios informed by experienced therapists, e.g. about measures of how to improve sleep or become more physically active. If not sufficient, a healthcare provider is available for help.
- Development of diagnosis-specific (e.g. COVID-19, infectious mononucleosis), and healthcare system-specific content of the intervention that can be added.
- Testing the prototype with a small number of patients using a think-aloud test strategy. Based on the feedback derived from the pilot, the intervention will be finalised. Following this, *Fit after infection* will be translated into the languages of the countries participating in the clinical trial
- Development of the active control condition consisting of a web-based app with relaxation training and general advice on a healthy lifestyle.

Task 4.3: Development of a training program for health care professionals (lead: AUMC; part.: HUS; UCL) (M11-15)

- Development of a training program for health care professionals, also informed by qualitative research on the perception of health care providers of PIFS and the intervention.
- Translation of the manual and training program into English.

Task 4.4: Development of recruitment strategies for the clinical trial testing the efficacy of *Fit after infection* (lead: HUS; part.: AHUS, AUMC, UNSW, APHP, RIVM, UCL) (M10-15)

- Optimisation of recruitment strategies for the different countries participating in the study informed by qualitative research on the experience of patients with respect to the doctor-patient relationship in PIFS and using the existing network of the partners, cohorts and social media. The qualitative work will focus on the perception of the patient to what extent a behavioural intervention is acceptable in light of the fact that a somatic disease was the trigger of the fatigue.

Task 4.5: Conducting a clinical trial testing the efficacy of *Fit after infection* (lead: AUMC; part.: HUS; AHUS; UNSW; APHP; RIVM; UCL) (M16-60)

- Setting up a screening procedure to determine the eligibility of patients for participation in the study.
- Finalising the assessment battery for the primary and secondary outcome measures, baseline characteristics and possible mediators and moderators of the treatment effect. Preparing the semi-structured interview for the qualitative evaluation of the intervention.
- Collaboration with WP3 which will assess neurobiological and other somatic markers possibly associated with a treatment response.
- Submitting the study protocol to the medical ethical board in the Netherlands for approval followed by arranging the approval of local ethical boards in the other countries which participate in the clinical trial.
- Training of research assistants who will screen and assess patients, and health care professionals who will deliver the intervention.
- Recruitment of patients at the sites following the recruitment strategies as developed in task 4.4.
- Screening of patients, performing baseline assessments and central randomisation of participants.
- Delivery of interventions with the supervision of healthcare professionals who support patients.
- Perform follow-up assessments and interviews.
- Data management, data cleaning and preparing the statistical plan.
- Evaluating and reporting the results of the study

Task 4.6: Charting the experiences of patients and healthcare staff (lead.: UCL; part.: AHUS; AUMC, HUS) (M1-60)

- Interviewing 12-15 healthcare staff per focus country (Norway, Finland, The Netherlands, 36-45 total).
- Interviewing 12-15 fatigue patients per focus country (36-45 total)
- Interviewing 20-25 intervention subjects per focus country (60-75 total) and 10-12 control group members per focus country (30-36 total)

Task 4.7: Health economic evaluation of the preventive intervention (lead: AHUS-HS; part.: AUMC) (M1-M60)

- Gather data on resource implications during the trial
- Calculate SF-6D based on RAND-36 data gathered in the RCT.
- Perform cost-utility analysis based on combinations of costs and QALYs for all jurisdictions in the RCT.

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WP number	5	Lead / Deputy	5.1.2e
WP title	Preparing for the future: A digital product portfolio counteracting PIFS for all players along the health care value chain		
Start date – End date of the WP		M25-M60	
Objectives: The main goal of WP5 is to collate outputs generated through WPs 1-4 and turn them into innovative, tailored, and applicable <i>products</i> that can be easily disseminated to and exploited by all players along the healthcare chain value as well as relevant patient groups. This product portfolio – the PIFS Platform - will be key to diminishing fatigue after endemic as well as epi-/pandemic infections, in line with the overarching aim of DEFINE. More specifically, we will:			
- Develop the web-based, modularly organised PIFS Platform containing: a) Clinical guidelines to be used by health personnel for diagnosis of PIFS according to a validated and operationalised case definition (from WP1); b) An AI-based prediction tool to be used by health personnel for early identification of patients at risk of developing PIFS after acute infection (from WP2); c) An app to be used by at-risk patients for the prevention of PIFS development (from WP4 – “Fit after infection”); d) An educational program for health personnel on the usage of the preventive intervention (from WP4). The PIFS platform will be developed following a structured and iterative process with a continuous focus on the end user's needs and requirements. - Develop a PIFS Secure Data Exchange Hub (PIFS SDEH) that will maintain the PIFS Platform data management and data integration when used by health personnel and patients, adhering to the principles of the GDPR and FAIR.			
AHUS, as project coordinator, is leading this WP to ensure consistency with the WPs 1-4 outputs.			
Description of work			
Task 5.1: Collating practical outputs from WPs 1-4 (lead: AHUS) (M25-60)			
- AHUS will continuously collate relevant outputs from WPs 1-4 to a designated server area that can be easily accessed by other participants in the WP. - AHUS will collate and structure end-user requirements and needs based on a survey of health personnel and patients, an advisory panel of patients and clinicians, and inputs from the Patient Advisory Board.			
Task 5.2: Further development of the AI-based prediction tool using clinical real-world data (lead: HUS; part.: AHUS) (M25-48)			
- HUS will adapt and test the feasibility of the predictive algorithm (from WP2) in real-world data from infectious disease patients (e.g. COVID-19, infectious mononucleosis, giardiasis) transformed to OMOP format and gathered in the Academic secure data analytics platform at HUS. - HUS will implement the AI-based prediction tool in an electronic health record system to ensure optimal functionality. The tool will be tested in both primary and secondary healthcare data, and the ability to identify patients at risk of PIFS will be reported.			
Task 5.3 Iterative development of the PIFS Platform (lead: NURO; part.: AHUS, HUS, AUMC) (M25-60)			
- NURO will develop the main PIFS Platform functionalities (UX) and interfaces (UI), implementing Open Source Privacy and Security Toolkits. - AHUS will develop practical clinical guidelines in collaboration with the Guidelines International Network (GIN) for arriving at a PIFS diagnosis in adults and adolescents, based upon the output of WP1; NURO will provide appropriate web design for inclusion in the PIFS platform modular structure. - HUS will develop the final AI-based algorithm for the identification of patients at risk of developing PIFS after infection (from WP2 and task 5.2 above); NURO will provide an appropriate web design for inclusion in the PIFS platform modular structure. - AUMC will develop the final “Fit after infection” app to be used by at-risk patients for the prevention of PIFS development (from WP4); NURO will provide an appropriate web design for inclusion in the PIFS platform modular structure. - AUMC will develop the final educational program for health personnel to accompany the “Fit after infection” app; NURO will provide appropriate web design for inclusion in the PIFS platform modular structure. - AHUS will oversee the quality and applicability of the final PIFS platform, in close collaboration with other consortium partners, the Patient Advisory Committee and the Scientific Advisory Board.			
Task 5.4: Data management strategy (lead: NURO; part.: CHINO) (M25-30)			
- NURO will undertake an iterative development of the PIFS Secure Data Exchange Hub (PIFS SDEH). - CHINO will oversee the legal and ethical issues pertaining to the PIFS SDEH.			
Task 5.5 Technical support and further development (lead: NURO) (M55-M60)			
NURO will provide technical support and refinement of the PIFS Platform and the PIFS SDEH.			

WP number	6	Lead / Deputy	5.1.2e
WP title	Ethics, data security and socioeconomic aspects		
Start date – End date of the WP	M1-M60		
Objectives: The project entails the construction of a large repository of data with varying levels of sensitivity and confidentiality. Hence the need to comply with the latest EU Ethics and Data Protection regulations and recommendations. The main objectives of WP6 are:			
• Ethics: This consortium will invest significant effort to ensure that all outputs are ethical and trustworthy. This is especially important with the AI-based tool, and the primary governing ethical principle will be <i>primum non nocere</i>—first, do no harm. • GDPR compliance and legal framework: We will develop an architecture and data repository that are completely compliant with GDPR, and ensure that data is stored in a suitably robust manner. • Data and architecture security: Considering the sensitivity of data, we will ensure that the created repository guarantees privacy and security by design and that the data sharing among partners implements state-of-the-art security standards. • Socioeconomic analysis: Analyse socioeconomic aspects of PIFS by comparing healthcare resource use among PIFS and non-PIFS both before infection and after the infection and diagnosis of PIFS			
Description of work			
Task 6.1: Delivering an ethical project. (lead: CHINO) (M1-60)			
• CHINO will identify applicable ethics requirements and issues surrounding the whole project considering medical ethics, EU Ethics Guidelines for Trustworthy AI, and the AI Act, and ensure their application. • If necessary, CHINO will coordinate the recruitment of external ethics advisors to sit on an ethics advisory panel. Their role will be to offer advice and assistance on any ethical aspects that are needed. • CHINO will produce ethics reports and workshops for the project partners.			
Task 6.2 Ensuring data privacy and GDPR compliance (lead: CHINO) (M1-60)			
• Understand the precise GDPR and privacy requirements to enable the necessary data sharing for this project. • Create or oversee the creation of several GDPR legal documents, including Data Processing Agreements, Registers of Processing Activities and Joint Controllership Agreements. • Ensure that partners’ Data Protection Officers and legal representatives contribute to and approve the created data processing agreements to enable data sharing.			
Task 6.3: Secure data sharing and architecture for DEFINE repository (lead: CHINO) (M6-48)			
GDPR mandates that health data may only be processed if it is protected using suitable organisational and technical measures. CHINO will:			
• Perform a gap assessment and eventually improve the technical and security measures already adopted by the COFFI JDC, based on minimising the risks identified in the previous tasks and according to the “Data protection by design and default” (art 25). • Instruct partners in implementing measures such as encryption, pseudonymisation, audit logging and consent management (art. 32). • Report on the final GDPR status of the project, including preparing the data protection impact assessment (DPIA). This work will feed into a final report on the overall compliance of the project across all relevant regulations, laws, and standards.			
Task 6.4: Assessment of the socio-economic impact of PIFS (lead: AHUS-HS) (M1-60)			
• Gather data from HUNT and MoBa cohorts. • Gather data from Norwegian registries for HUNT and MoBa cohort participants. • Merge data from cohorts and registries and compare healthcare resource consumption among PIFS and non-PIFS before and after infection. • Perform separate analyses of social service use and work participation among HUNT and MoBa participants related to PIFS status.			

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WP number	7	Lead / Deputy	5.1.2e
WP title	Communication, dissemination and exploitation		
Start date – End date of the WP	M1-M60		
Objectives: The main goal of WP7 is to raise awareness and disseminate results for the project as a whole and our key innovations. To this end, we will:			
• Develop and plan a dissemination and communication strategy to ensure the widest possible outreach of the project in a multi-stakeholder Communication and Dissemination Plan. • Deliver cross-media communication activities to raise awareness (Task 7.1). • Disseminate the project results to the scientific community and complementary research initiatives (Task 7.2). • Exploit the commercial and non-commercial opportunities of the DEFINE solution, developments and outcomes to stakeholders interested in the further use and development of results (Task 7.3).			
Description of work			
Task 7.1: Audience-targeted communication and engagement (lead: accelCH; participants: all partners & networks) (M1-60)			
Raising awareness for the project to society, and patients and informing healthcare providers on the DEFINE solution are key to our public engagement strategy. Section 2.2.1 describes all activities to help achieve this.			
• Communication and Dissemination Plan (CDP) to maximise the impact of the project results, accelCH will set up a multi-channel and multi-stakeholder outreach strategy with input from all partners (D7.2). In the CDP, we will define messages tailored to specific target groups; specify public engagement and dissemination measures; and set up monitoring processes to evaluate the progress of outreach measures. accelCH will monitor the implemented measures to assess the individual activities and adapt any activities required to maximise impact. • To support dissemination and communication activities throughout the project, accelCH will set up and maintain the project website (D7.1), which will notably function as the main source of information and resources related to the project, partners, latest developments, publications, and public deliverables for all stakeholders. • accelCH with the input from all partners will develop digital and print material incl. factsheets, infographics, press releases, and audio-visual material such as videos to explain to different audiences the key objectives and impacts of the DEFINE project and innovations. All material shall be available on the website. • Patient engagement led by AHUS to ensure the active engagement of patients in the project including the implementation of patient-oriented lectures, surveys and an interactive patient-centred website page to interest relevant stakeholders to follow the project as it develops through the communication tools that will be set up. • Multi-stakeholder surveys to engage with key audiences and receive and implement feedback.			
Task 7.2: Disseminate scientific and technological results (lead: UNSW; participants: all; duration: M1-60)			
• All partners will present their findings through oral presentations, posters, specific sessions, and conference papers, at international conferences such as IACFS/ME, WONCA Europe, European Forum for Primary Care. • Comply with the EU's Open Science policy and guarantee free access to all publications. • Contribute to the EC's Knowledge Centre on Health Promotion and Disease Prevention, European COVID-19 Data Platform by sharing relevant project outcomes via their platform. • Cluster Event organised by accelCH and AHUS with other relevant EU-funded projects on non-communicable diseases to ensure knowledge transfer and to collaboratively overcome barriers as well as policy and decision-makers to present key results and outcomes from DEFINE. • Final project event organised by accelCH at the EU Health Summit. The consortium will invite members from the established networks including members from the European Commission, decision-makers from EU member states and COFFI's existing networks. to present the final project results and the developed policy guidelines.			
Task 7.3: Exploit the commercial and non-commercial opportunities (lead: AUMC; part.: all) (M37-60)			
• Roadmap for Exploitation developed by AHUS (D7.7, M54) to ensure the commercial and non-commercial uptake of project results including the development of an IP and innovation strategy and management as well as exploitation plans in the short-, mid- and long-term. • Training program, developed by AUMC, consisting of patient guidelines for app Fit after infection usage, a clinical manual describing how to use and evaluate the digital solution, to be used by general practitioners and other primary care providers. These learning materials will cover explanations of the approach taken, how to deliver an effective preventive intervention for patients, setup and use of the portal. • Policy guidelines - AUMC will prepare policy guidelines, which will include recommendations on future guidelines and international regulations based on results from the clinical trial (WP4). • Strategic grant planning to be conducted by accelCH with input from the whole consortium to identify future funding opportunities for individual or joint results and innovations.			

WP number	8	Lead / Deputy	5.1.2e
WP title	Coordination, data and innovation management		
Start date – End date of the WP	M1-M60		
Objectives: The main goal of WP8 is to ensure an efficient and effective implementation of the DEFINE Research and Innovation Action through an organisational structure with clear roles and responsibilities and well-defined management procedures. More specifically, we will:			
• Ensure effective coordination and decision-making in the project • Facilitate efficient organisation, communications and administration • Deliver timely reporting and executing financial management • Assess potential risks, execute the contingency plan and manage the quality of work • Oversee legal and ethics compliance for the overall project and in collaboration with WP6 • Manage the innovation process, including data and IP management in collaboration with WP6 and WP7			
Description of work			
Task 8.1: Coordination and governance (lead: AHUS; participants: all) (M1-60)			
• Establish the project-internal bodies and management team. • Set up external monitoring structures ensuring ethical and scientific oversight.			
Task 8.2: Organisation, communications, and administration (lead: accelCH/AHUS; participants: all) (M1-60)			
• Set up and maintain the secured, private online Document Management System (DMS), accelCLOUD, operated by accelCH, which will be linked to the public project website (see WP7). • Provide and maintain project templates, contact lists and communication manual. • Organise all meetings at the consortium level and WP leader calls. Meetings will be combined with other project activities such as scientific workshops and other dissemination measures. • Monitor collaboration between the project participants and the progress of work.			
Task 8.3: Reporting and financial management (lead: AHUS; participants: all) (M1-60)			
• Compile and review technical input from all beneficiaries for the regular internal progress reports. • Compile and submit the periodic reports and the final report to the EC within 60 days after the end of each reporting period. All reports will follow the “Guidelines on project reporting” for Horizon Europe projects. • Distribute the EU funding (pre-financing, interim and final payments) to the beneficiaries according to the payment scheme as defined in the Consortium. • Monitor the appropriate use of resources and assist all beneficiaries in financial matters. • Approve cost financial statements of beneficiaries as part of the periodic reports to the EU.			
Task 8.4: Quality and risk management (lead: AHUS, accelCH; participants: all) (M1-60)			
• Produce a Quality Assurance Plan to ensure a high level of quality of project activities. • Monitor the work progress regarding quality aspects and early risk detection in order to execute the contingency plan (see Section 3.1). accelCH has developed a Horizon Europe project-specific Excel-based Risk Monitoring tool that will be used and maintained throughout the lifetime of the project. • Undertake two risk assessments before the start of the clinical trial and during its implementation (M14, M36).			
Task 8.5: Contracts management and legal compliance (lead: AHUS, CHINO; participants: all) (M1-60)			
• Maintain, amend and update, if necessary, the Grant Agreement. • Monitor legal compliance of partners with the Consortium Agreement. • Coordinate ethical issues with WP6, the privacy advisors at AHUS and the Regional Committee for Medical Research Ethics in Norway.			
Task 8.6: Data management (lead: CHINO; participants: all) (M1-60)			
• FAIR data management: Make the DEFINE research data findable, accessible, interoperable and reusable, if possible, in real-time, at the latest shortly after generation (FAIR principles) to ensure it is soundly managed. • Data Management Plan (DMP): The DMP will be submitted by M6 and be compliant with existing legal EU regulations on data protection and international standards. An update of the DMP will be conducted by M42. • PEARL analysis: Development of practical solutions for Political, Ethical, Administrative, Regulatory and Legal (PEARL) barriers that hamper the timely and openly sharing data through DEFINE.			
Task 8.7: Innovation management (lead: AHUS; participants: accelCH, CHINO, support from all) (M1-60)			
• Promote an open access policy in collaboration with the WP7 leader. • Monitor the dissemination and exploitation of results as laid down in the Consortium Agreement. • Guide the innovation process from a clinical and business perspective. • Monitor IP and implementing the project’s exploitation strategy.			

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Table 10: List of deliverables (Table 3.1c)

No.	Name and short description	Lead	Type	Level	Due
D1.1	Literature review of case definitions of PIF/PVF, ME/CFS, long COVID	NUFSOM	R	PU	4
D1.2	Data review: Review of ability of case definition(s) of PIF/PVF, ME/CFS, long COVID to separate cases from controls	NUFSOM	R	PU	9
D1.3	Expert panel: consensus on definition of PIFS	NUFSOM	R	SEN	10
D1.4	Expert panel: testing of new definition of PIFS	NUFSOM	R	SEN	21
D2.1	Operating Joint Data Center , with a merged and harmonised dataset	AHUS	DATA	SEN	9
D2.2	Multivariate regression model of PIFS risk factors across infections	AHUS	R	PU	18
D2.3	Refined multivariate regression model of PIFS risk factors across different infections	AHUS	R	PU	24
D2.4	Amendable risk factors with causal relationship to PIFS	FHT	R	PU	30
D2.5	Risk-factor identification tool: Supervised methods to identify risk factors	FHT	OTHER	SEN	24
D2.6	AI tool based on machine learning methods: AI tool using ML methods for patient identification	FHT	OTHER	SEN	30
D3.1	Harmonised imaging data: Imaging data jointly stored, processed and prepared for harmonised statistical analysis across COFFI sites	UiO	R	PU	6
D3.2	Brain functional and morphometric correlates of PIFS across sites: MRI findings from PIFS case-control comparisons & clinical correlates	UiO	R	PU	18
D3.3	Validated experimental test-suite: Experimental paradigm for assessing and manipulating fatigue states and their brain network dynamics	UiO	OTHER	PU	12
D3.4	Harmonised and richly phenotyped functional imaging data: Collected, quality assured and processed experimental and brain imaging data from recruited PIFS patients (n: 50) and healthy/recovered controls (n: 50)	UiO	DATA	PU	36
D3.5	PIFS case-control comparison of brain network configurations modulating fatigue states in PIFS patients and healthy controls	UiO	R	PU	48
D3.6	Effects on preventive intervention on brain network configuration: Longitudinal brain imaging data from the PIFS patients	UiO	R	PU	60
D3.7	Insight in immunological, (epi)genetic and neuroendocrinological risk factor's impact on immune cell function	AHUS	R	PU	36
D4.1	Review of literature on (preventive) interventions for PIFS	HUS	R	PU	5
D4.2	Study initiation package incl. registration nb, protocol, ethical approvals	AUMC	R	SEN	15
D4.3	Prototype app/therapeutic chatbot available in different languages	AUMC	OTHER	SEN	15
D4.4	Final version interventions: Preventive intervention and active control	AUMC	OTHER	SEN	15
D4.5	Treatment manual and training program for health care professionals	AUMC	DEM	SEN	14
D4.6	Mid-term recruitment report across clinical sites and risk analysis	AUMC	R	SEN	36
D4.7	Health economic evaluation: Finalised cost-utility analysis	AHUS	R	SEN	48
D4.8	Report on the status of posting results in applicable registries	HUS	R	SEN	58
D5.1	End user requirements collated and structured for the PIFS platform	AHUS	R	SEN	30
D5.2	Data management strategy: Establishment of the PIFS SDEH	NURO	DEM	SEN	30
D5.3	Patient phenotypes and risk prediction in real world data	HUS	R	PU	42
D5.4	Identification of patients at risk and early detection in real world	HUS	R	PU	48
D5.5	PIFS platform established: incl. the complete product portfolio	NURO	DEM	PU	60
D6.1	Reports on ethics and its application within the project	CHINO	R	SEN	12,42
D6.2	Summary of regulatory compliance incl. legal and technical provisions	CHINO	R	SEN	24,60
D6.3	Data security architecture and interim compliance update	CHINO	R	SEN	30
D6.4	Socio-economic assessment: Findings from socio-economic analyses	AHUS-HS	R	SEN	36
D7.1	Project website , including social media	accelCH	DEC	PU	2
D7.2	Communication and dissemination plan incl. strategies, measures, KPIs	accelCH	R	PU	6
D7.3	Patient talks , including surveys	AHUS	R	PU	24
D7.4	Interim & final impact assessment reports to monitor effectiveness	accelCH	R	SEN	30, 60
D7.5	Cluster event to foster synergies with other projects.	accelCH	R	PU	40
D7.6	Policy guidelines for policy and decision makers	AUMC	R	PU	50
D7.7	Roadmap for exploitation to support uptake of results	AHUS	R	SEN	54
D7.8	Final event to present the results and outcomes	accelCH	DEC	PU	60
D8.1	Governance report: Governance bodies and decision-making processes	AHUS	R	SEN	2

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D8.2	Quality assurance plan: Guidelines to ensure a high level of quality	accelCH	R	SEN	3
D8.3	Data Management Plan overall and per WP. Update in M42	CHINO	DMP	SEN	6, 42
D8.4	Risk assessment reports before and during the clinical trial	accelCH	R	SEN	14, 36
D8.5	Innovation reports: Reports on available and future IP	AHUS	R	SEN	30, 60

*Type: R: Document, report; DEM: Demonstrator, pilot, prototype, plan designs; DEC: Websites etc.; DATA: Data sets, etc.; DMP: Data management plan; ETHICS: Ethics issues; SECURITY: Security issues; OTHER: Software, etc. **Dissemination level: PU – Public, fully open; SEN – Sensitive

Table 11: List of milestones (Table 3.1d)

No.	Milestone name	WP	Lead	Means of verification	Due
M1	DEFINE website live	7	accelCH	Website URL and D7.1 submitted	1
M2	Governance bodies established	8	AHUS	D8.1 submitted	2
M3	Operating Joint Data Center	2	AHUS	D2.1 submitted	9
M4	Legal framework for data sharing	6	CHINO	All parties are ready to share necessary data	12
M5	Validated test suite for fatigue states and their brain network dynamics	3	UiO	D3.3 submitted	12
M6	Preventive intervention available and implemented	4	AUMC	Intervention available and usability demonstrated in pilot	15
M7	First patient randomised	4	AUMC	Start clinical trial	16
M8	A case definition of PIFS developed and tested	1	NUFSom	Case definition developed and fitted into the COFFI JDC cohort study patients	21
M9	Draft innovation report approved	8	AHUS	Draft D8.5 available	28
M10	Amendable risk factors with causal relationship to PIFS	2	FHT	A risk factor model drafted for publication	30
M11	The AI algorithm reads real-world clinical data	5	HUS	Proven feasibility of the algorithm in real world data	30
M12	PIFS patients and controls recruited	3	UiO	D3.4 submitted	36
M13	PIFS Platform functionalities and interfaces defined	5	NURO	A report on the functionalities and interfaces of the PIFS platform	36
M14	Cluster event implemented	7	accelCH	D7.5 submitted	40
M15	Predicting PIFS from clinical records	5	HUS	The prediction tool makes PIFS risk estimates from patient health record systems	48
M16	Last follow-assessment	4	AUMC	Last patient complete follow-up	54

Table 12: Critical risks for implementation (Table 3.1e) #@RSK-MGT-RM@#

Description of risk	Likelihood/severity	WPs	Proposed risk-mitigation measures (lead)
Expert panel not able to come to a consensus definition for PIFS	Low/High	1	Use of the Delphi process. (NUFSom)
Formal/legal obstacles relating to data sharing from certain COFFI cohorts into the JDC	Medium/Low	2	Extended contact or negotiation with hosting institutions. The project may proceed without all COFFI cohorts included in the JDC; most cohorts can provide sufficient statistical power. (AHUS)
Not feasible to apply the case definition of PIFS across all population-based cohorts	Medium/Low	2	The project may proceed without all population-based cohorts included; a majority of cohorts will still provide sufficient statistical power. (AHUS)
Data sharing approval for imaging data declined due to international privacy regulations	Medium/Low	3	Apply federated harmonised analysis pipelines which do not require sharing of sensitive data. (UiO)
Lack of experimental control and low sensitivity/specificity for paradigm assessing and manipulating fatigue states	Medium/Medium	3	Apply existing and validated experimental paradigms for assessing and manipulating general states of cognitive effort, assumed to be closely linked to fatigue states. (UiO)
Difficulty recruiting patients	Medium/High	3, 4	Different strategies have been developed to facilitate recruitment incl. self-referral. (AHUS)
Therapeutic chatbot algorithm suboptimal	Medium/Medium	4	Extensive experience in designing chatbots. (AUMC)
Attrition of patients in clinical trial	Medium/Medium	4	Contact with health care professionals and different techniques applied in the app. (AUMC)
Outputs from WPs 1-4 are delayed	Medium/Low	5	Work can be flexibly directed to different tasks dependent on progress in other WPs; in a worst-case scenario, preliminary results from WPs 1-4 can be used until final outputs are available. (AHUS)

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Inadequate information on the infection and clinical presentation of PIFS in patient health records	Medium/Medium	5	Natural language processing methodology will be used to extract useful information from clinical notes. (HUS)
Getting access to sufficient data to ensure robust and unbiased AI models	Low/High	6	Clinical partners to provide a contact person to help facilitate access to data. Partners already committed to data sharing. (CHINO)
Potential resistance to use of AI-based clinical guidelines by clinicians making it hard to assess effectiveness	Medium/Low	6	All AI models will be created in accordance with the EU Ethics Guidelines for Trustworthy AI. The project partners will ensure use of the Ethics guidance in their own institutions. (CHINO)
Withdrawal of partner	Low/Medium	8	Try and resolve any conflict. Each WP has a co-leader to ensure replacement. Failing that, suitable alternatives will be considered. (AHUS)

Resources: The requested EU contribution amounts to € 6,895,025. The Australian and Swiss governments will provide additional € 743,500 for the participation of the associated partners UNSW and accelCH. These numbers are realistic given the ambition and relatively large size of the consortium. The potential financial benefit of DEFINE far exceeds the requested funding and offers a high gain to the EU and its societies.

The distribution of the staff efforts (Table 13) reflects the importance of the clinical studies, and is crucial to achieve the development, testing and validation targets. WP4 is a large RCT, running for five years, including preparatory work and leading to a multicentre study across Europe.

Among the other direct costs, all clinical sites have been allocated € 10,000 for communication costs related to the recruitment of patients and controls. The foreseen subcontracting involves support needed for AI/ML activities at AHUS within WP2 (€ 50,000), the development of the therapeutic chatbot and the corresponding platform at AUMC in WP4 (€ 120,000 each), along with the adaptation, to be performed by a software company, of two research platforms ([tekenradar](#) and [infectieradar](#)) to select patients that are eligible for the intervention trial at RIVM. A total of € 30,000 has been set aside by AHUS as contributions to COFFI participating institutions to provide access to their cohorts in WP2.

Table 13: Summary of staff efforts (Table 3.1f)

#	Short name	WP1	WP2	WP3	WP4	WP5	WP6	WP7	WP8	Total PM
1	AHUS	6	48	45	48	15	12	6	20	200
2	HUS	0	0	0	54	31	0	1	1	87
3	AUMC	4	0	0	98	6	0	6	1	115
4	UfO	0	0	99	0	2	0	1	1	103
5	NUFSOM	15	0	2	0	0	0	1	1	19
6	APHP	0	0	0	21	0	0	1	1	23
7	RIVM	0	0	0	18	0	0	1	1	20
8	UNSW	15	0	0	21	0	0	4	1	41
9	UCL	0	0	0	9	0	0	1	1	11
10	FHT	0	40	0	0	2	0	1	1	44
11	NURO	0	0	0	0	36	0	1	1	38
12	CHINO	0	6	0	0	4	42	1	3	56
13	accelCH	0	0	0	0	0	0	15	14	29
Total PM		40	94	146	269	96	54	40	47	786

Table 14: 'Subcontracting costs' items (Table 3.1g)

1	AHUS	Cost (€)	Description of tasks and justification
	Subcontracting	5.1.1.c	external support for AI/ML activities
3	AUMC	Cost (€)	Description of tasks and justification
	Subcontracting	5.1.1.c	Development of the chatbot (€ 5.1.2.e) and of the platform (€ 5.1.2.e) (WP4)
7	RIVM	Cost (€)	Description of tasks and justification
	Subcontracting	5.1.1.c	Adaptation of research platforms to select patients that are eligible for the intervention trial (WP4)
11	NURO	Cost (€)	Description of tasks and justification
	Subcontracting	5.1.1.c	Development activities for 2D/3D design support (e-learning front-end, dashboard, gamification interfaces, templates, etc.)

Table 15: 'Purchase costs' items for partners which purchase costs exceed 15% of personnel costs (Table 3.1h)

5	NUFSOM	Cost (€)	Justification
	Travels	5.1.1.c	Consortium meetings (5*3 persons*€ 5.1.1.c), travel and accommodation for conferences (€ 5.1.1.c)
	OCS		Structured Interview/Survey Development, Evaluation (€ 5.1.1.c), Open Access costs (€ 5.1.1.c), Software & IT supply (€ 5.1.1.c)
	Total	€ 45,900.00	
6	APHP	Cost (€)	Justification
	Travels	5.1.1.c	Consortium meetings (5*2 persons*€ 5.1.1.c), travel and accommodation for conferences (€ 5.1.1.c)
	OCS		Communication/public relations costs for patient recruitment (€ 5.1.1.c), GP participation (€ 5.1.1.c), Open Access costs (€ 5.1.1.c)
	Total	€ 35,000.00	
11	NURO	Cost (€)	Justification
	Travels	5.1.1.c	Consortium meetings (5*3 persons*€ 5.1.1.c), technical meetings on site (€ 5.1.1.c)
	Equipment	5.1.1.c	Secure Server Infrastructure (Web, API, Databases, etc) (€ 5.1.1.c)
	OCS		Unity assets buy-in for serious game development (€ 5.1.1.c)
	Total	€ 40,000.00	

Table 16: 'Other costs categories' items (Table 3.1i)

2	HUS	Cost (€)	Justification
	Internally invoiced goods and services	5.1.1.c	Access to supercomputer facilities
	Virtual access to research infrastructure		Findata register use fee

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3.2 Capacity of participants and consortium as a whole #@CON-SOR-CS@# #@PRJ-MGT-PM@#

The DEFINE network is led by experienced and internationally recognised researchers, who are leading and/or are involved in numerous European and international initiatives and organisations in fatigue following infections. DEFINE will benefit from the expertise of four university hospitals, six research organisations, and three SMEs.

- **Multidisciplinarity and complementary expertise:** Each participant brings unique expertise to the network and across the development and implementation processes, i.e. on clinical medicine; infectious diseases; clinical and experimental psychology; neurobiology and brain imaging; epidemiology; neuroendocrinology and immunology; digital health; AI/ML; data sciences; health economics; socioeconomics; and legal and ethical aspects, as described in Section 1.2.3.
- **Access to infrastructure:** All DEFINE partners have the necessary infrastructure and state-of-the-art equipment to ensure the successful development and implementation of DEFINE into clinical practice. The consortium will benefit from the unique COFFI Joint Data Center at AHUS, which includes pooled clinical data from 17 COFFI prospective cohorts, making it by far the largest database of its kind in the world. UiO provides access to a High-Performance Computing platform for storage of sensitive brain imaging and experimental data, and state-of-the-art facilities for brain MRI and cognitive experiments (incl. EEG). CHINO offers a bespoke compliance development platform (Chino.io Toolkit) to enable compliance with the GDPR technical requirements, including secure storage, data encryption, pseudonymisation, consent management and audit log. Further details on partners' infrastructure can be found in the participants' profiles in Part A.



Figure 15: DEFINE consortium overview

- **Role and adequate resources:** Each partner has a specific role, as described in each Work Package in Section 3.1, and has been allocated adequate resources to contribute to the project objectives (see Section 3.1).
- **Wide European and global dimension:** Five EU Member States, two associated countries (Norway and the UK) and three non-associated third countries (Australia, Switzerland, and the US) are represented in the consortium. They all have national funding to study PIFS and will all participate in this endeavour. The clinical sites are based in five different European countries. This allows for the project outcomes to be applied to many different healthcare systems and settings. The involvement of the partners in European and global networks as well as the presence of international Advisory Boards (see p. 2) further widen the outreach potential of DEFINE.
- **Private sector involvement:** Three SMEs will significantly contribute to the project, namely NURO, CHINO, and accelCH. NURO is an international R&D and software company focused on interactive applications, notably in digital health. CHINO is a legal-tech and cloud technology company that supports health IT companies and innovators to ensure compliance with privacy and security regulations related to the processing of sensitive data. Building on over 20 years of experience in the management and dissemination of EU projects, accelCH will contribute to the monitoring, dissemination, exploitation, and communication of project results with dedicated tools. accelCH has organised three successful Cluster Events in the fields of [digital health](#), [manufacturing](#) and [renewable energy](#), in which more than 20 EU-funded projects had the opportunity to present their results.
- **Other countries and international organisations:** The consortium include NUFSoM, UNSW, and accelCH which are located respectively in the United States, Australia, and Switzerland. The UNSW Kirby Institute has a long track record of research on diverse aspects of infectious diseases, including prevention, treatment and pathophysiology. The UNSW team leader, Prof. Lloyd was recognised as a Member of the Order of Australia, for service to medicine and the community, particularly in research in infectious diseases. Dr. Katz at NUFSoM is well-known for his significant research and academic contributions and has been conducting NIH-funded research related to chronic fatigue syndrome since 1997. Both Prof. Lloyd and Dr. Katz are key members of COFFI. NUFSoM, as a US-based entity, is eligible for funding in the Horizon Europe Health cluster calls. Funding for accelCH will be provided by the Swiss State Secretariat for Education, Research and Innovation ([SERI](#)), while UNSW participation will be funded through [a specific call](#) of the Australian National Health and Medical Research Council supporting Australian participation in collaborative research under Horizon Europe.

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**Fit after INfEction: a randomised controlled trial testing
the efficacy of a behavioural intervention aimed at
preventing Post-Infective Fatigue Syndrome (FINE trial)**

Call: HORIZON-HLTH-2023-DISEASE-03-07 —
Relationship between infections and non-communicable diseases

Clinical Study Document

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1 Description of the clinical study

1.1 Title, acronym, unique identifier of the clinical study

Title: Fit after INfEction: a randomised controlled trial testing the efficacy of a behavioural intervention aimed at preventing Post-Infective Fatigue Syndrome (PIFS)

Acronym: FINE

1.2 Study rationale

Persistent fatigue is prevalent in individuals following many acute infectious diseases (Ceban et al., 2022; Hickie et al., 2006; Hulme, Hudson, Rojczyk, Little, & Moss-Morris, 2017; Reukers et al., 2019). Fatigue during the acute phase of an infection is part of the stereotyped acute sickness response, an adaptive reaction to the infection. However, fatigue often persists after the typical recovery period and can have detrimental effects on the patients' functioning, quality of life and societal participation (Reukers et al., 2019; Verveen, Wynberg, et al., 2022). If this disabling fatigue and related symptoms persist for more than 6 months and cannot be explained by the presence of another physical or mental condition, a diagnosis of Post-Infective Fatigue Syndrome (PIFS) can be made. Persistent, disabling fatigue is common after infectious diseases. For example, at least 10% of patients following COVID-19 (Van der Maaden et al., 2022), 5% of patients following Lyme disease (Ursinus et al., 2021), and 20% of patients following Q-fever report chronic fatigue and related symptoms that lead to significant disability (Reukers et al., 2019). PIFS leads not only to impairments in patients' health but also to high illness-related economic costs (Pheby et al., 2020). Therefore, timely intervention to prevent patients recovering from an acute infectious disease from progressing into persistent fatigue has the potential to alleviate the long-term impact of endemic infectious diseases on health and functioning. With the latest PIFS now recognised to be a prevalent sequel of the COVID-19 epidemic, the overall ambitions of the DEFINE consortium will include a focus on this context. Moreover, developing a transdiagnostic intervention will make us better prepared for the next pandemic by ensuring that we can intervene in a timely fashion to prevent acute fatigue from developing into PIFS.

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

PIFS is most likely multi-factorial determined but its pathophysiology remains largely unknown (Verveen, Muller, et al., 2022). Existing evidence suggests that the severity of the acute infection, emotional distress, female gender and low physical fitness are significant predictors of the development of PIFS (Katz et al., 2018; Verveen et al., 2022). There is also ample evidence that behavioural factors play a role in the persistence of fatigue following infection and more generally in long-term medical conditions (Fritschi & Quinn, 2010; Hofman, Ryan, Figueroa-Moseley, 5.1.2e & Morrow, 2007; Hulme et al., 2017; Menting et al., 2018). Examples of these factors are sleep problems, inactivity or an unevenly distributed activity pattern. This implies that a behavioural intervention may be beneficial in preventing acute fatigue following an infection becoming chronic and developing into PIFS.

There is already some evidence that behavioural interventions can reduce fatigue and disability in existing PIFS. A recent study by one of the DEFINE partners found that cognitive behaviour therapy (CBT) aimed at post-infective fatigue following COVID-19 led to a significant reduction in the severity of fatigue and functional impairment compared to care as usual (Kuut et al., submitted). The majority of patients were no longer severely and persistently fatigued following treatment, and this result was maintained at follow-up 1 year after the end of treatment. Previously, the same approach was found effective in the treatment of PIFS following Q-fever (Keijmel et al., 2017). In both studies the intervention was based on a cognitive-behavioural model of PIFS which assumes that the infection triggers the onset of fatigue whereas cognitive-behavioural factors, like a disrupted sleep-wake pattern,

may maintain fatigue and slow down or even prevent recovery. Interventions based on this model have also proved to be successful in reducing persistent fatigue in patients with other long-term conditions (Menting et al., 2017; Okkersen et al., 2018; Poort et al., 2020). Positive effects were not only found in adults but also in adolescents (5.1.2e et al., 2021; Nijhof et al., 2023).

In addition to the close similarities in the symptom complex in PIFS following several different infections (Hickie et al., 2006), the fact that fatigue following both Q-fever and COVID-19 can be reduced with a similar behavioural intervention suggests that fatigue is a transdiagnostic phenomenon (Goertz et al., 2021; Menting et al., 2017). This enables the development of generic interventions for PIFS that may contribute to its management irrespective of the specific infection which triggers the symptoms. This fits well within the Horizon Europe call aimed at improving the preparedness to face the next pandemic, as a truly transdiagnostic intervention for PIFS could be swiftly implemented. For this, an evidence-based transdiagnostic intervention should be developed that has been tested in patients who are fatigued following different endemic infections.

Aside from CBT, other behavioural approaches like graded exercise programs or psycho-education have been shown to be able to reduce fatigue following an infection or in other long-term medical conditions characterised by fatigue (Andersen, Rowland, & Somerfield, 2015; Kim et al., 2019). Ideally, a behavioural intervention would incorporate different evidence-based elements that together can reduce fatigue following an intervention.

Most behavioural interventions for fatigue have been tested in populations with longstanding symptoms when the fatigue and functional impairments have already become entrenched. There is evidence that a long symptom duration is associated with less favourable outcomes of behavioural interventions (Janse, Bleijenberg, & Knoop, 2019). It is likely that an early intervention, starting shortly after the symptom has commenced, can help prevent the evolution of PIFS - but this has not been empirically tested. An effective preventative intervention could potentially significantly contribute to reducing the long-term negative consequences on health and societal costs of infectious diseases.

Behavioural interventions for PIFS, especially CBT, are generally intensive, necessitating a considerable time investment from both therapists and patients. One way to reduce the intensity of the treatment is to offer the intervention online, supported by contacts with a healthcare provider. This approach has been successfully applied in the CBT trial for PIFS following COVID-19 (Kuut et al., submitted). It is likely that patients with a short symptom duration need an even less intensive approach. For a subgroup, psycho-education may well suffice, while other patients need more support. The development of internet-supported interventions has already made the treatment of fatigue more efficient and less burdensome (Abrahams et al., 2017; Menting et al., 2017). A more recent development is the use of chatbots as an effective Artificial Intelligence-based tool to help patients implement behavioural interventions and give feedback on their progress without the direct engagement of a health care provider (Vaidyam et al., 2019; Aggarwal et al., 2023). Therapists are then only needed for troubleshooting or for more complex problems. These developments will greatly facilitate the development of a preventative intervention for PIFS that delivers stepped care, ranging from psycho-education to AI-supported interventions to direct therapeutic intervention by a health care provider. Such an efficient intervention format could, due to its largely online format, be initiated almost immediately when a care need arises and is scalable to reach a wide patient group at a limited cost.

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

The aforementioned CBT studies mainly included patients already meeting the criteria of PIFS, i.e., suffering from persisting fatigue with associated disability lasting more than six months (Keijmel et al., 2017; Kuut et al., submitted). To the best of our knowledge, no preventative intervention for PIFS has been developed and investigated in a randomised controlled trial (RCT). The two CBT studies in patients

with PIFS showed that the majority of patients were no longer severely fatigued following the intervention (Keijmel et al, 2017; Kuut et al, submitted). In the COVID-19 study, patients also reported reduced functional impairment, concentration problems, and other somatic symptoms following treatment. CBT in this context is a safe intervention with no evidence of deterioration of fatigue (Heins et al., 2010; Keijmel et al., 2017; Kuut et al., submitted). There is one published exercise trial in COVID-19 which also found a reduction in fatigue, but the intervention was intensive with three supervised exercise sessions per week for 8 weeks (Jimeno-Almazan et al., 2022). No adverse events were reported. We searched clinical trial registers with the search terms ‘post-infectious’, ‘post-infective’, ‘fatigue’, infection, prevention, and intervention and did not find ongoing clinical studies testing a behavioural intervention aimed at preventing the development of PIFS.

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

There is limited evidence regarding the mechanism of action of the interventions in PIFS which lead to a significant reduction of symptoms. Mediation analysis in the study testing the efficacy of CBT for PIFS following Q-fever supported the assumed role of cognitive-behavioural factors in the perpetuation of PIFS (Breukers et al., 2019). It was found that a change in self-efficacy with respect to fatigue mediated the treatment response. Research on other behavioural interventions suggests that in addition an increase in physical functioning and fitness, reduction of sleep-wake cycle problems and depression, and a change in fatigue and activity-related beliefs can mediate improvement in persistent fatigue in long-term medical conditions (Abrahams et al., 2019; de Gier et al., 2023; van den Akker et al., 2018).

1.3 Objectives of the clinical study

a) Primary Objective:

To determine the efficacy of a behavioural intervention aimed at preventing Post-Infective Fatigue Syndrome (PIFS) compared to an active control condition in adolescent and adult patients reporting persistent severe fatigue following an acute infection.

b) Secondary Objectives:

i) To determine the efficacy of a behavioural intervention aimed at:

- 1) Reducing the prevalence of PIFS according to the case definition to be formulated in WP1 of DEFINE;
- 2) Reducing fatigue severity;
- 3) Improving physical and social functioning;
- 4) Fostering workability and school attendance;
- 5) Relief of concentration problems;
- 6) Reduction of other persistent physical symptoms;

compared to an active control condition in adolescent and adult patients reporting persistent severe fatigue following an acute infection.

ii) To determine the cost-utility of the behavioural intervention compared to an active control condition in adolescent and adult patients reporting persistent severe fatigue following an acute infection.

iii) To determine potential adverse effects of the behavioural intervention.

iv) To explore whether the behavioural intervention impacts on brain network dynamics as assessed by functional brain imaging and neuroendocrine-immunological interactions as assayed by molecular and cell physiology studies as outlined in WP3.

1.4 Characteristics of the study population

Patients are eligible for entry into the study if they:

1. were diagnosed with an acute infectious disease. The way the infection is diagnosed will differ depending on the health care system of participating countries and the recruitment strategy applied:
 - a) Diagnosed by a GP or other physician with a symptomatic infectious disease, confirmed by lab findings, e.g. symptomatic COVID-19 confirmed by a positive PCR or rapid antigen test (RAT) for SARS-CoV-2 (*Finland, France, Netherlands, Norway, Australia*);
 - b) Specific antibody responses towards Epstein-Barr Virus (EBV) antigens including viral capsid antigen (VCA) IgM and IgG, and EBV nuclear antigen (EBNA) IgG assayed in serum samples; qualitative detection of heterophile antibodies will be performed if results from the three specific tests are inconclusive. A serological pattern confirming recent acute EBV infection is required for inclusion (VCA IgM positive, VCA IgG negative, EBNA IgG negative, heterophile antibodies positive; or VCA IgM positive, VCA IgG positive, EBNA IgG negative) (*Norway, Australia*);
 - c) Recruitment via a national website for patients following a tick bite (www.tekenradar.nl) or following a positive COVID-19 rapid antigen self-test (RAT) (www.infectieradar.nl). Patients who meet the criteria for a clinical diagnosis of Lyme disease confirmed by contacting the patient's GP and online uploading a picture of the skin manifestation (www.tekenradar.nl), and patients uploading a picture of a positive RAT test for COVID-19 and reporting a definite onset of documented fever ($>38^{\circ}\text{C}$) and associated symptoms of the acute sickness response leading to functional impairments in the acute phase of the illness (www.infectieradar.nl) (*Netherlands*);
 - d) Diagnosed by a GP or other physician with a symptomatic acute infectious disease without objective confirmation but with a definite onset of documented fever ($>38^{\circ}\text{C}$) and/or associated symptoms of the acute sickness response leading to functional impairments in the acute phase of the illness, i.e. absence of work or school and/or substantial reduction of other usual daily activities (*Netherlands, Finland, France, Australia*).

Recruitment of participants with strategies a), b), and c) are defined as 'definite' infectious disease onset, and strategy d) as 'likely' infectious disease onset.

2. are between 3 to 6 months after the onset of the symptomatic infectious disease. Three months is chosen because there is substantial spontaneous recovery of post-infective fatigue in the first few months after the onset of symptoms (see e.g., Verveen et al., 2022).
3. experiencing severe fatigue (≥ 35 for adults and ≥ 40 for adolescents on the fatigue subscale of the Checklist Individual Strength [CIS-fatigue] (Worm-Smeitink et al., 2017; Nijenhof et al., 2011). The fatigue must have started with the onset of the fever and/or associated symptoms of the acute infectious disease, without a symptom-free interval thereafter.
4. report physical and/or social disability (≤ 65 on the SF-36 physical functioning subscale (Ware, 1993)) and/or a score of ≥ 10 on the Work and Social Adjustment Scale [WSAS] (Mundt, Marks, Shear, & Greist, 2002) or [WSAS-Y] (Jassi et al., 2020) or school absence ($<75\%$ attendance in the last 2 weeks prior to assessment) in the case of adolescents.;
5. are 12 years of age or older;
6. have sufficient command of the language of the country they reside;
7. have access to and can use a smart phone, tablet or computer with internet access.

Patients will be excluded if they:

1. have a known physical or mental condition that can explain their fatigue. In two countries (*Norway and Australia*) patients will be thoroughly assessed for alternative conditions that may explain persistent fatigue, following a previously established algorithm involving clinical and laboratory examination (Selvakumar et al., 2023). In The Netherlands, Finland and France this will be assessed using questionnaire data as well as data from GPs health records;
2. are pregnant;
3. report a current demanding life event that makes it impossible for the patient to follow the treatment.

1.4.1 Details on sample size and power calculation

The primary outcome of this study is PIFS caseness, defined as being severely fatigued for more than 6 months and reporting substantial functional impairment (see further for a detailed operationalisation). Previous cohort studies using validated questionnaires to assess fatigue following infectious disease found that prevalence rates of severe fatigue decline steeply in the first three months after the onset of symptoms (e.g. Verveen et al., 2022). On the basis of studies on the course of fatigue following an infection, we estimate that the prevalence of severe and disabling fatigue will decrease one-third from 12 weeks up to 6 months without treatment with a declining recovery rate in this period (Verveen et al., 2022; Hickie et al., 2006). This would imply that a maximal of one-third (i.e., $\approx 33,33\%$) of severely fatigued patients would show spontaneous recovery if all were recruited at 3 months (12 weeks) post-infection, i.e. lower limit of the recruitment window. If we assume a placebo effect in the active control condition leading to a further decrease of caseness of 12 percent this would result in about 55 percent of patients in the active control condition group still meeting the criteria for caseness at the primary endpoint (Cho, Hotopf, & Wessely, 2005). If the effect of the experimental intervention is twice as large as the expected placebo effect of the active control condition (i.e., 24%), 43% of patients (i.e., 100% - 57 %) would be a case at the primary end point. Including 750 patients, i.e. 150 patients from each country, and a drop-out rate of 20 percent would give a power of 84 percent to detect the difference in caseness of 12% (55%-43%) between the active control condition and the intervention using a two-sided alpha of .05 with a two group χ^2 test.

1.5 Design of the clinical study

The proposed study is a pragmatic 2-arm randomised controlled trial (RCT) in which patients who have recovered from an acute infection but suffer from ongoing severe and debilitating fatigue will be randomised to either *Fit after Infection* or an active control condition in a 1:1 ratio. Both interventions have a maximal duration of 4 months. Assessments will take place before randomisation (T0), at 4,5 months (T1) and a follow-up six months after T1 (T2).

Recruitment will take place in 5 different countries among consecutive patients visiting outpatient clinics of participating hospitals, from referrals of general practitioners, prospective cohorts of patients with an infection, direct contact with microbiological laboratories, and self-referrals.

1.6 Type of intervention

Experimental intervention: *Fit after infection*

Fit after infection consists of a web-based app with a therapeutic chatbot combined with consults with a healthcare provider trained to deliver the low-intensity intervention. The intervention will be offered in a stepped care format, starting with psycho-education on post-infective fatigue, followed by behavioural interventions supported by a therapeutic chatbot, and if this does not suffice, by video consults with trained health care providers. On the basis of feedback from the patient and progress made in the web-based app as evaluated by the healthcare provider, it will be decided if patients should

progress to the next level of care. In this way, optimal care is delivered in an efficient way which will ease large-scale implementation if *Fit after infection* significantly reduces the prevalence of PIFS.

The web-based app consists of modules which are based on existing evidence-based (cognitive) behavioural interventions for PIFS following Q-fever and COVID-19 respectively (Keijmel et al., 2013; Kuut et al., 2021). Eight modules will be available aimed at: 1) psycho-education on fatigue and the role of behaviour in reaching recovery or symptom relief; 2) goal setting (e.g. resumption of school or work); 3) regulation of the sleep-wake pattern; 4) graded activity; 5) changing fatigue-related beliefs; 6) managing pain; 7) social support; 8) realising goals. Modules 2 to 8 consist of psycho-education on the subject and its relation to post-infective fatigue followed by behavioural interventions. Further information about each module:

1. In the module ‘psycho-education’, general information about post-infective fatigue and other symptoms is provided and how a cognitive-behavioural approach of fatigue can help recovery or give symptom relief.
2. In the module ‘goal setting’, patients formulate treatment goals they aim to achieve, assuming fatigue will diminish during the intervention (e.g., return to work, resuming social and leisure activities). The progress made on these goals will regularly be evaluated within the web-based app.
3. In the module ‘regulation of the sleep-wake pattern’, patients start to regulate their sleep-wake patterns and follow sleep hygiene practices in order to stop the dysregulation of circadian rhythms and reduce their sleep problems.
4. The module ‘graded activity’ targets a low or fluctuating physical activity pattern. Patients with a low activity pattern immediately start with a gradual increase in their daily physical activity (e.g. walking, cycling). Patients with a fluctuating activity pattern learn first to evenly distribute their activities during the day and across the week, and will then subsequently gradually increase their physical activity. Following this, a comparable program of graded increases in cognitive activities will be implemented to counter the complaint of neurocognitive difficulties (‘brain fog’) All patients will, following a successful increase of physical and cognitive activities subsequently increase their social activities.
5. The module ‘changing fatigue-related beliefs’ targets dysfunctional cognitions regarding fatigue. Information is provided on how catastrophizing about fatigue and non-accepting fatigue beliefs can negatively influence outcomes. Patients formulate more helpful beliefs in response to fatigue. Furthermore, patients learn how to shift their attention away from fatigue towards other activities or the environment to reduce their excessive focus on fatigue.
6. The module ‘managing pain’ aims to help patients to cope with persistent widespread pain, which is not uncommon in PIFS. The module targets dysfunctional cognitions with respect to pain and patients are helped to deal with pain in such a way that it does not limit them in the gradual increase of activities.
7. The module ‘social support’ targets low perceived social support and negative interactions with respect to symptoms. Patients learn how to communicate with significant others about their fatigue, be assertive and adapt to the expectations they have from the support and help of others.
8. In the module ‘realising goals’ patients step-by-step realise their goals, this will include work or study resumption, increasing mental and social activities and other goals. Patients also learn to let go of the regular sleep-wake pattern and the even distribution of activities. In this module, patients also are asked to evaluate their progress and determine whether they are no longer severely fatigued. Lastly, how relapse can be prevented is addressed.

The intervention will be personalised, based on a baseline assessment before the start of treatment. Relevant modules will be selected on the basis of questionnaires and a short intake interview. The

modules on social support and on pain will only be offered if data from the baseline assessment indicate that this is required. Some infectious disease-specific information will be inserted in the intervention to better match the generic, transdiagnostic intervention with the experience of the patient suffering from fatigue that developed after a specific infectious disease (e.g., by using the words ‘Lyme disease’ instead of ‘infection’ in texts for patients who developed symptoms following Lyme disease).

Using Natural Language Programming techniques, an AI-powered therapeutic chatbot will be developed to aid patients in the implementation of interventions. The chatbot can provide CBT-based counselling conversations that involve, for example, advice on behavioural or cognitive strategies to improve sleep or enhance physical activity, or give comments to homework assignments. These chatbot-led conversations will be based on scenarios (‘pipelines’) informed by experienced therapists. The conversational pipelines of the chatbot have already been developed in another Horizon Europe project (TIMELY), whereby the aim of the chatbot was to support the (largely overlapping) needs of Cardiac Rehabilitation patients (Sun et al., 2023), and will be adapted for its specific use in patients with post-infective fatigue. In patients in whom the combination of psycho-education and support of the chatbot-based counselling is not sufficient to alleviate symptoms or adequately adapt behaviour, a healthcare provider will be made available for help as a third step-up in care within the web-based app.

Two versions of the intervention will be made available, one suitable for adolescents between 12 and 18 years, and one for adults (>18 years). The research group of the leader of WP4 and other partners have experience with the development and testing of internet-supported behavioural interventions for persistently fatigued adolescents (5.1.2e et al., 2021; Nijhof et al., 2023). The modules and type of interventions will be the same as for adults but adapted to the age of the patient and to the fact that adolescents are at school. Parents will be involved in the treatment of the adolescents, especially in the age group 12-15 years.

The duration of the intervention is a maximum of 4 months.

The contents of the intervention will be refined based on the output from WP2 (determining risk factors for PIFS) and WP3 (scrutinizing potential causal mechanisms of PIFS) of the DEFINE project. The intervention may be further adapted on the basis of a review that will be done in WP4 on (preventative) behavioural interventions for PIFS. On the basis of the literature, evidence-based strategies to prevent PIFS or reduce persistent fatigue will be described and if possible integrated in *Fit after Infection*. During the development of the intervention, the material will be discussed in a focus group together with members of the consumer panel of COFFI and other patients who recovered from PIFS. By co-creation, the content of the intervention will be optimised. The last phase in the development of the intervention will be testing the prototype with a small number of patients using a think aloud test strategy (Boren & Ramey, 2000). On the basis of the feedback derived from the pilot, the intervention will be finalised. Following this, *Fit after infection* will be translated into the languages of the non-Dutch countries participating in the clinical trial (English, French, Norwegian, Finnish).

Active control conditions: Relaxation training and general health advice

The active control condition consists of a web-based app offering an already existing relaxation training (van Kessel et al., 2008) and a second module containing more general advice on a healthy lifestyle (e.g. healthy food intake and stress reduction). This app will also be available in two versions, one for adults and one for adolescents. It will also consist of psycho-education, behavioural assignments and contact with a health care provider who will provide guidance on relaxation training and a healthy lifestyle.

In both interventions, all patients have a short intake with a trained healthcare provider face-to-face or via video consultation. Video consultations are available when the patient needs more guidance than offered in the app to prevent attrition and optimise treatment results. The treatment duration has a maximum of 4 months and will end with a second short evaluation via video consultation.

The *Relaxation training and general health advice* will also be translated into the languages of the countries participating in the clinical trial.

Training of health care provider and treatment integrity

Health care providers working at the five clinical sites, preferably cognitive-behavioural therapists, will be trained in 3-day program provided by the AUMC. The training consists of discussing each treatment module and practicing the interventions in role-playing with simulation patients, being professional actors. Furthermore, an introduction to the online platform, exercises in writing e-mails and giving online feedback are part of the training. Two-weekly, the therapist will receive supervision via a secured video connection by experienced therapists from the AUMC. Adherence to the protocol for treatment integrity will be determined via recordings of video-consults (with informed consent of patients and safely stored on a secured server) and analysis of anonymised email responses (5%).

A short web-based training/information program will be developed for GPs and other physicians to aid recruitment and optimise the information on the intervention for patients.

1.7 Description and timing of study procedures

Participants

See inclusion and exclusion criteria 1.4 (characteristics of the study population). After (self) referral, interested patients (and their parents in the case of adolescents) will be contacted by telephone by the researcher or research assistants to inform them about the study. Depending on the recruitment strategy patients are self-referred, physician referred, or recruited based on tests results at microbiological laboratories (*Norway*) or via the RIVM (*Netherlands*). In the case of a physician referred patient, a patient who was recruited via RIVM (after self-referral through 'Tekenradar' and "Infectieradar"), or a patient recruited based upon microbiological laboratory tests, the inclusion criteria 1 (infectious disease as onset of symptoms) and exclusion criterion 1 (a somatic or psychiatric condition that can explain the fatigue) will already be checked by a physician. For self-referrals, these eligibility criteria will be checked by contacting the patient's GP with the permission of the patient.

Written informed consent should be signed by the parents and patient in the case of adolescents between the age of 12 and 16, and by patients when they are 16 years or older. After obtaining informed consent, online screening questionnaires will be administered by the researcher or research assistant to verify the remaining eligibility criteria (see 1.4), or (*in Norway and Australia*) supplemented by clinical examination and standard laboratory assessment. The subscale fatigue severity of the CIS-questionnaire is used to screen for the presence of severe fatigue. For the presence of limitations in physical and/or social functioning, the subscale physical functioning of the Short Form Health Survey (SF-36) and the Work and Social Adjustment Scale (WSAS or WSAS-Y for adolescents) will be used. In adolescents, data on school absence in the previous two weeks is gathered. Adult participants will be screened for the presence of a depressive disorder with the Beck Depression Inventory for Primary Care (BDI-PC) (Beck, Guth, Steer, & Ball, 1997) for exclusion criterion 1, i.e. the presence of a psychiatric condition that can explain the fatigue. If the score on the BDI-PC is ≥ 4 the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) will be conducted by a trained research assistant via phone to determine if patients meet the criteria for major depressive disorder. This will mostly be a likely explanation for the fatigue and in that case, patients will not be included. Instead, the GP is contacted for referral to appropriate treatment with the consent of the patient. For adolescents, the same procedure will be used, but the children's depression inventory questionnaire is used as a screener (Kovacs, 1985) and the M.I.N.I. interview for adolescents (MINI-KID) (Sheehan et al., 2010).

Randomisation

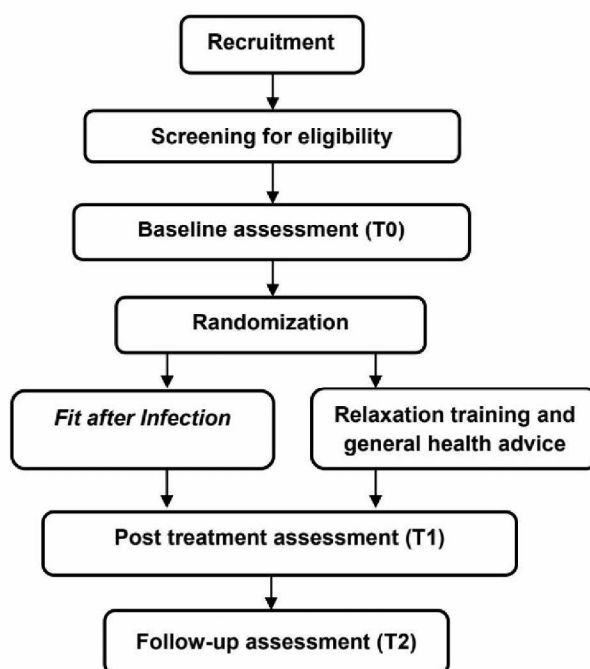
Allocation of participants to either *Fit after Infection* or the active control condition will be stratified based on age (12-18, >18 years); (2) type of infectious disease (COVID-19, Lyme, EBV, other) and time between symptom onset and randomisation (≤ 18 and >18 weeks).

A web-based randomisation programme in Castor EDC is used to generate the randomisation sequence ("Castor Electronic Data Capture," 2019). The allocation ratio is 1:1. Block randomisation with randomly selected block sizes (i.e. 2, 4 or 6) is used. The randomisation will be performed centrally by a research assistant in the AUMC and will be communicated by email (and telephone in European sites) to each of the sites. The research assistants, the researchers and the participants will be blinded to the allocation sequence. The researcher who will send the online assessments will also be blinded to allocation. Due to the nature of the intervention, blinding to allocation is not feasible for health care providers delivering the intervention and participants. Data will be analysed by an independent statistician using a data file which is blinded for treatment allocation. Participants who drop out of the study will not be replaced.

Procedure

Eligible and consenting participants will start with the baseline assessment (T0). Following T0, participants will be randomised to either *Fit after Infection* or the active control condition. The intake session will be planned within 1 week after randomisation, and eighteen weeks after randomisation all participants will be assessed again (T1). T1 is the post-intervention assessment and primary endpoint of this study. At follow-up (T2), 6 months after T1, all participants will be assessed again. A flowchart of the study design is shown in Figure 1.

Figure 1. Study flowchart



Outcome measures

Outcome measures consist of self-reported questionnaires, which will be assessed at T0, T1, and T2. See Table 1 for the measurements at all time points. The questionnaires will be administered online using Castor EDC which is hosted at AUMC on a secure server. Castor EDC will also be used as electronic case report form. Participants will receive an e-mail with a personal link to fill out the questionnaires. For optimal retention, participants will be contacted by the research assistant at the clinical site if they have not completed the questionnaires within one week. When participants who are not willing to complete all measurements at T1 and/or T2 will be asked to fill in a minimum set of questionnaires to determine caseness which is the primary outcome.

Table 1. Measures used in the study

Timepoint*		-T1	0	T0	T1	T2
Enrolment:	Eligibility screen	x				
	Informed Consent	x				
	Allocation		x			
Interventions:	Fit after Infection			↔		
	Active control condition			↔		
Primary and secondary outcomes						
Fatigue	Checklist Individual Strength (CIS), subscale fatigue severity	x		x	x	x
	Chalder Fatigue scale (CFQ)			x	x	x
Duration of fatigue	Self-report item				x	x
Physical functioning	Short Form Health Survey (SF-36) subscale physical functioning	x		x	x	x
Concentration problems	CIS subscale concentration problems			x	x	x
Social functioning	Work and Social Adjustment Scale (WSAS/WSAS-Y)	x		x	x	x
	SF-36 subscale social functioning			x		
Somatic symptoms	Patient Health Questionnaire 15 somatic symptoms (PHQ-15), adult and adolescent version			x	x	x
School attendance	Self-report (adolescents)	x		x	x	x
Workability	MTA Productivity Cost Questionnaire (IPCQ) (adults)			x	x	x
Cognitive-behavioural variables						
Sleep	Insomnia Severity Index (ISI) (adults)			x		
	Sickness Impact Profile, subscale sleep-rest (SIP-SR)			x		
Cognitions: Self-efficacy	Self-Efficacy Scale (SES)			x		
Cognitions: Catastrophizing	Jacobson-Fatigue Catastrophizing Scale (J-FCS) (adults)			x		
Cognitions: Focus on fatigue	Illness Management Questionnaire (IMQ)			x		
Activity	Activity interview			x		
Social support	Van Sonderen Social Support Inventory, discrepancy (SSL-D) and interactions (SSL-I) (adults)			x		
Pain	SF-36 subscale pain			x	x	
Other outcomes						
Brain network dynamics, neuroendocrine-immunological interactions	<i>Only at AHUS, Norway:</i> Brain fMRI, molecular and cell physiology assays exploiting Peripheral Blood Mononuclear Cells (PBMC)			x	x	
Mental health	Patient Health Questionnaire, somatic, anxiety and depressive symptoms (PHQ-SADS) (adults)			x		
Depression	Beck Depression Inventory-Primary Care (BDI-PC) (adults)	x				
	Mini-International Neuropsychiatric Interview (M.I.N.I.) (adults)	x				
	The Children's Depression, Inventory (CDI) (adolescents)	x				
	Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (adolescents)	x				
Anxiety	Spielberger State-Trait Anxiety Inventory for Children, (STAIC) (adolescents)			x		
Expectations about treatment	Treatment Outcome Expectations Questionnaire (TOEQ)			x		
Adverse events	Self-report items				x	

Exploratory outcome measures (only at AHUS, Norway)

In addition, a subset of patients (recruited at AHUS clinical site in Norway) will undergo clinical examination, standard laboratory assessments, biobanking of blood samples, and functional brain imaging at T0 and T1.

Functional brain imaging involves the application of brain fMRI during rest as well as during experimental tasks. By manipulating the cognitive effort required to successfully perform a task while simultaneously assessing the corresponding brain activity using fMRI, we will be able to map the functional brain network dynamics associated with the objective and subjective experience of cognitive effort and mental fatigue. Importantly, we will be able to assess whether the intervention promotes a coordinated alteration of fatigue and effort perceptions, task performance and brain network dynamics.

The biobanking of blood will enable the storage of viable Peripheral Blood Mononuclear Cells (PBMC). *In vitro*, PBMC (and cell subpopulations) cultures will be co-cultured with neuroendocrine mediators, such as cortisol and catecholamines for investigations of neuroendocrine-immunological interactions and their potential alterations as a consequence of the intervention. Read-outs will be both at the mRNA, protein and cell physiology level.

Primary outcome

PIFS caseness is the primary outcome and is defined as being severely fatigued and functionally impaired for longer than six months. Fatigue severity is assessed by the subscale fatigue severity of the Checklist Individual Strength (Worm-Smeitink et al., 2017). The CIS consists of 20 items scored on a 7-point Likert scale and measures four dimensions of fatigue, i.e. fatigue severity, concentration problems, motivation and activity. The CIS-fatigue consists of eight items, each item is scored on a 7-point Likert scale with a higher score indicating more severe fatigue. The cut-off score for severe fatigue is ≥ 35 (Worm-Smeitink et al., 2017) for adults and ≥ 40 for adolescents (Nijhof et al., 2011). Previous research supports the reliability and validity of the CIS.

Limitations in physical functioning are assessed by the subscale physical functioning of the SF-36 which consists of ten items scored on a 3-point scale (Ware, 1993). The weighted subscale score ranges from 0 to 100, with a higher score indicating less limitations. A score of ≤ 65 is indicative of substantial limitations in physical functioning. The SF-36 is a reliable and valid instrument and has previously also been applied in chronically fatigued adolescents (Stulemeijer, de Jong, Fiselier, Hoogveld, & Bleijenberg, 2005). Social disability is assessed by the WSAS (Mundt et al., 2002) which consists of five items assessing different domains of functioning, e.g. work and social leisure activities, scored on an 8-point Likert scale. A score of ≥ 10 is indicative of significant functional impairment. The WSAS is a reliable and valid instrument (Thandi, Fear, & Chalder, 2017). A version for adolescents of the WSAS has been developed and will be used in the study using the same cut-off score for significant impairment (Jassi et al., 2020). The duration of symptoms will be self-reported using a separate question (Kuut et al., 2021).

Patients are seen as (still) meeting the criteria for PIFS if they score:

- ≥ 35 (for adults) or ≥ 40 (adolescents) on the CIS-fatigue and have a symptom duration of 6 months or longer
- AND
- ≤ 65 on the physical functioning subscale and/or ≥ 10 on the WSAS (adults) or WSAS-Y (adolescents).

As the aforementioned case definition may differ from the PIFS case definition developed with international partners in WP1 which will become available in month 24 of DEFINE we will also apply this international case definition at T1 and T2 (secondary outcome).

Secondary outcomes

- Fatigue severity assessed with the CIS-fatigue subscale and Chalder Fatigue Questionnaire (CFQ), a widely used questionnaire, consisting of 11 items. Likert scoring will be used (range 0–3; total score 0–33) in preference to binary scoring, as it was suggested that more variance results in greater sensitivity in detecting change. The CFQ is reliable and valid (Worm-Smeitink et al., 2016). A higher score on the CFQ reflects more severe fatigue (Cella & Chalder, 2010).
- Functional impairment assessed with the physical functioning subscale of SF-36 and the WSAS or WSAS-Y.
- School attendance of adolescents based on self-report of adolescents and parents expressed as attended hours/obliged hours * 100% over a period of two weeks (Nijhof, Bleijenberg, Uiterwaal, Kimpfen, & van de Putte, 2012).
- With the MTA Productivity Cost Questionnaire (iPCQ) absenteeism and loss of productivity because of illness of the patient (in case of adults) or of caring for a sick child in the previous 4 weeks is assessed. It consists of 12 questions. The iPCQ is a valid and reliable questionnaire (Bouwman et al., 2014).
- Quality-adjusted life years (QALY) calculated from the SF-36 inventory will be combined with cost data gathered from all the five sites to obtain a cost-utility analyses of the intervention.
- Problems concentrating are assessed by the subscale concentration of the CIS which consists of five items scored on a 7-point Likert scale. The scores range from 5 to 35, with a higher score indicating more difficulties in concentrating (Goedendorp, Knoop, Gielissen, Verhagen, & Bleijenberg, 2014).
- Somatic symptom severity is assessed by the somatic symptoms scale of the Patient Health Questionnaire (PHQ) (Kroenke, Spitzer, & Williams, 2002). The PHQ-15 consists of 15 items referring to somatic symptoms. Each symptom is scored on a 3-point scale with scores of 5, 10 and 15 indicating low, medium, and high symptom severity. Research supports the reliability and validity of the PHQ-15 (Kroenke, Spitzer, Williams, & Lowe, 2010). An adapted version of the PHQ-15 is available for adolescents, the items assessing menstrual cramps and pain during sexual intercourse are deleted from this version (Johnson, Harris, Spitzer, & Williams, 2002).
- In WP1 at month 24 a refined case definition of PIFS will be available, this will then be applied to the participants.

Qualitative outcomes

Qualitative research conducted in Norway, Finland and the Netherlands (the qualitative focus countries) will provide insights and understandings into study members' experiences of and perspectives on the *Fit after Infection* intervention. In doing so, the qualitative research will support and inform (1) the training of healthcare staff who will deliver the intervention; (2) patient recruitment; and (3) the intervention. Semi-structured interviews will be conducted with:

- 12-15 healthcare staff per focus country (36-45 total), to support and continually improve the staff training and subject recruitment processes
- 12-15 fatigue patients per focus country (36-45 total), to support patient recruitment – e.g., by exploring patient attitudes towards using a chatbot counselling tool
- 20-25 intervention subjects per focus country (60-75 total) and 10-12 control group members per focus country (30-36 total). The key outcome will be an in-depth understanding of participants' experiences and perspectives on the intervention. Analysis of these experiences and perspectives will provide insights into the mechanisms, processes, pathways and contexts associated with intervention outcomes (Pawson, Greenhalgh, Harvey, & Walshe, 2004; Pawson & Tilley, 1997).

Interviews will be transcribed in the national language and analysed using Reflexive Thematic Analysis (Braun & Clark, 2019). The analysis will be written up in English. The thematic analysis process will be iterative, with country-specific analyses being complemented in an ongoing fashion with cross-country analyses (Chapple & Ziebland, 2018). Throughout the data collection and analysis process, the qualitative research team will work closely with the project's quantitative researchers, to facilitate integrated mixed methods analysis of the processes, mechanisms, experiences, pathways and perspectives underlying intervention outcomes.

Exploratory outcomes

Brain network dynamics as assessed by fMRI; neuroendocrine-immunological interactions as assessed by laboratory assays exploiting viable PBMC. Cf. details above.

Demographics and patient characteristics

The demographic characteristics include age, sex, relationship/cohabitation status, level of education and employment status. Patient characteristics include length, weight, morbidities, the start date of symptoms of the infectious disease, data on the lab findings or other objective findings with respect to the infectious disease. All characteristics are assessed by self-report during screening with the exception of data on objective findings with respect to the infectious disease which will be collected with permission of the patient from their medical or pathology record.

Fatigue-related behaviours, cognitions and emotions

Based on the cognitive behavioural model for fatigue in PIFS and fatigue in other long-term conditions, several fatigue-related behaviours, cognitions and emotions will be assessed. In adults these are dysfunctional beliefs are assessed by the Jacobsen - Fatigue Catastrophizing Scale (J-FCS) (Jacobsen, Andrykowski, & Thors, 2004), Illness Management Questionnaire (IMQ) (Ray, Weir, Stewart, Miller, & Hyde, 1993) and the Self-Efficacy Scale (SES) (Heins, Knoop, Burk, & Bleijenberg, 2013). Social support will be assessed with the Van Sonderen Social Support Inventory (SSL-I and SSL-D) (Bridges, Sanderman, & van Sonderen, 2002), and pain assessed by the subscale pain of the SF-36 (Ware, 1993). Mental health will be assessed by the patient health questionnaire, somatic, anxiety and depressive symptoms (PHQ-SADS) (Kroenke et al., 2010). Social functioning will be assessed by the subscale social functioning of the SF-36 (Ware, 1993). Expectations about treatment will be assessed by the Treatment Outcome Expectations Questionnaire (TOEQ) (Heins, Knoop, & Bleijenberg, 2013). Sleep quality will be assessed with the Insomnia Severity Index (ISI) (Bastien, Vallières, & Morin, 2001) and by the sleep and rest activity subscale of the Sickness Impact Profile (SIP-SR) (Bergner, Bobbitt, Pollard, Martin, & Gilson, 1976).

In adolescents, the IMQ and SES will be used to assess beliefs with respect to fatigue. Social support will be assessed by the therapist during intake and the TOEQ is used to assess treatment expectations. Anxiety will be evaluated with the Spielberger State-Trait Anxiety Inventory for Children, STAIC (Papay & Spielberger, 1986). Pain will be assessed with the SF-36 pain subscale and sleep problems with the SIP-SR.

In case of significant pain symptoms (SF-36 <40), the pain module is indicated. If patients score above >40 on the SSL-D the social support module is indicated (adults) or when a lack of social support is evident from the intake session (adult and adolescent). In both adults and adolescents, the activity pattern will be assessed using a validated structured interview to determine if a patient immediately starts with graded activity or first needs to undertake activity pacing - dividing activities more evenly (Scheeres, Knoop, van der Meer, & Bleijenberg, 2009).

Demographics and patient characteristics and *Fatigue-related behaviours, cognitions and emotions* will only be assessed at T0. At T1 and T2 only the primary and secondary outcomes are assessed (see Table 1).

Adverse events (AE's)/serious adverse events (SAE's)

At T1, all participants will be asked to report if they experienced new symptoms or an increase in existing symptoms during the intervention. All AE's reported by the participant or observed by the health care providers or research staff will be recorded and reported.

Handling and storage of data and documents

Personal data will be handled confidentially and coded in compliance with the EU General Data Protection Regulation Act. Identifiable patient information will be coded for all study procedures at the clinical site. Only the PI of the clinical site and one of the researchers will be allowed to access the key file with both participant codes and identifying participant data. Deidentified data will be stored at the Department of Medical Psychology of the AUMC.

Participant withdrawal

Participants can leave the study at any time for any reason without any consequences. The reasons for withdrawal will be documented. The researchers can also withdraw a participant from the study in case of incorrect enrolment. Participants are informed of their possibility to withdraw from the study during the intake and in the information letter. Despite leaving or being withdrawn from the study, treatment can be continued. The investigator or the treating physician can decide to withdraw a participant from the study for urgent (medical) reasons which will be documented. Participants that are withdrawn from the study will not be replaced.

Statistical analyses

Descriptive statistics (i.e. participant characteristics) will be presented in tables, with separate columns for participants randomised to CBT vs. participants randomised to the active control condition. Categorical variables (e.g. sex, relationship status) will be presented in participant numbers (n) and percentages (%). Continuous variables (e.g. age, CIS-fatigue baseline score) will be presented in means and standard deviations or, if appropriate due to skewness of data, as median with its interquartile range. Participant numbers, dropout and reasons for dropout will be presented in the study flow-chart.

In all analyses, two-sided p values of < 0.05 will be considered to indicate statistical significance. All analyses will be conducted in SPSS. The primary study parameter will be analysed according to intention-to-treat, i.e. all randomised participants will be included in the analysis and analysed in the group to which they were randomly allocated. Missing values will be replaced with multiple imputations using chained equations. A total of five data sets will be imputed and pooled according to Rubin's rules (Rubin, 1996; Rubin, 2004). The imputation model will include all baseline sociodemographic and clinical characteristics assessed at baseline and follow-up measurements. The difference in the proportion of patients being cases at T1, the primary endpoint, between the *Fit after Infection* and active control condition will be tested with a logistic regression analysis. This analysis will be repeated 1) for the proportion of patients being cases at T2 and 2) for T1 and T2 with the case definition formulated in WP1 and available at month 24 of DEFINE. The latter is a secondary outcome.

The differences between both conditions for the other secondary outcomes will be tested using a mixed linear model. The model will include the secondary outcome measure as a dependent variable, condition (*Fit after Infection* versus the active control condition), time (T1, T2), condition-by-time interaction as fixed effects, a random intercept and the score on the secondary outcome measure at baseline as covariate. It will be examined if the main effect of the condition from the mixed linear model, i.e. the mean difference in the secondary outcome across T1 and T2 while controlling for baseline fatigue, is statistically significant. If the main effect of the condition is found to be statistically significant, the statistical significance of the between group differences at the separate time points (T1 and T2) will be interpreted. Cohen's d effect sizes for the secondary outcome will be calculated by dividing the

parameter estimate for the mean difference in scores on the secondary outcome between both conditions from the mixed linear model by the pooled standard deviation of both conditions combined. Effect size magnitudes will be interpreted as small (0.2), medium (0.5) and large (0.8).

To explore the robustness of our findings from the primary analysis, four sensitivity analyses will be conducted. First, per protocol analysis will be conducted with treatment completion operationalised by including participants who have filled out the treatment goals and opened the standard modules of the intervention and second, a per protocol analysis with participants who have completed the intervention according to their health care provider. Third, the extent to which, somatic co-morbidity, age (12-15, 16-18, >18 years); type of infectious disease (COVID-19, Lyme, EBV, other); definite vs likely diagnosis of infectious disease, sex, and time since the symptoms commenced have an impact on the primary outcome will be explored. Fourth, the analysis will be repeated but the missing values in the *Fit after infection* and active control condition will be replaced with the same response rate to the intervention as in the active control condition.

Possible detrimental effects of the intervention will be determined in two ways: by registering AE and SAE and by computing and reporting the prevalence of clinically significant exacerbation for fatigue severity as assessed with the CFQ, physical functioning (SF-36) and social functioning (WSAS). Indicating an RCI >1.96 between two measurements, we set a clinically significant exacerbation at a RCI <-1.962.

2 Preparedness status

2.1 Development of the clinical study protocol

2.1.1 Scientific advice from regulatory and health technology assessment bodies

The clinical study was discussed with several experts on PIFS, e.g. with the Scientific Advisory Committee of COFFI and infectious diseases specialists.

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

The clinical trial will follow the International Conference on Harmonisation (ICH) guidelines in general and specifically guidelines E6 (good clinical practice), E8 (general considerations for clinical trials), E10 (choice of control group in clinical trials), E17 (multi-regional clinical trials), and E3 (clinical study reports). The overall methods adhere to internationally accepted guidelines for data management and protocol development, standard operating procedures (SOP) and relevant ethical requirements in all countries.

A protocol paper including the statistical analysis plan will be submitted for publication. Findings of the RCT will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) statement extension for pragmatic trials.

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

The clinical trial protocol will be prepared by the trial steering committee with members nominated by each partner covering specific expertise in ethics, statistics, clinical research, study conduction, database and infrastructure, and legal aspects. CHINO will advise on ethical and legal issues. The Consumer Advisory Committee of COFFI was involved in the design of the study, and representatives will be on the trial steering committee. Furthermore, patients or patient representatives will, via focus groups together with other consumers who recovered from PIFS, be involved in the development of the intervention (co-creation). Patients suffering from fatigue following infection will be invited to participate in usability tests of the web-based app (and will receive treatment without being randomised).

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

2.2.1 How the consortium will ensure access to regulatory expertise necessary to get advice on, and management of, regulatory affairs activities in all concerned jurisdictions?

The AUMC has research support with expertise in regulatory affairs in all concerned jurisdictions. Each co-applicant has significant expertise and experience in regulations in their own jurisdiction. Additional advice will be sought from experts who are knowledgeable about the regulations in Australia. CHINO will advise all partners on regulatory affairs.

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

AUMC will with the support of CHINO submit all required documents to the ethical board of the AUMC. Once the trial is approved by them AUMC and CHINO will seek local approval in collaboration with the partners in the EU countries (France and Finland), as well as in Norway and Australia.

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

2.3.1 Details about the sponsor(s)

The main sponsor of the trial will be Amsterdam University Medical Centers, located in Amsterdam, the Netherlands. This is a large university hospital and has extensive experience with conducting large, multi-center international clinical studies. Their legal department and WP leader will, with the help of CHINO establish a consortium agreement and data-transfer agreement with all participating centers.

2.3.2 Composition, role and functioning of the planned board

The planned board includes the project coordinator of DEFINE (i.e. AHUS), the clinical trial project manager, a statistician, leader and co-leaders of Work Package 4, and patient representatives from the COFFI Consumer Advisory Committee. This group has a specific focus on the clinical trial to ensure smooth organisation and harmonisation, effective accrual and to react rapidly in case of any difficulties. In addition, this subgroup approves any new decision regarding the clinical trial or its database. In particular, they approve any amendment to the protocol after which the ethical board of the AUMC will be asked to give permission.

3 Operational feasibility

3.1 How the availability of the intervention(s) is secured throughout the entire implementation phase

We will ensure that the software platform is available for the duration of the project with video-consults which will be part of the contract with the software company. Therapists will be hired for the duration of the project. The IP on the intervention will belong to the DEFINE consortium and can be made available to software platforms for internet interventions of commercial parties in different languages and includes a treatment manual. A '*PIFS portal*' will become available for digital tools developed in DEFINE (WP5). An educational program will be developed for health care providers to train them in delivering the intervention, and will also be made available through the *PIFS portal*. Finally, via the COFFI network, it is possible to implement this intervention with the help of its members in different countries. Implementation is also guaranteed by the activities of WP7 (dissemination and implementation).

3.2 How the study population will be recruited

3.2.1 Clinical sites contributing to the recruitment of the study population

Five clinical sites will recruit patients for the trial. There are sites in the Netherlands, Finland, France, Norway and Australia.

3.2.2 Will recruitment of the study population be of competitive nature between the clinical sites?

The recruitment will not be of competitive nature, each center will recruit 150 patients.

3.2.3 What evidence supports the ability of the individual clinical sites to recruit the required number of study participants within the planned timeline?

The involvement of international study groups with recognised expertise in the conduction of clinical trials will represent a guarantee of success in selecting well-performing clinical sites. All clinical sites have treatment centers where patients are treated for PIFS ensuring that they can deliver the interventions skillfully (via video consults). All sites have access to patients with infectious diseases or have access to networks of GP's who can recruit patients. AUMC has extensive experience with leading multi-center trials testing (web-based) interventions for chronic fatigue in different conditions. The leader of WP4 previously conducted a multi-center, international trial as WP-leader in a Horizon 2020 program and was co-principal investigator in studies in the US and Germany. AHUS has decades of experience in carrying out clinical trials among adolescents and adults with PIFS. At present, AHUS is leading two clinical trials on the post-COVID-19 condition; both of them involving a cognitive-behavioural intervention. One of these trials has completed patient recruitment, with a total of 310 post-COVID-19 condition sufferers enrolled over a period of 12 months. Also, AHUS has a well-established infrastructure for clinical examination and biobanking of clinical trial participants. For recruitment in the Netherlands, RIVM uses two online platforms for prospective follow-up of acute infections, www.tekenradar.nl and www.infectieradar.nl. Patients can self-report acute infections on these platforms, i.e. Lyme disease (tekenradar) and COVID-19 (Infectieradar), and are then followed up for the development of severe fatigue. For Lyme disease, the diagnosis will be mainly clinical, and will be confirmed through the patient's GP, further supported by a picture of the clinical skin manifestation uploaded on the online platform. For COVID-19, the diagnosis will be confirmed through antigen self-tests, as supplied by the Infectieradar researchers. When reporting severe fatigue between 3 and 6 months after onset of disease, participants are invited for the intervention trial, and can refer themselves to the clinical trial site of the AUMC, after which they are screened for inclusion by a research assistant.

In France, the recruitment will result from different channels. Some patients will be recruited in an outpatient clinic of Hotel Dieu Hospital (Paris), the CASPer-COVID unit, referenced by the health regional agency of the Paris area for managing post-COVID conditions since September 2021. Patients with symptoms (including 90% with fatigue) persisting more than 3 months after a COVID-19 are self-referred or referred to by their general practitioners. More than 300 patients have been referred to the unit in one year. As only one-third of those patients have fatigue lasting for less than 6 months, the recruitment will be completed with the help of two GP networks. The first one consists of 75 GP's from the Paris Area, involved in an ongoing trial called EMPATY, a large RCT involving 720 patients with long COVID, that aims at ameliorating the quality of life of the patients by educating their GP about somatic syndrome disorders' diagnosis and care. The trial is ongoing and will be completed at the time DEFINE will start. The second network is the "Réseau Sentinelles" a research and health monitoring network in primary care in metropolitan France. Created in November 1984, it was developed under the joint supervision of the National Institute of Health and Medical Research (Inserm) and Sorbonne University. This network is based on the voluntary participation of nearly 1300 general practitioners (about 2.2% of French general practitioners), spread over the entire metropolitan area, who collect

epidemiological data on several health indicators in real-time. These GP-s have a long experience of participating in epidemiological studies regarding various infectious diseases (influenza, acute diarrhoea, chickenpox, measles, mumps, viral hepatitis, HIV and COVID-19). The GP will be in charge of screening patients with post-infective fatigue and ask for their consent to participate in the study, and a research assistant will call the patient to ensure they meet the inclusion criteria. The diagnosis of the previous acute infection will be based on the GP's diagnostic, either purely clinical or with microbiological documentation (especially for Lyme's disease, EBV and COVID-19).

In Australia, recruitment will occur from referrals to the infectious diseases specialist practice of Professor Andrew Lloyd at the University of New South Wales in Sydney and to the multidisciplinary outpatient CBT intervention service with an integrated academic research framework, which he leads – the UNSW Fatigue Clinic and Research Program (<https://www.fatigueclinic.unsw.edu.au>). Professor Lloyd is Australia's leading clinical researcher in relation to post-infective conditions and receives referrals from across the country. Similarly, the UNSW Fatigue Clinic and Research Program is Australia's only integrated centre of research and clinical services focused on improving the health of people who have chronic fatigue states, including PIFS. With the advent of the COVID-19 pandemic, approximately 50% of the current referrals to the Clinic are for Long COVID. Professor Lloyd also leads the Long COVID initiative of the Australian Centre for Preparedness Research on Infectious Diseases Emergencies (APPRISE). The APPRISE Long COVID initiative is currently coordinating a network of 20 existing prospective cohorts following patients from acute COVID in both tertiary and primary care, and is also establishing a new prospective cohort across three state-wide primary care networks for ongoing Long COVID surveillance. This latter primary care network along with recruitment systems and data collection systems is being developed as a sustainable platform for future post-infective sequela. This combination of existing referral networks will be utilised for recruitment into the FINE protocol.

In Finland, the patients will be recruited via a network of GPs that have an interest in functional disorders. This is an active network of approximately 800 GPs all over Finland. The network is coordinated by the Clinic for Functional Disorders at Helsinki University Hospital, which is the only specialised clinic in this field in the country. This network has held monthly meetings since the beginning of 2020 and holds a Teams group for information sharing. The educational program will be tested in this network. The GPs in the network screen patients for the study, ask for their consent and refer the eligible patients for the study. The therapist support for the trial will be provided by the Clinic for Functional Disorders at Helsinki University Hospital.

3.3 Any additional supply necessary to carry out the required study procedures

The intervention consists of a web-based app and thus is highly feasible. The web-based app for the active control condition is already available in Dutch. The *Fit after Infection* app will be developed during the clinical study period. Both the active control condition and *Fit after Infection* will be translated into the languages necessary (English, French, Norwegian, Finnish) after pilot testing. No additional supply will be necessary. Clinical data will be transmitted through a web-interface using local computers with an internet connection. Software platforms for the web-based app are commercially available and in accordance with EU regulations, the User Interface (suitable for both iOS and Android mobile devices) to support the conversational pipelines for the therapeutic chatbot is already developed by the AUMC/UvA in another Horizon Europe project (TIMELY) and will be used with their permission in the current project.

The functional brain imaging will be carried out by the DEFINE partner UiO. The PBMC experiments will be performed by DEFINE partner AHUS.

3.4 Plans on data management aspects

A detailed data management plan (DMP) will be prepared during protocol development. Actions will be taken to ensure that data management is EU General Data Protection Regulation (GDPR) compliant and aligned with the FAIR (Findable, Accessible, Interoperable and Reusable) principles. This applies to the entire chain of data management, from planning, storage, quality assurance procedures, data monitoring by external, qualified personnel at all sites, analyses, reporting and open repository requirements.

3.5 How reporting obligations to regulatory bodies and ethics committees will be met

The study protocol will be submitted for ethical approval by the medical ethical review board of the AUMC. The leader of WP4 will submit a summary of the progress of the trial to the ethics committee once a year. Information will be provided on the date of inclusion of the first subject, the number of subjects included, the number of subjects that have completed the trial, SAEs and amendments. Use of the software platform and therapeutic chatbot will be in compliance with the EU Medical Device Regulations. In the Netherlands, the study is subject to on-site monitoring in accordance with the quality assurance advice of the Dutch Federation of University Medical Centres regarding research involving human subjects. On-site monitoring will most likely be based on the risk classification ‘negligible’. Local ethical approval will be requested in each of the clinical sites after the medical ethical review board of the AUMC gives its approval to the study. According to national guidelines we will report on the progress of the study to the ethical board in each country.

3.6 Sponsor’s responsibilities

The sponsor of the clinical study is responsible for ensuring that the study is adequately monitored. Quality assurance by monitoring clinical sites will be coordinated by the Department of Clinical Research Monitoring in the AUMC, according to Dutch guidelines.

Data management will additionally be the responsibility of the sponsor, which will be supported by the Department of Research Data Management in the AUMC.

A communication plan will be set up before the trial start that will define the strategy for communication between the sponsor, study sites and all stakeholders involved to ensure proper oversight of all processes, with respect to the milestones described in 3.7.

3.7 Plans for major study milestones

The study milestones are stated in Part B and include the following:

Milestone	Month
Finalised study protocol and submission to the ethics committee	8
Ethics approval of study in first countries, finalisation of site contracts, initiation of trial sites	12
First patient in	16
50% of patients in	30
Last patient in	44
Interim analysis (25% patients in, 50% patients in, 75% patients in)	-
Data analysis and model development	54
Model validation	
Study closing, workshop, symposium, end report	60

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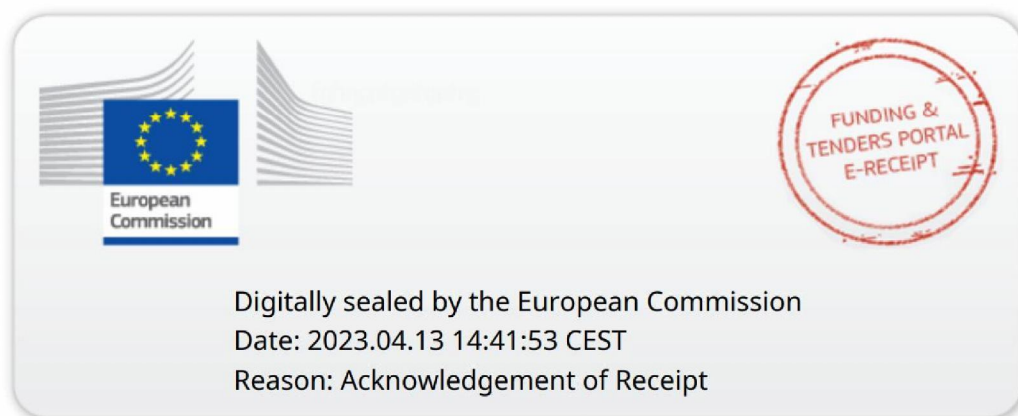
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