iPROLEPSIS

D5.1 / Study initiation package (iPROLEPSIS-PDPID study)

Editor	**Contractual delivery date**	**Actual delivery date**
Batoul Hojeij (EMC)	December 2023	October 2024
Deliverable type	**Dissemination level**	**Version - date**
R - Document, report	PU – Public	2.0 - 14/10/2024

Deliverable ID

Project acronym	iPROLEPSIS
Project full title	Psoriatic arthritis inflammation explained through multi-source data analysis guiding a novel personalised digital care ecosystem
Grant Agreement ID	101095697

Deliverable number	D5.1
Deliverable title	Study initiation package
Work package	WP5 – Clinical studies
Deliverable type	R - Document, report
Dissemination level	PU – Public
Version - date	2.0 - 14/10/2024

Contractual delivery date	December 2023
Actual delivery date	October 2024

Lead partner	EMC
Editor	Batoul Hojeij (EMC)
Contributors	Batoul Hojeij (EMC); Jolanda Luime (EMC); Nikos Athanasopoulos (AUTH); Ilja Tchetverikov (CICERO); Georgios Apostolidis (AUTH); Eleni Vasileiou (AUTH); Vasilis Charisis (AUTH); Cátia Gonçalves (PSR); Ana Rodrigues (PSR); Laura Coates (OUXF); Theodoros Dimitroulas (AUTH); Maria Mutilinaiou (AUTH)
Reviewed by	Juliana Valle (TUM) Francesca Levi-Schaffer (HUJI)
Approved by	Leontios Hadjileontiadis (AUTH, Project Coordinator)

Keywords	Digital biomarker; disease activity; flare; psoriatic arthritis

Document history

Version	Date	Contributors	Action / status
0.1	24/11/2023	EMC	Document structure (table of contents) ready
0.1	11/12/2023	EMC, AUTH	Document first draft
0.1	11/12/2023	EMC	Ready for internal review
0.1	19/12/2023	TUM	Reviewed by Juliana Valle (TUM)
0.1	21/12/2023	HUJI	Reviewed by Francesca Levi-Schaffer (HUJI)
0.2	22/12/2023	EMC, AUTH	Document revision 1
0.3	21/02/2024	EMC, AUTH	Document revision 2
0.4	29/02/2024	AUTH	Approved by the Project Coordinator
1.0	29/02/2024	AUTH	Submitted to the EC by the Project Coordinator
1.1	03/10/2024	EMC	Revision of document based on PO's feedback: 1) latest protocol version 2) study registration in ClnicalTrials.gov 3) update on ethics
1.2	04/10/2024	AUTH	Review
1.3	09/10/2024	EMC	Addressed AUTH comments
2.0	14/10/2024	AUTH	Approved by the Project Coordinator and submitted to the EC

Contents

List of figures 9

List of tables 10

List of abbreviations 11

Executive summary 13

1 Introduction 14

- 1.1 Document scope 14
- 1.2 Document structure 14

2 Study protocol 15

- 2.1 Protocol ID 15
- 2.2 Summary 16
  - 2.2.1 Rationale 16
  - 2.2.2 Objectives 16
  - 2.2.3 Study design 17
  - 2.2.4 Study population 17
  - 2.2.5 Intervention (if applicable) 17
  - 2.2.6 Main study parameters/endpoints 17
  - 2.2.7 Nature and extent of the burden and risks associated with participation, benefit and group relatedness: 18
- 2.3 Introduction and rationale 18
  - 2.3.1 Digital biomarkers 19
  - 2.3.2 Gut microbiome 22
- 2.4 Objectives 23
  - 2.4.1 Primary objective: 23
  - 2.4.2 Secondary objectives: 23
- 2.5 Study design 24
- 2.6 Study population 24
  - 2.6.1 Population (base) 24
  - 2.6.2 Inclusion criteria 25
  - 2.6.3 Exclusion criteria 25
  - 2.6.4 Sample size calculation 25
- 2.7 Treatment of subjects 25
  - 2.7.1 Investigational product/treatment 25
  - 2.7.2 Use of co-intervention (if applicable) 25
  - 2.7.3 Escape medication (if applicable) 25
- 2.8 Investigational product 26
  - 2.8.1 Name and description of investigational product(s) 26

- 2.8.2 Summary of findings from non-clinical studies 26
- 2.8.3 Summary of findings from clinical studies 26
- 2.8.4 Summary of known and potential risks and benefits 26
- 2.8.5 Description and justification of route of administration and dosage 26
- 2.8.6 Dosages, dosage modifications and method of administration....26
- 2.8.7 Preparation and labelling of Investigational Medicinal Product 26
- 2.8.8 Drug accountability 26

2.9 Non-investigational product....27

- 2.9.1 Name and description of non-investigational product(s)....27
- 2.9.2 Summary of findings from non-clinical studies 27
- 2.9.3 Summary of findings from clinical studies 27
- 2.9.4 Summary of known and potential risks and benefits 27
- 2.9.5 Description and justification of route of administration and dosage 27
- 2.9.6 Dosages, dosage modifications and method of administration....27
- 2.9.7 Preparation and labelling of Non-Investigational Medicinal Product....27
- 2.9.8 Drug accountability 27

2.10 Methods....27

- 2.10.1 Study parameters/endpoints 27
- 2.10.2 Randomisation, blinding and treatment allocation....30
- 2.10.3 Study procedures 30
- 2.10.4 Withdrawal of individual subjects 34
- 2.10.5 Replacement of individual subjects after withdrawal 34
- 2.10.6 Follow-up of subjects withdrawn from treatment 34
- 2.10.7 Premature termination of the study 34

2.11 Safety reporting....37

- 2.11.1 Temporary halt for reasons of subject safety 37
- 2.11.2 AEs, SAEs and SUSARs 37
- 2.11.3 Annual safety report 37
- 2.11.4 Follow-up of adverse events 37
- 2.11.5 [Data Safety Monitoring Board (DSMB) / Safety Committee] 37

2.12 Statistical analysis....38

- 2.12.1 Primary study parameter(s) 38
- 2.12.2 Secondary study parameter(s)....40
- 2.12.3 Other study parameters 40
- 2.12.4 Interim analysis (if applicable)....42

2.13 Ethical considerations 42

- 2.13.1 Regulation statement....42

    - 2.13.2 Recruitment and consent 42
    - 2.13.3 Objection by minors or incapacitated subjects (if applicable) 43
    - 2.13.4 Benefits and risks assessment, group relatedness 43
    - 2.13.5 Compensation for injury 44
    - 2.13.6 Incentives (if applicable) 44
  - 2.14 Administrative aspects, monitoring and publication 44
    - 2.14.1 Handling and storage of data and documents 44
    - 2.14.2 Monitoring and Quality Assurance 46
    - 2.14.3 Amendments 46
    - 2.14.4 Annual progress report 46
    - 2.14.5 Temporary halt and (prematurely) end of study report 46
    - 2.14.6 Public disclosure and publication policy 46
  - 2.15 Structured risk analysis 47
    - 2.15.1 Potential issues of concern 47
    - 2.15.2 Synthesis 47
- 3 Study protocol amendments 47
- 4 Ethics 48
  - 4.1 Netherlands 49
    - 4.1.1 Status 49
    - 4.1.2 Participating centres 49
    - 4.1.3 PIF 49
    - 4.1.4 Forms 50
  - 4.2 UK 50
    - 4.2.1 Status 50
    - 4.2.2 Participating centers 50
  - 4.3 Portugal 50
    - 4.3.1 Status 50
    - 4.3.2 Participating centers 50
  - 4.4 Greece 50
    - 4.4.1 Status 50
    - 4.4.2 Participating centers 50
  - 4.5 Study registration in registry 51
    - 4.5.1 Status 51
- 5 Clinical study and eCRF management system setup, rollout and maintenance 51
- 6 Conclusions 55
- References 56
- Appendices 61

Appendix I Questionnaires 61
  I.1 Questionnaires Netherlands (Dutch)...61
Appendix II Ethical approvals 62
  II.1 Netherlands.. **Error! Bookmark not defined.**
  II.1.1. Initial letter of approval from the MREC Erasmus MC for iPROLEPSIS-PDPID study .... **Error! Bookmark not defined.**
  II.1.2 Letters of the amendments approval by the MREC Erasmus MC for iPROLEPSIS-PDPID study.. **Error! Bookmark not defined.**
  II.1.3 Local approval letter study site ASZ....................... **Error! Bookmark not defined.**
  II.1.4 Proof/letter of initial local approval for 5 local sites in the Netherlands ....**Error! Bookmark not defined.**
  II.2 UK .... **Error! Bookmark not defined.**
  II.2.1. Initial letter of approval by the HRA and HRA and Health and Care Research Wales .... **Error! Bookmark not defined.**
  II.2.2 Proof/letter of initial local approval for local sites in UK**Error! Bookmark not defined.**
  II.3 Greece .... **Error! Bookmark not defined.**
  II.4 Portugal.. **Error! Bookmark not defined.**
Appendix III PIF...63
  III.1 Latest PIF and consent form Netherlands (Dutch) 63
  III.2 Latest PIF UK, Portugal, Greece (Dutch)................. **Error! Bookmark not defined.**
  III.3 PIF UK (draft original version, for translation purposes)..64
IV Appendix Forms..65
  IV.1 ABR form Netherlands 65
  IV.2 Research declaration template Netherlands...66
  IV.3 Clinical trial agreement template Netherlands 68
  IV.4 Risk classification Netherlands...95
  IV.5 Data management plan Netherlands...96

List of figures

Figure 1 Impact of cytokines on sleep patterns (Irwin, 2019). 20
Figure 2 Sleep deprivation, immune and inflammatory responses. 20
Figure 3 Immune-Stress Axis.Adapted from neuro-immune crosstalk in the pathology of hypertension (Calvillo et al., 2019)..21
Figure 4 Mechanical stress and biologic actors possibly involved in on bone remodelling in PsA. 22
Figure 5 Interactions between microbiota, intestinal epithelium and immune cells in RA. 23
Figure 6 Features captured by smartwatch. 26
Figure 7 Flow chart of study procedures. 31
Figure 8 Mock-ups of the miPROLEPSIS application under development. 35
Figure 9 Mock-up for physical activity measurement by miPROLEPSIS application. 35
Figure 10 Start screen and flare registration button in miPROLEPSIS application. 36
Figure 11 Example of daily questionnaires in the miPROLEPSIS application. 36
Figure 12 Mock-ups of the PsAI application in use. 37
Figure 13 Hand images processing pipeline for evaluating nail and joints condition. 41
Figure 14 Data architecture (smartphone and smartwatch)..45
Figure 15 Dataflow of the video assessment application...45
Figure 16 OpenClinica Dashboard...52
Figure 17 Example for eCRF versioning. 53

List of tables

Table 1 List of participating centers from Netherlands, UK, Portugal, and Greece. 24
Table 2 Type and scope of data collected by the miPROLEPSIS app. 33
Table 3 Amendments of PDPID study protocol 47
Table 4 Committees and Authorities for obtaining ethical approval for the PDPID study 48
Table 5 OC User roles defined for the study. 54

List of abbreviations

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AI	Artificial intelligence
App	Application
AR	Adverse Reaction
AUC	Area under curve
AUTH	Aristotle University of Thessaloniki
BMI	Body mass index
CA	Competent Authority
CASPAR	ClASsification criteria for Psoriatic ARthritis
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CRP	C reactive protein
CSP	Common spatial patterns
CV	Curriculum Vitae
DAPSA	Disease Activity Psoriatic Arthritis
DEPAR	Dutch south west Early Psoriatic ARthritis
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
Erasmus MC	Erasmus university medical center
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDL	Geometric deep learning
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
GRCQ	Global Rating of Change Questionnaire
HAQ	Health Assessment Questionnaire
IB	Investigator’s Brochure
IC	Informed Consent
ICC	Intra-class correlation coefficient
IMP	Investigational Medicinal Product
IQR	Interquartile range
LDA	Low disease activity
LEI	Leeds Enthesitis Index
IMPD	Investigational Medicinal Product Dossier
MDA	Minimal disease activity
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MIC	Minimal important changes
MDD	Minimal detectable difference
MONITOR	Multicentre ObservatioNal Initiative in Treat to target Outcomes in Psoriatic Arthritis
NA	Not applicable
OC	Open Clinica
PASDAS	Psoriatic Arthritis Disease Activity Score

PASS	Patient acceptable symptom state
PHQ9	Patient Health Questionnaire-9
PIF	Patient information forum
PPG	Photoplethysmography
PRO	Patients’ Reported Outcome
PsA	Psoriatic Arthritis
PSAID	Psoriatic Arthritis Impact of Disease
PSR	Portuguese Society of Rheumatology
PSS	Perceived Stress Scale
RA	Rheumatoid arthritis
REM	Remission
Reuma.pt	Portuguese Registry of Rheumatic Diseases
(S)AE	(Serious) Adverse Event
SD	Standard deviation
SF36	36-item Short Form Survey
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: AVG
UK	United Kingdom
URD	Unobtrusive Remote Disease activity monitoring
VAS	visual analogue scale
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen
WPAI	Work Productivity and Activity Impairment
WP	Work package

Executive summary

Psoriatic arthritis (PsA) is an immune mediated inflammatory arthritis occurring in patients with psoriasis. Patients with PsA experience difficulties in dealing with unpredictable disease activity which can affect their quality of life. Development of a digital biomarker using smart devices such as smartphone and smartwatch would allow for an unobtrusive remote monitoring of disease activity in these patients. Besides, understanding what factors trigger flare would allow for a better disease control.

The iPROLEPSIS-PDPID study is a multicentre observational cohort study that aims to develop an unobtrusive and affordable digital biomarker capable of detecting changes in disease activity including flare in patients with PsA, and to identify triggers of flare in these patients. The study will be conducted in four countries (Netherlands, UK, Portugal and Greece) and will involve patients with PsA. Therefore, an ethical approval will be required from each country to be able to initiate the study in. Application of ethical approval requires submission of multiple documents, such as country specific forms, study protocol, patient information file and consent form, patient assessment tools, and information on participating centers and principal investigators. By the time of writing, of the participating countries, ethical approval has been granted to initiate the study in the Netherlands (Erasmus MC), UK (University of Oxford), Greece (Hipokrateion Hospital Thessaloniki), and Portugal (local site: Hospital de Santa Maria). The Erasmus MC is the sponsor of the study.

The deliverable D5.1 is the initial deliverable for Task T5.1 and Task T5.2, which are part of work package (WP) 5. In this report, we provide the study registration number in Netherlands and the forms that were required to obtain the ethical approval. Besides, we provide information on the eCRF management system of the study. Data obtained from task T5.2 (iPROLEPSIS-PDPID study) will be analysed in WP3.

1 Introduction

Psoriatic arthritis (PsA) is an immune mediated inflammatory arthritis occurring in patients with psoriasis (Tiwari & Brent, 2023). Patients with PsA experience difficulties in dealing with unpredictable disease activity which can have consequences on their daily living. Development of novel smartphone- and smart watch digital biomarker would allow for an unobtrusive remote monitoring of disease activity in these patients. Indeed, the daily use of these devices allows for real-time disease activity monitoring, as compared to clinical assessment of disease during routine clinical visits. Besides, understanding what factors trigger flare would allow for a better disease control.

The iPROLEPSIS-PDPID study is a multicentre observational cohort study which will recruit patients with PsA from four different countries (Netherlands, UK, Portugal, Greece). The study aims to develop an unobtrusive and affordable digital biomarker capable of detecting changes in disease activity including flare in patients with PsA to assist patients on their disease activity status and to identify triggers of flare in patients with PsA.

When researching with human subjects, research needs to be reviewed and approved by a medical ethical review committee (MREC). This is required to ensure that the research participants and their rights are protected, and that research is carried according to high ethical standards. Since the iPROLEPSIS-PDPID study involves human subjects (patients with PsA), application for ethical approval is therefore required from each participating country to be able to conduct the research in. In general, the study application file includes country specific forms, study protocol, patient information file and consent form, patient assessment tools, and information on participating centers and principal investigators. Once approved, the study will be registered under a specific study registration number. Ethical approval has been granted to initiate the iPROLEPSIS-PDPID study in the Netherlands, UK, Greece and Portugal. Of note, the Erasmus MC is the sponsor of the study.

1.1 Document scope

The deliverable D5.1 is the initial deliverable for Task T5.1 and Task T5.2, which are part of work package (WP) 5. Here, we report the study protocol of the multicentre iPROLEPSIS-PDPID study, and the study number, ethical approval, and the forms required for the inclusion of the first patient in the Netherlands. Moreover, we provide information on the eCRF management system of the study. Data obtained from task T5.2, will be analysed in tasks T3.1, and T3.2, and the creation of artificial intelligence (AI) model will be performed in task T3.5 in WP3.

1.2 Document structure

The document consists of 5 sections: (1) introduction, (2) study protocol, (3) Ethics, (4) Clinical study and eCRF management system setup, rollout and maintenance, (5) conclusion. In section 1, the introduction provides an overview on the multicentre iPROLEPSIS-PDPID study. Section 2 includes the study protocol. Section 3 includes information on study protocol amendments. Section 4 provides information on the study number, patient information file (PIF), participating centers, and forms. Section 5 provides information on the eCRF system that will be implemented for the study. Section 6 provides conclusion for the document with future steps.

2 Study protocol

2.1 Protocol ID

Protocol title PsA digital phenotyping and inflammation drivers study

Protocol ID NL84429.078.23

Short title PsA digital phenotyping and inflammation drivers study (iPROLEPSIS-PDPID)

EudraCT number Not Available

Version 7.0

Date 03-07-2024

Coordinating investigator/project leader Jolanda Luime

Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) Jolanda Luime, Ilja Tchetverikov

Multicenter research Country leads: UK, Laura Coates; Portugal, Ana Rodrigues; Greece, Theodoros Dimitroulas

Local centers are presented in **Table 1**.

Sponsor (in Dutch: verrichter/opdrachtgever) Erasmus MC

Subsidising party EU

Independent expert (s) Dr. Paul van Daele

Pharmacy NA

Protocol signature sheet

2.2 Summary

2.2.1 Rationale

The level of disease activity in PsA and the perception thereof by the patients determines the actions the rheumatologist takes to optimise treatment outcomes among patients with this disease. Currently, disease activity is measured by a combination of clinical measures and patients' self-reported symptoms and functional ability. This requires the patients to visit the outpatient clinic at regular intervals, which during the Covid-19 pandemic was not always possible. The use of questionnaires to collect *Patients' Reported Outcomes* (PRO's) is a feasible option for monitoring patients at a distance. However, from a long-term perspective, survey fatigue is a known limiting factor of PRO's. Currently, there is no valid alternative for unobtrusive remote disease activity monitoring.

The widespread use of smart devices by the general population, such as smartphones or smartwatches, provides opportunities to develop and study possibilities for Unobtrusive Remote Disease activity monitoring (URD) using behavioural data captured by the sensors embedded within the smartphones/smartwatches. We hypothesize that a high level of disease activity in PsA will lead to changes in physical activity as registered by a patient's smartphone and smart watch as compared to a low disease activity state. We also hypothesize that the information acquired by digital biomarkers will be comparable to the information received through clinical measures and PROs. Additionally, digital biomarkers are likely to provide information on other disease characteristics such as tiredness and sleep problems. Adding these will enhance the discriminative ability of our approach. Last but not least, we hypothesize that patients will see the use of smartphone data as a privacy-wise safe and fair deal in return for better inside in their disease. And in low disease activity the use of digital biomarkers could reduce the amount of follow-up appointments at the out-patient clinic.

2.2.1.1 Overarching Aim

To develop an unobtrusive and affordable digital biomarker capable of detecting changes in disease activity including flare in patients with PsA to assist patients on their disease activity status and need of follow-up visits and for a better disease control by improved insights on what triggers a flare.

2.2.2 Objectives

2.2.2.1 Primary objective:

To develop and internally validate a novel and interpretable machine learning model for detecting flare in PsA patients using integrated accelerometer data, keystroke dynamics and screen time metrics (i.e., digital biomarker) to assess changes in their physical activity patterns against clinical defined flare by the rheumatologist. Accelerometer data are captured by both smartphone and smartwatch.

To develop and internally validate machine learning models that capitalize on sleep, fatigue, pain, stress, mechanical stress, composition of gut microbiome, genetic risk and environmental exposure for flare prediction (either clinically established or evaluated by the digital biomarker) in patients with PsA.

2.2.2.2 Secondary objectives:

To assess construct validity of the novel and interpretable machine learning model for detecting flare in PsA patients using integrated accelerometer data, keystroke dynamics and screen time metrics (digital biomarker) to assess changes in physical activity patterns against the continuous measure of clinical composite scores of disease activity and impact of disease used by the rheumatologist and impact of disease as reported by the patient.

To develop and internally validate a novel and interpretable machine learning model for changes in joint and skin appearance that relates to flare in PsA patients using video analysis of hand, posture and gesture and photos of the hands and feet against clinically defined flare by the rheumatologist.
To determine intra-person reliability of the AI-driven digital biomarker system.
To determine clinically relevant changes in the AI-driven digital biomarker system.
To determine minimal detectable difference in the AI-driven digital biomarker system.
To assess the intra-person variation of stress, mechanical stress and changes in gut microbiome on the occurrence of flare.
To identify genetic contribution to disease activity and pain.
To evaluate costs and effects of the digital biomarker of future care to current care.
To evaluate the compliance and satisfaction of the users with the smartphone- and smartwatch-based measurement of disease activity and flare.

2.2.3 Study design

One-year international multicentre prospective observational cohort.

2.2.4 Study population

Patients with psoriatic arthritis will be recruited from four different countries: Netherlands, Portugal, United Kingdom (UK) and Greece. In Netherlands and UK, patients will be recruited from centers participating in the DEPAR and MONITOR cohorts, respectively. In Portugal, patients will be recruited from centers participating in Portuguese Registry of Rheumatic Diseases (Reuma.pt), which is a project from the Portuguese Society of Rheumatology (PSR). In Greece, patients will be recruited from the outpatient clinic of Rheumatology Department of Hipokrateion Hospital Thessaloniki. The following inclusion criteria apply: (i) Psoriatic Arthritis per diagnosis of the rheumatologist, (ii) age 18 years or older and competent, (iii) using a smart phone, (iv) agree to use smartwatch, and (v) have good command of the local language. Exclusion criteria include (i) less than 18 years of age and (ii) incapacitated patients.

2.2.5 Intervention (if applicable)

None.

2.2.6 Main study parameters/endpoints

Absence of flare in psoriatic arthritis evaluated every 3 months, defined as:

Patients
‘At this time, is your psoriatic arthritis in remission, if this means: you feel your disease is as good as gone?’ (for REM)
‘At this time, are you in low disease activity, if this means: your disease is in low activity but it’s not as good as gone?’ (for LDA).

Doctors
’At this time, is the psoriatic arthritis in remission, if this means: the absence of clinical and laboratory evidence of significant inflammatory disease activity?’
‘At this time, is the psoriatic arthritis in low or minimal disease activity?’[1]

Patient Acceptable Symptom State (PASS)
‘If you were to remain for the next few months as you were during the last 48 hours, would this be acceptable or unacceptable for you?’ yes/ no

---

[1] The study is powered on low or minimal disease activity as noted by the doctor.

2.2.7 Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Patients with PsA experience difficulties in dealing with unpredictable disease activity which can have consequences on their daily living. With the introduction of smart devices, they could have better understanding on the disease influence on their physical activity patterns, stress levels, sleep, pain, stiffness, and fatigue. During the study, patients will benefit from the features provided by the Garmin Smart watch Vivoactive 5, such as physical activity and heart rate.

Digital monitoring of patients will be performed continuously for a year using a smart watch that will be provided for patients to wear daily, and a data capturing application (app) that will be installed on their smartphone. The data capturing app will collect -unobtrusively- the keystroke dynamics and the accelerometer/gyroscope data of the smartphone. The levels of pain, fatigue and stiffness will be also monitored via questions provided by the app on these symptoms. These are very short questions that appear one time a day for the first 14 days and are answerable within a few seconds. In addition, the app allows the patients to self-register a disease flare by pressing the flare button. Once patient registers a flare, these questions will appear again. When flare button is off, patients are inquired every two weeks if they are flare free. Besides, photos of hands and feet and videos of hands, posture and gesture will be collected at baseline, every 6 weeks and when patient experiences disease flare. Photos captured by the patient must contain only hands and feet, otherwise they will be discarded. Regarding the videos of hands, posture, and gesture, only the time series of hand/body landmarks from the raw videos will be saved (no raw videos will be stored).

Patients will be assessed at baseline and followed-up every 3 months for a total duration of one year. Each study visit requires around 30 minutes. Patients are clinically assessed for disease activity at study center and are requested to fill out questionnaires, at baseline and every 3 months. Saliva collection for DNA analysis is performed at baseline only, using a salivary collection kit at the study center or at home. For microbiome analysis, patients are provided with a home kit to collect stool at baseline and when experiencing disease flare in which they seek help from the rheumatologist. In the Netherlands, additional stool sample collection is requested from patients attending centers that are participating in DEPAR at months 6 and 12. Depending on the hospital facilities, patients can bring samples back during their hospital visit or send it to a central location via postal mail. To analyse cortisol from hair, 3 cm of hair will be sampled at study center from posterior vertex at baseline and every 3 months.

Burden on patients include more outpatient clinical visits than standard care, response burden, continuous use of smartwatch and continuous monitoring of patient activity for 12 months, taking photos and videos, providing hair and stool samples, and providing saliva for DNA analysis.

2.3 Introduction and rationale

PsA is a chronic immune mediated inflammatory arthritis occurring in patients with psoriasis and is usually serum rheumatoid factor negative (Tiwari & Brent, 2023). PsA affects around 20% of patients with psoriasis, is equally distributed amongst the sexes, has a tendency to be more prevalent in areas distant from the Equator and appears in most patients before age 65 (Alinaghi et al., 2019; Chandran & Raychaudhuri, 2010). The disease manifestation can be heterogeneous between subjects, and the resulting musculoskeletal impairment can interfere with physical function as well as quality of life of patients (Gudu & Gossec, 2018). Depending on disease activity, patients can experience burden at physical, psychological, social, and economic levels (Gudu & Gossec, 2018; Lee et al., 2010). In general, the treatments aim for a disease remission state, which means absence of inflammation and related symptoms.

Currently, disease activity is measured by a combination of clinical measures, as well as patients' self-reported symptoms and functional ability. The use of questionnaires to collect patient reported outcome (PRO's) is a feasible approach, however, from a long-term perspective, survey fatigue is a known limiting factor. On the other hand, the widespread use of smart devices by the general population, such as smartphones or smartwatches allows for *Unobtrusive Remote Disease activity monitoring* (URD) using behavioural data captured by the sensors embedded within the smartphones/smartwatches. Besides, the daily use of these devices allows for real-time disease activity monitoring, as compared to clinical assessment of disease during routine clinical visits.

Here we introduce some of the main disease domains that could be monitored digitally, namely: physical activity, fatigue, sleep, stress, mood, mechanical stress; and biologically, namely, the gut microbiome.

2.3.1 Digital biomarkers

2.3.1.1 Physical activity

Measuring physical activity by activity trackers is an upcoming research field in the field of Rheumatology. Most of them being performed in Rheumatoid Arthritis (RA) (Andreu-Perez et al., 2017; Davergne et al., 2021; Davergne et al., 2019; Gossec et al., 2019; Nowell et al., 2019), some in Axial spondylarthropathy (Gossec et al., 2019) and few in combined arthritis patient samples (Keogh et al., 2020; Perraudin et al., 2018). Aims and setting differed over the studies. Actconnect (Gossec et al., 2019) comes closest to what we aim for: identifying early bouts of inflammation that require intervention. They used an actigraph worn at the wrist and found that changes in walking speed seems indicative for self-reported flares. A similar device was worn in another study on morning stiffness in rheumatoid arthritis (RA) (Keogh et al., 2020). Changes in movement patterns within a patient allowed to distinguish RA from healthy controls. The only study reporting activity assessment in PsA patients focussed on foot pain (Walha et al., 2022). Another RA study tested something similar for hand function (Patanè et al., 2022).

2.3.1.2 Fatigue

(Andreu-Perez et al., 2017; Davergne et al., 2021; Davergne et al., 2019; Gossec et al., 2019; Keogh et al., 2020; Nowell et al., 2019; Patanè et al., 2022; Perraudin et al., 2018; Walha et al., 2022) One of the less understood problems in psoriatic arthritis is fatigue. This is commonly measured by questionnaires. There are no studies yet that try to capture fatigue in a digital way. Studies of fatigue in other fields have shown that fatigue could be measured in several ways: tracking eye movements on the phone (Valliappan et al., 2020), capture voice data (Laganas et al., 2022), keypad stroke dynamics (Lam et al., 2021).

2.3.1.3 Sleep

Sleeping patterns change due to inflammation (**Figure 1**) and change in sleeping patterns could elicit inflammation (**Figure 2**) (Garbarino et al., 2021; Ibarra-Coronado et al., 2015; Irwin, 2019). No data are yet available among PsA nor RA patients. One study described the protocol for measuring sleeping patterns using a smart watch (Crouthamel et al., 2021).

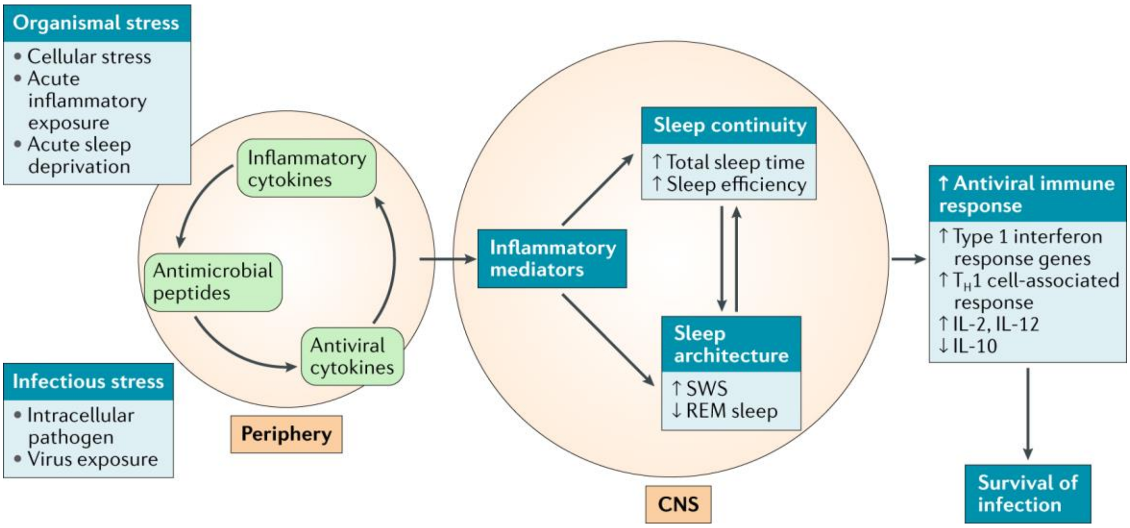


Figure 1 Impact of cytokines on sleep patterns (Irwin, 2019).

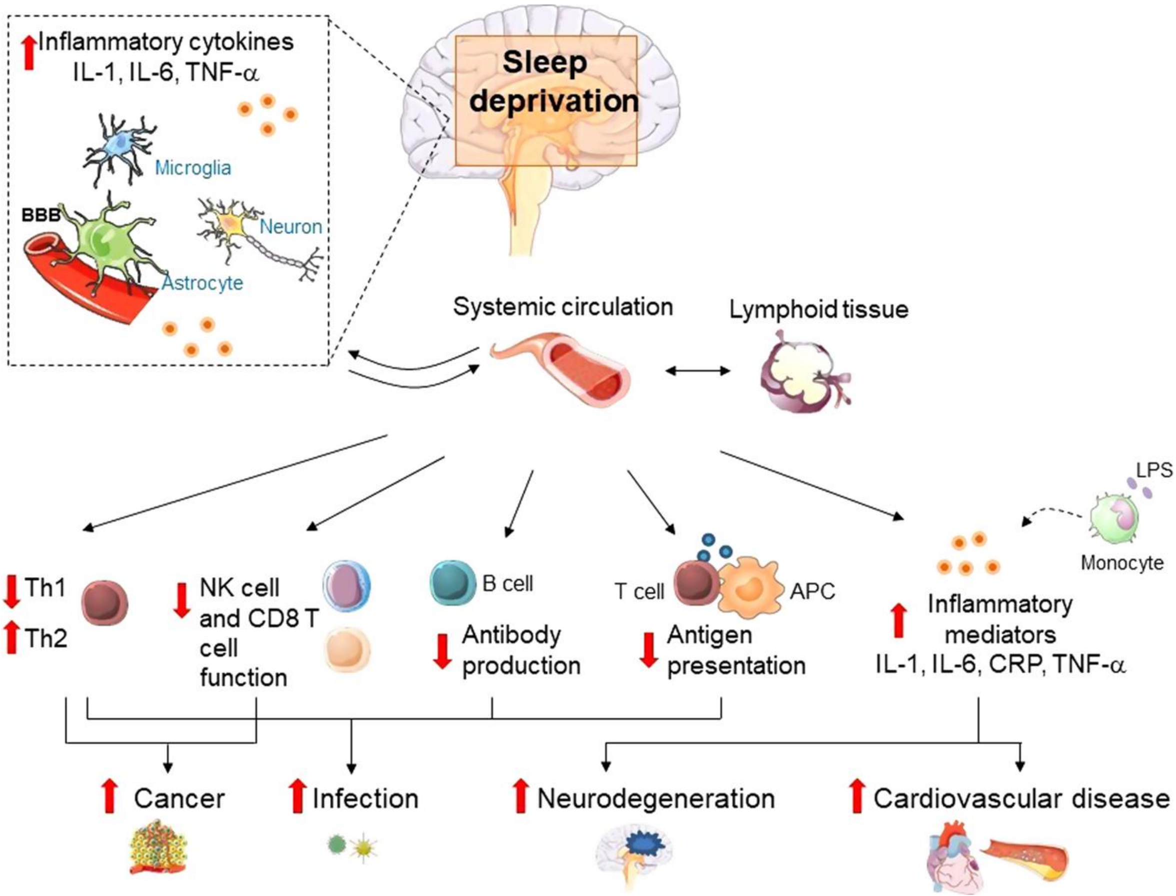


Figure 2 Sleep deprivation, immune and inflammatory responses.

Sleep deprivation, as induced experimentally or in the context of habitual short sleep, has been found to be associated with alterations in the circulating numbers and/or activity of total leukocytes and specific cell subsets, elevation of systemic and tissue (e.g., brain) pro-inflammatory markers including cytokines (e.g., interleukins (IL), tumour necrosis factor (TNF)-α), chemokines and acute phase proteins (such as C reactive Protein (CRP)), altered antigen presentation (reduced dendritic cells, altered pattern of activating cytokines, etc.), lowered Th1 response, higher Th2 response, and reduced antibody production. Furthermore, altered monocytes responsiveness to immunological challenges such as lipopolysaccharide (LPS) may contribute to sleep deprivation-associated immune modulation. Hypothesized links between immune dysregulation by sleep deprivation and the risk for immune-related diseases, such as infectious, cardiovascular, metabolic, and neurodegenerative and neoplastic diseases, are shown (Garbarino et al., 2021).

2.3.1.4 Mood

Fatigue, pain, lack of sleep and inflammation influences mood. Currently, mood is not looked at in systematic way by the rheumatologists. Although scientific studies look at depression and anxiety, the common way to do this is by questionnaire. Among other things keypad stroke dynamics may have the potential to assess changes in mood (Mastoras et al., 2019).

2.3.1.5 Stress

There is a continuous talk between the immune system and the stress axis to adapt the body to changes in the environment (**Figure 3**) (Russell & Lightman, 2019). In people with PsA this translates to the immune system alerting the stress system when inflammation occurs causing distress in people leading them to feel not their best version of themselves. Also, if external stressors activate the stress axis for longer time it results in a pro-inflammatory status of the immune system. Recent developments in digital biomarkers show that capturing the heartrate variability by smart devices allows to study stress continuously (Kim et al., 2018). Combined with measuring chronic hyperactivity of hypothalamic-pituitary-adrenal axis by cortisol levels in hair (Gonzalez et al., 2019) it provides a personal stress profile. This has not been done in the field of rheumatology.

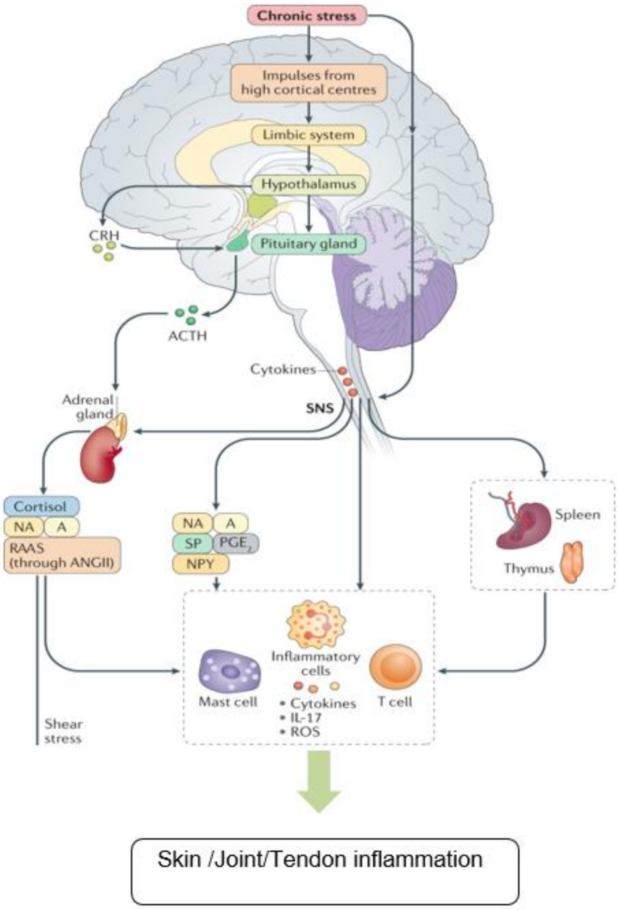


Figure 3 Immune-Stress Axis.Adapted from neuro-immune crosstalk in the pathology of hypertension (Calvillo et al., 2019).

2.3.1.6 Mechanical stress

Mechanical stress on joints and tendons occurs every day in normal life. The repair process of the small amounts of tissue damages is part of normal tissue remodelling. In PsA patients this mechanism gets easily disturbed causing longstanding inflammation at tendon insertions at the bone (**Figure 4**) (Gracey et al., 2020; Perrotta et al., 2021; Van Mechelen & Lories, 2020). It is also likely to play a role as a hit the inflammation mechanism in arthritis (Gracey et al., 2020). Up to now no studies actively sought to measure mechanical stress in real-life. Data are currently collected by questionnaires and indirectly discovered by history taking.

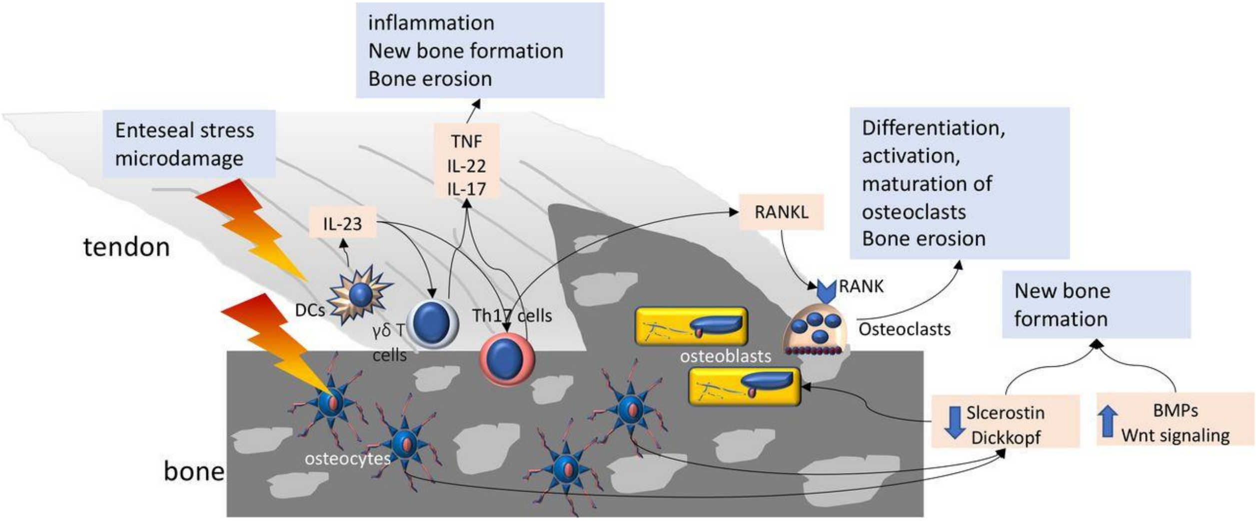


Figure 4 Mechanical stress and biologic actors possibly involved in on bone remodelling in PsA. Mechanical stress and microdamage could enhance IL-23 production which stimulates IL-17 production by γδT cells and Th17 cells. Proinflammatory cytokines contribute to inflammation and bone damage. RANKL may also be produced by T cells and contributes to maturation, activation, and differentiation of osteoclasts. Finally, mechanical stress may reduce the production of sclerostin and Dickkopf proteins by osteocyte. Together with the increase of Wnt signalling and BMPs activity, new bone formation is enhanced. IL, interleukin; RANKL, Receptor Activator of Nculear Factor-kBBone Morphogenic protein; TNF, tumour necrosis factor (Perrotta et al., 2021).

2.3.2 Gut microbiome

Changes of the complex interplay between the gut microbiota and the cells of the immune system in the inner lining of the gut seems a trigger in the inflammatory mechanism of PsA (**Figure 5**) (Miguens Blanco et al., 2020). The changes in the gut microbiome composition which are more likely to cause this are currently unknown. The studies already performed mainly investigate cross sectional gut microbiome signature in patients (Zhang et al., 2020). It is likely that these profiles over time change depending on stress and food intake. Recent studies in depression show that due to distress people start to eat different foods causing the composition of gut microbiota to change. The microbiota composition resembled patterns they also saw in irritable bowel syndrome patients, a disease originating in the same group of immune-mediated inflammatory disease (Valles-Colomer et al., 2019).

Currently, there are no studies available that evaluate AI-driven digital biomarkers for remote assessment and monitoring of people with PsA. Two early studies in the field RA using activity trackers show promising results for the detection of flares (Davergne et al., 2021; Gossec et al., 2019). One focused on the prediction of flares as defined by the clinician while the other assessed the prediction of self-defined flares by the patients. Therefore, we hypothesize that a high level of disease activity in PsA will lead to changes in physical activity as registered by a patient’s smartphone and smart watch as compared to a low disease activity state, and that the information acquired by digital biomarkers will be comparable to the information received through clinical measures and PROs. Additionally, digital biomarkers are likely to provide information on other disease characteristics such as tiredness and sleep problems

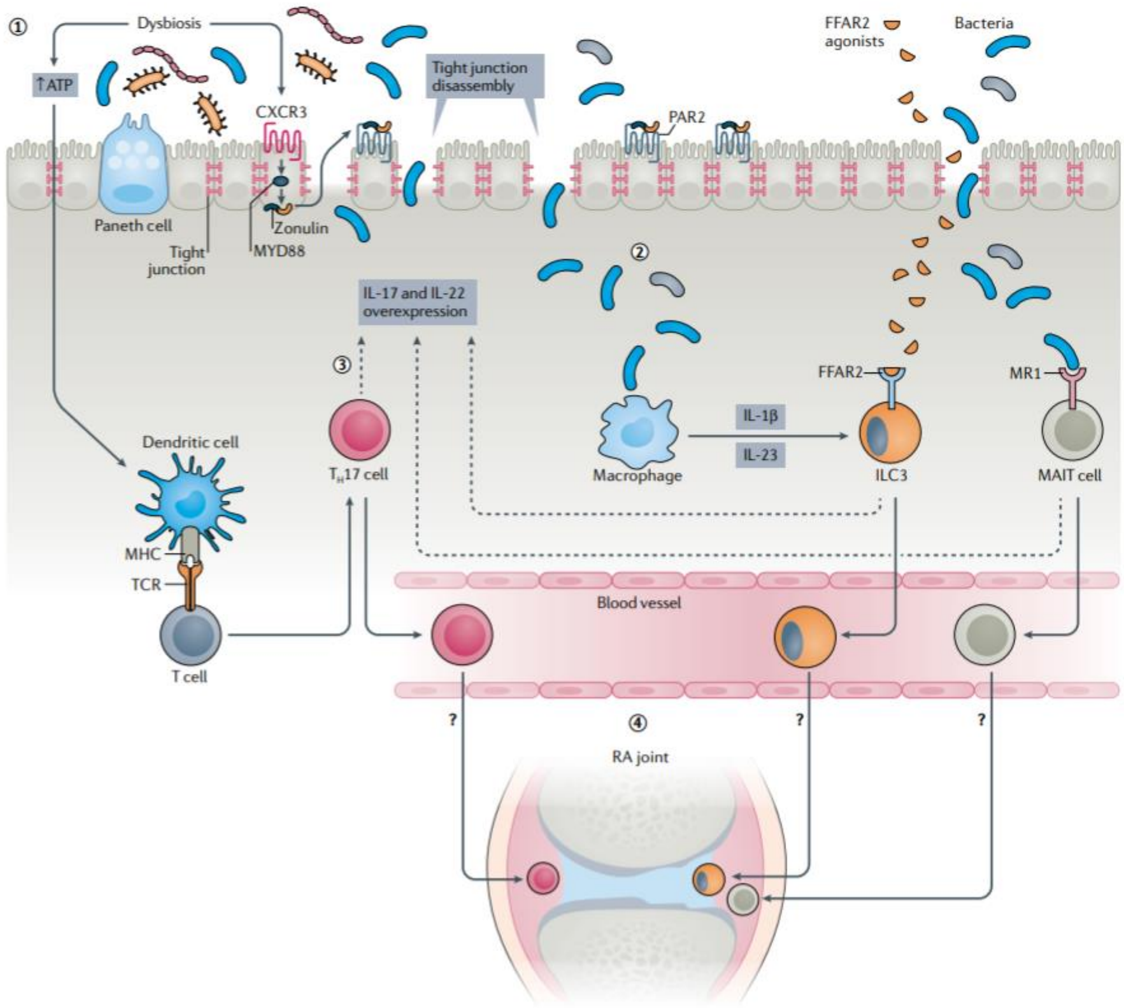


Figure 5 Interactions between microbiota, intestinal epithelium and immune cells in RA. Linking the gut to the joint in RA, similar mechanisms are at play in PsA (Zaiss et al., 2021).

2.4 Objectives

2.4.1 Primary objective:

To develop and internally validate a novel and interpretable machine learning model for detecting flare in PsA patients using integrated accelerometer data, keystroke dynamics and screen time metrics (i.e., digital biomarker) to assess changes in their physical activity patterns against clinical defined flare by the rheumatologist. Accelerometer data are captured by both smartphone and smartwatch.

To develop and internally validate machine learning models that capitalize on sleep, fatigue, pain, stress, mechanical stress, composition of gut microbiome, genetic risk, and environmental exposure for flare prediction (either clinically established or evaluated by the digital biomarker) in patients with PsA.

2.4.2 Secondary objectives:

To assess construct validity of the novel and interpretable machine learning model for detecting flare in PsA patients using integrated accelerometer data, keystroke dynamics and screen time

metrics (digital biomarker) to assess changes in physical activity patterns against the continuous measure of clinical composite scores of disease activity and impact of disease used by the rheumatologist and impact of disease as reported by the patient.
To develop and internally validate a novel and interpretable machine learning model for changes in joint and skin appearance that relates to flare in PsA patients using video analysis of hand, posture and gesture and photos of the hands and feet against clinically defined flare by the rheumatologist.
To determine intra-person reliability of the AI-driven digital biomarker system.
To determine clinically relevant changes in the AI-driven digital biomarker system.
To determine minimal detectable difference in the AI-driven digital biomarker system.
To assess the intra-person variation of stress, mechanical stress and changes in gut microbiome on the occurrence of flare.
To assess genetic contribution to disease activity and pain.
To evaluate costs and effects of the digital biomarker of future care to current care.
To evaluate the compliance and satisfaction of the users with the smartphone- and smartwatch-based measurement of disease activity and flare.

2.5 Study design

One-year international multicentre prospective observational cohort in patients diagnosed with PsA.

2.6 Study population

2.6.1 Population (base)

Patients with PsA will be recruited from four different countries: Netherlands, Portugal, United Kingdom (UK) and Greece. In Netherlands and UK, patients will be recruited from centers participating in the DEPAR and MONITOR cohorts, respectively. In Portugal, patients will be recruited from centers participating in Portuguese Registry of Rheumatic Diseases (Reuma.pt), which is a project from the Portuguese Society of Rheumatology (PSR). In Greece, patients will be recruited from the outpatient clinic of Rheumatology Department of Hipokrateion Hospital Thessaloniki. The list of participating centers from each country is depicted in **Table 1**.

Table 1 List of participating centers from Netherlands, UK, Portugal, and Greece.

Country	Participating center
Netherlands (DEPAR cohort)	Erasmus MC (leading)
	Albert Schweitzer (ASZ)
	Reinier de Graaf ziekenhuis (RDGG)
	Maasstad ziekenhuis (MSZ)
	Amphia
	Admiraal de Ruyter Ziekenhuis (Adrz)
	Haga ziekenhuis
	Franciscus Gasthuis & Vlietland (SFG)
	Reumazorg ZWN (RZWN)
	Medisch Spectrum Twente (MST)
United Kingdom (MONITOR cohort)	University of Oxford
Portugal (Reuma.pt/PSR)	Hospital de Santa Maria

	Hospital Egas Moniz
Greece	Hippokrateion Hospital Thessaloniki

2.6.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
18 years or older and competent
Diagnosed with PsA
Using a smart phone
Agree to use smartwatch
Good command of local language

2.6.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
Less than 18 years of age
Incapacitated patients

2.6.4 Sample size calculation

2.6.4.1 Detection of flare

We estimate that between 20-50% will have a clinical detectable flare (inflammation) within one year of disease monitoring (Gossec et al., 2019). As we currently have no details on the test performance of the AI-driven digital biomarker we aim to have a sensitivity of 90% and a specificity of 80% of the biomarker with a conservative estimation to identify 25% of patients having a flare in a year. Using these numbers would require 180 participating patients including a 20% drop out rate (Buderer, 1996). However, given the different data sources we use to get our initial biomarker and our second study objective on prediction of flare we used the sample size for our other primary objective.

2.6.4.2 Prediction of flare

To answer research questions on prediction for flare, we used the generally accepted rule of thumb with a prevalence of 25% flare and 10 patients per event. Within 554 patients, 139 patients (25%) will have a flare, allowing for 12 variables plus the intercept in the prediction model (Harrell et al., 1996; Steyerberg et al., 2001). These variables will include age, sex, initial disease activity state, sleep, keystroke dynamics (3 features), activity by accelerometer data (3 features), sleep, stress and screen time. With some compensation for lost to follow-up we aim to include 600 patients (150 patients per country).

2.7 Treatment of subjects

Patient are treated according to usual care. Measurements are strictly observational and are not used for intervention nor for clinical decision making.

2.7.1 Investigational product/treatment

NA

2.7.2 Use of co-intervention (if applicable)

NA

2.7.3 Escape medication (if applicable)

NA

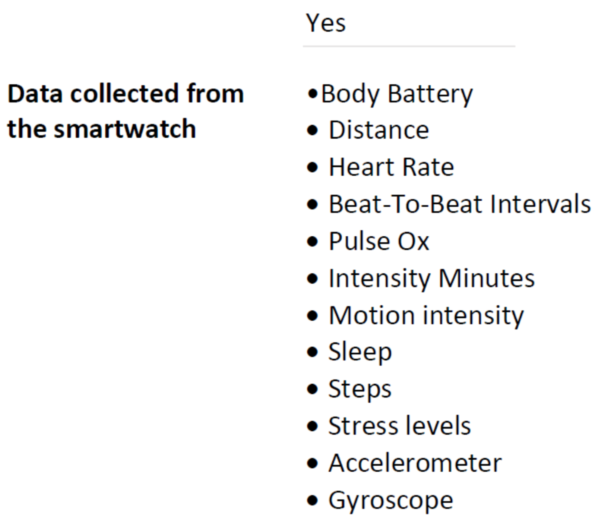
2.8 Investigational product

2.8.1 Name and description of investigational product(s)

The following products will be used to develop a digital biomarker set for the assessment of disease activity:

Mobile phone app that captures accelerometer data, screen time, keystroke dynamics to assess psychomotor impairment caused by the disease activity (including mood decline), hand and feet photos, and hand/gesture/posture videos. Photos captured by the patient must contain only hands and feet, otherwise they will be discarded. Regarding the videos of hand/body landmarks, only the time series of hand/body landmarks from the raw videos will be saved (no raw videos will be stored).

Garmin Smart watch Vivoactive 5 that captures accelerometer data, heart rate, heart rate variability, recognises physical activity, calculates stress based on heart rate and activity pattern and sleep parameters as provided by the smartwatch (**Figure 6**).



	Yes
Data collected from the smartwatch	•Body Battery • Distance • Heart Rate • Beat-To-Beat Intervals • Pulse Ox • Intensity Minutes • Motion intensity • Sleep • Steps • Stress levels • Accelerometer • Gyroscope

Figure 6 Features captured by smartwatch.

2.8.2 Summary of findings from non-clinical studies

NA

2.8.3 Summary of findings from clinical studies

No clinical studies yet.

2.8.4 Summary of known and potential risks and benefits

No risks are expected.

2.8.5 Description and justification of route of administration and dosage

NA

2.8.6 Dosages, dosage modifications and method of administration

NA

2.8.7 Preparation and labelling of Investigational Medicinal Product

NA

2.8.8 Drug accountability

NA

2.9 Non-investigational product

2.9.1 Name and description of non-investigational product(s)

Device to collect stool: OMNIgene.GUT kit to collect stool which includes a simple paper tool with an accompanying tube.
Device to collect saliva: ORAGene.DNA kit to collect saliva which includes a tube and allows for collected saliva to be stored at room temperature.

2.9.2 Summary of findings from non-clinical studies

Both devices are tools that are regularly used to collect materials from subjects in clinical care.

2.9.3 Summary of findings from clinical studies

Both devices are tools that are regularly used to collect materials from subjects in clinical care.

2.9.4 Summary of known and potential risks and benefits

The devices to collect stool and saliva have no potential risks.

2.9.5 Description and justification of route of administration and dosage

NA

2.9.6 Dosages, dosage modifications and method of administration

NA

2.9.7 Preparation and labelling of Non-Investigational Medicinal Product

NA

2.9.8 Drug accountability

NA

2.10 Methods

2.10.1 Study parameters/endpoints

2.10.1.1 Main study parameter/endpoint

Absence of flare in PsA evaluated every 3 months defined as (Coates et al., 2021; Gorlier et al., 2019):

Patients
‘At this time, is your psoriatic arthritis in remission, if this means: you feel your disease is as good as gone?’ (for REM)
‘At this time, are you in low disease activity, if this means: your disease is in low activity but it’s not as good as gone?’ (for LDA).

Doctors
‘At this time, is the psoriatic arthritis in remission, if this means: the absence of clinical and laboratory evidence of significant inflammatory disease activity?’
‘At this time, is the psoriatic arthritis in low or minimal disease activity?’[2]

Patient Acceptable Symptom State (PASS) (Gorlier et al., 2019)
‘If you were to remain for the next few months as you were during the last 48 hours, would this be acceptable or unacceptable for you?’ yes/ no

2.10.1.2 Secondary study parameters/endpoints

Based on clinical evaluation and the patient reported outcomes the following composites of disease activity and impact of disease will be calculated at baseline and during each follow-up period every three months (please refer to the data collection sheet):

---

[2] The study is powered on low or minimal disease activity as noted by the doctor.

Minimal disease Activity (MDA) (Coates et al., 2010) as defined by patient meeting 5 out of 7 of the following criteria: (i) tender joint count ≤1; (ii) swollen joint count ≤1; (iii) Psoriasis Area and Severity Index ≤ 1 or body surface area ≤3%; (iv) tender entheseal points ≤ 1 (v) patient pain visual analogue scale VAS ≤15; (vi) patient global activity VAS ≤20; (vii) Health Assessment Questionnaire (HAQ) ≤0.5.

Psoriatic Arthritis Disease Activity Score (PASDAS) (Helliwell et al., 2013) calculated as a composite score using the following criteria: physician global VAS, patient global VAS, SF36 PCS, swollen joint count, tender joint count, Leeds Enthesitis Index, tender dactylitis count, and CRP.

Disease Activity Psoriatic Arthritis (DAPSA) (Schoels et al., 2010) calculated as a summation score of the following: tender and swollen joints (TJC68, SJC66), patient global assessment VAS, patient pain VAS and CRP.

Likert scale questions daily from the PsAID (Gossec et al., 2014):
Severity of pain (PSAID 1). When in pain, follow-up question: “did you use painkillers or NSAIDs?”
Severity of fatigue (PSAID2)
Sleep (PSAID 7)

10-point Likert scale for severity of stiffness (morning stiffness)

In addition the following flare questions will be asked at baseline, follow-up visits, and when patients experience disease flare in which they seek help from the rheumatologist (Sousa et al., 2023):

Doctors
‘At this time, is the disease in flare (i.e., significantly worsened/more active compared to usual)?’ yes/no

Patients
‘At this time, are you having a flare of your psoriatic arthritis, if this means the symptoms are worse than usual?’ yes/no

2.10.1.3 Other study parameters

2.10.1.3.1 Digital biomarkers (collected continuously):

Phone captured
Keypad time-related data and metadata
Accelerometer and gyroscope sensor data
Screen time
Hand and feet photos
Hand, gesture, and posture videos (no raw videos will be stored)

Smart watch captured
Sleeping time and type
Accelerometer data
Screen time
Body battery / Stress levels
Heart rate and Beat-to-beat intervals
Motion intensity
Pulse Ox
Steps
Physical activity intensity and categories as captured by the device
Distance

The digital parameters will be provided as raw data from smartwatch (e.g., heart rate) or if they are calculated from other parameters (e.g., respiration rate) as determined by smartwatch.

Motion data, collected from smartphone and Garmin sensors, are considered a primary source, since we aim to validate algorithms for smartphone-based digital biomarkers, as smartphones can be considered an unobtrusive and affordable approach to measurement of flare/disease activity. As people will not always carry their smartphone with them, data are added from the smartwatch to see whether the missing accelerometer data of the phone will cause detection problems in flare. Furthermore, the smartwatch allows for data collection on sleeping behaviour, to test whether changes in sleeping patterns elicit flare. The smartphone will allow capturing a bit of this information extracted via screen time, as patients may use their smartphone as an alarm clock and if they wake up during the night also look at the time in the night on their phones. The smartwatch is also used for assessing stress as it measures heart rate and heart rate variability.

2.10.1.3.2 Clinical assessment:

Medical history
Age
Sex
Years of disease
Medication over the year of the study
Comorbidity
Care activities
Job title, shift work and frequent flying
Handedness and typing fingers
Onset of flare

Clinical evaluation
66/68 joint count for swelling and tenderness
6 tendon count for enthesitis using Leeds Enthesitis Index (LEI)
Body Surface Area for skin
BMI
Abdominal circumference
CASPAR score calculation for the classification of PsA which include (Taylor et al., 2006): (i) evidence of current psoriasis, or personal or family history of psoriasis, (ii) dactylitis, (iii) juxtaarticular new bone formation, (iv) nail dystrophy, and (v) negative for rheumatoid factor.

2.10.1.3.3 Biological markers:

Saliva
DNA (selected genetic variants)

Stool
Gut microbiome

Hair
Hair cortisol levels

Blood (standard care)
Inflammatory blood marker CRP obtained from medical records as part of standard care.

2.10.1.3.4 Questionnaires (Appendix I):

Demographics
VAS pain and patient global
HAQ to measure physical function (Fries et al., 1980)
Psoriatic Arthritis Impact of Disease (PSAID) (Gossec et al., 2014)
36-item Short Form Survey (SF36) for general health assessment (Ware & Gandek, 1994)
EQ5d for general health assessment (Lee et al., 2013)

Work Productivity and Activity Impairment (WPAI) (Tillett et al., 2019)
Patient Health Questionnaire (PHQ9) for depression assessment (Kroenke et al., 2001)
Life events
Health care usage
Global Rating of Change Questionnaire (GRCQ) to evaluate disease activity change (Jaeschke et al., 1989)
Perceived Stress Scale (PSS) (Cohen et al., 1983)
Digital literacy
Questionnaire for stool analysis
Questionnaire for hair cortisol analysis

2.10.1.3.5 Environment:

Humidity
Temperature
Air Pollution (namely, NO, NO2, NOx, O3, PM10, PM25, SO2)

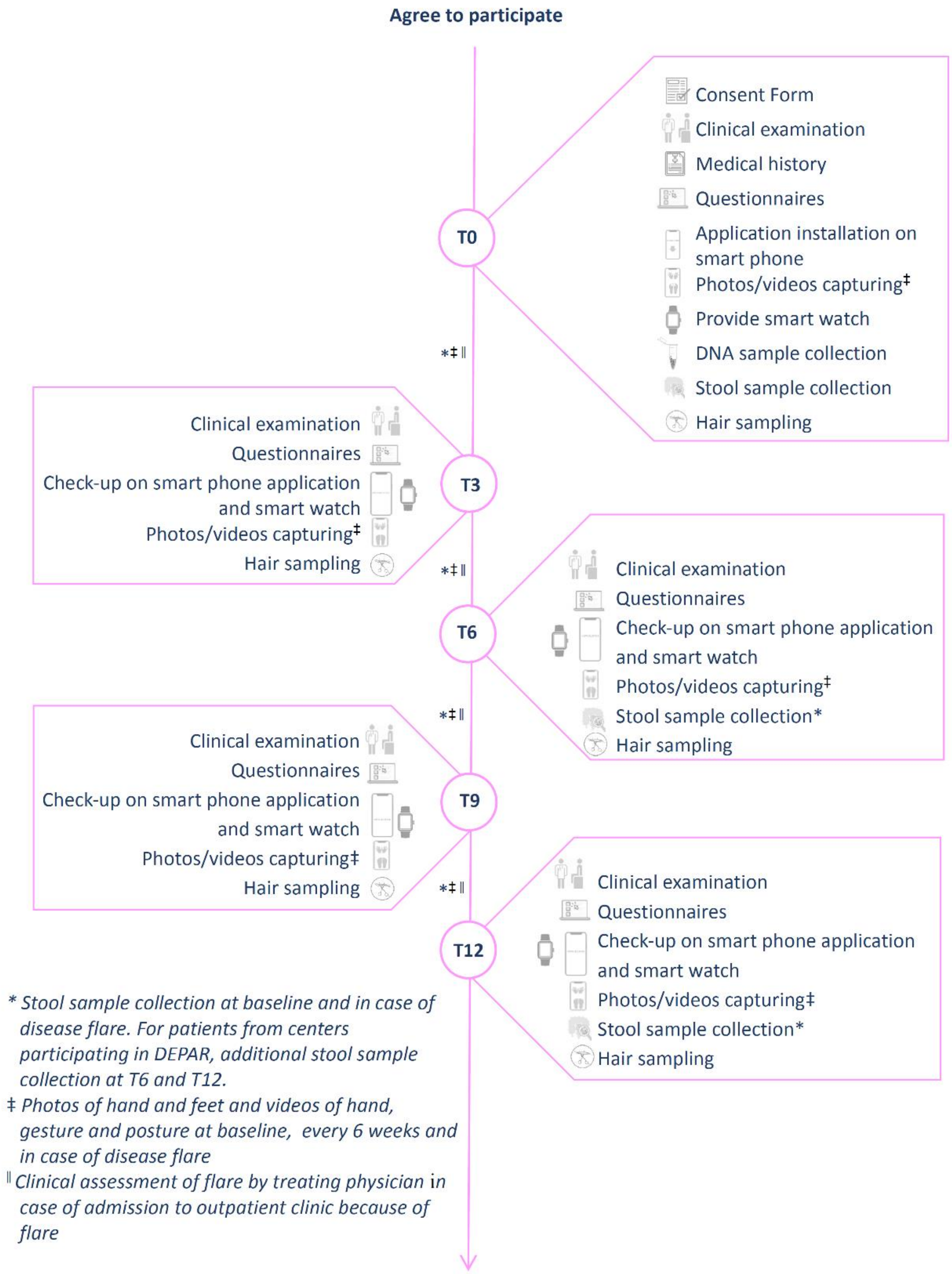
2.10.2 Randomisation, blinding and treatment allocation

NA

2.10.3 Study procedures

Flow chart of study procedures is depicted in **Figure 7**. Before baseline assessments patients are screened if they meet all of the inclusion criteria: (i) being diagnosed with PsA; (ii) age 18 years or older and competent; (iii) familiar with the use of a smart phone; (iv) agree to use smartwatch; and (v) have good command of the local language. Briefly, patients are invited by their rheumatologist. If they agree to participate, then during the first visit (T0), they will provide the informed consent, have medical history taken, be clinically examined and be requested to fill online questionnaires. In addition, they will have their hair sampled and be provided with research kit which includes a smart device, a stool sample collection (tubes plus stool collection devices and envelops) and a DNA sample collection tool. The patients will also have the app installed on their smartphone. Besides, a button in the phone app will be available to allow patients to register self-determined disease flare which would allow to monitor flare during the study. A control question will appear every two weeks to check if patients were indeed flare free if they did not use the button.

Following baseline assessment, patients will be follow-up every 3 months. During each follow-up period, patient will be clinically examined, requested to fill out online questionnaires and have a check-up on their smart device. Moreover, patients will have their hair sampled, and provided with restock of materials for stool collection. Besides, as part of standard care when the patient visits the outpatient clinic seeking help because of high level of disease activity, assessment for flare will be also performed by the treating physician. In such case, standard care procedures will be followed according to protocols of the participating center.



** Stool sample collection at baseline and in case of disease flare. For patients from centers participating in DEPAR, additional stool sample collection at T6 and T12.*

‡ Photos of hand and feet and videos of hand, gesture and posture at baseline, every 6 weeks and in case of disease flare

‖ Clinical assessment of flare by treating physician in case of admission to outpatient clinic because of flare

Figure 7 Flow chart of study procedures.

2.10.3.1 (Routine) Laboratory tests

As part of routine clinical practice, the following parameters are measured in blood in the local laboratories of the participating hospitals: C-reactive protein (CRP); HLA-B27.

2.10.3.2 Questionnaires

Before each visit patients will fill out online questionnaires at home, which will be checked at the corresponding visit. If patients did not fill out the online questionnaire, they are given the opportunity to do so at the study visit.

2.10.3.3 Stool samples

For the (change in) microbiota composition, stool samples will be collected in a tube including an integrated spoon attached to the lid at baseline (T0) and when patient experiences disease flare for which they seek help from the rheumatologist at the hospital. Additional stool sample collection is requested from patients attending centers that participate in DEPAR at T6 and T12. The participants are given instructions to store their sample in their own fridge immediately upon acquiring it, preferably 24 hours prior to the visit. Samples are brought in by the patient at the moment of the visit. Food intake over the last 3 days prior to the time of collection will be monitored by a short survey. After arrival at the laboratory, the samples will be homogenized and stored until analysis at -80°C. Bacterial DNA will be extracted from the stool samples and the sequences of region V3-V4 of the 16S rRNA bacterial gene will be amplified using barcoded primers with Illumina adapters. Bacterial libraries are prepared according to 16S Metagenomic Sequencing Library Preparation protocol (Part # 15,044,223 Rev. B, Illumina, San Diego, CA, USA). Sequencing will be performed on an Illumina MiSeq platform using a MiSeq Reagent Kit v3 (600 cycles). Analysis of stool samples will be performed at the Erasmus MC.

2.10.3.4 Saliva samples

For the study of genetics, DNA from saliva will be collected. Patients are requested to provide liquid saliva in a tube. The collection tube can be stored at room temperature (around a year) and does not require cold shipping. Analysis of salivary DNA will be performed at the Erasmus MC.

Patients will be tested for pre-specified genetic variants (in form of single nucleotide polymorphisms) of genes of interest and polymorphisms in human leukocyte antigen that have been shown to be related to PsA (e.g., HLA-B27, HLA-C06). Concerning genes of interest, selection is mostly based on genes involved in immune-inflammatory pathways involved in PsA (e.g., TNF-a, IL-23R, IL-6, JAK-STAT) and in drug metabolism and transport for medications used in treatment of PsA (e.g., CYP2C9, ABCB1).

2.10.3.5 Hair sampling

For the measurement past stress, 3 cm of hair will be cut at the study center near scalp at the posterior vertex at baseline (T0) and each follow-up period (T3, T6, T9 and T12). Since hair grows at a rate of 1cm per month, 3 cm of hair would represent average cortisol release of the past three months (Staufenbiel et al., 2013). Hair samples will be stored at room temperature and analysed according to protocols of clinical chemistry department of Erasmus MC.

2.10.3.6 Phone app

The miPROLEPSIS phone app will be used in this study which is currently under development (**Figure 8**). The app will be installed on the patient smartphone and utilized as a data collector, which will be then used for algorithms development and training. The app will not present any recommendations to the patient that will affect decision making related to their health conditions. Being utilized as a data collector only, the app is not considered medical software.

Table 2 provides information on the type and scope of data collected by miPROLEPSIS app. Briefly, the app is used to measure physical activity (**Figure 9**), the length of sleep, self-registered flare and registering daily pain, fatigue, sleep and morning stiffness in the first 14 days of the study. The app registers motion by means of 3-axis accelerometer of the phone and keystroke dynamics via an additional keyboard layer. Screen time is used as a proxy for sleep gathering Bed Time and waking up Time. A button in the start screen of the app allows to self-register a disease flare (**Figure 10**). A control question will appear every two weeks to check if patients were indeed flare free if they did not use the button. Also, images of both hands and feet, and videos of both hands, posture and gesture will be collected using the phone camera at baseline, every 6 weeks and when patient experiences disease flare as they can be useful to identify early signs of inflammation as well as to predict upcoming inflammation. Daily questions will be automatically sent for the first 14 days at the start of the study and if a flare occurs at daily intervals up to the moment the flare is gone (**Figure 11**). When patients register no flare, a control question will appear every two weeks to check if patients were indeed flare free if they did not use the button. All data collected by the miPROLEPSIS app will be available to patients.

Since the miPROLEPSIS app is under development, we provide mock-ups of the PsAI app (**Figure 12**) that has been developed and is currently in use in the PsAI pilot study (NL81628.078.22).

For the video assessment, a separate application with minimal features has been developed to accompany the miPROLEPSIS app. The new application will be triggered (called) by the miPROLEPSIS app when the user is ready to perform each video movement assessment test and it will close automatically when the test finishes. During the test, the application will process the camera frames and compute the skeletal data.

Table 2 Type and scope of data collected by the miPROLEPSIS app.

Type	From	Scope
Keyboard data	Keyboard application integrated with miPROLEPSIS patient app	Collecting typing dynamics is a key component for data collection related to hand function
Images (toes and nails)	Smartphone camera sensor used through miPROLEPSIS patient app	Assessing PsA symptoms related to nails and toes
Video Assessment	Smartphone camera sensor used through miPROLEPSIS patient app	Hand/gesture/posture analysis for the assessment of range movement
Accelerometer data	Smartphone accelerometer sensor	Assessing physical activity levels
User inputs	Questionnaires provided in the miPROLEPSIS patient app	Patient assessment on his/her condition and lifestyle (pain, flare, sleep)
Physical activity (steps, etc.)	Wearable device (Garmin Vivoactive 5) connected via Bluetooth with the smartphone	Assessing activity patterns
Sleep (duration, stages, quality)	Wearable device (Garmin Vivoactive 5) connected via Bluetooth with the smartphone	Assessing sleep status and disorders
Stress (summary, continuous data)	Wearable device (Garmin Vivoactive 5) connected via Bluetooth with the smartphone	Assessing body response to stress
Heart Rate and HRV	Wearable device (Garmin Vivoactive 5) connected via Bluetooth with the smartphone	Assessing body response to stress

2.10.3.7 Garmin smart watch Vivoactive 5

The patient is provided with the Garmin Vivoactive 5 device at baseline (T0) and requested to return it at the end of data collection period (T12) or if they drop-out. The Vivoactive 5 device is used to collect data on physical activity, heart rate, heart rate variability and the quality of sleep. The Vivoactive 5 device registers motion by means of 3-axis accelerometer. In addition, it records sleep (Bed Time, Get Up Time, Time in Bed, Total Sleep Time –hours-, Onset

Latency -minutes-, Sleep Efficiency -proportion-, wake after sleep onset and number of awakenings), environmental light and skin temperature.

The collected data from Garmin is downloaded from the miPROLEPSIS app by Wellics software (developer in the project), which allows extracting, visualizing and exporting collected both company-processed data, as well as raw data. Of note, patients will be informed on the possibility of using Garmin application provided by the Garmin, but the application is not used in any of study outcomes.

2.10.3.8 Weather and pollution data

Weather and pollution data will be collected from open-source data in the near neighborhood of the patient's home and work location. This will be done based on the postal code provided by the patient, average working hours and travel amount during work. For patients that travel a lot for work we will use general weather data of the area they travel in. Most weather institutions in the participating countries collect weather data on hourly basis. Air pollution is measured in lower location resolution because of specific stations needed to collect the data. The nearest station will be used to determine the extent of air pollution using the air pollution data integration of the university of Exeter (Gonzalez, 2023).

2.10.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

2.10.4.1 Specific criteria for withdrawal (if applicable)

NA

2.10.5 Replacement of individual subjects after withdrawal

NA

2.10.6 Follow-up of subjects withdrawn from treatment

NA

2.10.7 Premature termination of the study

NA

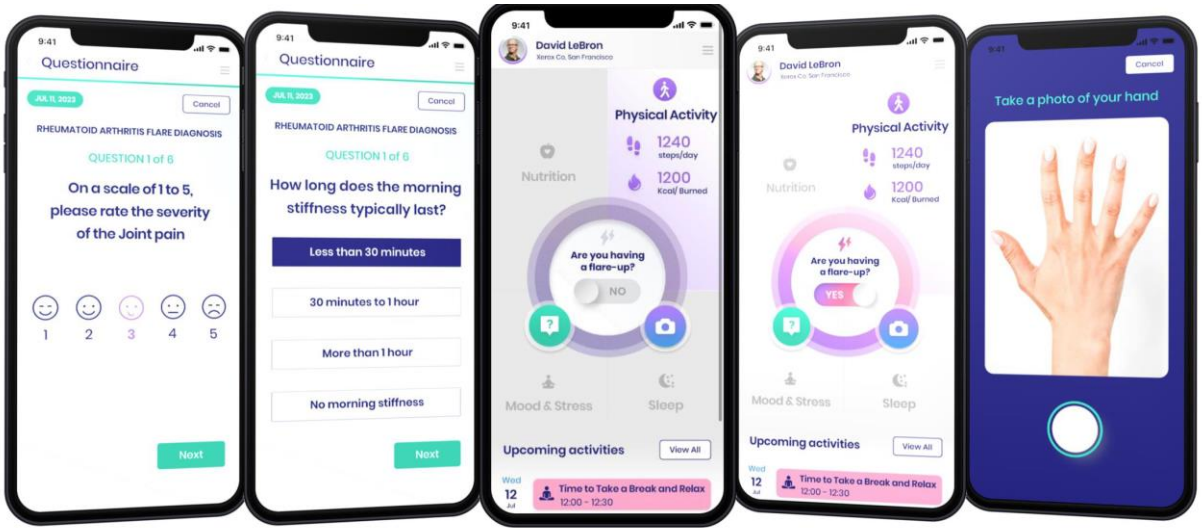


Figure 8 Mock-ups of the miPROLEPSIS application under development.

Indication that wearable is connected

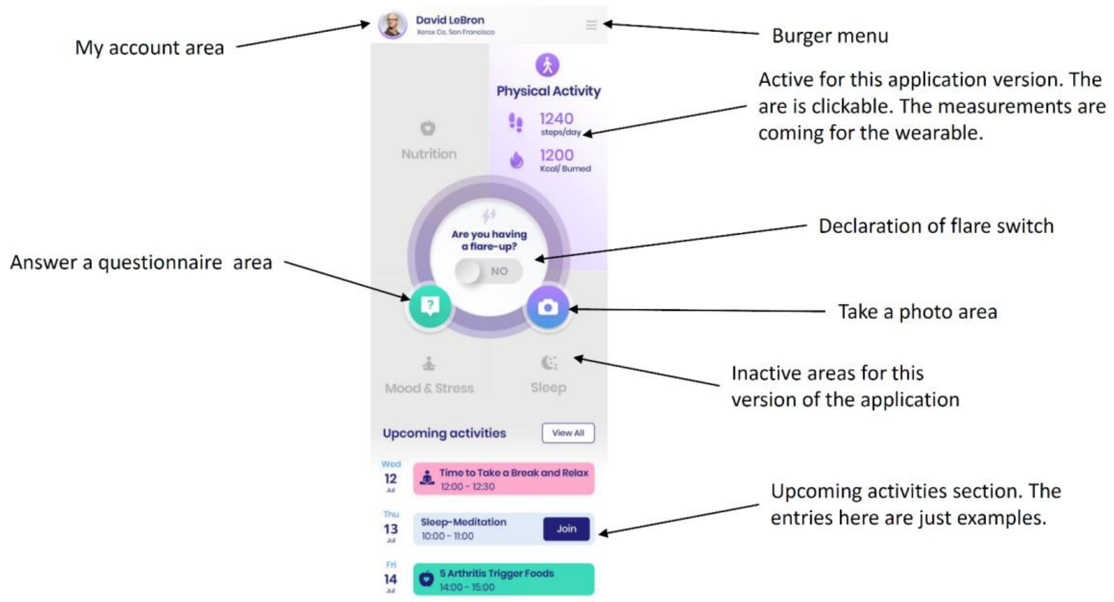
Notification button

Graphical representation of steps through time (measured through wearable)

Different physical activity metrics list measured either from wearable or through phone. In this case these are just examples to demonstrate how information is going to be.

Upcoming physical activities area. The entries here are just examples to demonstrate how information is going to be presented. For this version of the application this area will be inactive.

Figure 9 Mock-up for physical activity measurement by miPROLEPSIS application.



My account area

Burger menu

Active for this application version. The are is clickable. The measurements are coming for the wearable.

Answer a questionnaire area

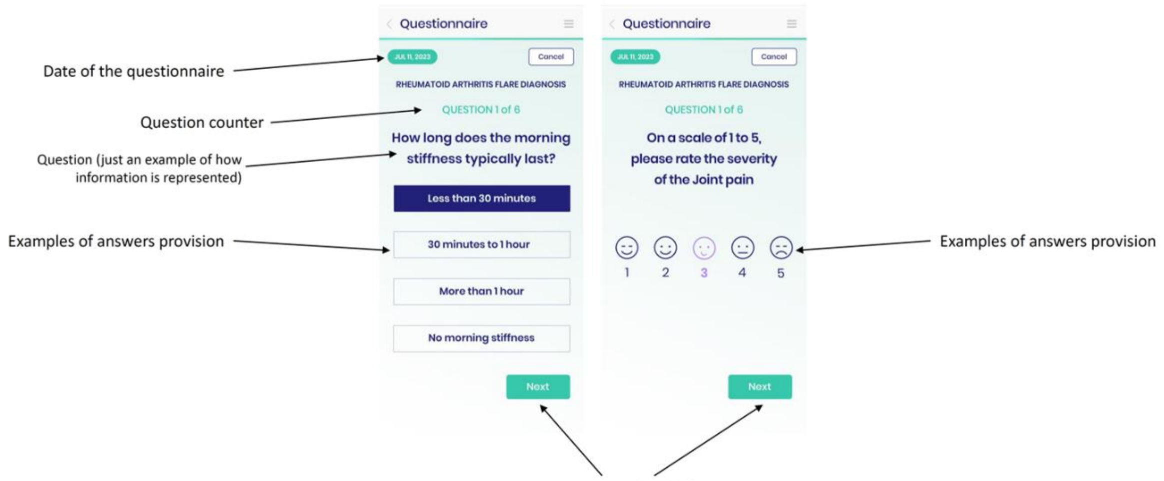
Declaration of flare switch

Take a photo area

Inactive areas for this version of the application

Upcoming activities section. The entries here are just examples.

Figure 10 Start screen and flare registration button in miPROLEPSIS application.



How long does the morning stiffness typically last?

On a scale of 1 to 5, please rate the severity of the Joint pain

Date of the questionnaire

Question counter

Question (just an example of how information is represented)

Examples of answers provision

Examples of answers provision

Button to proceed with the next question

Figure 11 Example of daily questionnaires in the miPROLEPSIS application.

Ontsteking van uw gewrichten, huid en pezen wordt gemeten met behulp van maten voor ziekteactiviteit. Die bestaan uit vragen die u zelf kan invullen, maar ook uit lichamelijk onderzoek waarvoor u naar het ziekenhuis moet komen. Dit is ten tijden van corona lastig geweest, maar ook misschien niet altijd nodig als uw ziekte rustig is. Daarom zouden we graag ziekte activiteit op een andere manier gaan meten.

In dit onderzoek gaan we kijken of gegevens verzameld met uw mobiele telefoon iets zeggen over uw ziekte activiteit. Mocht blijken dat dit een goede manier is, dan kunnen we in de toekomst ziekteactiviteit op afstand meten, waardoor u minder vaak naar het ziekenhuis hoeft te komen. Ook kan het voor u een hulpmiddel zijn om een betere balans te vinden in het leven.

De volgende gegevens worden verzameld:

```
1 STILL_AR-1054 secs 2023-06-11T12:54
                     :41.942+02:00
2 ON_BICYCLE_AR-102 secs 2023-06-11
                         T12:56:07.6
                         54+02:00
3 STILL_AR-342 secs 2023-06-11T13:01:
                    50.097+02:00
4 WALKING_AR-80 secs 2023-06-11T13:
                     03:10.099+02:00
5 RECORDING-80 secs 2023-06-11T13:03
                    :10.455+02:00
6 WALKING-90 secs 2023-06-11T13:03:2
                  0.573+02:00
7 STILL-970 secs 2023-06-11T13:19:31.4
                 86+02:00
8 STILL_AR-998 secs 2023-06-11T13:19:
                    48.497+02:00
9 WALKING_AR-83 secs 2023-06-11T13:
                     21:11.956+02:00
10 RECORDING-100 secs 2023-06-11T13:
                      21:12.357+02:0
                      0
11 WALKING-110 secs 2023-06-11T13:2
                    1:22.443+02:00
12 STILL-152 secs 2023-06-11T13:23:55.
                  593+02:00
13 STILL_AR-177 secs 2023-06-11T13:2
                     4:09.622+02:00
14 WALKING_AR-287 secs 2023-06-11T1
```

Deze vragenlijst is gebaseerd op de PsAID12 vragenlijst en bestaat uit 3 vragen over pijnklachten, slaapkwaliteit en vermoeidheid.

Figure 12 Mock-ups of the PsAI application in use.

2.11 Safety reporting

2.11.1 Temporary halt for reasons of subject safety

NA

2.11.2 AEs, SAEs and SUSARs

2.11.2.1 Adverse events (AEs)

NA: The study design is a prospective cohort that undergoes no intervention. No AE are expected to occur due to the daily use of their own smart phone. Patients will be provided with a leather band for the smartwatch if they suffer from skin irritation from the silicon strap that comes standard with the Garmin watch to prevent any skin discomfort.

2.11.2.2 Serious adverse events (SAEs)

NA: The study design is a prospective observational cohort that undergoes no intervention. No SAE are expected to occur due to the wearable or daily of the own smart phone.

2.11.2.3 Suspected unexpected serious adverse reactions (SUSARs)

NA: The study design is a prospective observational cohort that undergoes no intervention. No SUSARs are expected to occur due to the wearable or daily of the own smart phone.

2.11.3 Annual safety report

NA

2.11.4 Follow-up of adverse events

NA

2.11.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

NA

2.12 Statistical analysis

2.12.1 Primary study parameter(s)

2.12.1.1 Preprocessing of data from smartphone and smartwatch for the detection and prediction of flare

2.12.1.1.1 Keyboard

The keyboard application will collect keyboard metadata when patient is typing. Each of these sessions will consist of sequences of 1) transient data, i.e., holding time, flying time and normalized pressure and 2) global data, i.e., typing session duration, length, delete rate. Specifically, the holding and flying times in a session will be calculated using the sequence of time stamps of corresponding to the press and release of each key in the typing session. Next, both transient and global data will be processed and combined to result the typing feature vector of each typing session. Subsequently, machine learning models will be fed with sequences of typing feature vectors to calculate typing digital biomarkers which represent the finger mobility/dexterity. The feature extraction and machine learning modelling pipelines will be based on the methodology proposed by Iakovakis et al (Iakovakis et al., 2018). The typing digital biomarkers will be scores the level of which will contribute to the detection of PsA specific inflammation.

2.12.1.1.2 Accelerometer data

The raw accelerometer data are tri-axial signals which represents the time changes of 3-DOF orientation. These signals consist of various components relative to physical activity and postural state. The processing of raw accelerometers will be based on analysing the signals on different spectral bands. The resulted components will be used for extracting features and, finally, the features will be fed to machine learning models to calculate scores the level of which will contribute to the detection of flare.

2.12.1.2 Reliability of AI-driven digital biomarker system

A pre-set number of tasks will be carried out to verify the reliability of the different digital measurements.

Accelometer data: Accelerometer data: test-retest reliability will be determined by assessing the degree of similarity between repeated features produced over a pre-specified period (e.g., consecutive days) using intra class correlation coefficient (ICC) values (Andrew P. Creagh, 2022). Accelerometer data will be captured by both smartphone and smartwatch and will be transformed into meaningful features representing the physical activity levels of the participants, and activity specific characteristics. This method will allow us to evaluate the reliability of the entire spectrum of the extracted features.

Keystroke dynamics: test-retest reliability will be determined by assessing the degree of similarity between features produced by consecutive typing sessions throughout a pre-specified period (Andrew P. Creagh, 2022). Each typing session consists of measurements of typing events, e.g., key press and release timestamps, and it is collected every time the patient types a text during the study. No specific task is required from the patient.

Heart rate: heart rate is highly variable due to influences of many biological systems – we will assess heart rate on consecutive nights between a fixed time period with movement in the same range.

Test-retest reliability will be assessed using the 2 consecutive measurements. This will be performed using a two-way mixed effect model with absolute agreement for a single rater/measurement intra-class correlation coefficient, (ICC) (2,1) (Koo & Li, 2016). Reliability is indicated using the ICC values classified as; poor ($ICC < 0.5$), moderate ($ICC = 0.5$ to 0.75), good ($ICC = 0.75$ to 0.9) and excellent ($ICC > 0.9$) (Streiner, 2014).

2.12.1.3 Validity of AI-driven digital biomarker system against flare

Construct validity of the new digital biomarker will be evaluated against the self-reported flare of disease activity by the patients and the flare definitions as noted under 8.1.1. (Lidwine B. Mokkink et al., 2010; L. B. Mokkink et al., 2010). In addition, we will use the PSAID as described under 8.1 using AUC with different cut offs for precision and recall.

2.12.1.4 Creating and evaluating a digital biomarker

To model individual evolution of digitally measured flare, we will apply a technique based in geometric deep learning (GDL). GDL is a field of machine learning that modifies key operations, as convolutions, to apply traditional Convolutional Neural Networks to 3D objects, graphs and manifolds. Inflammatory processes, like PSA, are multi-scale processes evolving processes expressing in different ways across different timescales that can be expressed as a manifold. The immune system responds to a trigger resulting in higher inflammation states that expresses as increase in pain, fatigue, stiffness, and decrease of range of motion and sleep. Such processes are distinguished because they evolve in a low-dimensional manifold in phase space. In a phase space, every degree of freedom or parameter of the system, in this study the components that resemble PsA disease activity, is represented as an axis of a multidimensional space; a one-dimensional system is called a phase line, while a two-dimensional system is called a phase plane. For every possible state of the system or allowed combination of values of the system's parameters, a point is included in the multidimensional space. The system's evolving state over time traces a path (a phase-space trajectory for the system) through the high-dimensional space. The phase-space trajectory represents the set of states compatible with starting from one particular initial condition, located in the full phase space that represents the set of states compatible with starting from *any* initial condition. As a whole, the phase diagram represents all that the system can be, and its shape can easily elucidate qualities of the system that might not be obvious otherwise. In classical statistical mechanics the concept of phase space provides a classical analogue to the partition function (sum over states) known as the phase integral (Alf Gerisch, 2017; Deisboeck et al., 2011; Fenichel, 1979).

We will apply common spatial patterns (CSP) method (Fenichel, 1979) to identify this low-dimensional manifold and use it as a prior in geometric deep learning (GDL) to build a predictive tool quantifying the risk of PsA flare. To optimise the learning conditions for the GDL, the CSP splits factors into fast and slow timescales in order to characterise the model by which timescales the manifold is defined. Think about the occurrence of inflammation causing change in accelerometer data sampling frequency on millisecond scale, pain evolving over hours, affecting sleep over days.

The GDL model will be evaluated against clinical measures of disease activity as noted under 8.1 using area under curve (AUC) with different cut offs for precision and recall. Internal validation will be performed using 1/3 bootstrap validation.

2.12.1.5 Determination of minimal import changes (MIC) and minimal detectable difference (MDD) in the AI-driven digital biomarker system

Change in the digital biomarker will be correlated with changes in daily pain, fatigue and self-reported stiffness and sleep levels, the self-reported flare button and the clinical markers of disease activity. Both MIC and MDD will be determined (de Vet et al., 2006).

Anchor-based and distribution-based methods will be adopted to triangulate the ranges of MIC. The anchor-based MIC estimate is calculated as the mean change score on the digital biomarkers, corresponding to patients that change from no-flare to flare and those that change from flare to no flare (Jaeschke et al., 1989). The distribution-based MIC estimate is determined using Cohen's effect size benchmark, which is widely accepted. An effect size of

0.5 of the no-flare score is advocated as a reasonable method to estimate the MIC (Norman et al., 2003).

For each of the parameters in digital biomarker we will determine normal levels of variation and those that for the individual person are beyond these band of normal variation (Polgar et al., 2021). Based on the bandwidth, we will determine the MDD.

2.12.1.6 Prediction of flare in PsA

In predicting PsA specific inflammation we will use 3 different outcomes: self-registered flare, flare as detected by the digital biomarker and the 3-month defined inflammation by the rheumatologist. Here we assume that symptoms like evolution of morning stiffness, pain, fatigue, reduction of physical activity, precede the flare, while being modified or elicited by changes in gut microbiome, sleeping pattern, heart rate. This will be happening on a genetic background while being modified by external parameters, including weather conditions and air pollution. These covariates will be evaluated using a survival analysis, also known as time-to-event analysis, employing DeepSurv (Katzman et al., 2018) to explore and understand the relationships between patients' covariates (e.g., clinical and genetic features). This then may allow for early individual patient warning that a flare is likely to occur. Using AUC different cut offs for precision and recall will be tested. Internal validation will be performed using 1/3 bootstrap validation technique.

2.12.1.7 Train-validation-test sets development

To split data samples in train, validation and test sets, random splitting will be used. The split ratio will be 80%-10%-10% (Lauritsen et al., 2020) initially. This split will be a starting point and can be adjusted based on the specific dataset size and nature of the problem.

2.12.1.7.1 Internal validation

We will apply Cross-validation (Müller, 2016), a resampling technique used in machine learning to assess how well a predictive model will generalize to an independent dataset. Cross-validation provides a more accurate estimation of a model's performance compared to a single train-test split. The basic idea behind cross-validation is to divide the dataset into multiple subsets, often referred to as folds. The model is trained on a subset of the data (training set) and then validated on the remaining data (validation or test set). This process is repeated multiple times, with different subsets of data used for training and validation in each iteration. The performance metrics from these iterations are then averaged to obtain a more reliable estimate of the model's performance. We will start by comparing the k-fold (Katzman et al., 2018) and leave-one-out methods (Müller, 2016), and we will explore the literature for advancements in cross validation methods.

2.12.2 Secondary study parameter(s)

For the secondary study parameters, same procedures will be applied as for primary study parameters in terms of data pre-processing, creating, and evaluating a digital biomarker, and determination of MIC and MDD (section 10.1).

2.12.2.1 Validity of AI-driven digital biomarker system against disease activity

Construct validity of the new digital biomarker will be evaluated against clinical measures of disease activity as noted under 8.1 using AUC with different cut offs for precision and recall (Lidwine B. Mokkink et al., 2010; L. B. Mokkink et al., 2010).

2.12.3 Other study parameters

2.12.3.1.1 Baseline characteristics

Descriptive statistics (mean (SD), median (IQR), minimum and maximum values), will be used to present baseline characteristics of study population.

2.12.3.1.2 Photos of hands and feet and videos hands, gestures, and postures

Images of both hands and feet will be collected using a smartphone camera. Each image will be processed with image processing and computer vision techniques to produce a feature vector relative to the condition of nails and joints of hands and toes. Firstly, a set of metrics will be calculated finger/toe-wise following the pipeline shown in **Figure 13**. A similar version of this processing approach was adopted by Webster et al (Webster DE, 2022). Next, the finger/toe-wise metrics and the skin tone bias (Firzpatrick skin tone) will be combined to result hand/feet imaging digital biomarkers.

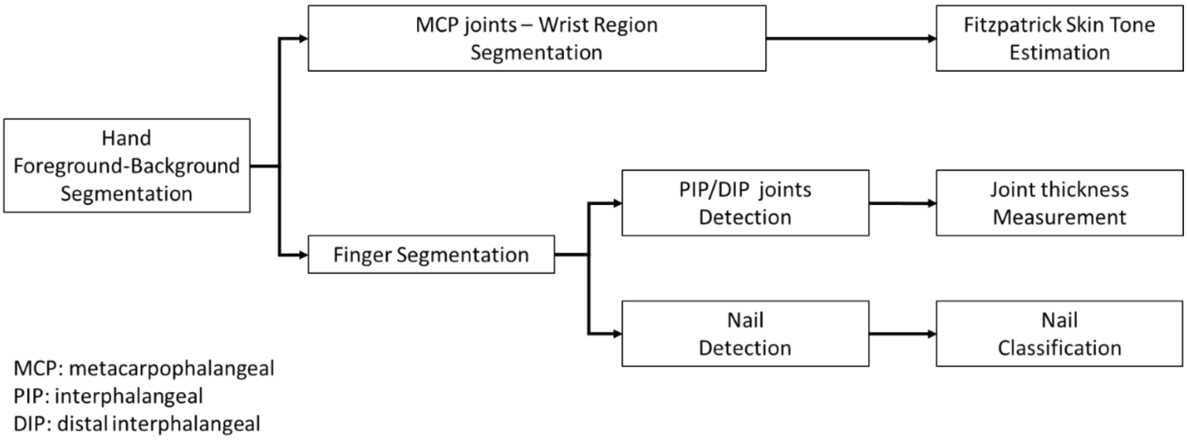


Figure 13 Hand images processing pipeline for evaluating nail and joints condition. The same abstract pipeline will be used for feet nail and joint evaluation.

Videos will be recorded during a set of range of motion assessment tests. From each recording, a set of initial body, hand and joint landmarks (i.e., skeleton) will be detected, and their coordinates will be tracked across subsequent video frames. The output from tracking the landmarks from a video will produce a set of time series with landmark coordinates. From these time series a few scores will be produced. These scores can be the ones that represent the similarity between the recorded hand/gesture/posture and a reference one and/or the absolute distance travelled by joints of interest. Other scores that can be calculated are the total number of successful test repetitions and the duration of the test. The exact type and number of scores that will be measured depend on the specific test. A tentative but not exhaustive list with the possible tests follows:

Sitting to standing: The subject moves from a sitting position to a standing position without using their hands.
Standing to sitting: The subject moves from a standing position to a sitting position without using their hands.
Reaching forward: While standing with straight legs, the subject reaches forward with their hand extended as far as possible.
Turning look behind: While standing straight, the subject turns to look behind them from both sides.
Picking up objects: The subject picks up an object from the floor.
Making fist: The subjects open and close their hands.
Making wrist movements: The subjects move their wrists upwards/downwards.

For the processing of the videos and time series existing open-source software tools will be used such as MediaPipe (https://github.com/google/mediapipe) as well as implementations of well-established algorithms such as the Fast Dynamic Timeseries Warping (Salvador, 2007).

2.12.3.1.3 Stress, mechanical stress, gut microbiome, genetics, and cost and effects

Descriptive statistics will be used to express the intra- and inter-person variation. For high resolution data, data will be summarised per day and the mean (SD), median (IQR), minimum and maximum values will be used to describe the distribution of the data. Linear mixed models will be used in the analysis.

Evaluation of the compliance and satisfaction of the users with the smartphone- and smartwatch-based measurement of disease activity and flare Patients will be asked to provide feedback on app performance after the end of the study. Descriptive statistics will be used in the analysis.

2.12.4 Interim analysis (if applicable)

NA

2.13 Ethical considerations

2.13.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (10, 6 September 2022) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and acts as applicable in each of the participating countries.

2.13.2 Recruitment and consent

2.13.2.1 The Netherlands

Patients participating in DEPAR (MEC 2012-549) and other patients with PsA not participating in DEPAR but attend the centres participating in DEPAR will be asked to participate. Patients are asked by their treating physician to participate during consultation. They receive a letter and the patient information leaflet and within 7 days will be approached by the research team to ask whether they want to participate. If they agree they sign the consent form. The physician will also ask the patients to provide consent for transferring their contact information including their phone number to the research team.

2.13.2.2 UK

Patients participating in MONITOR (17/SC/0556) and other patients with PsA under NHS follow up at the UK sites will be asked to participate. MONITOR is an ongoing cohort that follows patients from the onset of their disease. Patients are asked by their treating physician to participate during consultation. They receive a letter and the patient information leaflet and within 7 days will be approached by the research team to ask whether they want to participate. If they agree they sign the consent form.

2.13.2.3 Portugal

PsA patients participating in REUMA.PT will be asked to participate. Reuma.pt has been approved by the National Data Protection Commission 14429/ 2017) and the ethics committees of participating centres. This registry is an ongoing cohort that follows patients being treated for rheumatic diseases at public and private health centres since 2008. Reuma.pt has been approved by the National Data Protection Commission 14429/ 2017) and the ethics committees of participating centres. This registry is an ongoing cohort that follows patients being treated for rheumatic and musculoskeletal diseases at public and private health centres since 2008. Patients will be asked by their treating physician to participate during consultation. They will receive a letter and the patient information leaflet and within 7 days will be approached by the research team to ask whether they want to participate. If they agree they sign the Reuma.pt informed consent form (if they have not yet signed it) and an informed consent specific for this study covering the variables that are not routinely collected in Reuma.pt, including data collected via the smartphone and smartwatch.

2.13.2.4 Greece

New and existing patients will be asked by their treating physician to participate in the iPROLEPSIS cohort. Patient will be followed for a year after they consent to participate. They receive a letter and the patient information leaflet and within 7 days will be approached by the research team to ask whether they want to participate. If they agree they sign the consent form.

2.13.3 Objection by minors or incapacitated subjects (if applicable)

NA

2.13.4 Benefits and risks assessment, group relatedness

Patients with PsA experience difficulties in dealing with unpredictable disease activity which can have consequences on their daily living. With the introduction of smart devices, they could have better understanding on the disease influence on their physical activity patterns, stress levels, sleep, pain, stiffness and fatigue. During the study, patients will benefit from the features provided by the Garmin Smart watch Vivoactive 5, such as physical activity and heart rate. On the other hand, burden on patients include more outpatient clinical visits than standard care, response burden, continuous use of smartwatch and continuous monitoring of patient activity for 12 months, taking photos and videos, providing hair and stool samples, and providing saliva for DNA analysis.

2.13.4.1 Digital biomarkers

Digital monitoring of patients will be performed continuously for a year using a smart watch that will be provided for patients to wear daily, and a data capturing app that will be installed on their smartphone. The data capturing app will collect -unobtrusively- the metadata of the keystrokes and the accelerometer/gyroscope data of the phone. In the app they have full control of the data they want to share. Photos of hands and feet and videos of hands, posture and gesture are captured by the patient. This means that they could stop with sharing (parts of) data at all times without asking our permission. Regarding the photos saving, they must contain only hands and feet. If other kind of images are taken, they will be discarded and not be saved. Regarding the videos saving, the time series of hand/body landmarks, which will be produced from the raw videos, will be saved (no raw videos will be saved) (See section 10.1, Data pre-processing). Photos of hands and feet and videos of hands, posture and gesture will be collected at baseline, every 6 weeks and when patient experiences disease flare. The levels of pain, fatigue and stiffness will be also monitored via questions provided by the app on these symptoms. These are very short questions that appear one time a day for the first 14 days and are answerable within a few seconds. In addition, the app allows the patients to self-register a disease flare by pressing the flare button. Once patient registers a flare, these questions will appear again. When flare button is off, patients are inquired every two weeks if they are flare free.

2.13.4.2 Clinical assessment

Clinical disease activity will be monitored at baseline and every 3 months, for a year (section 8, Methods). For most patients this will be a regular visit to the physician. Each study visit requires around 30 minutes. If they only visit their physician each 6 months or at even longer intervals, they are asked to have additional 3-month appointments for clinical disease activity assessment.

2.13.4.3 Questionnaires

Patients are requested to fill questionnaires at baseline and every 3 months, for a year (section 8, Methods). As most participants already participate in a study, we will use their already available self-reported measures. If they are diagnosed less than 12 months ago no additional work is required. If they have participated for longer than 12 months, they may receive additional questions if we could not combine the current data collection with their regular study visit.

2.13.4.4 DNA

Saliva collection for DNA analysis is performed at baseline. The saliva collection kit than can be returned to the researchers by physically taking it to the hospital at the visit or be send to a central collection point via postal mail.

2.13.4.5 Gut Microbiome

All patients will receive a home kit to collect stool at baseline and when experiencing disease flare for which they seek help from the rheumatologist, for a year. In Netherlands, patients that participate in the stool extension from centers participating in DEPAR centers will be asked to collect at months 6 and 12. Depending on the hospital facilities they can bring it in at their hospital visit or send it to a central location via postal mail.

2.13.4.6 Cortisol

Three centimeters of hair will be sampled from posterior vertex at study center at baseline and every 3 months, for a year. Sampled hair will be stored at room temperature.

2.13.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The METC Erasmus MC has granted the sponsor dispensation from the statutory obligation to provide additional insurance, because participating in the study is without risks.

2.13.6 Incentives (if applicable)

Patients can be reimbursed for travel- and parking costs in case they need an additional visit to the hospital for a physical assessment.

2.14 Administrative aspects, monitoring and publication

2.14.1 Handling and storage of data and documents

Data are handled confidentially. The database with personal details including name, address, and birthdate, is separated from the clinical research database as well as the sensor database. Each of the patients receive a Study ID as key. The reference table with the key and the personal details is accessible by the research coordinator and on individual level in electronic case report form (eCRF) by the research nurse in each of the participating centres.

Data from smartphones and smartwatches will be transferred to miPROLEPSIS app then to the cloud-based data management system (**Figure 14**). Flow of data from the video assessment app is shown in **Figure 15**. The infrastructure that will be used for the data storage and analysis will be hosted by a trusted cloud provider (Hetzner which servers are located in the EU) under a direct contract with INTRAsoft. Data infrastructure will offer access only to authorised users. User authentication mechanisms and interfaces for secure data exchange with the Cloud-based back-end will be provided. Moreover, physical security is provided by Hetzner whose data centers are certified in accordance with ISO/IEC 27001. Hetzner offers a Data Processing Protection Agreement that can ensure the General Data Protection Regulation (GDPR) compliance. The privacy policy can be found here: https://www.hetzner.com/legal/privacy-policy. Finally, data are de-identified before entering the cloud-based data management system.

The handling of personal data complies with the EU General Data Protection Regulation and the General Data Protection Regulation.

Given the nature of the way we capture data we added information on privacy to the patient information forum (PIF) and a supplemental file is provided to the patient on how Garmin deals with their data.

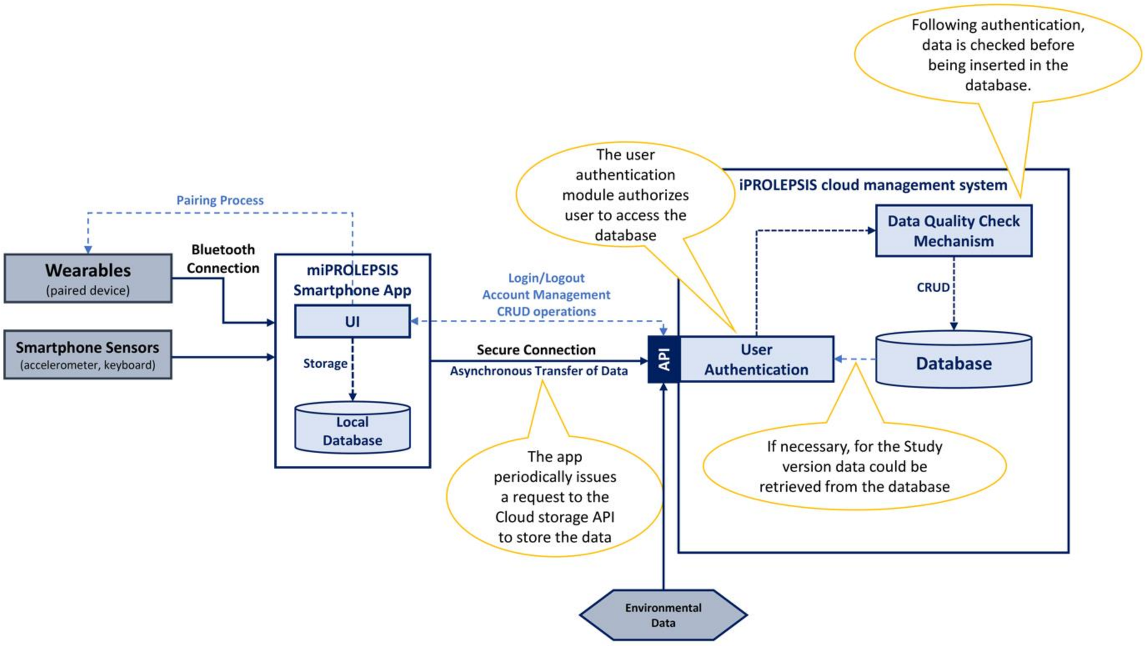


Figure 14 Data architecture (smartphone and smartwatch).

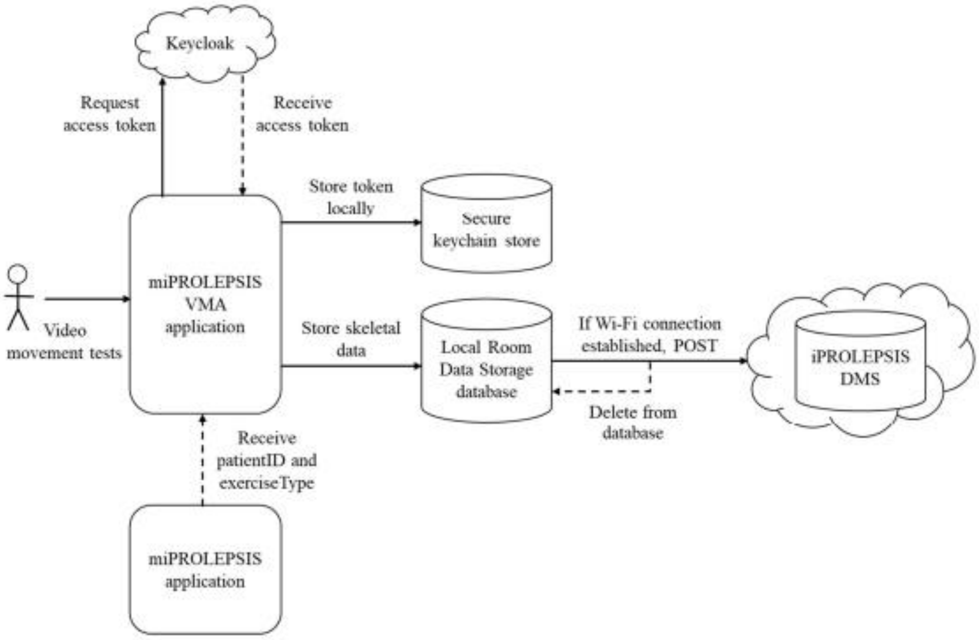


Figure 15 Dataflow of the video assessment application.

2.14.2 Monitoring and Quality Assurance

For the phone and wearable data, data quality checks will be in place on daily basis during the extract, transform and load (ETL) procedures from the device to the central storage. For the clinical and questionnaire data the following systems are in place

2.14.2.1 The Netherlands

In DEPAR, clinical data are checked yearly in the participating hospitals. As most of the data entry is entered and immediately validated in the clinical research database this only includes verification of medication and diagnosis.

2.14.2.2 UK

In the UK, the data entry is entered and immediately validated in the clinical research database. All studies may be monitored or inspected by the University team.

2.14.2.3 Portugal

In Portugal, data are directly entered in the clinical research database – Reuma.pt. Data quality checks will be performed by the Reuma.pt coordinating team. Data protection will be monitored and audited by the Reuma.pt data protection officer.

2.14.2.4 Greece

In Greece, a clinical research database will be generated in which the data entry is entered and immediately validated. All studies may be monitored or inspected by the University team.

2.14.3 Amendments

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority but will be recorded and filed by the sponsor.

2.14.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

2.14.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

2.14.6 Public disclosure and publication policy

Scientific communication will be through the usual channels and in accordance with the CCMO publication policies. Results shall be disclosed through publication in peer-reviewed scientific journals. In the case of negative outcomes results shall be made available, as appropriate, through publication or through trial registers, websites (for instance www.biomedcentral.com), databases and so. Raw data of the project will be available upon request but will not be publicly available in these phases of the project.

2.15 Structured risk analysis

2.15.1 Potential issues of concern

2.15.1.1 Level of knowledge about mechanism of action

NA

2.15.1.2 Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

NA

2.15.1.3 Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

NA

2.15.1.4 Selectivity of the mechanism to target tissue in animals and/or human beings

NA

2.15.1.5 Analysis of potential effect

NA

2.15.1.6 Pharmacokinetic considerations

NA

2.15.1.7 Study population

Adult patients with PsA are included. They suffer from a chronic condition that affects their physical activity patterns in daily life, work, social participation and other activities such as sports and leisure time activities.

2.15.1.8 Interaction with other products

NA

2.15.1.9 Predictability of effect

This is part of the research questions to be answered.

2.15.1.10 Can effects be managed?

NA

2.15.2 Synthesis

This study has no specific risk other then what patients will experience during their daily lives with the disease.

3 Study protocol amendments

Four amendments to the study protocol have been submitted and approved by the MREC Erasmus (Appendix II), as well as the MREC of UK. The original approved version of the protocol is version 3, while version 7 (Section 2) is the latest version of the protocol. The list of amended items are shown in **Table 3**.

Table 3 Amendments of PDPID study protocol

Amendment number	Amendment items
Amendment 1	▪ Frequency of photo and video capturing ▪ Version of the Garmin smartwatch

(protocol version 4)	▪ Additional questionnaire to assess the digital literacy
Amendment 2 (protocol version 5)	▪ Adding additional questions related to flare in the secondary ▪ parameters ▪ Excluding the type task ▪ Changing the name of the participating hospital in Greece ▪ Adding participating centers in the Netherlands ▪ Adding two additional questionnaires for the analysis of stool and hair cortisol ▪ Excluding respiratory rate from smartwatch data
Amendment 3 (protocol version 6)	▪ Excluding the walking task ▪ Adding participating centers in the Netherlands ▪ Adding additional Video app for performing the video assessment. ▪ Changes to the PIF regarding the storage of participant email addresses and the collection of hair samples
Amendment 4 (protocol version 7)	▪ Amending the privacy statement in section 10.4 of the PIF ▪ Adding one participating center in the Netherlands

4 Ethics

For initiation of the iPROLEPSIS-PDPID study, ethical approval needs to be obtained from each participating country (i.e., Netherlands, UK, Portugal and Greece). Until the date of the deliverable submission, ethical approval has been obtained from the Netherlands (Erasmus MC), UK (UOXF), Greece (AUTH), and Portugal (**Table 4**). The Erasmus MC is the sponsor of the study.

Definite start date of the study (inclusion of first patient) September 4, 2024

Table 4 Committees and Authorities for obtaining ethical approval for the PDPID study

Country	Ethics Committee (EC) / Competent Authority CA) / Any other additional regulatory approval (OTH)	Initial Projected Submission Date	Actual Submission Date	Final Approval Date (latest amendment)
Netherlands	EC: MREC Erasmus MC	June 2023	Aug 2023	July 2024 (Initial approval: Nov. 2023)
	OTH 1: WOAC ASZ	Dec 2023	Jan 2024	July 2024
	OTH 2: RvB Amphia	Dec 2023	Jan 2024	July 2024
	OTH 3: LHC Adrz	Dec 2023	Feb 2024	August 2024
	OTH 4: RvB MSZ	Dec 2023	Jan 2024	July 2024
	OTH 5: RvB RDGG	Dec 2023	Jan 2024	Sep 2024
	OTH 6: RvB RZWN	June 2024	Jun 2024	August 2024
	OTH 7: Wetenschapsbureau SFG	Feb 2024	Sep 2024	Not obtained yet (expected in Oct-Nov 2024)
	OTH 8: Wetenschapsbureau Haga	Feb 2024	April 2024	Not obtained yet (expected in Oct-Nov 2024)

	OTH 9: Wetenschapsbureau MST	July 2024	Sep 2024	Not obtained yet (expected Oct-Nov 2024)
UK	EC: HRA Health and Care Research Wales	Nov 2023	Nov 2023	Feb 2024
	OTH 1: St Georges ethical committee	March 2024	May 2024	Aug 2024
	OTH 2: Royal free London ethical committee	March 2024	May 2024	Sep 2024
	OTH 3: NOC ethical committee	March 2024	May 2024	Sep 2024
	OTH 4: NHS Lothian	March 2024	May 2024	Oct 2024
	OTH 5: Wales – Wrexham Maelor Hospital ethical committee	March 2024	May 2024	Oct 2024
Portugal	EC: MREC NOVA Medical School	Nov 2023	Nov 2023	Not obtained yet (expected Oct 2024)
	OTH 1: Committee ULSSM	Feb 2024	April 2024	Oct 2024
Greece	EC: MREC Hipokrateion Hospital Thessaloniki	Nov 2023	Jan 2024	Initial approval: May 2024

4.1 Netherlands

4.1.1 Status

The iPROLEPSIS-PDPID study has been approved by the MREC Erasmus MC. The letters of initial approval letters and amendments approval by the MREC Erasmus MC are provided in Appendix II. Besides Erasmus MC, local approvals have been obtained from 6 additional local sites.

The study ID Netherlands NL84429.078.23

Country Ethics Committee (EC) MREC Erasmus MC

MEC number Netherlands MEC-2023-0470

Inclusion of first patient September 4, 2024. This is the definite start date of the study. The first study participant was included from ASZ site. Approval letter for including first patient (ASZ site) is shown in Appendix II.

4.1.2 Participating centres

Table 1 provides an overview on the participating centers in the Netherlands. Approval to participate in the iPROLEPSIS-PDPID study has been obtained from 7 sites including the Erasmus MC (Appendix II), and submission of study file for local approval is ongoing for 3 additional local sites.

4.1.3 PIF

Two versions of the PIF are included in the study file for the iPROLEPSIS-PDPID study and were approved by the MREC Erasmus MC. One version for the Netherlands and another version for UK, Portugal and Greece. The Dutch versions of the latest PIF are shown in Appendix III.

4.1.4 Forms

For the iPROLEPSIS-PDPID study file, documents specific for the Netherlands include ABR form, research declaration, clinical trial agreement, risk classification and data management plan (Appendix IV). Research declaration and clinical trial agreement should be completed and signed by each participating center in the Netherlands.

Besides the abovementioned documents, list of participating centers, CVs of principle investigators form each participating center, and the CV of the independent physician are also included in the study file.

4.2 UK

4.2.1 Status

The iPROLEPSIS-PDPID study has been approved by the HRA and Health and Care Research Wales on 26/02/24 (Appendix II).

The study ID UK 332916

4.2.2 Participating centers

Approval to participate in the iPROLEPSIS-PDPID study has been obtained from 5 local sites (Appendix II).

4.3 Portugal

4.3.1 Status

PSR submitted the study protocol to the MREC of NOVA Medical School in November 2023. There has been delays in the assessment of study file by the MREC of NOVA Medical School. Alternatively, PSR started applying for local approval at each study site (N=3) as of April 2024. Approval to participate in the iPROLEPSIS-PDPID study has been obtained from one local site (Appendix II).

The study ID Portugal 124/2023/CEFCM

4.3.2 Participating centers

The number of local centers that are invited to participate in the iPROLEPSIS-PDPID study is 5-6 centers. Approval has been obtained from one site (Appendix II).

4.4 Greece

4.4.1 Status

The iPROLEPSIS-PDPID study has been approved by the MREC of Hipokrateion Hospital Thessaloniki in May 2024 (Appendix II). Greece can start recruitment before amendments approval by the MREC.

The study ID Greece 5549/31.01.24

4.4.2 Participating centers

Hipokrateion Hospital Thessaloniki is the participating center.

4.5 Study registration in registry

4.5.1 Status

The study has been registered in ClinicalTrials.gov under the study ID number of Netherlands (NL84429.078.23) and posted in April 2024.

The study ID ClinicalTrials.gov NCT06347237

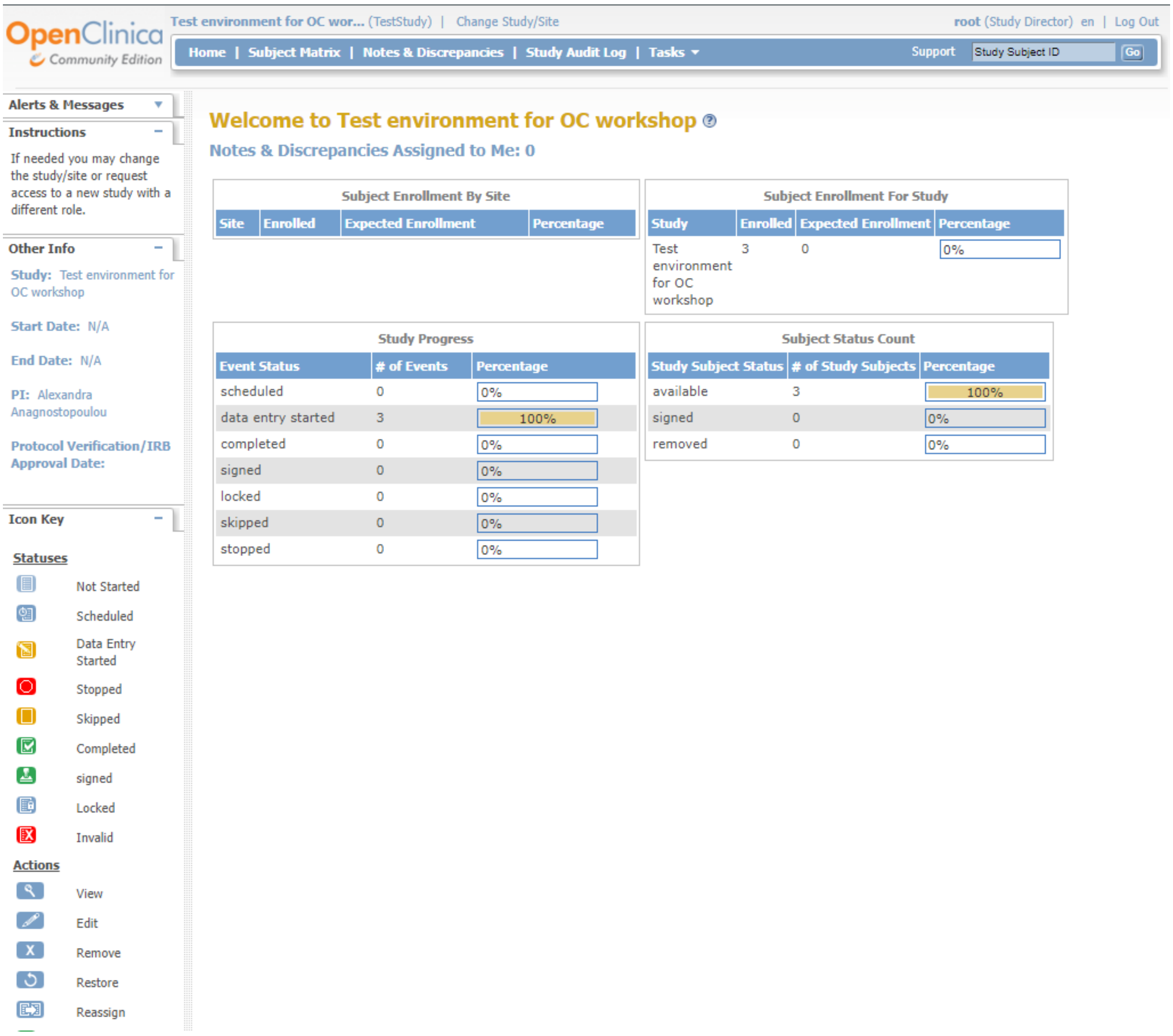
5 Clinical study and eCRF management system setup, rollout and maintenance

To store the clinical data, several programs were considered and because it is open-source, free, user-friendly and has strong community support, the OpenClinica platform was installed on a Virtual Machine (VM) Server in the secure premises of AUTH (**Figure 16**). The IT Department of AUTH has the ISO/IEC 27001 Certificate which ensures cyber security protection.

The technical requirements of the VM are 4GB of RAM, 4 x AMD Opteron(tm) Processor 6376 CPU and a storage of 100GB. The Operating System that runs all the applications is Ubuntu Server 22.04.03 LTS (jammy). The version of the OpenClinica platform is 3.13 Open Community Edition, licensed under LGPLv2.1 and all data are stored in a PostgreSQL Database version 9.5. The web location of the OpenClinica Platform for the project is iprolepsisvm.ee.auth.gr/OpenClinica. When install the platform an administrative user is created and has the role of the Study Director and is a unique role and user.

In parallel for the maintenance of the system, an automatic backup system has been created which operates daily via the method of incremental backup. In that way only copies data that has been changed or created since the previous backup file. We achieve smaller data volume and the restoring process become faster.

There is a versioning mechanism in OC platform enabled where every change or creation from a user, keeps a version to ensure CRF integrity (**Figure 17**). If the integrity of the CRF is failed, the integrity check will show a warning message which describe the problem.



Welcome to Test environment for OC workshop

Notes & Discrepancies Assigned to Me: 0

If needed you may change the study/site or request access to a new study with a different role.

Study: Test environment for OC workshop

Start Date: N/A

End Date: N/A

PI: Alexandra Anagnostopoulou

Protocol Verification/IRB Approval Date:

Subject Enrollment By Site

Site	Enrolled	Expected Enrollment	Percentage

Subject Enrollment For Study

Study	Enrolled	Expected Enrollment	Percentage
Test environment for OC workshop	3	0	0%

Study Progress

Event Status	# of Events	Percentage
scheduled	0	0%
data entry started	3	100%
completed	0	0%
signed	0	0%
locked	0	0%
skipped	0	0%
stopped	0	0%

Subject Status Count

Study Subject Status	# of Study Subjects	Percentage
available	3	100%
signed	0	0%
removed	0	0%

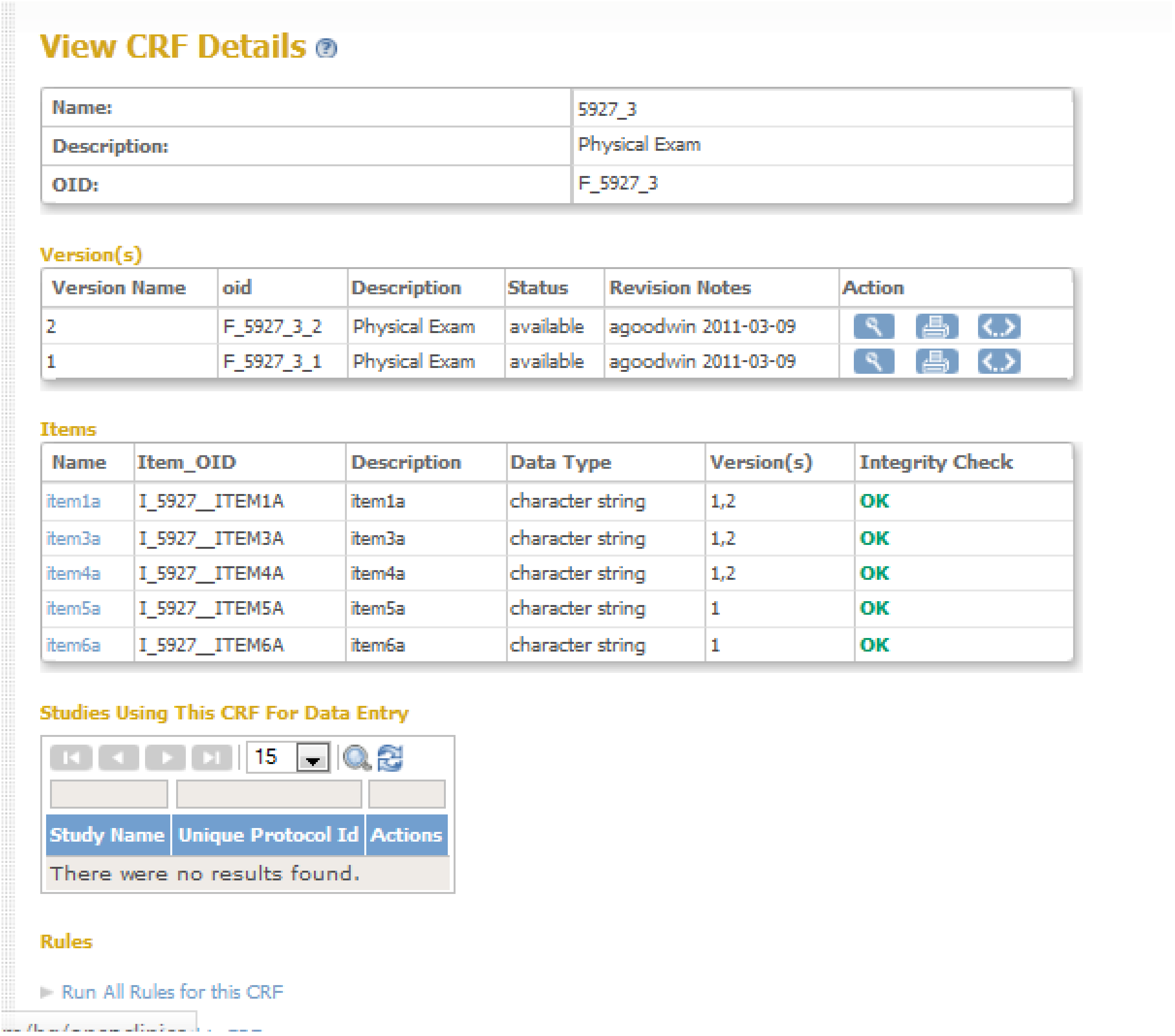
Statuses

- Not Started
- Scheduled
- Data Entry Started
- Stopped
- Skipped
- Completed
- signed
- Locked
- Invalid

Actions

- View
- Edit
- Remove
- Restore
- Reassign

Figure 16 OpenClinica Dashboard.



View CRF Details

Name:	5927_3
Description:	Physical Exam
OID:	F_5927_3

Version(s)

Version Name	oid	Description	Status	Revision Notes	Action
2	F_5927_3_2	Physical Exam	available	agoodwin 2011-03-09	
1	F_5927_3_1	Physical Exam	available	agoodwin 2011-03-09	

Items

Name	Item_OID	Description	Data Type	Version(s)	Integrity Check
item1a	I_5927__ITEM1A	item1a	character string	1,2	OK
item3a	I_5927__ITEM3A	item3a	character string	1,2	OK
item4a	I_5927__ITEM4A	item4a	character string	1,2	OK
item5a	I_5927__ITEM5A	item5a	character string	1	OK
item6a	I_5927__ITEM6A	item6a	character string	1	OK

Studies Using This CRF For Data Entry

Study Name	Unique Protocol Id	Actions
There were no results found.		

Rules

Run All Rules for this CRF

Figure 17 Example for eCRF versioning.

OpenClinica (OC) (OpenClinica » Driving the Future of Digital Clinical Trials)[3] has two distinct user types: (i) Administrator (Technical and Business, or System encompassing both); (ii) User (**Table 5**).

The system administrator can access all studies and data, manages user accounts, schedules and approves data import and export jobs, and is responsible for server operations and maintenance. The role of the OC System Administrator during the lifecycle of the study will be undertaken by an AUTH researcher.

There are 5 different roles a user can have: a) Study Director, b) Data Manager, c) Data Specialist, d) Data Entry Person, and e) Monitor. Only the Study Director, Data Manager, and Data Entry Person will be assigned to the project. The actions these roles can take are presented in the table below.

---

[3] OpenClinica » Driving the future of digital clinical trials, https://www.openclinica.com/

Table 5 OC User roles defined for the study.

User Roles	Study Setup	Submit Data	Monitor & Manage Data	Extract Data
Study Director/Data Manager	• View (view metadata, print) & Build (access, view, edit, set study status, create and edit CRFs, create and edit events, create and edit group classes, create and edit rules, create and edit sites) • Access, view roles, assign, and set/remove users	• Create & Add Subjects • View (view, enter data, or reassign CRF version), edit, & remove Subject • Set, review and resolve notes and discrepancies of entered data on Events • Add and schedule Events • Filter, edit, lock/unlock, remove/restore, change status of Events • Import data	• View Study Audit log and Source Data Verification (to ascertain completion, accuracy and verifiability of CRF data) • Set, view, run, remove/restore, and test rules for data entry • View groups (if applicable) • View, create, edit, replace, remove/restore CRFs and different versions of the same CRF	• Create, view and edit datasets to be exported • Remove/restore datasets for export
Data Entry Person	No actions allowed	• Create & Add Subjects • View and enter data to CRF • Set and review notes and discrepancies • Filter, edit, lock/unlock, and change the status of events • Import Data	No actions allowed	No actions allowed

Four (4) different studies have been set up, one per pilot site. The role of Study Director has be assigned to the System Administrator, and up to two (2) Data managers have been created for each OC study., while the role of Data Entry Person will be assigned upon request from the Data manager of each OC study. As the role of Date Entry Person can complete a limited number of actions, no limit has been set to the number of such roles that may be assigned.

eCRFs encapsulating data from clinical assessments (**section 2.10.1.3.2**) and questionnaires (**section 2.10.1.3.4**) will be set up in OC to be compatible with the OMOP standard (*Data Standardization – OHDSI*, n.d.)[4]. Two harmonisation rounds have been carried out between the pilot sites to make able the use of the same eCRFs across the different OC studies. AUTH and MONITOR will be utilising OC as a data capture system, i.e., these pilot sites will be using the OC interface to directly input data collected from participants to the OC server, while DEPAR and Reuma.pt will use their systems for data collection and then export their dataset and import them to OC (Appendix IV.5). Datasets from DEPAR and Reuma.pt will be

---

[4] Data Standardization – OHDSI, https://www.ohdsi.org/data-standardization/

harmonized prior to the upload. The data management software used in DEPAR is the Gemstracker. For Reuma.pt, data are stored in an SQL database and no clinical data management software like is used. Alternatively, healthcare professionals enter data through a website (Rheumatic disease Portuguese Register); this website functions as an eCRF. Of note, data will be shared pseudonomised via a secure connection to the data storage platform at Hetzner in Germany. Identifiable data (name, address, etc) will stay in the country of origin. data are stored under a study-id for the clinical data. All data extracted from the phone and the smartwatch will already be pseudonymised using the study id. The provider (Hetzner) offers a Data Processing Agreement that in case of processing personal data, it can verify compliance with the General Data Protection Regulation (GDPR).

6 Conclusions

Patients with PsA experience difficulties in dealing with unpredictable disease activity which can affect their quality of life. Development of a digital biomarker using smartphone and smartwatch would allow for an unobtrusive monitoring of the disease activity in these patients. Besides, understanding what factors trigger flare would allow for a better disease control.

The key takeaways of deliverable D5.1 are:

- The iPROLEPSIS-PDPID study is a multicentre observational cohort study that aims to develop an unobtrusive and affordable digital biomarker capable of detecting changes in disease activity including flare, and to identify triggers of flare in patients with PsA.
- The study will be conducted in four countries: Netherlands, UK, Portugal and Greece.
- The study involves patients with PsA. Therefore, ethical approval is required from each of the participating countries in the study.
- Ethical approval has been granted for initiating iPROLEPSIS-PDPID study in the Netherlands, UK, Greece and Portugal.
- The OpenClinica platform will be used in the collection and storage data of the iPROLEPSIS-PDPID study.

Future steps include obtaining ethical approvals from MREC of NOVA Medical School in Portugal as well as local approvals from centres participating in each country, and inclusion of patients from each participating country.

References

Alf Gerisch, R. P., Jens Lang. (2017). *Multiscale Models in Mechano and Tumor Biology: Modeling, Homogenization, and Applications*.

Alinaghi, F., Calov, M., Kristensen, L. E., Gladman, D. D., Coates, L. C., Jullien, D., Gottlieb, A. B., Gisondi, P., Wu, J. J., Thyssen, J. P., & Egeberg, A. (2019). Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies. *J Am Acad Dermatol*, *80*(1), 251-265 e219. https://doi.org/10.1016/j.jaad.2018.06.027

Andreu-Perez, J., Garcia-Gancedo, L., McKinnell, J., Van der Drift, A., Powell, A., Hamy, V., Keller, T., & Yang, G. Z. (2017). Developing Fine-Grained Actigraphies for Rheumatoid Arthritis Patients from a Single Accelerometer Using Machine Learning. *Sensors (Basel)*, *17*(9). https://doi.org/10.3390/s17092113

Andrew P. Creagh, V. H., Hang Yuan, Gert Mertes, Ryan Tomlinson, Wen-Hung Chen, Rachel Williams, Christopher Llop, Christopher Yee, Mei Sheng Duh, Aiden Doherty, Luis Garcia-Gancedo, David A. Clifton. (2022). Digital health technologies and machine learning augment patient reported outcomes to remotely characterise rheumatoid arthritis. https://doi.org/https://doi.org/10.1101/2022.11.18.22282305

Buderer, N. M. (1996). Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. *Academic Emergency Medicine*, *3*(9), 895-900.

Calvillo, L., Gironacci, M. M., Crotti, L., Meroni, P. L., & Parati, G. (2019). Neuroimmune crosstalk in the pathophysiology of hypertension. *Nat Rev Cardiol*, *16*(8), 476-490. https://doi.org/10.1038/s41569-019-0178-1

Chandran, V., & Raychaudhuri, S. P. (2010). Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. *J Autoimmun*, *34*(3), J314-321. https://doi.org/10.1016/j.jaut.2009.12.001

Coates, L. C., Fransen, J., & Helliwell, P. S. (2010). Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis*, *69*(1), 48-53.

Coates, L. C., Robinson, D. E., Orbai, A. M., Kiltz, U., Leung, Y. Y., Palominos, P., Canete, J. D., Scrivo, R., Balanescu, A., Dernis, E., Meisalu, S., Ruyssen-Witrand, A., Eder, L., de Wit, M., Smolen, J. S., Lubrano, E., & Gossec, L. (2021). What influences patients' opinion of remission and low disease activity in psoriatic arthritis? Principal component analysis of an international study. *Rheumatology (Oxford)*, *60*(11), 5292-5299.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav*, *24*(4), 385-396. https://www.ncbi.nlm.nih.gov/pubmed/6668417

Crouthamel, M., Mather, R. J., Ramachandran, S., Bode, K., Chatterjee, G., Garcia-Gancedo, L., Kim, J., Alaj, R., Wipperman, M. F., Leyens, L., Sillen, H., Murphy, T., Benecky, M., Maggio, B., & Switzer, T. (2021). Developing a Novel Measurement of Sleep in Rheumatoid Arthritis: Study Proposal for Approach and Considerations. *Digit Biomark*, *5*(3), 191-205. https://doi.org/10.1159/000518024

Davergne, T., Kedra, J., & Gossec, L. (2021). Wearable activity trackers and artificial intelligence in the management of rheumatic diseases : Where are we in 2021? *Z Rheumatol*, *80*(10), 928-935. https://doi.org/10.1007/s00393-021-01100-5 (Tragbare Aktivitätstracker und künstliche Intelligenz in der Behandlung rheumatischer Erkrankungen : Stand der Dinge im Jahr 2021.)

Davergne, T., Pallot, A., Dechartres, A., Fautrel, B., & Gossec, L. (2019). Use of Wearable Activity Trackers to Improve Physical Activity Behavior in Patients With Rheumatic and Musculoskeletal Diseases: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)*, *71*(6), 758-767. https://doi.org/10.1002/acr.23752

de Vet, H. C., Terwee, C. B., Ostelo, R. W., Beckerman, H., Knol, D. L., & Bouter, L. M. (2006). Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. *Health Qual Life Outcomes*, *4*, 54. https://doi.org/10.1186/1477-7525-4-54

Deisboeck, T. S., Wang, Z., Macklin, P., & Cristini, V. (2011). Multiscale cancer modeling. *Annu Rev Biomed Eng*, *13*, 127-155. https://doi.org/10.1146/annurev-bioeng-071910-124729

Fenichel, N. (1979). Geometric Singular Perturbation-Theory for Ordinary Differential-Equations. *Journal of Differential Equations*, *31*(1), 53-98. https://doi.org/Doi 10.1016/0022-0396(79)90152-9

Fries, J. F., Spitz, P., Kraines, R. G., & Holman, H. R. (1980). Measurement of patient outcome in arthritis. *Arthritis Rheum*, *23*(2), 137-145.

Garbarino, S., Lanteri, P., Bragazzi, N. L., Magnavita, N., & Scoditti, E. (2021). Role of sleep deprivation in immune-related disease risk and outcomes. *Commun Biol*, *4*(1), 1304. https://doi.org/10.1038/s42003-021-02825-4

Gonzalez, D., Jacobsen, D., Ibar, C., Pavan, C., Monti, J., Fernandez Machulsky, N., Balbi, A., Fritzler, A., Jamardo, J., Repetto, E. M., Berg, G., & Fabre, B. (2019). Hair Cortisol Measurement by an Automated Method. *Sci Rep*, *9*(1), 8213. https://doi.org/10.1038/s41598-019-44693-3

Gonzalez, U. (2023). *Spatio-temporal Models for Air Pollution*. University of Exeter.

Gorlier, C., Orbai, A. M., Puyraimond-Zemmour, D., Coates, L. C., Kiltz, U., Leung, Y. Y., Palominos, P., Canete, J. D., Scrivo, R., Balanescu, A., Dernis, E., Talli, S., Ruyssen-Witrand, A., Soubrier, M., Aydin, S. Z., Eder, L., Gaydukova, I., Lubrano, E., Kalyoncu, U., . . . Gossec, L. (2019). Comparing patient-perceived and physician-perceived remission and low disease activity in psoriatic arthritis: an analysis of 410 patients from 14 countries. *Ann Rheum Dis*, *78*(2), 201-208. https://doi.org/10.1136/annrheumdis-2018-214140

Gossec, L., de Wit, M., Kiltz, U., Braun, J., Kalyoncu, U., Scrivo, R., Maccarone, M., Carton, L., Otsa, K., Sooäär, I., Heiberg, T., Bertheussen, H., Cañete, J. D., Sánchez Lombarte, A., Balanescu, A., Dinte, A., de Vlam, K., Smolen, J. S., Stamm, T., . . . Taskforce, E. P. (2014). A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. *Ann Rheum Dis*, *73*(6), 1012-1019.

Gossec, L., Guyard, F., Leroy, D., Lafargue, T., Seiler, M., Jacquemin, C., Molto, A., Sellam, J., Foltz, V., Gandjbakhch, F., Hudry, C., Mitrovic, S., Fautrel, B., & Servy, H. (2019). Detection of Flares by Decrease in Physical Activity, Collected Using Wearable Activity Trackers in Rheumatoid Arthritis or Axial Spondyloarthritis: An Application of Machine Learning Analyses in Rheumatology. *Arthritis Care Res (Hoboken)*, *71*(10), 1336-1343. https://doi.org/10.1002/acr.23768

Gracey, E., Burssens, A., Cambré, I., Schett, G., Lories, R., McInnes, I. B., Asahara, H., & Elewaut, D. (2020). Tendon and ligament mechanical loading in the pathogenesis of inflammatory arthritis. *Nat Rev Rheumatol*, *16*(4), 193-207. https://doi.org/10.1038/s41584-019-0364-x

Gudu, T., & Gossec, L. (2018). Quality of life in psoriatic arthritis. *Expert Rev Clin Immunol*, *14*(5), 405-417. https://doi.org/10.1080/1744666X.2018.1468252

Harrell, F. E., Jr., Lee, K. L., & Mark, D. B. (1996). Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*, *15*(4), 361-387. https://doi.org/10.1002/(sici)1097-0258(19960229)15:4<361::Aid-sim168>3.0.Co;2-4

Helliwell, P. S., FitzGerald, O., Fransen, J., Gladman, D. D., Kreuger, G. G., Callis-Duffin, K., McHugh, N., Mease, P. J., Strand, V., & Waxman, R. (2013). The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). *Annals of the Rheumatic Diseases*, *72*(6), 986-991.

Iakovakis, D., Hadjidimitriou, S., Charisis, V., Bostantzopoulou, S., Katsarou, Z., & Hadjileontiadis, L. J. (2018). Touchscreen typing-pattern analysis for detecting fine motor skills decline in early-stage Parkinson's disease. *Sci Rep*, *8*(1), 7663. https://doi.org/10.1038/s41598-018-25999-0

Ibarra-Coronado, E. G., Pantaleon-Martinez, A. M., Velazquez-Moctezuma, J., Prospero-Garcia, O., Mendez-Diaz, M., Perez-Tapia, M., Pavon, L., & Morales-Montor, J. (2015). The Bidirectional Relationship between Sleep and Immunity against Infections. *J. immunol. res.*, *2015*, 678164.

Irwin, M. R. (2019). Sleep and inflammation: partners in sickness and in health. *Nat Rev Immunol*, *19*(11), 702-715. https://doi.org/10.1038/s41577-019-0190-z

Jaeschke, R., Singer, J., & Guyatt, G. H. (1989). Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*, *10*(4), 407-415. https://doi.org/10.1016/0197-2456(89)90005-6

Katzman, J. L., Shaham, U., Cloninger, A., Bates, J., Jiang, T., & Kluger, Y. (2018). DeepSurv: personalized treatment recommender system using a Cox proportional hazards deep neural network. *BMC Med Res Methodol*, *18*(1), 24.

Keogh, A., Sett, N., Donnelly, S., Mullan, R., Gheta, D., Maher-Donnelly, M., Illiano, V., Calvo, F., Dorn, J. F., Mac Namee, B., & Caulfield, B. (2020). A Thorough Examination of Morning Activity Patterns in Adults with Arthritis and Healthy Controls Using Actigraphy Data. *Digit Biomark*, *4*(3), 78-88. https://doi.org/10.1159/000509724

Kim, H. G., Cheon, E. J., Bai, D. S., Lee, Y. H., & Koo, B. H. (2018). Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature. *Psychiatry Investig*, *15*(3), 235-245. https://doi.org/10.30773/pi.2017.08.17

Koo, T. K., & Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med*, *15*(2), 155-163. https://doi.org/10.1016/j.jcm.2016.02.012

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*, *16*(9), 606-613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Laganas, C., Iakovakis, D., Hadjidimitriou, S., Charisis, V., Dias, S. B., Bostantzopoulou, S., Katsarou, Z., Klingelhoefer, L., Reichmann, H., Trivedi, D., Chaudhuri, K. R., & Hadjileontiadis, L. J. (2022). Parkinson's Disease Detection Based on Running Speech Data From Phone Calls. *IEEE Trans Biomed Eng*, *69*(5), 1573-1584. https://doi.org/10.1109/TBME.2021.3116935

Lam, K. H., Meijer, K. A., Loonstra, F. C., Coerver, E., Twose, J., Redeman, E., Moraal, B., Barkhof, F., de Groot, V., Uitdehaag, B., & Killestein, J. (2021). Real-world keystroke dynamics are a potentially valid biomarker for clinical disability in multiple sclerosis. *Mult Scler*, *27*(9), 1421-1431. https://doi.org/10.1177_1352458520968797

Lauritsen, S. M., Kristensen, M., Olsen, M. V., Larsen, M. S., Lauritsen, K. M., Jorgensen, M. J., Lange, J., & Thiesson, B. (2020). Explainable artificial intelligence model to predict acute critical illness from electronic health records. *Nat Commun*, *11*(1), 3852. https://doi.org/10.1038/s41467-020-17431-x

Lee, C. F., Luo, N., Ng, R., Wong, N. S., Yap, Y. S., Lo, S. K., Chia, W. K., Yee, A., Krishna, L., Wong, C., Goh, C., & Cheung, Y. B. (2013). Comparison of the measurement properties between a short and generic instrument, the 5-level EuroQoL Group's 5-dimension (EQ-5D-5L) questionnaire, and a longer and disease-specific instrument, the Functional Assessment of Cancer Therapy-Breast (FACT-B), in Asian breast cancer patients. *Qual Life Res*, *22*(7), 1745-1751. https://doi.org/10.1007/s11136-012-0291-7

Lee, S., Mendelsohn, A., & Sarnes, E. (2010). The burden of psoriatic arthritis: a literature review from a global health systems perspective. *P T*, *35*(12), 680-689. https://doi.org/ptj35_12p680

Mastoras, R. E., Iakovakis, D., Hadjidimitriou, S., Charisis, V., Kassie, S., Alsaadi, T., Khandoker, A., & Hadjileontiadis, L. J. (2019). Touchscreen typing pattern analysis for remote detection of the depressive tendency. *Sci Rep*, *9*(1), 13414. https://doi.org/10.1038/s41598-019-50002-9

Miguens Blanco, J., Borghese, F., McHugh, N., Kelleher, P., Sengupta, R., Marchesi, J. R., & Abraham, S. (2020). Longitudinal profiling of the gut microbiome in patients with psoriatic arthritis and ankylosing spondylitis: a multicentre, prospective, observational study. *BMC Rheumatol*, *4*(1), 60. https://doi.org/10.1186/s41927-020-00155-2

Mokkink, L. B., Terwee, C. B., Knol, D. L., Stratford, P. W., Alonso, J., Patrick, D. L., Bouter, L. M., & De Vet, H. C. W. (2010). The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. *BMC medical research methodology*, *10*(1), 1-8.

Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L., Bouter, L. M., & de Vet, H. C. (2010). The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res*, *19*(4), 539-549. https://doi.org/10.1007/s11136-010-9606-8

Müller, A. C., & Guido, S. . (2016). *Introduction to machine learning with Python: a guide for data scientists*. O'Reilly Media, Inc.

Norman, G. R., Sloan, J. A., & Wyrwich, K. W. (2003). Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*, *41*(5), 582-592. https://doi.org/10.1097/01.Mlr.0000062554.74615.4c

Nowell, W. B., Curtis, J. R., Nolot, S. K., Curtis, D., Venkatachalam, S., Owensby, J. K., Poon, J. L., Calvin, A. B., Kannowski, C. L., Faries, D. E., Gavigan, K., & Haynes, V. S. (2019). Digital Tracking of Rheumatoid Arthritis Longitudinally (DIGITAL) Using Biosensor and Patient-Reported Outcome Data: Protocol for a Real-World Study. *JMIR Res Protoc*, *8*(9), e14665. https://doi.org/10.2196/14665

Patanè, M., Carmisciano, L., Hysa, E., Gotelli, E., Sulli, A., Paolino, S., Smith, V., & Cutolo, M. (2022). Engineered glove to evaluate hand disability in rheumatoid arthritis: A pilot-study. *Joint Bone Spine*, *89*(1), 105272. https://doi.org/10.1016/j.jbspin.2021.105272

Perraudin, C. G. M., Illiano, V. P., Calvo, F., O'Hare, E., Donnelly, S. C., Mullan, R. H., Sander, O., Caulfield, B., & Dorn, J. F. (2018). Observational Study of a Wearable Sensor and Smartphone Application Supporting Unsupervised Exercises to Assess Pain and Stiffness. *Digit Biomark*, *2*(3), 106-125. https://doi.org/10.1159/000493277

Perrotta, F. M., Lories, R., & Lubrano, E. (2021). To move or not to move: the paradoxical effect of physical exercise in axial spondyloarthritis. *RMD Open*, *7*(1). https://doi.org/10.1136/rmdopen-2020-001480

Polgar, O., Patel, S., Walsh, J. A., Barker, R. E., Clarke, S. F., Man, W. D., & Nolan, C. M. (2021). Minimal clinically important difference for daily pedometer step count in COPD. *ERJ Open Res*, *7*(1). https://doi.org/10.1183/23120541.00823-2020

Russell, G., & Lightman, S. (2019). The human stress response. *Nat Rev Endocrinol*, *15*(9), 525-534. https://doi.org/10.1038/s41574-019-0228-0

Salvador, S., & Chan, P. . (2007). Toward accurate dynamic time warping in linear time and space. *Intelligent Data Analysis*, *11*(5), 561-580.

Schoels, M., Aletaha, D., Funovits, J., Kavanaugh, A., Baker, D., & Smolen, J. S. (2010). Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. *Ann Rheum Dis*, *69*(8), 1441-1447. https://doi.org/10.1136/ard.2009.122259

Sousa, M., Lubrano, E., Smolen, J. S., Gorlier, C., de Wit, M., Coates, L. C., Kalyoncu, U., Ruyssen-Witrand, A., Leung, Y. Y., Scrivo, R., Canete, J. D., Palominos, P., Meisalu, S., Balanescu, A., Kiltz, U., Aydin, S. Z., Gaydukova, I., Dernis, E., Fautrel, B., . . . Gossec, L. (2023). Patient-defined flares and disease activity worsening in 222 patients with psoriatic arthritis from 14 countries. *Joint Bone Spine*, *90*(3), 105511. https://doi.org/S1297-319X(22)00171-3 [pii]

10.1016/j.jbspin.2022.105511

Staufenbiel, S. M., Penninx, B. W., Spijker, A. T., Elzinga, B. M., & van Rossum, E. F. (2013). Hair cortisol, stress exposure, and mental health in humans: a systematic review. *Psychoneuroendocrinology*, *38*(8), 1220-1235. https://doi.org/10.1016/j.psyneuen.2012.11.015

Steyerberg, E. W., Eijkemans, M. J., Harrell, F. E., Jr., & Habbema, J. D. (2001). Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. *Med Decis Making*, *21*(1), 45-56. https://doi.org/10.1177/0272989x0102100106

Streiner, D. L. a. N., G.R., Cairney, J. (2014). *Health Measurement Scales: A Practical Guide to Their Development and Use.* (5nd ed.). Oxford University Press. https://doi.org/https://doi.org/10.1093/med/9780199685219.001.0001

Taylor, W., Gladman, D., Helliwell, P., Marchesoni, A., Mease, P., Mielants, H., & Group, C. S. (2006). Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum*, *54*(8), 2665-2673. https://doi.org/10.1002/art.21972

Tillett, W., Lin, C. Y., Zbrozek, A., Sprabery, A. T., & Birt, J. (2019). A Threshold of Meaning for Work Disability Improvement in Psoriatic Arthritis Measured by the Work Productivity and Activity Impairment Questionnaire. *Rheumatol Ther*, *6*(3), 379-391. https://doi.org/10.1007/s40744-019-0155-5

Tiwari, V., & Brent, L. H. (2023). Psoriatic Arthritis. https://doi.org/NBK547710 [bookaccession]

Valles-Colomer, M., Falony, G., Darzi, Y., Tigchelaar, E. F., Wang, J., Tito, R. Y., Schiweck, C., Kurilshikov, A., Joossens, M., Wijmenga, C., Claes, S., Van Oudenhove, L., Zhernakova, A., Vieira-Silva, S., & Raes, J. (2019). The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat Microbiol*, *4*(4), 623-632. https://doi.org/10.1038/s41564-018-0337-x

Valliappan, N., Dai, N., Steinberg, E., He, J., Rogers, K., Ramachandran, V., Xu, P., Shojaeizadeh, M., Guo, L., Kohlhoff, K., & Navalpakkam, V. (2020). Accelerating eye movement research via accurate and affordable smartphone eye tracking. *Nat Commun*, *11*(1), 4553. https://doi.org/10.1038/s41467-020-18360-5

Van Mechelen, M., & Lories, R. (2020). Spondyloarthritis on the Move: Biomechanical Benefits or Harm. *Curr Rheumatol Rep*, *22*(8), 35. https://doi.org/10.1007/s11926-020-00913-8

Walha, R., Gaudreault, N., Dagenais, P., & Boissy, P. (2022). Spatiotemporal parameters and gait variability in people with psoriatic arthritis (PsA): a cross-sectional study. *J Foot Ankle Res*, *15*(1), 19. https://doi.org/10.1186/s13047-022-00521-y

Ware, J. J. E., & Gandek, B. (1994). The SF-36 Health Survey: Development and use in mental health research and the IQOLA Project. *International Journal of Mental Health*, *23*(2), 49-73.

Webster DE, H. R., Perez Chada L, Tummalacherla M, Tediarjo A, Yadav V, Chaibub Neto E, MacDuffie W, DePhillips M, Sieg E, Catron S. (2022). Clinical validation of digital biomarkers and machine learning models for remote measurement of psoriasis and psoriatic arthritis. *medRxiv*. https://doi.org/https://doi.org/10.1101/2022.04.13.22273676

Zaiss, M. M., Joyce Wu, H. J., Mauro, D., Schett, G., & Ciccia, F. (2021). The gut-joint axis in rheumatoid arthritis. *Nat Rev Rheumatol*, *17*(4), 224-237. https://doi.org/10.1038/s41584-021-00585-3

Zhang, X., Chen, B. D., Zhao, L. D., & Li, H. (2020). The Gut Microbiota: Emerging Evidence in Autoimmune Diseases. *Trends Mol Med*, *26*(9), 862-873. https://doi.org/10.1016/j.molmed.2020.04.001

Appendices

Appendix I Questionnaires

*Information can be provided upon reasonable request.

Appendix II Ethical approvals

Appendix letters of approval:

- II.1.1: Initial letter of approval by the MREC Erasmus MC (sponsor)– Netherlands: required for first patient inclusion
  II.1.2: Letters of amendments approval by the MREC Erasmus MC (sponsor) – Netherlands: required for first patient inclusion
  II.1.3: Letter of approval by the local site ASZ which included first patient – Netherlands: required for first patient inclusion
  II.1.4: Letter/proof of initial approval by the 5 other local sites in the Netherlands. Letters/proof of amendments approval are available upon request.
- II.2.1: Letters of approval by the HRA and Health and Care Research Wales – UK
  II.2.2: Letter/proof of initial approval by local sites in UK.
- II.3: Letter of approval by the MREC Hipokrateion Hospital Thessaloniki – Greece
- II.4: Letter of approval by local site Unidade Local da Saúde de Santa Maria – Portugal

* Information can be provided upon reasonable request.

Appendix III PIF

III.1 Latest PIF and consent form Netherlands (Dutch)

*Information can be provided upon reasonable request.

III.3 PIF UK (draft original version, for translation purposes)

*Information can be provided upon reasonable request.

IV Appendix Forms

IV.1 ABR form Netherlands

*Information can be provided upon reasonable request.

IV.2 Research declaration template Netherlands

Form version dd 01-07-2015

Research Declaration

To be issued by the Head of Department, healthcare group manager or a person in a similar position[5] on behalf of the local (principal) investigator: name local investigator

To the submitting party of the research file titled: PsA digital phenotyping and inflammation drivers
Study with file number NL84429.078.23 for the purpose of review by the competent medical research ethics committee (MREC/CCMO).

I hereby declare that the investigators and centre are in possession of sufficient expertise and facilities to conduct this research. This includes:

- *the appropriate levels of expertise and competence of research investigators and support personnel at our centre;*
- *ensuring all those who contribute to the research are informed in a professional manner on the research protocol at our centre;*
- *the suitability and availability of facilities at our centre to allow for faithful compliance with the research protocol.*

***Appendix**: recent cv local (principal) investigator*

Liability insurance
The liability for losses caused by the research subject's death or injury on account of the persons conducting the research is covered by the liability insurance of name policy holder which was taken out by name insurance company. [6]

Execution of the research
Effectuation of the execution of the research in this centre may only commence *after* the reviewing committee has reviewed its feasibility in this centre and has issued a positive decision to this effect *and after the centre's board of directors has subsequently granted its consent for the research to start*.

Position (i.e., Head of dept.) of name department or centre,

Name signatory Signature……………………………………

Place, date

Appendices

---

[5] *The investigator only signs the research declaration when there is no immediate supervisor – such as a Head of department, healthcare group manager or a person in a similar position – at the organisational level or such a level does not exist*

[6] *An Insurance policy must be taken out to cover the liability of the person conducting the study or the sponsor of the study, unless their obligations with respect to their liability are otherwise sufficiently safeguarded*

- *Recent cv of the local (principal) investigator in the participating centre (without publication list)*

To avoid any misunderstandings, once this document has been completed and signed please send it to the official applicant as stated in the ABR form.

IV.3 Clinical trial agreement template Netherlands

Template Investigator Initiated Clinical Study January 2019 – the Netherlands

Clinical Study Site Agreement

(Template agreement for investigator initiated clinical studies with human subjects, conducted in the Netherlands by academic (NFU) and non-academic (STZ) hospitals and NKI/AvL)

Scope of use:

This template clinical study agreement is created in joint cooperation between the University Medical Center's (UMC's) in The Netherlands, supported by the Nationale Federatie van Universitair Medische Centra (NFU); the Vereniging STZ (Samenwerkende Topklinische opleidingsZiekenhuizen) on behalf of STZ-hospitals; and the Stichting Het Nederlands Kanker Instituut - Antoni van Leeuwenhoek Ziekenhuis (NKI/AvL).

The creation and use of this template is supported and endorsed by the Dutch Clinical Research Foundation (DCRF).

This template can be modified as agreed upon between the Parties for accommodating the correct party structure, study-specific requirements, financial arrangements or any other terms and conditions which are relevant for the purpose of the collaboration. During the negotiations any modifications should be marked and explained.

Clinical Study: PsA digital phenotyping and inflammation drivers study

Protocol: NL84429.078.23
Sponsor ("verrichter"):

Study Drug/Equipment (if applicable): Mobile application

Funder: HORIZON-HLTH-2022-STAYHLTH-02-01 [No 101095697]

Target: 150 patients with psoriatic arthritis

The undersigned,

A. Erasmus MC, located at Doctor Molewaterplein 40, 3015 GD Rotterdam, duly represented by R. Dolhain, Department Head Rheumatology Research Erasmus MC (hereinafter referred to as “**Sponsor**”)

and

B. [*insert name of the site institution*], located at [*insert registered address*], duly represented by [*insert name(s) and function(s)*]
(hereinafter referred to as “**Study Site**”)

and

in the presence of:

Study Site’s employee, [*insert name of physician*]

(hereinafter referred to as “**Site Investigator**”)

WHEREAS,

- the Parties each are involved in patient care, research, and education;
- the Sponsor and Study Site jointly and in particular J.J. Luime (hereinafter the “**Principal Investigator**”), researcher employed by Sponsor who has designed the Clinical Study identified hereof;
- This Clinical Study is financially and/or in-kind supported by HORIZON-HLTH-2022-STAYHLTH-02-01 (hereinafter: the “**Funder**”) by means of a clinical study grant provided to Sponsor under Funder’s grant terms which are, in whole or in part, annexed hereto as Annex 3 if and to the extent applicable to Study Site;
- the Study Site has facilities and personnel with the requisite skills, experience, and knowledge required to support the performance of the Clinical Study by the Site Investigator;

- the Sponsor wishes to engage the Study Site and Site Investigator to perform part of the Clinical Study and Site Investigator and Study Site, having reviewed the Protocol and relevant Clinical Study information, is willing to participate in the Clinical Study.

In consideration of the undertakings and commitments set forth herein, the Parties agree to enter into this Clinical Study Site Agreement.

1. Definitions

The following words and phrases have the following meanings:

a. "**Affiliate**" means any business entity which controls, is controlled by, or is under the common control of, a Party. For the purposes of this definition, a business entity shall be deemed to control another business entity if it owns, directly or indirectly, in excess of 50% of the voting interest in such business entity or the power to direct the management of such business entity or to elect or appoint 50% or more of the members of the management of such business entity;
b. "**Agreement**" means this agreement comprising its recitals, clauses, schedules and any annexes attached hereto, including the Protocol and including any written amendments to the Agreement agreed between the Parties;
c. "**Auditor**" means a person who is authorised by Sponsor and/or Funder to carry out a systematic review and independent examination of clinical study related activities and documents to determine whether the evaluated Clinical Study related activities were conducted, and the data were recorded, analysed and accurately reported according to the Protocol, (if applicable) the standard operating procedures of Sponsor, ICH-GCP and the applicable regulatory requirements;
d. "**Authorisation**" means the authorisation of a clinical study, or any protocol amendments, in accordance with article 2, and (if applicable) 13i and 13k, of the Dutch *Medical Research Involving Human Subjects Act*;
e. "**CCMO**" means the Dutch clinical trial authority, namely the Central Committee on Research involving Human Subjects (in Dutch: "Centrale Commissie Mensgebonden Onderzoek" or "CCMO");
f. "**Clinical Study**" means the investigation as defined in the cadre above, (also) to be conducted at the Study Site in accordance with the Protocol;
g. "**Clinical Study Subject**" means a person enrolled to participate in the Clinical Study;
h. "**Competent Authority**" means the authority appointed to evaluate the Clinical Study in accordance with 13i of the Dutch *Medical Research Involving Humans Subjects Act*, based on article 9 of the European Clinical Study Directive 2001/20/EC;
i. "**Confidential Information**" means any and all information, data and material of any nature belonging or entrusted to a Party and/or its Affiliate(s), or which is a trade secret,

which such Party (the "**Disclosing Party**") may disclose in any form to the other Parties (each a "**Receiving Party**") pursuant to this Agreement, the release of which is likely to prejudice the interests of the Disclosing Party;

j. "**CRF**" means the case report form in a format prepared by Sponsor and documenting the administration of the Investigational Product (if applicable) to Clinical Study Subjects as well as all tests and observations related to the Clinical Study and "**eCRF**" means a CRF in electronic form;

k. "**Effective Date**" the date this Agreement comes into effect, being the date of the last Party's signature to this Agreement;

l. "**Ethics Committee**" means the accredited medical research ethics committee competent to review the Clinical Study in accordance with applicable Law, and to which the Protocol has been submitted for approval;

m. "**GDPR**" means Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation);

n. **"ICF"** means the Informed Consent Form as approved by the Ethics Committee, in which the Clinical Study Subject consents to his participation in the Clinical Study, including a consent, as defined in article 4 paragraph 11 of the GDPR, regarding the processing of the Clinical Study Subject's Personal Data which shall meet the requirements relating thereto of the GDPR;

o. "**ICH-GCP**" means the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95 together with such other good clinical practice requirements as are specified in Directives 2001/20/EC and 2005/28/EC of the European Parliament and the Council relating to medicinal products for human use and in guidance published by the European Commission pursuant to such Directives;

p. "**Independent Committee**" means a committee such as a Data and Safety Monitoring Board ("DSMB"), which is a group of individuals with pertinent expertise that have oversight of and reviews on a regular basis accumulating data from one or more ongoing clinical studies and that advise the Sponsor regarding the continuing safety of Clinical Study Subjects and those to be recruited to the Clinical Study, as well as the continuing validity and scientific merit of the Clinical Study;

q. "**Intellectual Property Rights**" means intellectual property rights including but not limited to patents, trade-marks, trade names, service marks, copyrights, rights in and to databases (including rights to prevent the extraction or reutilisation of information from a database), design rights, topography rights and all rights or forms of protection of a similar nature or having equivalent or the similar effect to any of them which may subsist anywhere in the world, whether or not any of them are registered and including applications for registration of any of them;

r. "**Investigational Product**" means the Study Drug and the control material, as further detailed in the Protocol;

s. "**Know How**" means all technical and other information which is not in the public domain (other than as a result of a breach of confidence), including but not limited to information comprising or relating to concepts, discoveries, data, designs, formulae, ideas, inventions, methods, models, procedures, designs for experiments and tests and results of experimentation and testing, processes, specifications and techniques, laboratory records, manufacturing data and information contained in submissions to regulatory authorities, whether or not protected by Intellectual Property Rights;

t. "**Law**" means any international, European Union and Dutch law and regulations, as well as generally accepted international conventions applicable to the performance of the Clinical Study. Such Law including but not limited to:

   - Directives 2001/20/EC and 2005/28/EC of the European Parliament and the Council relating to medicinal products for human use and in guidance published by the European Commission pursuant to such Directives and any implementation in Study Site's national Law (if applicable)
   - the Dutch Medical Research Involving Human Subjects Act (*Wet Medisch-wetenschappelijk Onderzoek met Mensen or WMO*),
   - the GDPR, and any applicable national implementing legislation,
   - the Dutch Medical Treatment Agreements Act (*Wet op de geneeskundige behandelingsovereenkomst* or *Wgbo*),
   - the ICH-GCP,
   - the directives on "the assessment of Clinical Trial Agreements (2011)" and on "External Review 2012)" issued by the CCMO,
   - the principles of the Dutch Code of Conduct regarding the adequate procurement, management and use of bodily human tissue published by the Federation of Dutch Medical Scientific Societies,
   - the Declaration of Helsinki, the most recent version,
   - and/or any successors of the above-mentioned Laws.

u. "**Party**" means the Sponsor or the Study Site or, *only if the Site Investigator is a separate Party to this Agreement*, the Site Investigator, and "**Parties**" shall mean the two or all of them jointly;

v. "**Personal Data**" means personal data as defined in article 4(1) of the GDPR, i.e. any information relating to an identified or identifiable natural person, e.g. such information of a Clinical Study Subject;

w. "**Protocol**" means the document as defined in the cadre at the beginning of this Agreement, detailing all aspects of the Clinical Study, and for which Authorisation has been obtained, a copy of which is attached as Annex 1 to this Agreement. The Protocol includes all amendments thereto for which Authorisation has been obtained;

x. “**Research Staff**” means the person(s) who will undertake the conduct of the Clinical Study at the Study Site on behalf of the Site Investigator and under the supervision of the Site Investigator;

y. “**Samples**” means any human biological materials, including but not limited to blood, body tissue, plasma and any other material containing human cells;

z. “**Site Investigator**” means the person who will take primary responsibility for the conduct of the Clinical Study at the Study Site, or any other person as may be agreed from time to time between the Parties as a replacement;

aa. **“Site Parties”** mean the Study Site and Site Investigator jointly;

bb. “**Study Drug**” means the study drug that is object of investigation, and which is to be used by Site Parties in accordance with the Protocol;

cc. “**Study Monitor**” means one or more persons appointed by the Sponsor to monitor compliance of the Clinical Study with ICH-GCP and the Protocol and to conduct source data verification;

dd. “**Target**” means the estimated number of Clinical Study Subjects to be included in the Clinical Study as referred to in the cadre above.

2. Obligations

2.1. The Parties agree to perform the Clinical Study in accordance with the Protocol, this Agreement and applicable Law.

2.2. The Parties represent and warrant that they each have the authority to enter into this Agreement. In case the Site Investigator is not a Party to this Agreement, Study Site shall ensure the performance of the tasks assigned to the Site Investigator under this Agreement and by no means will the Site Investigator be held liable hereunder in person in the event that he/she is not a Party to this Agreement. The Study Site will ensure the availability of and/or access to any resources necessary to perform the Clinical Study at the Study Site, including departments, facilities and Research Staff and support personnel, and the Study Site certifies (in Dutch: “verklaart”) that the Site Investigator holds the necessary registration and has the necessary qualifications, expertise and time to perform the Clinical Study.

2.3. The Study Site shall notify the Sponsor if the Site Investigator ceases to be associated with the Study Site where the Clinical Study will be conducted or if he/she is otherwise unavailable to continue as Site Investigator, and Study Site shall use all reasonable endeavours to find a qualified successor acceptable to the Sponsor. Replacement of the Site Investigator is subject to authorisation by the Ethics Committee. If subject to the foregoing no mutually acceptable replacement can be found, within reasonable time as not to hinder the safe continuation of the Clinical Study at the Study Site and provided that the Sponsor will not unreasonably withhold its approval of the proposed replacement of Site Investigator, each Party may terminate this Agreement pursuant to clause 11.2.g below.

3. Clinical study governance and compliance

3.1. The Sponsor shall be responsible for obtaining and maintaining Authorisation for the Clinical Study and (substantial) amendments to the Protocol.

3.2. In the event of any substantial amendments being made to the Protocol, the amendments shall be signed by the Site Investigator and shall be implemented after Authorisation and a favourable opinion of the Ethics Committee. The Site Investigator shall not consent to any change in the Protocol requested by the Ethics Committee or Competent Authority without the prior written consent of the Sponsor.

3.3. The Clinical Study shall be performed at the Study Site. The Site Investigator shall be responsible for obtaining permission (in Dutch: “onderzoeksverklaring”) from the representatives of the Study Site to perform the Clinical Study at the Study Site, which shall include the engagement of the Research Staff and, to the extent applicable, other departments.

3.4. The Sponsor shall be responsible for submitting the Clinical Study for listing on a free, publicly accessible clinical study registry.

3.5. The Site Investigator shall submit CRF/eCRFs to the Sponsor as outlined in the Protocol.

3.6. The Site Parties shall make and retain records regarding the Clinical Study as required by the Protocol, applicable Law, and in accordance with the Study Site’s standard archiving procedures. Site Parties will retain such records for the minimum period of time required under applicable Law. If indicated by Sponsor that such is reasonably required for regulatory purposes, Site Parties shall retain the records for a longer period of time, and to the extent applicable, at Sponsor’s expense.

4. Liabilities, indemnification and insurance

4.1. Sponsor shall arrange insurance cover in respect of its potential liability for damages to Clinical Study Subjects resulting from the Clinical Study in accordance with the requirements set out in the WMO and the Decree on Obligatory Insurance for Medical Studies involving Human Subjects of 1 July 2015, unless this requirement has been waived by the Ethics Committee, in which case the indemnification obligations of Sponsor under this clause 4 shall not apply and Parties shall be entirely liable for their own actions, including those of any and all of their employees, students, agents and Affiliates hereunder.

4.2. Subject to the limitations set out hereinafter, and without prejudice to clause 4.1 above, Sponsor, being the insurance holder as set out in clause 4.1 above, shall indemnify (in Dutch: “schadeloosstellen”) and hold harmless (in Dutch: “vrijwaren”) Study Site, its employees, the Site Investigator and the Research Staff (the “**Indemnitees**”) against all claims, demands, actions or proceedings (to include any settlements or ex gratia payments made with the consent of the Parties hereto and reasonable legal and expert costs and expenses) made or brought (whether successfully or otherwise): (i) by or on behalf of any Clinical Study Subject for personal injury or death arising out of the administration or use of the Investigational Product during or as a result of the Clinical Study, or (ii) of any clinical intervention or procedure provided for or required by the Protocol, to which the Clinical Study Subject would not have been exposed but for its participation in the Clinical Study.

4.3. Without prejudice to clause 4.1 above, Sponsor’s indemnification and defence of the Indemnitees shall not apply to any claim or proceeding pursuant to clause 4.2, and Sponsor shall not be liable:

(a) to the extent that said personal injury (including death) is caused by any of the Indemnitees’ failure to comply with this Agreement or the Protocol; or

(b) to the extent that said personal injury (including death) is caused by gross negligence, wilful recklessness or wilful conduct or wilful misconduct (in Dutch: "bewuste roekeloosheid of opzettelijk handelen of nalaten”) of any of the Indemnitees.

4.4. Parties shall keep each other reasonably informed of developments in relation to any such claim or proceeding. Parties will consult with each other on the nature of any defence to be advanced.

4.5. Parties will each give to the other such help as may reasonably be required for the efficient conduct and prompt handling of any claim or proceeding made or brought by or on behalf of Clinical Study Subjects (or their dependants).

4.6. Except in the event of intentional behaviour or gross negligence of a Party, in no event will a Party’s liability towards the other Party include any indirect damages (indirect damages meaning: loss of profit, loss of revenue, and loss of business opportunities).

4.7. The aggregate liability of the Site Parties for a claim or proceeding of Sponsor under this Agreement shall be limited to EUR 500.000, except and to the extent such claim or proceeding is made for damages caused by: **A)** gross negligence, wilful recklessness or wilful conduct or wilful misconduct (in Dutch: "bewuste roekeloosheid of opzettelijk handelen of nalaten”) of any of the Site Parties and cannot be so restricted or excluded by Law, or **B)** claims or proceedings between the Parties arising from the joint and several liability in connection with the joint controllership of the Parties under the GDPR as further laid down in clause 7 below.

4.8. Parties shall take out and/or maintain an insurance cover, or have a system of self-insurance in place, in amounts sufficient to cover their potential liability under this Agreement.

5. Clinical study subject recruitment and enrollment

5.1. The Site Parties shall use reasonable endeavours to recruit the Target of Clinical Study Subjects to the Clinical Study as indicated in the cadre above. Site Investigator shall make sure that the Clinical Study Subjects (and/or their legal representatives, if applicable) will, in accordance with applicable Law, be duly informed prior to their participation in the Clinical Study, in a language the Clinical Study Subjects (and/or their legal representatives, if applicable) can fully understand on all aspects of the Clinical Study which are deemed relevant in their decision to participate, and give informed consent. Site Investigator shall inform each Clinical Study Subject of the collection, the use and the transfer of Personal Data and the Clinical Study Subjects rights in respect of such processing as set forth in articles 13 and 14 GDPR, as well as the essence of the arrangement between the Parties as joint controllers referred to in article 26 paragraph 1 GDPR.

5.2. If circumstances or events have occurred or will occur that will substantially delay or are likely to substantially delay the progress of recruitment or enrolment of the Clinical Study Subjects, the Site Investigator shall without undue delay inform the Sponsor in writing. In each such event Parties shall discuss the consequences of the delay and each Party shall undertake reasonable endeavours to agree on measures to handle the delay.

5.3. In the event that the Clinical Study is part of a multi-centre clinical study, the Site Investigator acknowledges and agrees that recruitment may be competitive, and that Sponsor may stop further recruitment of Clinical Study Subjects at the Study Site when the recruitment target for all investigational sites for this Clinical Study has been met, even if the Study Site has not yet recruited the Target.

6. Quality assurance and control

6.1. The Site Parties shall permit the Study Monitor, Auditor and any official with a legal right to inspect and access all relevant documentation and source data for monitoring of the progress of the Clinical Study, the proper collection and recording of Clinical Study data, the welfare of the Clinical Study Subjects, and altogether the good quality of the Clinical Study and compliance with applicable Law and, if applicable and communicated to the Site Parties in writing, Sponsor's standard operating procedures. The Study Monitor and Auditor's access will be arranged at mutually convenient times and on reasonable notice with no additional costs for the Study Monitor, Auditor or Sponsor. The Study Monitor and Auditor will comply with all internal policies and regulations of the Site Parties during such inspection, to the extent these are sufficiently communicated to the Study Monitor or Auditor. For the avoidance of any doubt, the Sponsor shall be responsible for the confidential handling of all Personal Data of Clinical Study Subjects and other patients which the Study Monitor or Auditor comes across with during their monitoring or auditing activities. Before the start of the monitoring or auditing visits, the Sponsor shall provide the Site Parties with the name of the appointed Study Monitor or auditor, and hereby warrants (in Dutch: "staat garant") that such Study Monitor or Auditor shall timely sign a confidentiality statement regarding the above by means of a specific letter. of the template for such letter is annexed to this Agreement below, as Annex 4.

6.2. The Site Parties shall promptly inform the Sponsor in writing of any intended or actual inspection, written enquiry and/or visit to the Site Parties by any regulatory authority in connection with the Clinical Study and forward to the Sponsor copies of any correspondence from any such regulatory authority relating to the Clinical Study. The Site Parties shall allow Sponsor's representatives to be present during any such visit.

6.3. The Site Parties shall take appropriate measures and/or corrective actions without delay as the Sponsor may reasonably require in order to solve all problems found and reported by the Study Monitors, Auditor or officers from regulatory authorities or during an inspection under clause 6.2.

6.4. The Site Parties shall permit authorized representatives of the Ethics Committee and Competent Authorities to have access to and verify information relating to the Clinical Study, as required by and in accordance with applicable Law. Parties acknowledge that the Clinical Study is subject to inspection by regulatory authorities worldwide and that such inspections may occur after the completion of the Clinical Study.

6.5. It is expressly agreed between the Parties that:

a) the Sponsor will not compensate the Site Investigator nor any member of the Research Staff for the assistance or guidance of representatives of the Ethics Committee, Competent Authority or other regulatory authority and

b) the assistance or guidance of Study Monitors or Sponsor's Auditors by the Site Investigator and the Research Staff shall not be compensated by Sponsor, unless expressly agreed otherwise in writing.

7. Confidentiality and data protection

Confidential Information

7.1. The Receiving Party shall ensure that only those of its officers and employees concerned with the carrying out of this Agreement have access to the Confidential Information of the Disclosing Party. The Receiving Party shall take all practicable steps to ensure that such persons abide by the same obligations of confidentiality as apply to the Receiving Party under this Agreement. The Receiving Party undertakes to treat as strictly confidential and not to disclose to any third party any Confidential Information of the Disclosing Party, except where disclosure is required by a regulatory authority or by law, in which case the Receiving Party shall inform the Disclosing Party in writing of such requirement and the information to be disclosed. Notification will be within a reasonable time prior to being required to make the disclosure or if such time is not available, immediately upon becoming known of the requirement to disclose, Confidential Information. The Receiving Party undertakes not to make use of any Confidential Information of the Disclosing Party, other than in accordance with this Agreement, without the prior written consent of the Disclosing Party. For purposes of this Agreement and subject to clause 10 (Publication and Authorship), the Clinical Study results generated by Site Parties as disclosed through the CRF shall be considered Confidential Information of Sponsor and this clause 7 shall not provide Site Parties the rights granted hereunder to the Disclosing Party, where it relates to such Clinical Study results owned by Sponsor.

7.2. The obligations of confidentiality and non-use set out in clause 7.1 shall not apply to information which the Receiving Party can show by competent evidence:

a. is or becomes part of the public domain by any other means than a wrongful act or breach of this Agreement by the Receiving Party;
b. was or becomes in the Receiving Parties' lawful possession prior to the disclosure without restriction on disclosure;
c. has been independently developed by the Receiving Party without the use of Confidential Information of the Disclosing Party;
d. has been obtained by the Receiving Party from a third party without breach of a confidentiality obligation; or
e. is published in accordance with clause 10 hereof.

Medical confidentiality, data protection and data controlling

7.3. In line with the current position of the CCMO, the Study Site and Sponsor are considered joint controllers for the processing of the Personal Data and will both

handle all Personal Data in accordance with the GDPR and any other to the performance of the Clinical Study applicable laws or regulations covering the protection of Personal Data (collectively “**Data Protection Law**”). Parties, will fully cooperate with each other as joint controllers and shall take the necessary measures in order to comply with the Data Protection Law, such cooperation shall duly reflect the respective roles and relationships of the joint controllers vis-à-vis the Clinical Study Subjects as data subjects, in particular as regards the exercising of the rights of these data subjects and the Parties’ respective duties to provide the information referred to in Articles 13 and 14 of the GDPR. Each joint controller shall maintain a record of processing activities under its responsibility.
In the event law and interpretation by the CCMO and/or a relevant data protection authority or a court decision should prescribe or indicate another qualification of the roles of the parties in clinical trial agreements, the Parties hereto shall consult with each other and shall adapt the qualification of their roles and change arrangements as may be deemed appropriate.

7.4. Each Party shall be responsible for its own processing of Personal Data in accordance with all Data Protection Law and with the ICFs obtained from Clinical Study Subjects and to the extent applicable, Personal Data consents obtained from the Site Investigator and Research Staff.

7.5. Both Sponsor and Study Site shall implement appropriate technical and organizational measures to meet the requirements of the GDPR.

7.6. If any Party becomes aware of a Personal Data breach in connection with this Clinical Study or the performance of this Agreement, that Party shall promptly notify the other Party/-ies, and the Party that is the controller of the relevant Personal Data shall also document the Personal Data breach and report the breach to the applicable regulatory authorities. In such case, Parties will fully cooperate with each other in order to fulfil the (statutory) notification obligations timely. A Personal Data breach refers to: a personal data breach as defined in article 4 paragraph 12 GDPR and further determined by articles 33 and 34 of the GDPR.

7.7. Each Party agrees to co-operate with any competent supervisory authority and to allow such supervisory authority to audit each Party’s compliance with the GDPR.

7.8. The Parties agree to adhere to the principles of medical confidentiality in relation to Clinical Study Subjects.

7.9. Sponsor shall provide an Ethics Committee approved ICF to Site Parties.

7.10. Sponsor acknowledges that Clinical Study Subjects – and/or their legal representatives on their behalf – may withdraw, in whole or in part, their initial informed consent. Site Investigator shall promptly notify Sponsor of any such withdrawal of the informed consent of a Clinical Study Subject, which may affect the use of such Clinical Study Subject's Personal Data under this Agreement. The Site Investigator will communicate with Sponsor on behalf of the Clinical Study Subject. However, the procedure followed upon such withdrawal of a Clinical Study Subject's consent will be according to the instructions, to the extent laid down in the Protocol and the ICF, and in accordance with the Aplicable (Data Protection) Law.

7.11. Sponsor shall refrain from tracing and/or identifying any Clinical Study Subject, except where Sponsor is under a legal obligation to do so. In the event any Clinical Study Subject, for any other than aforementioned reason, becomes identifiable to Sponsor, Sponsor agrees to preserve, at all times, the confidentiality of information pertaining to such Clinical Study Subjects.

Site Investigator's (and Research Staff's) personal information

7.12. Where applicable, Sponsor shall inform the Site Investigator, and to the extent applicable other Research Staff involved in the Clinical Study as well, of the collection, the use and the transfer of his/her/their Personal Data and his/her/their rights in respect of such processing as set forth in articles 13 and 14 GDPR, as well as the essence of the arrangement between the Parties as joint controllers referred to in article 26 paragraph 1 GDPR. Site Parties agree to help Sponsor obtain any express consents, as may be necessary in accordance with applicable Data Protection Law from the Site Investigator, and to the extent applicable and necessary from other Research Staff involved in the Clinical Study as well, for any intended processing of his/her/their Personal Data by Sponsor.

8. Intellectual property

8.1. All Intellectual Property Rights and Know How owned by or licensed to any of the Parties prior to and after the date of this Agreement, other than any Intellectual Property Rights and Know How arising from the Clinical Study, are and shall not be affected by this Agreement.

8.2. The Parties shall jointly own the Intellectual Property Rights and Know How arising directly from the Clinical Study ("**Joint IP**").

8.3. The Site Investigator will promptly inform the Sponsor of any invention or discovery arising from and directly relating to the Clinical Study, and Study Site hereby assigns rights in relation to all Intellectual Property Rights in relation to such invention or discovery, and will provide reasonable assistance to the Sponsor in filing or prosecuting Intellectual Property Rights, at the expense of the Sponsor.

8.4. Nothing in this clause 8 shall be construed so as to prevent or hinder the Site Parties from using the Know How generated during their conduct of the Clinical Study for their normal hospital, non-commercial research and education activities, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Rights of the Sponsor.

8.5. *Protection, maintenance and costs of Joint IP:* After completion of the Clinical Study at all participating sites the Parties shall make additional arrangements with regard to application, acquisition and/or maintenance of the Joint IP. The Sponsor is designated as lead party therein.

Site Parties understand and agree that other participating sites may also have a right to the Joint IP. Sponsor shall ensure that such other participating sites adhere to the same terms and conditions with regards to Joint IP as Site Parties.

Sponsor shall timely discuss with the other participating sites any intended applications, reports etc. related to the Joint IP in order to give the other participating sites the opportunity to comment there on.

Each Party shall, and shall ensure that its employees, researchers, research fellows, individuals equivalent to those persons, give full cooperation and shall execute all documents, deeds and so forth as may reasonably be required in connection with the registration, protection and/or maintenance of that Joint IP.

8.6. In case Sponsor has an agreement on Intellectual Property Rights with a Funder, that agreement shall prevail over this clause 8 in case of conflict. In such case, Sponsor shall be obliged to fully inform the Study Site on all relevant aspects of such agreement within reasonable time prior to the execution of this Agreement.

8.7. In case a third party brings a claim or initiates proceedings against the Site Parties for the use of Intellectual Property Rights owned by or provided through Sponsor in conducting the Clinical Study in accordance with this Agreement, Sponsor shall indemnify the Site Parties against such claims or proceedings, provided the Site Parties shall have notified Sponsor promptly in writing of it and shall, upon Sponsor’s request and at Sponsor’s costs, have permitted Sponsor to have full control and discretion over the claim or proceeding using legal representation of its own choosing under the same conditions as set forth in clause 4.5-4.6.

9. Publicity

9.1. The Sponsor will not use the logo or name of the Study Site, Site Investigator, nor of any member of the Research Staff, for promotional purposes, in any publicity, advertising or news release without the prior written approval on a case-by-case basis of the Study Site or Site Investigator, such approval not to be unreasonably withheld. The Study Site and Site Investigator will not, and will ensure that the

Research Staff will not, use the name or logo of the Sponsor or of any of its employees for promotional purposes, in any publicity, advertising or news release without the prior written approval of the Sponsor on a case-by-case basis, such approval not to be unreasonably withheld.

9.2. The Site Parties will not issue and will ensure the Research Staff will not issue any information or statement to the press or public, including but not limited to advertisements for the enrolment of Clinical Study Subjects, without, where appropriate, the review and the issue of a favourable decision from the Ethics Committee and the prior written permission of the Sponsor.

10. Publication and authorship

Principles and multi-centre publication

10.1. The Sponsor, Study Site and the Site Investigator each acknowledge the importance of public disclosure/publication of information collected or generated as a result of or related to the Clinical Study, under the condition that public disclosure/publication takes place under the provisions of this clause 10.

10.2. Upon completion of the Clinical Study (whether prematurely or otherwise) the Site Investigator and Sponsor may co-operate in producing a report of the Clinical Study detailing the methodology, results and containing an analysis of the results and drawing appropriate conclusions.

10.3. As the Clinical Study is a multi-centre study, any publication based on the results obtained at the Study Site (or a group of sites) shall not be made before the first multi-centre publication or presentation, which shall be coordinated by Sponsor, unless otherwise agreed in writing, or as provided for in this clause 10. Notwithstanding the foregoing, if a multi-centre publication is not published within twelve (12) months after completion of the Clinical Study and lock of the Clinical Study database at all research sites that are part of the multi-centre Clinical Study or any earlier termination or abandonment of the Clinical Study, the Site Investigator and/or members of the Research Staff shall have the right to publish or present the methods and results of the Clinical Study in accordance with the provisions of this clause 10.

Publications by Site Investigator

10.4. Subject to clause 10.3 above, the Sponsor agrees that the Site Investigator and/or members of the Research Staff shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of its own choosing, methods and results of the Clinical Study, subject to the terms of this clause 10 and of any publication policy described in the Protocol, provided any such policy does not obstruct publication unreasonably.

10.5. Material for public dissemination will be submitted to the Sponsor for review at least thirty (30) days prior to submission for publication, public dissemination, or review by a publication committee. If Sponsor does not respond within this period, Site Parties are free to proceed with the intended publication or presentation without further delay.

10.6. The Site Investigator and/or Research Staff agree that all reasonable scientific comments made by the Sponsor in relation to a proposed publication or presentation shall be considered for incorporation into the publication or presentation.

10.7. During the period for review of a proposed publication referred to in clause 10.5 above, the Sponsor shall be entitled to

a. make a reasoned request to the Site Investigator and/or Research Staff that publication be delayed for an additional period of sixty (60) days (following the thirty (30) day period referred to in clause 10.5 in order to enable the Sponsor to take steps to protect its proprietary information and/or Intellectual Property Rights and/or Know How and the Site Investigator and/or Research Staff shall not unreasonably withhold their consent to such a request; and

b. cause the Site Investigator and/or Research Staff to remove from the intended publication any Sponsor Confidential Information received by Site Investigator that does not constitute results of the Clinical Study.

Authorship and copyrights

10.8. Publications will be in accordance with international recognized scientific and ethical standards concerning publications and authorship, including the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, established by the International Committee of Medical Journal Editors. Copyrights concerning publications of the Clinical Study remain with the authors of the publication, regardless of any other provisions regarding intellectual property rights.

11. Term and termination

11.1. This Agreement commences on the Effective Date and shall continue in force until the earlier of:

a. completion of the Clinical Study, close-out of the Study Site and completion of the obligations of the Parties under this Agreement; or

b. early termination in accordance with clauses 11.2 or 11.3 of this Agreement;

11.2 Each Party may terminate this Agreement upon written notice to the other Parties with immediate effect in the following events only:

a. if the approval by the Ethics Committee is not granted or irrevocably revoked;

b. if it can be reasonably assumed that the Clinical Study must be terminated in the interests of the health of the Clinical Study Subjects;

c. if it becomes apparent, following confirmation of the Ethics Committee or the Independent Committee, that continuation of the Clinical Study cannot serve a scientific purpose;

d. if the Sponsor and/or the Study Site become or are declared insolvent or a petition in bankruptcy has been filed against it or if one of them is dissolved;

e. if circumstances beyond a Party's control occur that render continuation of the Clinical Study unreasonable as outlined in clause 13;

f. if one of the Parties fails to comply with the obligations arising from the Agreement and, if capable of remedy, is not remedied within 30 days after receipt of written notice from the other Party specifying the non-compliance and requiring its remedy, unless the severity of the failure to comply does not reasonably justify the premature termination of the Clinical Study; or

g. if the Site Investigator is no longer able (for whatever reason) to act as investigator for this Clinical Study and no mutually acceptable replacement has been found in accordance with clause 2.3.

11.3 Sponsor may terminate this Agreement upon written notification to the Site Investigator and the Study Site with immediate effect, in the following events: a) for lack of recruitment at the Study Site, in case the Clinical Study is conducted at one site only; or

b) in case of a multicentre study, if termination at the Study Site does not affect performance of the Protocol.

The foregoing provided however, that this clause 11.3 shall not apply and Sponsor shall have no right to terminate this Agreement if any Clinical Study Subject has signed the ICF, at the Study Site.

11.4 At close-out of the Study Site following termination or expiration of this Agreement the Site Investigator and the Study Site shall, upon first request, immediately return to the Sponsor or destroy with confirmation thereof all Confidential Information, Equipment and/or unused materials or unused Study Drug and/or unused Investigational Product provided by Sponsor in accordance with Sponsor's instructions, except for copies to be retained in order to comply with Site Parties' archiving obligations or for evidential purposes.

12. Financial provisions / study drug / material / equipment

12.1. The Sponsor will provide solely if and to the extent as set out in Annex 2.

12.2. See Annex 2

12.3. Any arrangements with the pharmacy of Study Site to the extent applicable will be in writing and must be in accordance with the Site Parties' internal policies, to the extent these are sufficiently communicated by the Site Parties. Any such agreements will be annexed to this Agreement.

12.4. The Site Parties shall not use or permit the Research Staff or any third party to use the Study Drug, material or equipment for any purpose other than the conduct of the Clinical Study and upon termination or expiration of this Agreement all unused Study Drug, material or equipment shall, at the Sponsor's option, either be returned to the Sponsor or disposed of in accordance with the Protocol or the Sponsor's written instructions.

13. Force majeure

13.1 No Party shall be liable to the other Parties or shall be in default of its obligations hereunder if such default is the result of war, hostilities, terrorist activity, revolution, civil commotion, strike, and epidemic or because of any other cause beyond the reasonable control of the Party affected. The Party affected by such circumstances shall promptly notify the other Parties in writing when such circumstances cause a delay or failure in performance and where they cease to do so.

14. Miscellaneous

14.1. Parties shall have the right to assign this Agreement to an Affiliate upon prior written notification of the other Party/Parties, any other assignment shall take place upon the prior written approval of the other Party/Parties. Any approval by a Party of an assignment, transfer or encumbrance by the other Party shall not release the assigning Party of any of its obligations under this Agreement due up until such assignment. Subject to the foregoing, this Agreement shall bind and inure to the benefit of the respective Parties and their successors and assignees.

14.2. Site Parties may not sub-contract the performance of all or any of their obligations under this Agreement without the prior written consent of the Sponsor, such consent not to be unreasonably withheld or delayed. Any Party who so sub-contracts shall be responsible for the acts and omissions of its sub-contractors as though they were its own.

14.3. Nothing in this Agreement shall be construed as creating a joint venture, partnership or contract of employment between the Parties.

14.4. Should there be any inconsistency between the Protocol and the terms of this Agreement, or any other document incorporated therein, the Protocol shall prevail in case such inconsistency concerns clinical matters, and the Agreement shall prevail the inconsistency concerns non-clinical matters. For the avoidance of doubt, Termination and Publication provisions of this Agreement shall always prevail above the Protocol.

14.5. The clauses 4 (Liabilities, Indemnification and Insurance); 6 (Quality Assurance and Control); 7.3-7.11 (Medical confidentiality, data protection and data controlling); 8 (Intellectual Property); 9 (Publicity); 10 (Publication and Authorship); 11.4 (Term and Termination); 12 (Financial Provisions/Study Drug/Material/Equipment); this clause 14.5 (Surviving Clauses); 14.6 (Governing Law); 15 (Human Samples) or other clauses contemplating performance after termination, shall survive termination or expiry of this Agreement. The provisions of clauses 7.1 and 7.2 (Confidential Information) shall remain in force for a period of five (5) years from the date of such termination or expiry.

14.6. This Agreement shall be exclusively governed by and construed in all respects in accordance with the laws of The Netherlands without regard to any of its conflicts of laws rules. Any claims, controversies or disputes arising out of or in connection with this Agreement which cannot be settled amicably between the Parties, shall be subject to the exclusive jurisdiction of the competent court in The Netherlands.

14.7. Each person signing this Agreement represents and warrants that he or she is duly authorized and has legal capacity to execute and deliver this Agreement. Each Party represents and warrants to the other that the execution and delivery of the Agreement and the performance of such party's obligations hereunder have been duly authorized and that the Agreement is a valid and legal agreement binding on such party and enforceable in accordance with its terms.

15. Human samples

15.1 As part of the Protocol, Samples derived from Clinical Study Subjects may be transferred to Sponsor or another organization indicated by Sponsor (hereinafter: "**Sponsor's Designee**"), however only if this is arranged for in the ICF. If this is done in non-anonymous form, Sponsor and Sponsor's Designee shall adhere to the provisions of the GDPR by concluding an industry standard processor agreement with each other.

15.2 Sponsor, and if applicable Sponsor's Designee, shall have the right to store, transfer and use the Samples only in accordance with the applicable Law (at least laws and regulations concerning the protection of privacy), the Protocol and ICF. Site Parties shall promptly notify Sponsor of any withdrawal of or changes in the informed consent of a Clinical Study Subject, which may affect the use of such Clinical Study Subject's Samples under this Agreement. In such event, Sponsor or Sponsor's Designee shall destroy, with written confirmation thereof, or return the affected Samples, where necessary and possible.

15.3 Upon termination or expiration of the Clinical Study, and at least at any time the Samples are no longer needed to be retained by Sponsor, or Sponsor's Designee, for purposes defined in the ICF, or as required per any applicable Law or regulation, the remainder of the Samples in Sponsor's or Sponsor's Designee's possession will be returned to the Site Parties, or retained by the Sponsor in accordance with clause 15.2 or destroyed by the Sponsor/Sponsor's Designee, as described in the Protocol and/or the ICF, with written confirmation thereof.

15.4 For the avoidance of any doubt, the control *(*in Dutch: “zeggenschap”*)* of the Samples remains at all times with the Clinical Study Subjects they are derived from, while the Site Parties and/or Sponsor are acting as custodian of the Samples, as described in the Protocol.

Annexes

Annex 1: Protocol

Annex 2: Financial Provisions/ Study Drug / Material / Equipment

Annex 3: Funding Conditions

Annex 4: Template Monitoring Letter

[The remainder of this page is intentionally left blank]

Signed on behalf of the **Sponsor**

Signature: …………………………………………
Name: …………………………………………
Title: …………………………………………

Date: …………………………………………

Signed on behalf of the **Study Site**

Signature: …………………………………………
Name: ……………………………
Title: ……………………………

Date: …………………………………………

[N.B. In case a “medisch specialistisch bedrijf” will cosign the Agreement: insert signature field for

Signed on behalf of the **MSB …………**

Signature: …………………………………………
Name: ……………………………
Title: ……………………………

Date: …………………………………………

[**if the Site Investigator is NOT a contracting Party insert:** The undersigned Site Investigator hereby declares that he/she has read the above Agreement between the Parties and that he/she acknowledges the provisions of the Agreement relative to his/her role, responsibilities and duties concerning the Clinical Study;]

Signed by the **Site Investigator**:

Signature: …………………………………………

Name: ……………………………

Title: ……………………………

Date: …………………………………………

ANNEX 1

Protocol

the most recent version of the Protocol has been incorporated by reference only

ANNEX 2

Financial provisions / study drug / material / equipment

Smartwatches, and stool and saliva collection kits are provided by the study team.

The participating center is reimbursed for the costs of research nurse work according to the Dutch CAO algemene ziekenhuizen gross salary per hour.

Equipment will be provided from Erasmus MC to the participating center by delivery services or physical delivery by study team.

ANNEX 3

Funding conditions

Please refer to the grant agreement

ANNEX 4

Template letter study monitor

Ziekenhuis naam (Study Site)

Adres

Postcode en plaats

[plaatsnaam Sponsor], [datum]

Betreft: Opdracht monitoren klinische studie

Geachte heer/mevrouw,

[naam Study Site] doet mee aan het ondergenoemde klinische onderzoek. Zoals bepaald in de Clinical Study Agreement over dit onderzoek is [naam Sponsor] verantwoordelijk voor monitoring. Namens [naam Sponsor] zal [naam monitor] (hierna “**Monitor**”) regelmatig in uw ziekenhuis aanwezig zijn om de studiedata te monitoren. Deze Monitor zal in overeenstemming met Good Clinical Practice (GCP) en/of ISO14155, het contract en het studieprotocol de studiedata aan de hand van de brondata verifiëren.

Monitor zal vertrouwelijk omgaan met alle gegevens die hij/zij inziet en Sponsor verklaart hierbij dat Monitor een geheimhoudingsverklaring heeft getekend.

Monitor heeft de volgende faciliteiten nodig van het ziekenhuis om te kunnen monitoren:

- toegang tot alle patiënten data, waaronder het elektronisch patiëntendossier (EPD) van de patiënten die deelnemen aan ondergenoemde klinische studie.
- Monitor heeft alleen een controlefunctie, derhalve heeft zij enkel recht op inzage in het EPD en geen schrijfrecht.
- Dit inzagerecht is daarbij beperkt tot de patiënten die deelnemen aan de ondergenoemde studie.

Naam studie:

Studie id:

Protocol nummer:

Deze verklaring geldt voor de duur van de studie en alleen voor de genoemde Monitor.

Met vriendelijke groet,

[naam tekenbevoegde] Raad van Bestuur [naam Sponsor]

IV.4 Risk classification Netherlands

*Information can be provided upon reasonable request.

IV.5 Data management plan Netherlands

*Information can be provided upon reasonable request.