D8.6.3 – SP8 Medical Informatics Platform – Results for SGA1 Period 2

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Abstract:	This Deliverable is the annual compound of HBP deliveries and results (outputs and outcomes) from Subproject 8 – Medical Informatics Platform. The live complete catalogue of HBP deliveries is accessible on-line from the HBP Collaboratory. The main deliveries from April-2016 to March-2018 have been: D8.6.1 – SP8 Medical Informatics Platform – Architecture and Deployment Plan D8.6.2 – SP8 Medical Informatics Platform – Results for SGA1 Period 1 D8.6.4 – SP8 Medical Informatics Platform – System Validation Plan D8.6.3 – SP8 Medical Informatics Platform – Results for SGA1 Period 2

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Table of Contents

List of Figures

List of Tables

1. Introduction

Thousands of brain images and terabytes of invaluable associated medical data are produced every day at a gigantic pace around the world.

Convergence of biology and technology and the increasing capabilities to perform comprehensive "omic" assessments of an individual, including detailed brain features (morphology, connectivity, functionality), DNA sequence analysis, proteome, metabolome, microbiome, autoantibodies, physiome, phenome, etc., provide the opportunity to discover new biological signatures of diseases, develop preventive strategies and improve medical treatment. Opportunities to use these data to improve health outcomes – to develop preventive strategies and improve medical care – is the motivation for the development of the Medical Informatics Platform.

The MIP aims to use this information from a distributed data sources, wherever they are, and provide data science tools to the clinical researchers to effectively analyse the vast amount of cross-centre, multi-dataset patient clinical and self-observational information and advance more rapidly in understanding the diseases. This will in turn allow identifying the associated biological changes and open real possibilities for early diagnosis, preventive actions and personalised medicine.

The MIP has three main goals:

1) Build the tools to federate clinical data, currently inaccessible outside hospital and research archives;
2) Recruit hospitals to contribute to and benefit by using the platform;
3) Develop tools for extracting biological signatures of diseases from multi-level data.

The MIP provides methods to analyse federated data from hospitals, research centres and biobanks. Clinical scientists can develop, share and release results of their research. The MIP aims to bring together people across professional and scientific fields encourages them to actively contribute to the design and development of the services which the MIP provides.

The users of the MIP are:

- Clinicians, for objective diagnoses and treatment of brain disease
- Neuroscientists, for the application and testing of new models and methods
- Pharmaceutical or biotech researchers, for disease target discovery

2. Key Scientific Results

This section of the document presents the key outputs and outcomes from Human Brain Project's Subproject 8 (SP8) – the Medical Informatics Platform (MIP). The key Subproject results are defined as the key benefits that the Medical Informatics Platform provides to its users – clinicians, neuroscientists and epidemiologists – and indirectly to the patients and the general population.

The table provides the mapping of the achieved SP8 key results at the end of the SGA1 phase to the corresponding strategic SP8 FPA objectives.

Table 1 – Mapping of the key results to strategic FPA objectives

Strategic FPA Objective	Key Result
FO2. Establish agreements or MoUs, in consultation with authorised representatives of involved HBP Partners, for access to hospital data, centralised large-scale clinical research databases and biobanks. Provide documentation, training and support to the users	Deployment and evaluation agreements with European hospitals and research centres
FO1. Design, implement and operate a federated clinical infrastructure comprising tools for harmonising heterogeneous clinical databases, data anonymisation, ontology-based query interfaces, federated search and distributed analysis of clinical data	Shared cross-centre multi-dataset clinical studies
FO3. Develop generic tools for data curation, quality control and provenance. Develop, implement and deploy tools to extract brain morphology, genomic, proteomic behavioural and cognitive features from clinical and research databases	Patient data processing
FO4. Develop, implement and deploy mathematical methods for predicting multi-level features of diseases; develop tools for identification of homogeneous disease using the biological signatures; construct unified models of brain diseases	Data analytics using integrated statistical methods and machine learning algorithms
FO5. Contribute data, novel disease classification for disease simulation and *in silico* experimentation	Clinical utility of the Medical Informatics Platform for disease simulation and *in silico* research

2.1 Deployment and evaluation agreements with hospitals

The Medical Informatics Platform is the unique distributed data analytics solution for clinical and fundamental researchers and epidemiologists. It provides advanced single- or cross-centre analysis of harmonised patients' clinical data, distributed across private execution environments in the participating hospitals.

During the Ramp-Up Phase of the Project, nineteen European university hospitals expressed interest in providing patient datasets, deploying and evaluating the Medical Informatics Platform. Deployment and Evaluation Agreements were signed with seven of them:

- **University Hospital in Lausanne, Switzerland** (CHUV)
- **Regional University Hospital in Lille, France** (CHRU Lille)
- **Research and Healthcare Institute in Brescia, Italy** (IRCCS Fatebenefratelli Brescia)

- **Metropolitan Hospital Niguarda in Milano, Italy** (ASST Grande Ospedale Niguarda)
- **University Medical Centre in Freiburg, Germany** (Universitätsklinikum Freiburg)
- **Medical University Plovdiv, Bulgaria**
- **Sourasky Medical Centre in Tel Aviv, Israel**

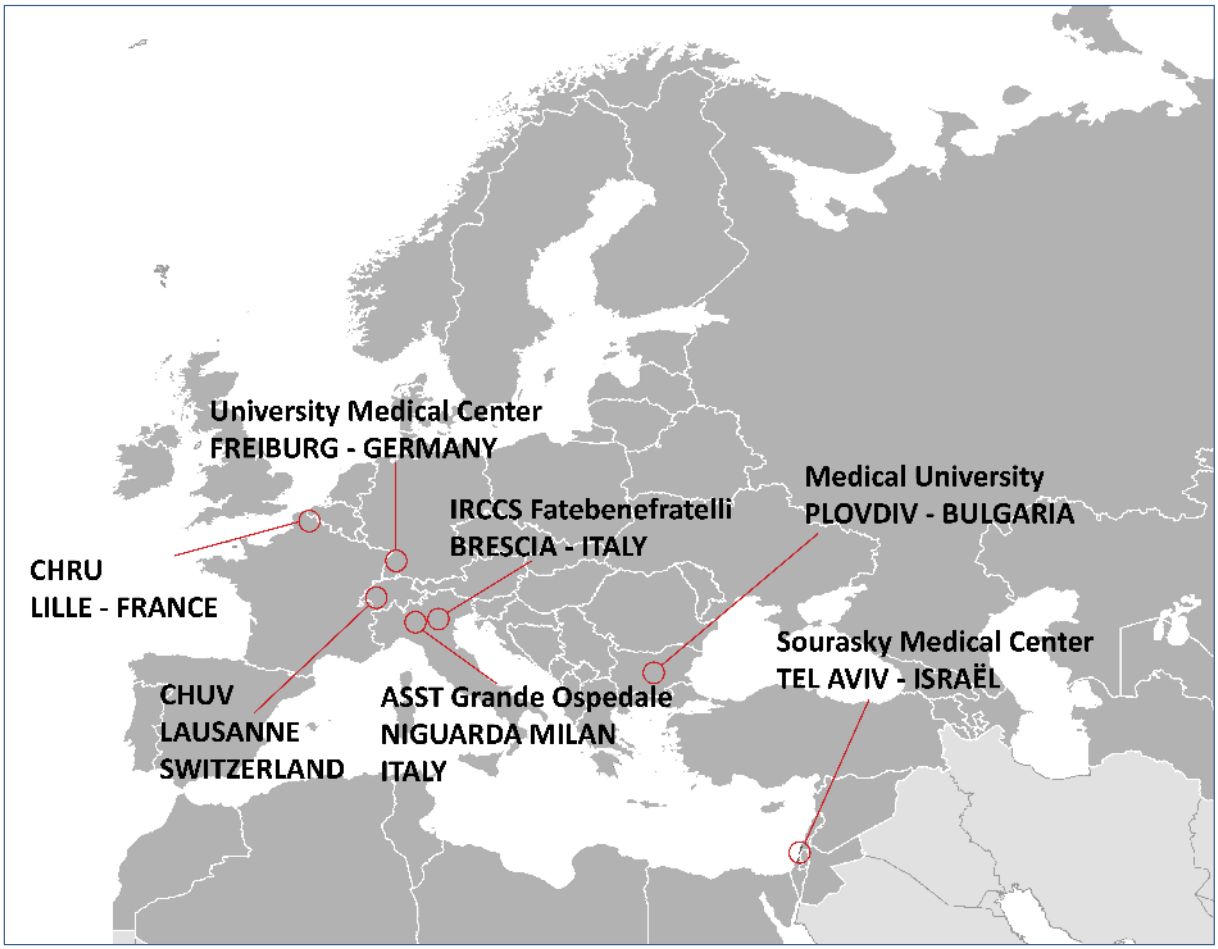

Figure 1 – Deployment and Evaluation Agreements with European University Hospitals

The criteria for selecting the seven European university hospitals for providing patient datasets, deploying and evaluating the MIP are provided in Table 2:

Table 2 – Criteria for selecting participating hospitals

Criteria	Description
Diversity	Hospitals in different countries. Objective: to test the MIP in different healthcare systems, using data of patients with different exposure to risk factors, disease prevalence, etc.
Size	Hospitals that have a significant number of patients and large patient datasets
Clinical Excellence	The best national hospitals with expertise in clinical neuroscience and clinical care, willingness to share data, with well-established ethics consent procedures
Available resources	Hospitals that have the personnel and IT equipment resources, and a long-term commitment to maintain the Medical Informatics Platform infrastructure
Influence	Hospitals that will promote Medical Informatics Platform through collaboration with other hospitals in the same region or country

The Medical Informatics Platform provides support for analysing diverse biomedical and other health-relevant patient data. That includes support for multi-centre, multi-dataset studies for bridging the gap between fundamental research and clinical practice.

Scientific research significance (Figure 10) – a realistic possibility to discover hidden data patterns by combining multi-centre patient clinical datasets with the available open research cohort data, such as ADNI, EDSD and PPMI, and compliance of the MIP platform concept with WHO's action areas – Information Systems for Dementia and Dementia Research and Innovation (Figure 11), were the reasons to select dementia and in particular Alzheimer's disease clinical study scenarios for the demonstration of MIP functionality and its scientific utility. Platform's scientific utility, defined as a key SP8 result, is discussed in the Chapter 2.5.

2.1.1 Achieved Impact

Clinicians and clinical researchers in the three selected university hospitals have been chosen because of the expertise in the domain of dementia syndromes and profiles of the available patient datasets (an overview is provided in Table 5). They contribute with the data of a significant number of patients with neurodegenerative and neurocognitive disorders, different types of dementia, high Alzheimer's disease incidence, and a variety of biological, cognitive, neuroimaging and other relevant patients' information.

Data profiles for three university hospitals from France, Italy and Switzerland, including the number of patients in each cohort dataset and the counts of patients with diagnosed Alzheimer's disease (AD), mild cognitive disorder (MCI), other neurodegenerative disorders, and cognitive normal (CN) control group are provided in Table 5.

In the cases of the Regional University Hospital in Lille, France (CHRU Lille) and the University Hospital in Lausanne (CHUV), patient cohort datasets consisted of the multiple visits per patient. The Data profile in Table 5 contains information about the first and the last visit recorded in the CHRU Lille's dataset and the first recorded visit of the patients in the CHUV. In the cases of Research and Healthcare Institute in Brescia, Italy (IRCCS FBF Brescia) the patient cohort dataset consisted of a single visit per patient and was already in the format of the Medical Informatics Platform.

2.1.2 Component / Technology Dependencies

Table 3 – Key technologies / components for deployment of the MIP in hospitals

Component ID	Component Name	Comment
102	**MIP Microservice Infrastructure**	Efficient and cost-effective deployment of the new or upgraded platform components in hospital or institute data centres and their integration in a federated MIP eco-system. This technology is a key for successful wide-scale deployment of the MIP and its progress on the TRL scale (Chapter 3)
2940	**Data De-identifier**	Optional service to hospitals and institutes in cases where they do not have their solution in place
2936	**MIP De-identification Profiles**	Efficient and sure configuration and management of de-identification profiles
2935	**MIP De-identification Strategy**	Formal specification document as a communication channel for the members of the DGDS committee responsible for establishing and maintaining data de-identification profiles for each participating hospital or institute

Key technologies for deployment of the MIP in hospitals are:

- **Docker microservice infrastructure –** architecture for fast deployment of services on bare metal or preconfigured virtual machines supporting clustering, security and monitoring. Support for continuous integration and continuous deployment. Microservices are implemented as small, encapsulated loosely coupled functions and components, enabling an incremental adoption of new technologies and independent deployment of new features with no or a minimal need for adaptation of the existing MIP eco-system
- **Patient data de-identification –** using Gnubila FedEHR Anonymizer data de-identification technology. It replaces all personally identifiable information from the patient data captured in CSV files with pseudonyms using out-of-the-box data de-identification techniques, such as generalisation, micro-aggregation, encryption, swapping and sub-sampling. Easy and efficient configuration of de-identification profiles. Data de-identifier uses checksum (SHA-512) as a data security mechanism for validation of the anonymisation profile files and detection of the unauthorised profile updates. The checksum is registered with the Gnubilla FedEHR Anonymiser's license.
- **Key organisational aspect: MIP Data Governance and Data Specification committee –** consists of the representative of hospitals' data management teams, biomedical experts (scientists and clinicians) and ethics committees. The MIP DGDS is responsible for the selection of datasets from participating hospitals and institutes – types, variety and volume of the data, specification of data vocabularies and data harmonisation rules, as well as specification of data de-identification rules in compliance with data protection regulations, such as EU/GDPR, CH/FADP and US/HIPAA

2.2 Shared cross-centre, multi-dataset clinical studies

Convergence of biology and technology and the increasing capabilities to perform comprehensive "omic" assessments of an individual, including detailed brain features (morphology, connectivity, functionality), DNA sequence analysis, proteome, metabolome, microbiome, autoantibodies, physiome, phenome, etc., provide the opportunity to discover new biological signatures of diseases, develop preventive strategies and improve medical treatment. Using these data to improve health outcomes – to develop preventive strategies and improve medical care – is the motivation for the development of the Medical Informatics Platform.

The MIP is distributed, cloud-ready patient data analysis ecosystem, which connects patients' data from hospitals and research cohort datasets and provides set of pre-integrated statistical methods and predictive machine learning algorithms for patient data exploration, data modelling, integration and execution of experiments (data analysis methods), and visualisation of the results.

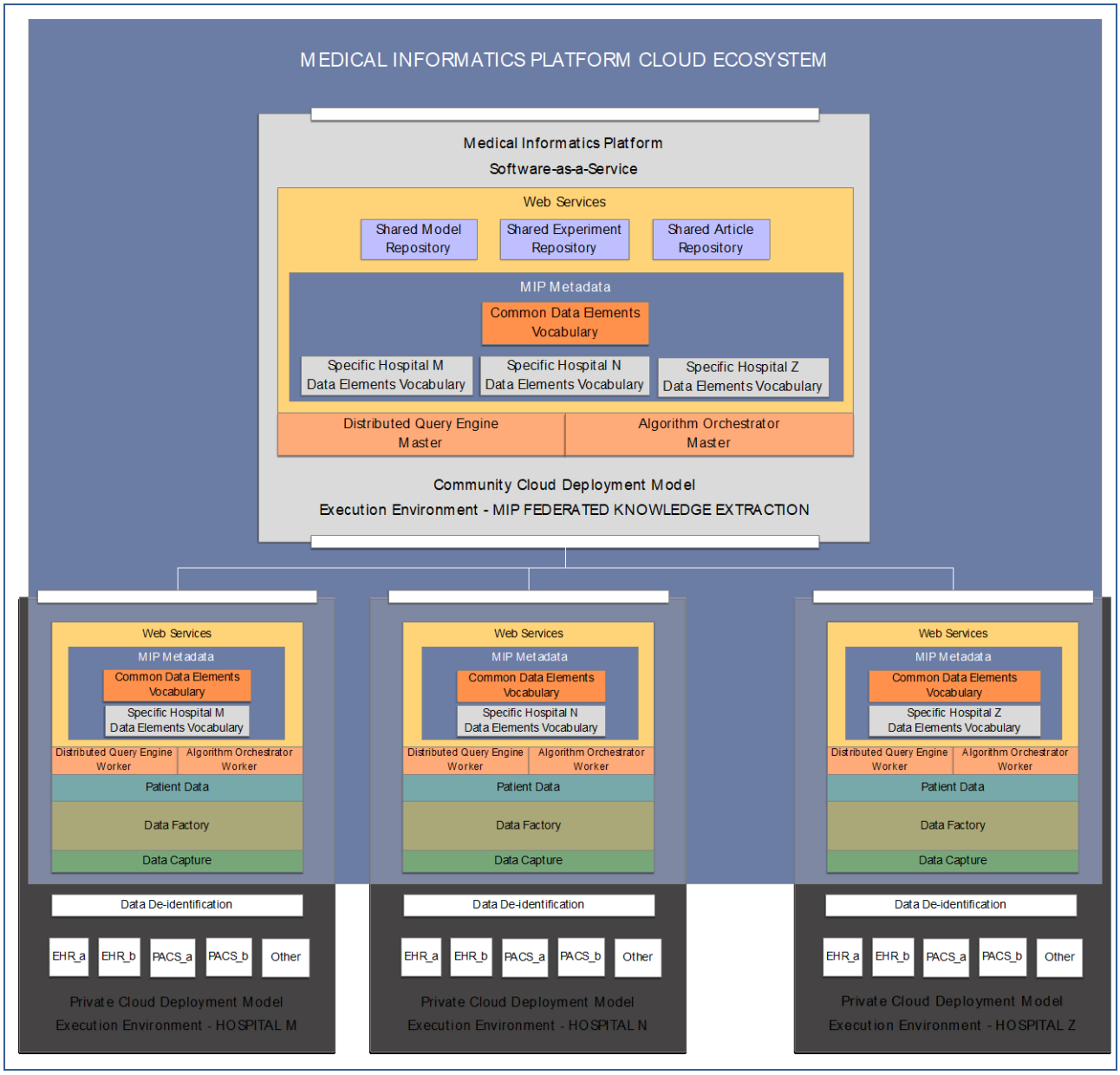

Figure 2 – Medical Informatics Platform Architecture

The Platform, developed during the SGA1 project phase, makes data on populations of patients broadly available for research use, by providing software-as-a-service to clinicians, neuroscientists and epidemiologists both for diagnosis and research in clinics and for collaborative neuroscience research using hospital data and open patient research cohort datasets.

Figure 2 illustrates the cloud-ready MIP federated knowledge extraction software-as-a-service deployed in community execution environment. The MIP community execution environment provides advanced multi-dataset, cross-centre descriptive and predictive analytics. It runs software that orchestrates the execution of statistical and machine-learning algorithms in private hospital MIP execution environments and aggregates the results. The algorithms are executed locally, in private hospital environments where the de-identified patient data is stored. Master orchestrator components that are running in community execution environment, connected to the distributed private MIP execution environments via web services, fetch the aggregate results of the algorithms executed in the private execution environments and aggregate them in a cross-centre data analysis result.

The MIP is engineered with a privacy by design approach. De-identified patient data stored in private hospital's execution environments are accessible only locally, either by the algorithms running there or by other means of data exploration within the private cloud, using the locally deployed web services.

Users of the MIP can access the community execution environment or the local private hospital execution environment through the MIP web portal. The MIP web applications allow for the statistical/aggregated (not individual) data exploration, selection of data types for analytics, execution of algorithms/experiments and visualisation of the results.

Figure 3 illustrates one instance of the web portal for the local execution environment in the University Hospital in Lausanne, Switzerland. Detailed functionality and results of system validation with the three participating hospitals are provided in Chapter 3.

Figure 3 - Medical Informatics Platform Web Portal

The hybrid community and private hospital deployment model, microservice architecture coupled with continuous integration and continuous deployment technology, distributed hospital patient data storage and federated algorithm execution are software architecture-related prerequisites to having a cross-centre data analytics.

This distributed, patient privacy preserving software architecture is a necessary but not a sufficient condition to having multi-dataset clinical studies. Hospital datasets have overlapping data types but different ontological representations. Data is described, stored and formatted in different data structures. For executing a multi-dataset analytics, data models need to be harmonised in a common MIP data model, which is shared and synchronised between the distributed private hospital instances and community execution environment (Figure 2).

The data model harmonisation is, therefore, a key technology enabler for cross-centre multiple dataset clinical studies. It is a well-defined process supported by the workflow orchestration, application ontology software architecture, and the organisation, which establishes and maintains the rules and controls the quality and the integrity of the data harmonisation process.

Data governance and data selection (DGDS) committee is a centrally coordinated MIP organisational entity responsible for establishing and maintaining data governance methodology and data harmonisation rules. The members of the DGDS committee are MIP software architects, with the expert medical committee consisting of the medical doctors and clinical researchers of participating hospitals and institutes and data managers, both from the participating hospitals and MIP R&D team.

Data harmonisation and re-harmonisation is an on-going process. With the introduction of a new dataset, the whole process has to be repeated, starting with the analysis of the incoming dataset ending with the synchronisation of (re-)harmonised data models across the distributed MIP ecosystem.

The process steps are provided in Table 4. The resulting common data model for three hospitals, which participated in MIP system validation, is illustrated in

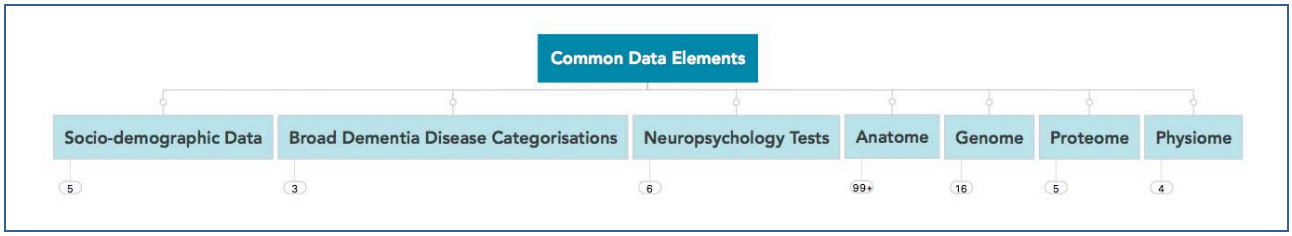

Figure 4 and Figure 5. Detailed description of the data models and data profiles for each of the three hospitals is provided in Chapter 3.

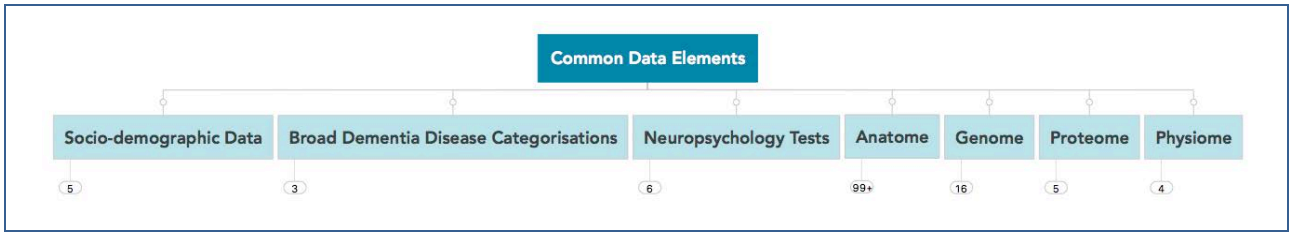

Figure 4 – MIP Common Data Element Groups

Diagnostic framework, i.e. the type and categorisation of diagnoses is typically hospital specific. Each hospital has its own naming classification of diseases. It is usually based on a standard classification, like ICD-10, but often a more detailed classification is needed for some disease domains. In case of the dementia disorders, for example, CHRU Lille has adopted the recommendation of the French *Banque Nationale de données Alzheimer* (BNA). CHUV Lausanne has recently provided their adaptation of the BNA disease classification, which is planned for integration in the next release of the MIP. System validation has been based on the old ICD-10 classification. To have multi-dataset analytics involving the diagnosis, MIP has introduced 3 broad dementia disease categorisations: Alzheimer, Parkinson and Neurodegenerative. Broad MIP disease

categories are mapped to the disease definitions of each of the diagnostic frameworks of participating hospitals based on the rules of the clinical experts.

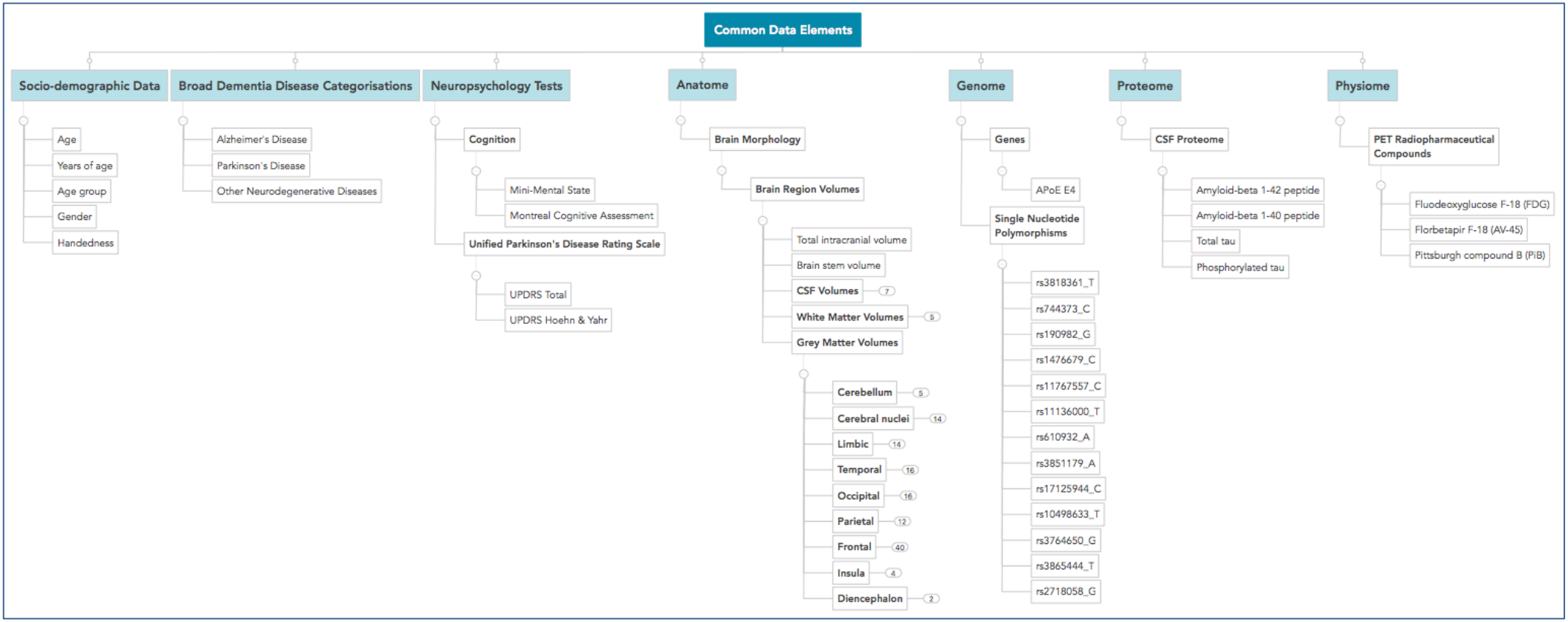

Figure 5 – MIP SGA1 Common Data Element Taxonomy

Note: Brain Volume group contains 135 data elements representing brain regions classified using the standard brain anatomy classification

Table 4 – High-level data model harmonisation process description

Activity Number	Activity	Description
1	**Analysis of the new dataset**	Initial profiling of the original de-identified patients' data exported from EHR's and research datasets in CSV format, stored in clinical research data warehouses or other OLAP systems (for example, I2B2). Analysis of the brain scan dataset, including the number of scan sessions, and preliminary examination of the DICOM file header information
2	**Understanding the meaning of the data**	Analysis of the formats and structures of received datasets. Informal description of the original data types confirmed and approved by originating hospital/institute experts
3	**Creation of data vocabularies / application ontologies**	Creation of data vocabularies/MIP application ontologies for: socio-demographic data, brain regions, genome, proteome, metabolome, physiome, phenome. Creation of hospital specific diagnostic framework, including mapping to MIP broad disease categories (see: Creation of hospital specific neuropsychological assessment framework
4	**Re-harmonisation of the common data model**	Updating of the MIP common data model in coordination with expert representatives of participating hospitals and institutes
5	**Update and formal approval of the Data Mapping and Transformation Specification**	Formal, version-controlled specification of the harmonisation and naming rules updated and formally approved by originating hospital/institute experts, MIP medical consultants and MIP software architects
6	**Integration of common and dataset-specific data models**	Integration and verification of common and dataset-specific data models in MIP testing environment. Regression testing using the open research cohort datasets

2.2.1 Achieved Impact

The Distributed MIP platform has been installed in the data centres of the three European university hospitals participating in the MIP SGA1 system validation project phase.

The datasets received from each of the three participating hospitals have been analysed, data vocabularies created, including the mapping of hospital-specific disease classification to the broad MIP neurodegenerative disease categories, based on the rules of their medical experts. The cross-comparison of the Alzheimer's disease related diagnostic dataset profiles are provided in Table 5.

Table 5 – Hospitals selected to participate in MIP system validation – data profiles

Hospital	Patient Count	Recorded Visit	Diagnosis				
			AD	**MCI**	**Other**	**CN**	**N/A**
CHRU Lille France	1,436	First	591	227	551	67	0
		Last	813	7	604	12	0
IRCCS FBF Brescia Italy	1,960	First	151	201	192	1,240	176
		Last	N/A	N/A	N/A	N/A	N/A
CHUV/CLM Lausanne Switzerland	699	First	164	78	414	41	2
		Last	N/A	N/A	N/A	N/A	N/A
ADNI	1,066		222	576	0	268	0
EDSD	368		141	76	0	151	0
PPMI	714		0	0	531	183	0
TOTAL	**6,243**		**1,164**	**1,116**	**1,846**	**1,941**	**176**

Diagnosis: AD – Alzheimer's disease, MCI – mild cognitive impairment, CN – cognitive normal, Other – other neurodegenerative disorder, N/A – disease information not available

Common data models (Figure 5) have been integrated and synchronised across the participating hospitals' private MIP execution environments. Both common and hospital-specific data models have been integrated in the central MIP community execution environment (Figure 2)

MIP SGA1 common data taxonomy is illustrated in Figure 5. Specific data taxonomies for each of the three hospitals participating in the SP8 system validation project phase are illustrated in Figure 6, Figure 7 and Figure 8.

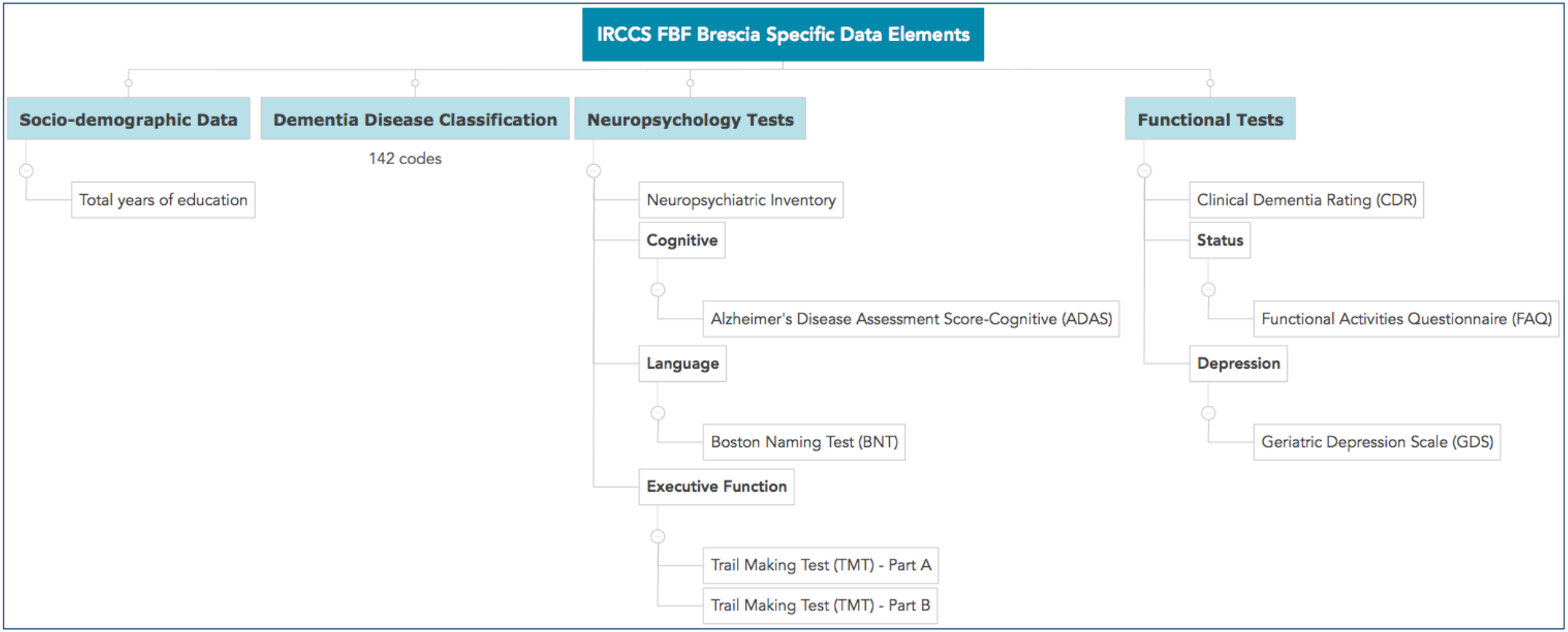

Figure 6 – IRCCS Brescia Specific Data Element Taxonomy

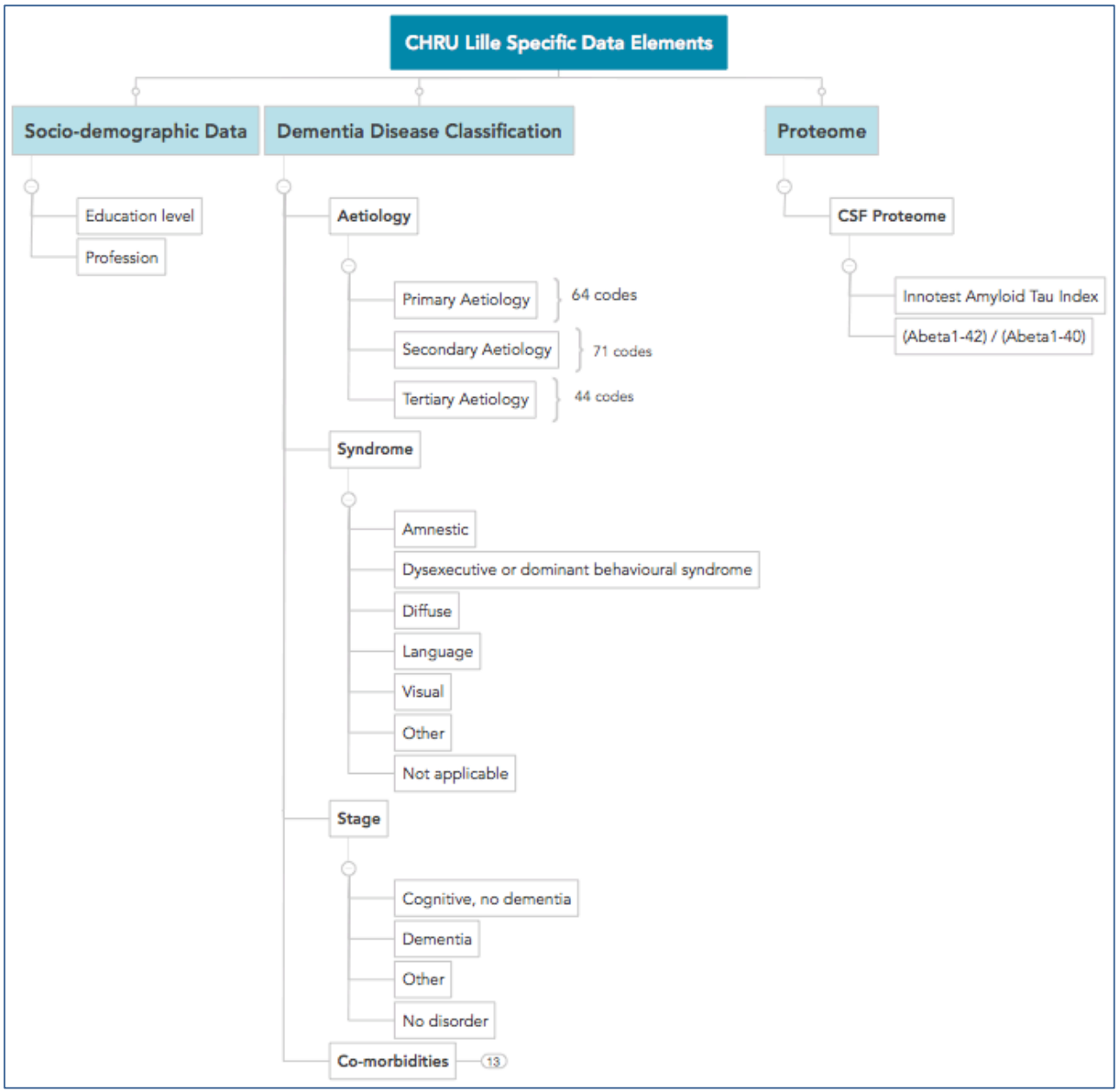

Figure 7 – CHRU Lille Specific Data Element Taxonomy

The distributed, privacy-preserving MIP software deployed across hospitals and institutes using a hybrid community-private deployment model with centralised orchestration of statistical inference and machine learning algorithms, and managed harmonisation and synchronisation of the data model provided the IT prerequisites for execution of cross-centre, multi-dataset clinical studies across the three university hospitals participating in the SP8 system validation project phase.

For example, using the unsupervised machine learning to train a classifier on CHRU Lille data, which differentiates between the frontotemporal dementia and Alzheimer's disease, then applying learned classifier to patient's data in IRCCS Brescia and CLM/CHUV Lausanne for a differential diagnosis between the two neurodegenerative disorders (see the detailed results in Chapter 2.4). Or, using the clinical and pathological data of deceased patients from the CHRU Lille dataset to train a machine-learning model that is used to predict the disease progression with patients in other two hospitals (detailed results in Chapter 2.5)

Chapter 3 contains results of the SP8 system validation project phase and their analysis, including the MIP system deployment across the private hospital execution environment, data harmonisation, data processing and feature extraction and execution of 4 clinical studies.

2.2.2 Component / Technology Dependencies

Table 6 – Key technologies / components for shared clinical studies

Component ID	Component Name	Comment
687	Data Governance Methodology	Providing rules and defining the framework for the on-going MIP data harmonisation, and management of both data harmonisation and data processing pipelines
587	Data Mapping and Transformation Specification	Version controlled specification of harmonisation and naming rules
2938	Algorithm Orchestrator	Managing of local or distributed execution of statistical inference and machine learning algorithms, controls machine learning model validation process as well as storing/retrieving of the predictive models in the Predictive Disease Models database. This component is a key technology for execution of data analytics methods and measurement of the accuracy of the resulting models
638	Query Engine	Querying of patients' health-relevant features stored in CSV files. This components is used by Distributed Query Processing Engine for local data retrieval
1595	Distributed Query Processing Engine - Master	Cross-centre, multi-dataset query and algorithm results aggregation. Provides a set of statistical inference algorithms as well as an unsupervised clustering algorithm (k-means)
1596	Distributed Query Processing Engine – Worker/Bridge	Retrieving the data using local instance of Query Engine, locally aggregating the results of the queries and user defined functions and forwarding the results to the Distributed Query Processing Engine Master for cross-centre result aggregation
633	Portal DB (Articles, Experiments, Models)	Web-based MIP front-end for data exploration, model building, experiment execution and creation and saving of scientific articles. User friendly selection of datasets and visualisation of their profiles, selection of variables (patient health-related features), selection of statistical or machine learning data analytic methods and visualisation of the results of selected statistical and predictive algorithms. Provides a web application for writing and saving draft scientific articles including the results of data analytics. Provides feature for sharing data models, learned statistics and learned predictive disease models and articles with the other registered users of the platform

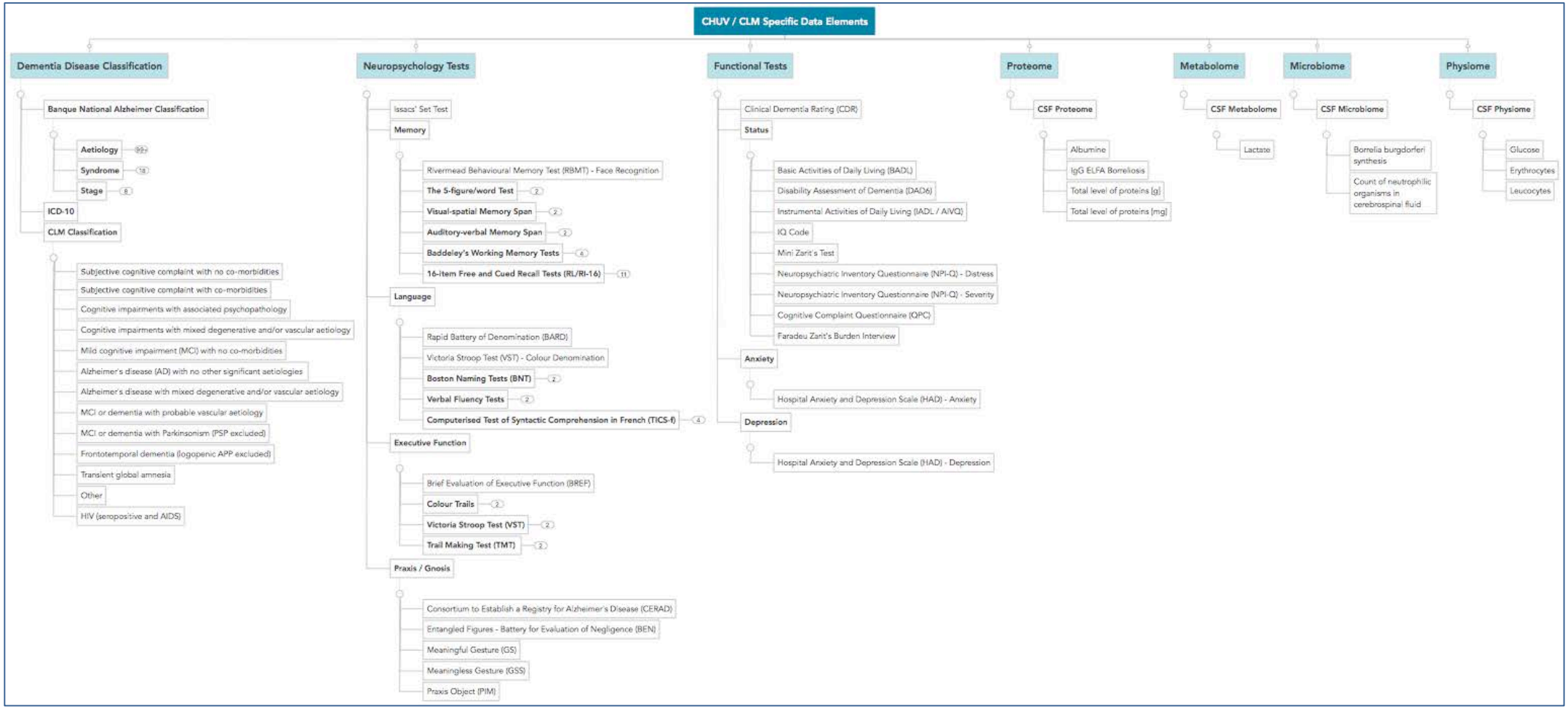

Figure 8 – CLM / CHUV Lausanne Specific Data Element Taxonomy

2.3 Patient data processing

Clinical studies that use a combination of patient datasets from their electronic health records, brain scans and open research cohort databases are challenging because data from different sources have different structures and use different coding systems.

Medical Informatics Platform performs harmonisation of data structures from different sources, permanently stores the data in a harmonised data structure and makes the data available to clinicians and researchers for further multi-centre, multi-dataset analysis. This process is becoming more and more significant since the need for multi-centre studies is rapidly growing and the volume of the available open research cohort data have a tendency to explode.

MIP Data Governance and Data Selection (DGDS) committee selects brain-relevant data elements (cognitive, neuromorphometric, biological, genetic, molecular and demographic) out of patients' EHRs from participating hospitals and open research cohort datasets, analyses metadata, and publishes data mapping rules in Data Mapping and Transformation Specification document.

The process for harmonisation of biomedical data for multi-centre clinical and research studies is performed by the components of the Data Factory sub-system. The components of this sub-system perform batch pre-processing of neuroimaging and I data, extraction of patients' biomedical features from different data sources, maps the extracted features to a harmonised data structure, and permanently stores harmonised features in the Feature Data Store sub-system.

The two sub-system's components are running in participating hospitals' execution environments. The harmonised feature data stored across participating hospitals are made available to Knowledge Extraction sub-systems statistical methods and machine learning algorithm for multi-centre, multi-dataset clinical and research studies.

The processes of the Data Factory sub-system are orchestrated as directed acyclic graphs of tasks in programmatically configurable pipelines using an open-source Apache Airflow workflow management platform. Alongside these processes, a set of supporting components are tracking and storing the data provenance and data quality metrics.

Personal identifiable information in patient datasets from participating hospitals have to be pseudonymised before the datasets are made available to the Medical Informatics Platform for further processing. Pseudonymisation process and its reversibility are out of the scope of the MIP.

Once pseudonymised, datasets extracted from different data sources – EHRs, PACS and open research cohort databases – are stored in a version controlled file system from which they are taken by the MIP data factory sub-system for cleaning and quality checking, extraction of patients' biomedical features, processing and conversion to a common harmonised biomedical features format.

2.3.1 Achieved Impact

- Number of brain scans successfully processed (CLM, Lille, Brescia)
  - Number of people with neurodegenerative diseases (per hospital and general)
  - Number of healthy controls (per hospital and general)
- Number of patient records processed (CLM, Lille, Brescia)
- Impact to clinical utility of the platform

2.3.2 Component / Technology Dependencies

Table 7 – Key technologies / components for patient data processing

Component ID	Component Name	Comment
671	Neuromorphometric Processing	Provides estimates of brain region volumes, CSF volumes and total intracranial volume
664	Airflow DAGs	Provides support for controlled and managed data processing. Orchestrates execution of data processing pipelines – neuromorphometric and patient's data processing, including quality control and data provenance storage mechanisms
2927	Data Catalogue	In conjunction with data processing pipeline workflow orchestration, provides support for controlled and managed data processing. Provides a permanent storage for the provenance of the processed data and corresponding data quality information throughout data processing stages
2926	Data Capture Database	Provides an intermediate storage of processed brain scan data and raw patient data. Staging data structure designed after the I2B2 star schema. Also allows direct import of the patient data from clinical research databases, based on I2B2
669	Common Data Elements Database	Normalised data ready for analysis. Developed using PostgreSQL, schema adapted to tensor-representation of the data. Despite the name, contains not only common data elements, but also hospital specific data elements.
1580	Online Data Integration Module	Visual data exchange tool MIPMap for manual user-friendly mapping of hospital variables to harmonised MIP variables, according to the Data Mapping and Transformation Specification

2.4 Data analytics using integrated statistical methods and machine learning algorithms

The Medical Informatics Platform is a data analytics solution that adds value to patient data by analysing data inter-connectedness across data collections. It provides powerful statistical and machine learning tools to clinicians and researchers for descriptive and predictive data analytics.

The Medical Informatics Platform uses advanced data analytics for:

- Computational neuro-anatomical data extraction using MATLAB-based SPM12 software for voxel-based statistical parametric mapping of brain image data sequences
- Distributed descriptive and predictive data analytics for discovery of biological signature of diseases using harmonised patients' biomedical feature data stored in participating hospitals

The advanced MIP data analytics provides results with measurable reliability and accuracy. Disease models are validated against the test datasets for estimating predictive model errors. The models and their estimated predictive errors are permanently stored in the Predictive Disease Model Repository.

The MIP Knowledge Extraction sub-system provides data analytics functions in both private hospital execution environments where the patient data is permanently stored, and community execution environment where the orchestration of the execution of statistical inference and machine learning algorithms performed.

The components of the Knowledge Extraction sub-system are deployed both within the private MIP execution environments in participating hospitals for local data analytics and within the community MIP execution environment for orchestration of the distributed data analytics and

aggregation of the results. The processing of patient's biomedical feature data stored in participating hospitals' Feature Data Store sub-systems is performed in the hospitals' execution environments. The remote MIP community execution environment then orchestrates the execution of and aggregates the results of locally run data analytics.

The two major complementary components of Knowledge Extraction sub-system are:

- Algorithm Factory for distributed machine learning algorithm execution, including model validation and benchmarking. It does not have out-of-the-box support for database query processing.
- Distributed Query Processing Engine for execution of distributed database queries extended with user-defined functions that can be used to implement statistical inference and machine learning models. It does not have out-of-the-box support for machine learning model validation and benchmarking.

Table 8 – List of supported machine learning algorithms

Name	Methods	Federation/Local	PFA cross-validation
java-jsi-clus-fire	Clustering methods	Local	no
java-jsi-clus-fr	Clustering methods	Local	no
java-jsi-clus-pct-ts	Clustering methods	Local	no
java-jsi-clus-pct	Clustering methods	Local	yes
java-jsi-streams-modeltree	Tree-based methods	local	yes
java-jsi-streams-regressiontree	Tree-based methods	Local	yes
java-rapidminer-knn	Classification	Local	yes
java-rapidminer-naivebayes	Classification	Local	
python-anova	Classical inference	Local and Federation	yes
python-correlation-heatmap	Classical inference	Local and Federation	no
python-distributed-kmeans	Clustering	Local and Federation	yes
python-histograms	Descriptive	Local and Federation	no
python-jsi-hedwig	Tree-based	Local	no
python-jsi-hinmine	Tree-based	Local	no
python-knn	Classification	Local	yes
python-linear-regression	Predictive linear regression	Local and Federation	yes
python-longitudinal	Longitudinal analyses	Local	yes
python-sgd-regression	Gradient descent	Local and Federation	yes
python-summary-statistics	Descriptive	Local and Federation	no
python-tsne	descriptive	Local	yes
r-3c	classification	Local	no
r-ggparci	Exploration	Local	no
r-heatmaply	Correlation	Local	no
r-linear-regression	Bayesian regression	Local and Federation	yes
Exareme k-means	Clustering	Federation	no
Exareme regression	Regression	Federation	no

Figure 9 provides an overview of the frequency of the MIP algorithm use during the SGA1 project period, including the users who have been validating the system at the end of the project period.

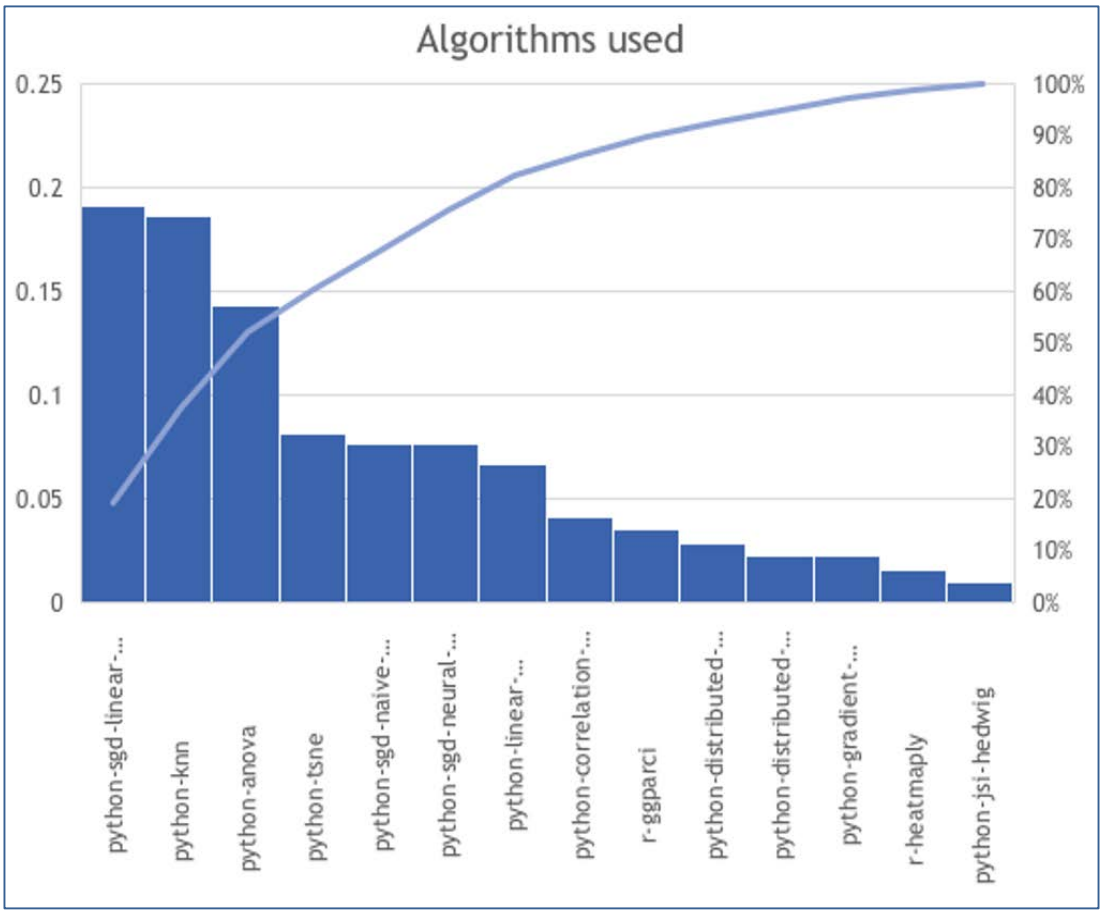

Figure 9 – HBP MIP Algorithm Usage

2.4.1 Component Dependencies

Table 9 – Key technologies / components for data analytics

Component ID	Component Name	HBP Internal	Comment
2938	Algorithm Orchestrator	No	Managing of local or distributed execution of statistical inference and machine learning algorithms, controls machine learning model validation process as well as storing/retrieving of the predictive models and the results of their benchmarking from the Predictive Disease Models database. This component is a key technology for execution of data analytics methods and measurement of the accuracy of the resulting models
647	Algorithm Repository	No	Management and inventory of the algorithm integration process. Algorithms are integrated as containerised microservices, using the TRL9 Docker technology
645	Model Benchmark and Validation	No	Execution of machine learning model benchmarking and validation process and storing the results in the Predictive Disease Models database. This component is a key for developing predictive models with measurable accuracy
646	Predictive Disease Models	No	Storing and retrieving of the learned predictive disease models, their validation results and the results of the statistical inference methods

2.5 Clinical utility of the MIP for disease simulation and *in silico* research

Alzheimer's disease and related neurodegenerative syndromes, defined by DSM-5 as neurocognitive disorders, are chosen for the evaluation of the platform's functionality and the assessment of its value for clinicians, researchers and epidemiologists.

The following characteristics make the neurodegenerative diseases scientifically significant and suitable candidates for demonstrating the value of a data analytics platform for multi-centre multi-dataset studies:

1) **A wide range of symptoms and clinical differences**

   Neurodegenerative diseases are varying, with symptoms ranging from progressive dysfunction of motor control to mood disorders and cognitive deficits, eventually expressed as full-blown dementia. With time, disabilities impair normal, autonomous life, and ultimately these patients will require total assistance.[3]

   Known aetiological differences and clinical presentations are equally as diverse as the symptoms of these disorders. This was recognised in 2016 by the French *Banque Nationale de données Alzheimer* (BNA), when it standardised aetiological diagnosis of dementia diseases in 43 different categories, classified in 9 different groups: Alzheimer's disease, other neurodegenerative disorders, vascular disorders, other diseases, encephalopathies, other organic disorders, psychiatric disorders, mental disorders and unknown diagnostics.

2) **Some fundamental biological commonalities**

   Despite the evident clinical differences among them, neurodegenerative diseases have some underlying commonalities. Pathology studies have revealed that the brains of patients with dementia syndrome have some abnormal nerve cells containing aggregates of damaged proteins. Also, vascular and inflammatory processes are known to contribute to the progression of many neurodegenerative diseases.

3) **No cure available, only palliative care**

   Effective treatments for relieving dementia syndrome symptoms and curing related neurodegenerative diseases are not available. While the scientific advances in Alzheimer's disease are expanding continuously, an ever-growing gap is developing between primary evidence, i.e. clinical data and the biology- or imaging-based research findings.

   Medical care and social assistance for patients and their families are essential. Moreover, education, diet, physical exercise, cognitive stimulation, and treatment of diabetes, hypertension, obesity, might improve cognitive status. These effects, however, are small and have to be confirmed.[4]

4) **High and ever-increasing demographic and socio-economic impact**

   According to the WHO report in December 2017[1], neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and other strongly age-related disorders, affect 47 million people worldwide. World population growth has been accompanied by a progressive increase in the number of older people. Life expectancy is already well above 80 years in developed countries and it is expected that the affected population will double over the next 30 years.

   In older people, the principal causes of death are still cardiovascular diseases and cancer. Neurodegenerative disorders, known to be strongly age-related, are among the top ten illnesses with no cure and no significant and sustainable relief of the disabling symptoms.

   The increase in the frequency of disabling, currently incurable neurodegenerative disorders is likely to have a devastating impact on individuals, families and societies, unless effective means to reduce the incidence and progression of these diseases are discovered. A delay in the onset of dementia by just five years would reduce the burden of Alzheimer's disease by

50%. Such a limited delay would be beneficial, yielding improved autonomy of the patient and relief to the commitment of the family and the public health spending.[3]

The primary scientific objective is to understand the causes, mechanisms and progression of these disabling diseases. The MIP aims to bridge the gap between fundamental research and real-world clinical data by integrating and statistically comparing clinical datasets with reference research cohort databases (i.e., "gold research standards"). The Platform serves the clinical and fundamental research communities worldwide as a globally accessible distributed information system for dementia, supporting studies by providing advanced federated analytics of diverse clinical and research datasets. As such, the MIP should be seen as the implementation of target action areas 6 and 7 of the WHO's Global Action Plan on the Public Health Response to Dementia 2017 – 2025. (Figure 11)

The MIP's Alzheimer's disease study scenarios compare real-world based evidence with "gold standard" research datasets to statistically define expected discrepancies and identify the sources of variance that may not be captured by the proposed models. The promise of the *in silico* research approach is a discovery of complex interactions between the diverse neuropathologies, contributions of biological, genetic and environmental factors, and a potential for learning about causal biomedical and environmental mechanisms. Failure to address the key elements of complex phenomena such as neurodegenerative diseases, likely results in costly and unsuccessful pharmaceutical and fundamental research. In most of the clinical trials, a simplified model (the "amyloid cascade") has been used. However, for a number of the participants in these studies, cognitive disorders are usually severe with widespread lesions, or neuropathologies cannot be explained merely by the accumulation of Beta-amyloid peptides in the brain tissue.

Currently, Alzheimer's disease (AD) clinical diagnostic criteria rely on symptoms that do not precisely reveal the underlying AD biological processes. These criteria cannot identify preclinical cases and objectively quantify the disease severity. A recent paper (Frisoni *et al.*)[5] concluded that "the provision of high-quality care to patients is negatively affected because the informative value of biomarkers cannot be used with full reliability in clinical practice". The group proposed a new strategic five-phase roadmap to foster the clinical validation of biomarkers in Alzheimer's disease. The five phases include:

- Providing sufficient evidence of analytical validity (phase 1)
- Evidence of clinical validity (phases 2 and 3), and
- Evidence of clinical utility (phases 4 and 5)

The implementation of this strategy requires standardisation of the methods used to extract biomarkers and the use of algorithms to combine multiple biomarkers. The essential MIP application is the use of routinely collected data at the hospitals for:

- Computing, testing and validating the research-originated biomarkers (MRI-derived, bio-specimens, etc.) against the clinical data.
- Improving the classification of different dementia subtypes using different patterns of cortical atrophy associated with cognitive decline.
- Refining the classification of varying dementia subtype using neuropathological examination.

Clinical study scenarios[7] proposed for the MIP system validation (Chapter 31 implement the five-phase strategy and the methodology proposed by Frisoni *et al*.

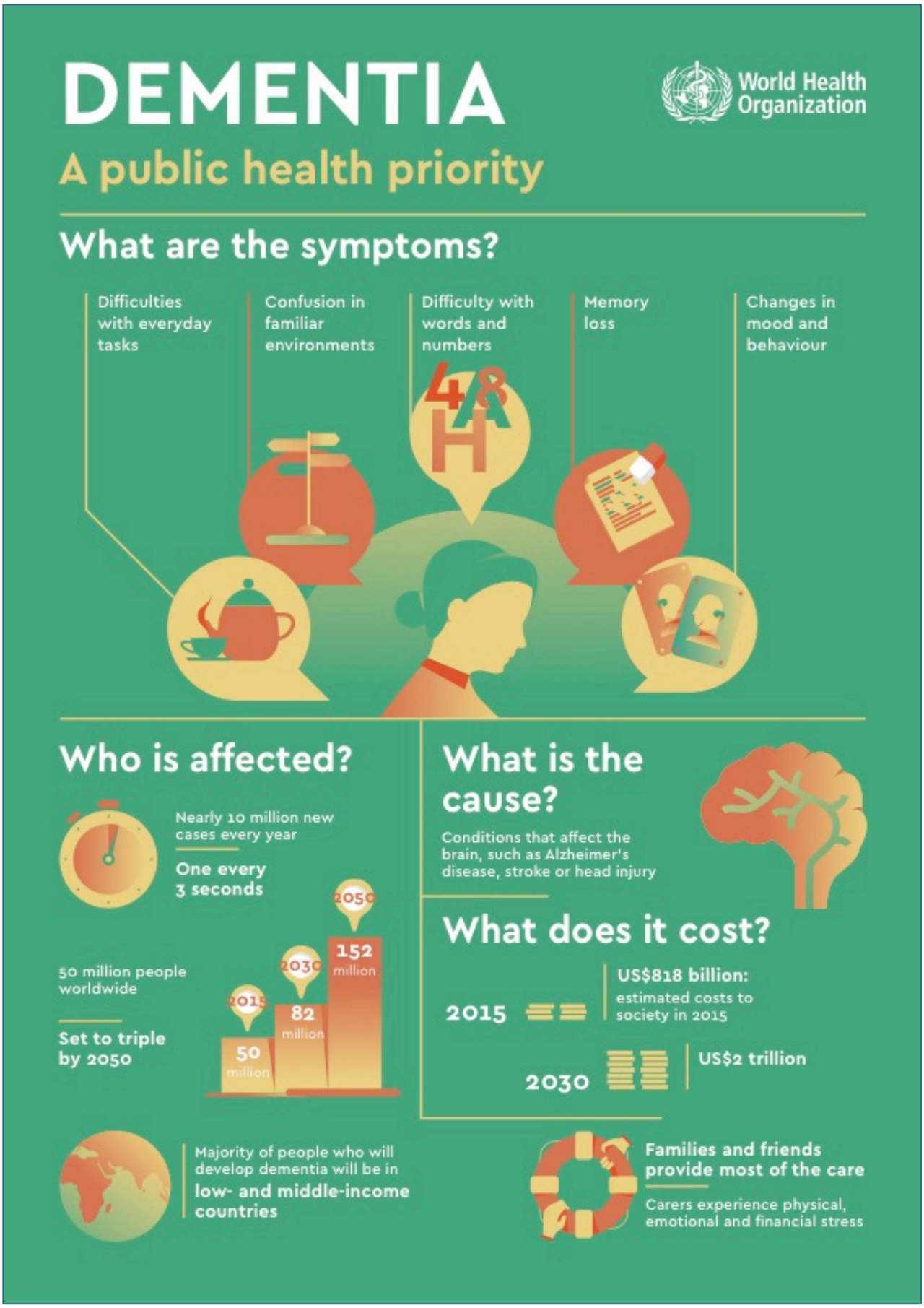

Figure 10 – World Health Organisation Dementia Infographics

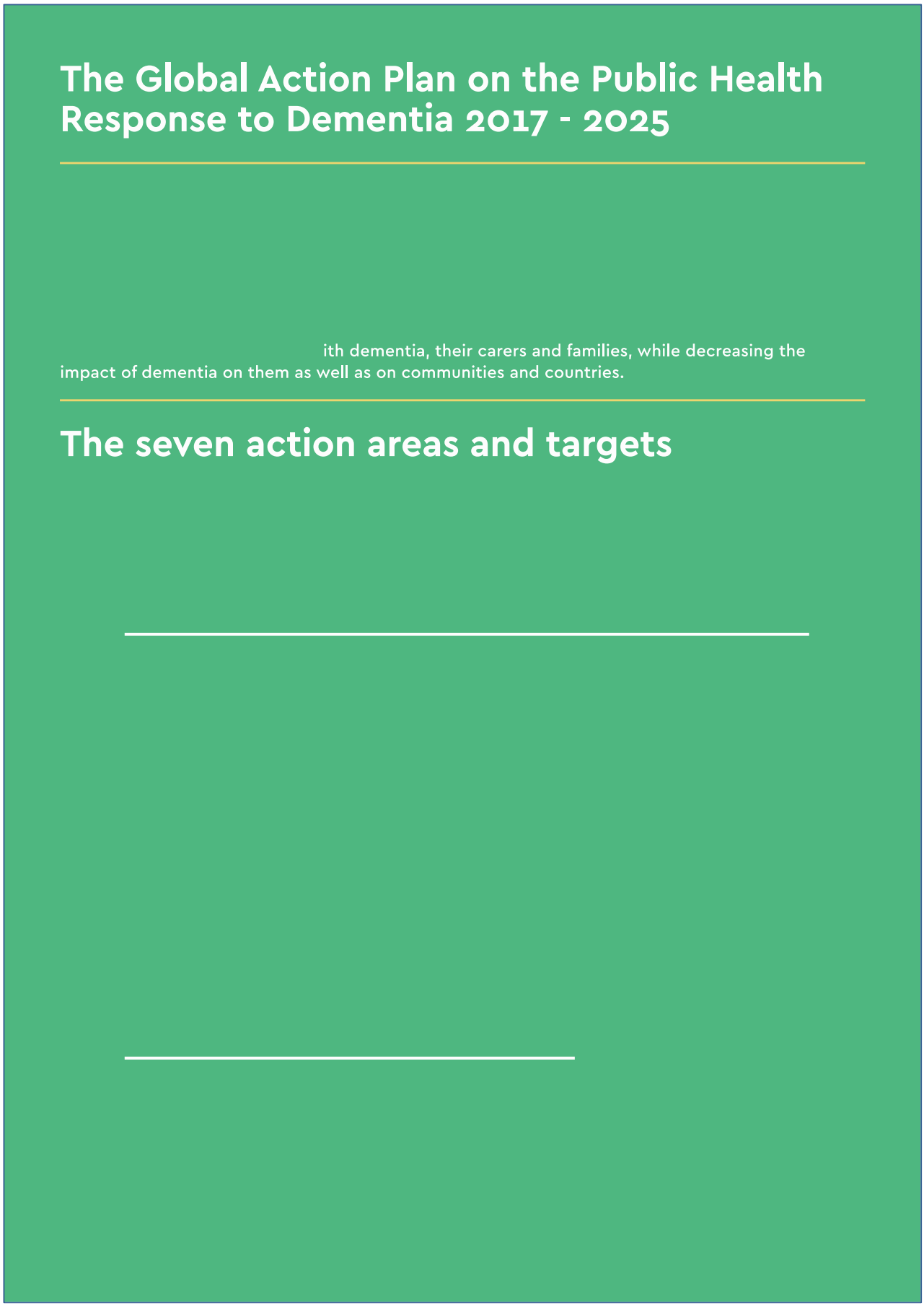

Figure 11 - Global Action Plan on the Public Health Response to Dementia

Table 10 – Measuring analytical and clinical validity and clinical utility of the MIP

MIP Diagnostic Measure	Measured Object	Description of the MIP Diagnostic Measure	Method of Measure
Analytical Validity	Data Quality	Measurement of the data quality – accuracy and reliability. Accuracy is the probability that the values of the patient's features in a dataset chosen for the study will be in the same expected range with the values of those features in the "gold standard" – control research cohort datasets. Reliability is the probability of repeatedly getting the same result of the data analysis when using MIP's integrated statistical methods and machine learning algorithms Analytical validity assessment is a prerequisite for accurate and reliable measurement of the feature's clinical validity. To measure feature's clinical validity, the data stored in MIP must be accurate and reliable Reliability of the predictive (machine-learning) models is measured using model validation methods integrated into the Medical Informatics Platform	Analytical validity of data – ANOVA, linear regression, logistic regression, visual methods: histogram, density plot, scatter plot, box plot Analytical validity of predictive models – cross-validation
Clinical Validity	Clinical Feature	Measurement of the feature's clinical performance: (1) clinical sensitivity (ability to identify those who have or will get the disease), (2) clinical specificity (ability to identify those who do not have or will not get the disease), (3) positive predictive value (PPV) – the probability that a person with a positive test result for a predictor, has or will get the disease, and negative predictive value (NPV) – the probability that a person with a negative test result for a predictor does not have or will not get the disease MIP can be used to measure clinical validity of the features (biomarkers and other relevant data), or to measure clinical validity of the descriptive and predictive mathematical models by executing integrated model validation methods. Clinical validity of the models with different set of features can be compared using ROC curves, C-statistics, etc. The more data available in the MIP – the number of patients and the diversity of their conditions and profiles, the more accurate and reliable the measurement of clinical validity	Clinical validity of features – ANOVA, linear regression, logistic regression; Visualisation – heatmap
Clinical Utility	Result of Analytics	Evaluation of the clinical utility of the results of the data analytics using the Medical Informatics Platform – diagnostic relevance: do the results of the predictive analytics confirm or change a diagnosis in a new group of patients, do they determine the aetiology for a condition or clarify the prognosis; disease outcomes: do the results of the predictive analytics lead to the improvement of health outcomes (e.g., reduce mortality or morbidity – prescriptive implication of machine learning models) or other outcomes that are important to patients, such as quality of life; familial and societal impacts: do the results of the predictive analytics	Machine learning models (supervised and unsupervised): univariate and multivariate linear and polynomial regression using gradient decent, KNN, Naïve Bayes; K-means; SVM

MIP Diagnostic Measure	Measured Object	Description of the MIP Diagnostic Measure	Method of Measure
		identify at risk family members, high-risk race/ethnicities, and the impact on health systems and/or population The important part of the assessment of the clinical utility of the results of predictive analytics is the evaluation of the accuracy of the hypothesis function. The method used in this release of MIP is cross-validation. The measured accuracy of the learned model shall determine the level of clinical utility of the model with the real patient population.	Validation of machine learning models using cross-validation integrated into the MIP

3. System Validation Results

The Medical Informatics Platform system validation project phase has been executed by clinical researchers in the following participating centres:

- Research and Healthcare Institute in Brescia, Italy
  (IRCCS Centro San Giovanni di Dio – Fatebenefratelli)
- Regional University Hospital Centre in Lille, France
  Centre Hospitalier Régional Universitaire de Lille
- University Hospital Centre in Lausanne, Switzerland
  Centre Hospitalier Universitaire Vaudois

Table 13 provides the summary of the MIP system validation in the three participating hospitals. Green indicates that the planned test scenarios were executed in all three hospitals. Orange indicated test passed in two out of three hospitals. Red indicates "no run".

Table 12 provides an overview of the tested use cases and front-end software components.

In summary, all the local and federated tests were passed/accepted in Brescia and Lausanne, while only local tests could not be executed in CHRU Lille. Indeed, at the time of system validation, we could not obtain from Lille's hospital the required authorizations to connect that hospital to the federation MIP platform installed in the community execution environment. As a result, Federated tests could not be run in Lille. In addition, Lille, which was expected to provide post-mortem data for testing the clinical system validation scenario 4, was unable to provide these data in an appropriate format, resulting in the impossibility to test that scenario in both the local and federated modes.

Most importantly, these two issues, relating to local administrative authorisation and data handling procedures, are completely independent from the MIP functionalities. In fact, all MIP local and federated functionalities could be appropriately tested, despite the above limitations (i.e. federated analyses could be run between Brescia and Lausanne, while scenarios 1 to 3 were to tests all other MIP features, appropriately).

Table 11 – Summary of the System Validation Scenario Execution

ID	Acceptance Criterion Description	Clinical Scenarios				Mode	
		CS1	CS2	CS3	CS4	Federated	Local
DATA PREPARATION							
A01	Variables are selected.	3 (3)	3 (3)	3 (3)	0 (1)	2 (3)	3 (3)
A01	Population of interest - within one hospitals and across- defined and described.	3 (3)	3 (3)	3 (3)	0 (1)	2 (3)	3 (3)
A01	Model of interest defined and built.	3 (3)	3 (3)	3 (3)	0 (1)	2 (3)	3 (3)
ANALYTICAL VALIDITY AND DATA QUALITY							
A02	Compare the variables from the clinic to the variable from the research data (e.g. ADNI).	3 (3)	3 (3)	3 (3)	0 (1)	2 (3)	3 (3)
A03	Compare the variables from the clinic to the variable from the research data and interaction between sites and disease diagnostics	3 (3)	3 (3)	3 (3)	0 (1)	2 (3)	3 (3)
CLINICAL VALIDITY							
A04	Test significance of the association between variable of interest and disease diagnostics	3 (3)	3 (3)	3 (3)	0 (1)	2 (3)	3 (3)

ID	Acceptance Criterion Description	Clinical Scenarios				Mode	
		CS1	CS2	CS3	CS4	Federated	Local
CLINICAL UTILITY							
A05	Train, test and validate predictive models against the selected cohort data.	2 (3)	2 (3)	2 (3)	0 (1)	2 (3)	2 (3)
A05	Compare the predicted label to the current diagnostic label	2 (3)	2 (3)	2 (3)	0 (1)	2 (3)	2 (3)
MODEL VALIDATION ACROSS HOSPITALS							
A06	Apply the selected model to the data of the other hospitals.	2 (3)	2 (3)	2 (3)	0 (3)	2 (3)	2 (3)
PUBLISH RESULTS							
A07	Save the results and output of the model (graph, table).	3 (3)	3 (3)	3 (3)	0 (1)	2 (3)	3 (3)
A07	Model is available for use by other users.	3 (3)	3 (3)	3 (3)	0 (1)	2 (3)	3 (3)

Note: The number in bold indicated the number of hospitals where the tests were passed and accepted. The number in parenthesis indicates the expected number.

Table 12 – Use Cases and Components Tested

ID	Functionality validated	Components validated	Validated	Location			
				Federation	CLM	Lille	FBF
A01	Data Preparation: • get the summary statics on all the variable of interest (number of patients/ mean and variance) • get information about the acquisition protocol and pre-processing methods • filter to select the patients by setting inclusion and exclusion criteria	UC_WEB_01 UC_WEB_02 MIP-EE web App	Yes				
A02	Analytical Validity and data quality Test if the variables are accurate and sensitive enough with a valid range by comparing the grey-matter volume atrophy from clinical scan to those from research scan.	UC_WEB_04 UC_WEB_05 MIP-EE web App	Yes				
A03	Analytical Validity and data quality Test if variables are reproducible in different setting (different scanners, different environment, or cohorts	UC_DTM_01 UC_DTM_02 MIP-interactive web-app	Yes				
A04	Clinical Validity: Test if the variables are associated with the disease	UC_DTM_01 UC_DTM_02	Yes				

ID	Functionality validated	Components validated	Validated	Location			
				Federation	CLM	Lille	FBF
	diagnostic (e.g. AD vs cognitively normal or with mild cognitive impairments) or disease outcome?	MIP-BSD webapp univariate linear regression and/or multivariate inference methods (e.g. Anova, MLM)					
A05	Clinical Utility: Test the predictive value and Performance of the test sensitivity (positive and negative predictive values)	UC_DTM_03 UC_DTM_04 UC_ACC_01 to UC_ACC_08 MIP-BSD webapp predictive models and machine learning tools (e.g. naïve Bayes, knn, rule based, tree classification)	Yes				
A06	Model validation across hospitals: Apply the selected model to the data of the other hospitals.	UC_DTM_03 UC_DTM_04 Use the MIP-BSD webapps to create a new model including the education variables. Use the MIP-BSD webapps to model comparisons Use the MIP-IA for further exploration					
A07	Publish results	UC_WEB_06 MIP-writing article webapp					

The following sub-chapters provide a detailed view of the user feedback during and after the execution of clinical system validation scenarios. The figures referenced in the tables are provided in the Appendix II of this document.

Video recordings of the execution of clinical validation scenarios are accessible on YouTube:

- IRCCS Brescia – https://youtu.be/whq9RM_fRLo
- CHRU Lille – https://youtu.be/UtbtWH4mp3o and https://youtu.be/XurBr2UBaLk
- CHUV – https://youtu.be/8bVN95SonmI

3.1 Research and Healthcare Institute - Brescia, Italy

Table 13 – Participants in the MIP System Validation from IRCCS Brescia

Project Identification			
Project name		Hospital	Version date
Medical Informatics Platform System Validation		IRCCS FBF Brescia	
Representatives			
Site	Role	Name	Email
HBP-MIP	Project Leader	Philippe Ryvlin	philippe.ryvlin@chuv.ch
	Deployment Manager	Jacek Manthey	jacek.manthey@chuv.ch
IRCCS - FBF Brescia Italy		Alberto Redolfi	aredolfi@fatebenefratelli.eu
	Researcher – Data-Driven Predictive Models Research experience 0.5 years Used the platform before: 5 times	Damiano Archetti	archetti.dam@gmail.com
	Research Fellow Clinical research experience: 14 years Used the platform before: Once	Michela Pievani	maxime.bertoux@chru-lille.fr

Table 14 – IRCCS Brescia Clinical Validation Scenario 1 – Acceptance Criteria Test Matrix

SYSTEM VALIDTION TEST CASE: CLINICAL UTILITY OF THE VOLUME OF MEDIAL TEMPORAL LOBE SUBREGIONS FOR AD DIAGNOSTIC							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
Data Preparation							
A01	Variables (hippocampal volume, diagnostic) are selected.	Figure 1	☒	☐	☒	☐	
A01	Population of interest - within one hospitals and across defined and described.	Figure 2	☒	☐	☒	☐	
A01	Model of interest defined and built.	Figure 3	☒	☐	☒	☐	Sometimes the upload of the dataset is slow. I needed to refresh the browser several times to fix this. Filters: The colours of the AND/OR labels are too similar, it is difficult to understand which one is active.
Analytical Validity and Data Quality							
A02	Compare the variables from the clinic to the variable from the research data (e.g. ADNI).	Figure 4	☒	☐	☒	☐	It would be useful to see the % for category data (e.g., gender, diagnosis).

SYSTEM VALIDTION TEST CASE: CLINICAL UTILITY OF THE VOLUME OF MEDIAL TEMPORAL LOBE SUBREGIONS FOR AD DIAGNOSTIC							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
							For MRI data, it would be useful to see the unit of measure (mm3, cm3, etc…). The SD should be placed near to the mean rather than after the range.
A03	compare the variables from the clinic to the variable from the research data and interaction between sites and disease diagnostics	Figure 5	☒	☐	☒	☐	
Clinical Validity							
A04	test significance of the association between variable of interest and disease diagnostics	Figure 6	☒	☐	☒	☐	
Clinical Utility							
A05	Train, test and validate predictive models against the selected cohort data.	Figure 7	☒	☐	☒	☐	
A05	Compare the predicted label to the current diagnostic label	Figure 8	☒	☐	☒	☐	
Model Validation Across Hospitals							
A06	Apply the selected model to the data of the other hospitals.	Figure 9	☒	☐	☒	☐	
Publish Results							
A07	Save the results and output of the model (graph, table).	Figure 9	☒	☐	☒	☐	
A07	Model is available for use by other users.	Figure 10	☒	☐	☒	☐	

Table 15 - IRCCS Brescia Clinical Validation Scenario 2 – Acceptance Criteria Test Matrix

SYSTEM VALIDATION TEST CASE: CLINICAL UTILITY OF CSF MARKERS FOR ALZHEIMER'S DISEASE: TOTAL AND PHOSPHORYLATED TAU, ABETA42							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
Data Preparation							
A01	Variables cerebrospinal fluid markers and diagnostic are selected.	Figure 1	☒	☐	☒	☐	Some outliers were detected on data inspection. If possible, outliers should be removed from the outset, otherwise they need to be removed later on using filters.

SYSTEM VALIDATION TEST CASE: CLINICAL UTILITY OF CSF MARKERS FOR ALZHEIMER'S DISEASE: TOTAL AND PHOSPHORYLATED TAU, ABETA42							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
A01	Population of interest (within one hospitals and across) defined and described.	Figure 2	☒	☐	☒	☐	Not clear whether CSF data can be directly compared - each hospital collects CSF with its own method, and the levels/range vary accordingly. E.g., CSF Abeta cut-off in Brescia is 600 ng/l, in ADNI 192 ng/l. It may be useful to add some details on the reference values for each dataset.
A01	Model of interest defined and built.	Figure 3	☒	☐	☒	☐	It would be useful to report the unit of measure for CSF levels
Analytical validity and data quality							
A02	Compare the variables against reference value	Figure 4	☒	☐	☒	☐	Reference values not found.
A03	Compare the variables against reference values assess interaction between disease diagnostics	Figure 5	☒	☐	☒	☐	
Clinical Validity							
A04	Test significance of the association between variable of interest and disease diagnostics	Figure 6	☒	☐	☒	☐	
Clinical Utility							
A05	Train, test and validate predictive models against the selected cohort data.	Figure 7	☒	☐	☒	☐	
A05	Compare the predicted label to the current diagnostic label	Figure 8	☒	☐	☒	☐	
A06	Compare CSF Model to MTL model	Figure 9	☒	☐	☒	☐	
Model Validation Across Hospitals							
A06	Apply the selected model to the data of the other hospitals.	Figure 9	☒	☐	☒	☐	
Publish Results							
A07	Save the results and output of the model (graph, table).	Figure 9	☒	☐	☒	☐	
A07	Model is available for use by other users.	Figure 10	☒	☐	☒	☐	

Table 16 – IRCCS Brescia Clinical Validation Scenario 3 – Acceptance Criteria Test Matrix

SYSTEM VALIDATION TEST CASE: DIFFERENTIAL DIAGNOSTIC BETWEEN FRONTO-TEMPORAL DEMENTIA AND ALZHEIMER'S DISEASE							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
Data Preparation							
A01	Variables all brain features and diagnostic are selected.	Figure 1	☒	☐	☒	☐	
A01	Population of interest (within one hospitals and across) defined and described.	Figure 2	☒	☐	☒	☐	
A01	Model of interest defined and built.	Figure 3	☒	☐	☒	☐	
Clinical utility							
A05	Train, test and validate predictive models against the selected cohort data.	Figure 4	☒	☐	☒	☐	There was an error in the output (a p value of 0.06 starred as significant).
Model Validation Across Hospitals							
A06	Apply the selected model to the data of the other hospitals.	Figure 9	☒	☐	☒	☐	
Publish Results							
A07	Save the results and output of the model (graph, table).	Figure 9	☒	☐	☒	☐	
A07	Model is available for use by other users.	Figure 10	☒	☐	☒	☐	

Table 17 – IRCCS Brescia Clinical Benefits – Acceptance Criteria Test Matrix

Did the systems meet the clinical objectives?				
Id	Description	Yes	No	
Primary Benefits				
1	Clinicians can explore own variable dataset in a well-structured interface (MIP EE) and can run data-mining algorithms on their own datasets	☒	☐	
2	Clinicians can compare specific patients and their measured variables against the whole cohort of the node, observe disease severity and therefore help them in their decision-making processes.	☐	☒	In the current form, the system is well-suited to carry out analyses at the group level, however less so for individual analysis or decision making. To do this, one would need to upload single-subject data on the system (I do not know if this is currently possible) and then compare this subject with a reference cohort (e.g., local dataset). The most intuitive way of doing this is to plot the position of the subject with respect to the reference population (e.g., below 5th percentile, below established cut-off).
3	Clinicians can visualize and interpret the quantitative measurements of the MRIs (outputted by the Data Factory) and further link	☒	☐	To fully interpret the data, however, more details are needed about each variable (e.g.,

	these measures to diagnostic, behaviour and clinical measurements.			reference values for that variable, unit of measurement, correction for TIV in case of MRI measures).
4	As data will be extracted with benchmarked industry tools and standards (within the Data Factory), the results are ready to be published in journals.	☐	☐	This depends on the type of tools (e.g., for structural MRI, fMRI, DTI, etc…) and their accuracy. In terms of publications, currently the system seems advantageous for the investigation of relatively simple research questions and the exploitation of huge dataset using out-of-the-box toolboxes. For more complex research questions, requiring higher precision or the combination of multiple modalities, researchers may still wish to use their own pipelines or sophisticated tools.
Secondary Benefits				
5	Models, articles and data mining experiments may be shared within the users of the node.	☒	☐	
6	The hospitals can explore the MIP software, its functionality, its potential and its technology before deciding to upgrade to the MIP Federation.	☒	☐	

Table 18 – IRCCS Brescia System Validation Survey

Possible Responses : Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
Login to the Medical Informatics Platform			
1	I experienced no issues with accessing the platform	Agree	In a previous occasion, I had some problems in accessing the platform when using an older Mac
2	Graphical user interface upon logging in is easy-to-understand to start using the platform	Strongly Agree	
Data inspection and selection			
3	The functions available for inspecting the data are appropriate, given the constraints imposed by the data privacy by design (no inspection of individual data is allowed).	Strongly Agree	
4	Graphical user interface is easy-to-use for inspecting the available data	Strongly Agree	
5	Graphical user interface is time-efficient for inspecting the available data	Neutral	Sometimes the system takes a long time to upload and visualize the data
6	The functions available for selecting the data are appropriate	Agree	
7	Graphical user interface is easy-to-use for selecting the data of interest	Strongly Agree	
8	Graphical user interface is time-efficient for selecting the data of interest	Neutral	See previous comment
Data analytics			

Possible Responses : Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
9	The analytical methods available fulfil our need to analyse the MIP datasets	Agree	
10	Graphical user interface is easy-to-use for selecting and executing the data analysis methods	Agree	
11	Graphical user interface is time-efficient for selecting and executing the data analysis methods	Agree	
12	The time required for processing data analysis is appropriate	Agree	
13	The results of the data analysis are presented in an informative and easy-to-understand manner	Neutral	Presentation of results is a bit scant, only statistics is reported. A summary of the population data together with statistics would be useful to have the entire picture handy (as done for example by other statistical packages such as SPSS or R).
14	The functions available to store, share and retrieve previously made analysis are appropriate	Strongly Agree	
General assessment			
15	I experienced issues related to the usage or performance of the system if you experienced issues, please provide a short description	Agree	Long time for data upload Sometimes the upload fails and gives an 'error' message During one test, the statistical output included an error (p values not significant was reported as significant)
UAT credibility			
16	Time spent on the UAT (in the format HH:MM)	2:00	
17	Test scenarios conducted during the UAT were representative of the data analytics experiments my institution will perform on a recurrent basis	Agree	
18	The questions raised during testing were appropriate	Agree	
19	The questions raised during testing covered all my concerns	Agree	
20	The testing was rigorously performed, allowing me to fully express my views and check for their appropriate retranscription	Strongly Agree	
Clinical research needs			
21	I understand the conceptual framework, functionalities, and research applications of the MIP local	Agree	
22	The MIP local is providing useful tools complementary to those currently available in my research environment for analysing my data	Agree	
23	I plan to execute further studies using MIP local on patient data from my hospital/institution	Neutral	Not yet decided
24	I understand the conceptual framework, functionalities, and research applications of the MIP federate	Agree	

Possible Responses : Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
25	The MIP federate is providing useful tools complementary to those currently available in my research environment for analysing my data	Agree	
26	I plan to execute further studies using MIP federate using the available open research cohort datasets	Neutral	Not yet decided
27	I plan to execute further studies using MIP federate using data from other hospitals available in the MIP community ecosystem	Neutral	Not yet decided
Final remarks			
28	Please include any other comments you wish to share with the Medical Informatics Platform project team		

3.2 Regional University Hospital Centre - Lille, France

Table 19 – Participants in the MIP System Validation from CHRU Lille

Project Identification			
Project name		Hospital	Version date
Medical Informatics Platform		CHRU Lille	
Representatives			
Site	Role	Name	Email
HBP-MIP	Project Leader	Philippe Ryvlin	philippe.ryvlin@chuv.ch
	Deployment Manager	Jacek Manthey	jacek.manthey@chuv.ch
CHRU Lille France	Professor, Head of Neurology Service Clinical research experience: years Used the platform before:	Florence Pasquier	florence.pasquier@chru-lille.fr
	Attachée de Recherche Clinique Research experience 6 years Used the platform before: over 25 times	Mélanie Leroy	melanie.leroy@chru-lille.fr
	Chargé de Recherche Inserm Clinical research experience: 13 years Used the platform before: 5 times	Maxime Bertoux	maxime.bertoux@chru-lille.fr mpievani@fatebenefratelli.eu

Table 20 – CHRU Lille Clinical Validation Scenario 1 – Acceptance Criteria Test Matrix

SYSTEM VALIDATION TEST CASE: CLINICAL UTILITY OF THE VOLUME OF MEDIAL TEMPORAL LOBE SUBREGIONS FOR AD DIAGNOSTIC							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
Data Preparation							
A01	Variables (hippocampal volume, diagnostic) are selected.	Figure 1	☐	☐	☒	☐	No computation between the variables is available (simple formula such as sum, average etc.)
A01	Population of interest - within one hospitals and across defined and described.	Figure 2	☐	☐	☒	☐	OK. “null data” for a significant number of participants.
A01	Model of interest defined and built.	Figure 3	☒	☐	☒	☐	OK
Analytical validity and data quality							
A02	Compare the variables from the clinic to the variable from the research data (e.g. ADNI).	Figure 4	☐	☐	☒	☐	Data are similar, there is a probable impact of age, which justify its addition as a covariate

SYSTEM VALIDATION TEST CASE: CLINICAL UTILITY OF THE VOLUME OF MEDIAL TEMPORAL LOBE SUBREGIONS FOR AD DIAGNOSTIC							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
A03	compare the variables from the clinic to the variable from the research data and interaction between sites and disease diagnostics	Figure 5	☐	☐	☒	☐	The group 'CN' is not representative of cognitively normal participants. TIV values are not available.
Clinical Validity							
A04	test significance of the association between variable of interest and disease diagnostics	Figure 6	☐	☐	☒	☐	OK, results were expected. Significant effect of age. No effect of category (AD vs CN).
Clinical utility							
A05	Train, test and validate predictive models against the selected cohort data.	Figure 7	☐	☐	☐	☒	K-nearest neighbour failed to provide any results.
A05	Compare the predicted label to the current diagnostic label	Figure 8	☐	☐	☐	☒	The platform was not able to provide us a result
Model Validation Across Hospitals							
A06	Apply the selected model to the data of the other hospitals.	Figure 9	☐	☐	☐	☒	The federated platform was not tested today
Publish Results							
A07	Save the results and output of the model (graph, table).	Figure 9	☐	☐	☐	☐	Not applicable
A07	Model is available for use by other users.	Figure 10	☐	☐	☐	☐	Not applicable

Table 21 - CHRU Lille Clinical Validation Scenario 2 – Acceptance Criteria Test Matrix

SYSTEM VALIDATION TEST CASE: CLINICAL UTILITY OF CSF MARKERS FOR ALZHEIMER'S DISEASE: TOTAL AND PHOSPHORYLATED TAU, ABETA42							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
Data Preparation							
A01	Variables cerebrospinal fluid markers and diagnostic are selected.	Figure 1	☐	☐	☒	☐	<Comments>
A01	Population of interest - within one hospitals and across defined and described.	Figure 2	☐	☐	☒	☐	<Comments>
A01	Model of interest defined and built.	Figure 3	☐	☐	☒	☐	Test the correlation between Ab42 and MMS values in the whole CHRU cohort that had a lumbar puncture. 2) Test the correlation between the right

SYSTEM VALIDATION TEST CASE: CLINICAL UTILITY OF CSF MARKERS FOR ALZHEIMER'S DISEASE: TOTAL AND PHOSPHORYLATED TAU, ABETA42							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
							hippocampus volume and the MMSE
Analytical validity and data quality							
A02	Compare the variables against reference value	Figure 4	☐	☐	☒	☐	Some participants have a MMSE equal to 30. We will check the diagnoses and clinical profile of these patients.
A03	compare the variables against reference values assess interaction between disease diagnostics	Figure 5	☐	☐	☒	☐	1) We cannot see the plot of the regression. Can we limit the analysis to participants for which the LP and the cognitive test has been made within x weeks ?
Clinical Validity							
A04	test significance of the association between variable of interest and disease diagnostics	Figure 6	☐	☐	☒	☐	Results were not expected for 1): Weird correlation between MMSE and Ab42; 2) Weird absence of correlation between hippocampus volume and MMSE.
Clinical utility							
A05	Train, test and validate predictive models against the selected cohort data.	Figure 7	☐	☐	☐	☒	The platform was not able to provide us a result
A05	Compare the predicted label to the current diagnostic label	Figure 8	☐	☐	☐	☒	The platform was not able to provide us a result
A06	Compare CSF Model to MTL model	Figure 9	☐	☐	☐	☒	Not done
Model Validation Across Hospitals							
A06	Apply the selected model to the data of the other hospitals.	Figure 9	☐	☐	☐	☒	The federated platform was not tested today
Publish Results							
A07	Save the results and output of the model (graph, table).	Figure 9	☐	☐	☐	☐	Not applicable
A07	Model is available for use by other users.	Figure 10	☐	☐	☐	☐	Not applicable

Table 22 – CHRU Lille Validation Scenario 3 – Acceptance Criteria Test Matrix

SYSTEM VALIDATION TEST CASE: DIFFERENTIAL DIAGNOSTIC BETWEEN FRONTO-TEMPORAL DEMENTIA AND ALZHEIMER'S DISEASE							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
Data Preparation							
A01	Variables all brain features and diagnostic are selected.	Figure 1	☒	☐	☒	☐	Test of the difference between the precuneus volume between AD and FTLD. Comparison of randomly picked prefrontal volumes between AD and FTLD.
A01	Population of interest - within one hospitals and across defined and described.	Figure 2	☒	☐	☒	☐	All centres then CHRU only.
A01	Model of interest defined and built.	Figure 3	☒	☐	☒	☐	While we obtain a significant difference, we cannot see the plot of the results, and therefore cannot infer the nature of the difference. We haven't obtained any significant differences on prefrontal volumes.
Clinical utility							
A05	Train, test and validate predictive models against the selected cohort data.	Figure 4	☐	☐	☒	☐	
Model Validation Across Hospitals							
A06	Apply the selected model to the data of the other hospitals.	Figure 9	☐	☐	☐	☐	The federated platform was not tested
Publish Results							
A07	Save the results and output of the model (graph, table).	Figure 9	☐	☐	☒	☐	
A07	Model is available for use by other users.	Figure 10	☐	☐	☒	☐	

Table 23 – CHRU Lille Clinical Benefits – Acceptance Criteria Test Matrix

Did the systems meet the clinical objectives ?				
Id	Description	Yes	No	
Primary Benefits				
1	Clinicians can explore own variable dataset in a well-structured interface (MIP EE) and can run data-mining algorithms on their own datasets	☒	☐	A guide of the algorithms would be useful.
2	Clinicians can compare specific patients and their measured variables against the whole cohort of the node, observe disease severity and therefore help them in their decision-making processes.	☐	☒	It would be useful but not created yet

Did the systems meet the clinical objectives ?				
Id	Description	Yes	No	
3	Clinicians can visualise and interpret the quantitative measurements of the MRIs (outputted by the Data Factory) and further link these measures to diagnostic, behaviour and clinical measurements.	☒	☐	Not individually
4	As data will be extracted with benchmarked industry tools and standards (within the Data Factory), the results are ready to be published in journals.	☒	☐	
Secondary Benefits				
5	Models, articles and data mining experiments may be shared within the users of the node.	☒	☐	
6	The hospitals can explore the MIP software, its functionality, its potential and its technology before deciding to upgrade to the MIP Federation.	☒	☐	

Table 24 - CHRU Lille System Validation Survey

Possible Responses : Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
Login to the Medical Informatics Platform			
1	I experienced no issues with accessing the platform	Strongly Agree	
2	Graphical user interface upon logging in is easy-to-understand to start using the platform	Strongly Agree	
Data inspection and selection			
3	The functions available for inspecting the data are appropriate, given the constraints imposed by the data privacy by design (no inspection of individual data is allowed).	Agree	
4	Graphical user interface is easy-to-use for inspecting the available data	Strongly Agree	
5	Graphical user interface is time-efficient for inspecting the available data	Agree	
6	The functions available for selecting the data are appropriate	Agree	
7	Graphical user interface is easy-to-use for selecting the data of interest	Agree	
8	Graphical user interface is time-efficient for selecting the data of interest	Agree	
Data analytics			
9	The analytical methods available fulfil our need to analyse the MIP datasets	Neutral	
10	Graphical user interface is easy-to-use for selecting and executing the data analysis methods	Agree	The only reserve is about naming the analysis twice before running it.
11	Graphical user interface is time-efficient for selecting and executing the data analysis methods	Agree	Agree
12	The time required for processing data analysis is appropriate	Neutral	It seems variable. Some are fast, some are not.

Possible Responses : Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
13	The results of the data analysis are presented in an informative and easy-to-understand manner	Disagree	Not possible to get the direction of the difference when using an ANOVA. Not clearly stated that results are (or are not) corrected for multiple comparisons
14	The functions available to store, share and retrieve previously made analysis are appropriate	Strongly Agree	
General assessment			
15	I experienced issues related to the usage or performance of the system if you experienced issues, please provide a short description	Agree	In my first session of use, the analysis did not show any results and was not finished after 5 days. In my last session, the system was unable to provide any results when running a K-nearest neighbour analysis.
UAT credibility			
16	Time spent on the UAT (in the format HH:MM)	06:00	
17	Test scenarios conducted during the UAT were representative of the data analytics experiments my institution will perform on a recurrent basis	Neutral	They are, but not entirely. My institution would like to perform other experiments that need to implement some basic tools such as TIV, averaging volumes, …
18	The questions raised during testing were appropriate	Agree	
19	The questions raised during testing covered all my concerns	Agree	But we would like to have estimated deadlines or expectations about when some of our demands will be met.
20	The testing was rigorously performed, allowing me to fully express my views and check for their appropriate retranscription	Strongly Agree	
Clinical research needs			
21	I understand the conceptual framework, functionalities, and research applications of the MIP local	Agree	But could be more specific about the public targeted, i.e. clinicians and/or researcher
22	The MIP local is providing useful tools complementary to those currently available in my research environment for analysing my data	Disagree	
23	I plan to execute further studies using MIP local on patient data from my hospital/institution	Agree	But need some tools to be implemented so that the MIP could replace standard statistics software.
24	I understand the conceptual framework, functionalities, and research applications of the MIP federate	Agree	Agree
25	The MIP federate is providing useful tools complementary to those currently available in my research environment for analysing my data	Agree	Agree
26	I plan to execute further studies using MIP federate using the available open research cohort datasets	Agree	Agree
27	I plan to execute further studies using MIP federate using data from other hospitals available in the MIP community ecosystem	Agree	Agree

Possible Responses : Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
Final remarks			
28	Please include any other comments you wish to share with the Medical Informatics Platform project team		

3.3 University Hospital Centre (CHUV) - Lausanne, Switzerland

Table 25 – Participants in the MIP System Validation from CHUV Lausanne

Project Identification			
Project name		Hospital	Version date
Medical Informatics Platform		CHUV Lausanne	
Representatives			
Site	Role	Name	Email
HBP-MIP	Project Leader	Philippe Ryvlin	philippe.ryvlin@chuv.ch
	Deployment Manager	Jacek Manthey	jacek.manthey@chuv.ch
CHUV Lausanne Switzerland	Professor, Head of Service – Leenaards Memory Centre Research experience 30 years Used the platform before: 30 times	Jean-François Demonet	jean-francois.demonet@chuv.ch
	Neurologist – Leenaards Memory Centre Clinical experience, including clinical trials in neurodegenerative diseases Used the platform before: 3 times	Olivier Rouaud	olivier.rouaud@chuv.ch

Table 26 - CHUV Lausanne Clinical Validation Scenario 1 – Acceptance Criteria Test Matrix

SYSTEM VALIDATION TEST CASE: CLINICAL UTILITY OF THE VOLUME OF MEDIAL TEMPORAL LOBE SUBREGIONS FOR AD DIAGNOSTIC							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
Data Preparation							
A01	Variables (hippocampal volume, diagnostic) are selected.	Figure 1	☒	☐	☒	☐	
A01	Population of interest - within one hospitals and across defined and described.	Figure 2	☒	☐	☒	☐	
A01	Model of interest defined and built.	Figure 3	☒	☐	☒	☐	
Analytical validity and data quality							
A02	Compare the variables from the clinic to the variable from the research data (e.g. ADNI).	Figure 4	☒	☐	☒	☐	
A03	compare the variables from the clinic to the variable from the research data and interaction between sites and disease diagnostics	Figure 5	☒	☐	☒	☐	
Clinical Validity							

SYSTEM VALIDATION TEST CASE: CLINICAL UTILITY OF THE VOLUME OF MEDIAL TEMPORAL LOBE SUBREGIONS FOR AD DIAGNOSTIC							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
A04	test significance of the association between variable of interest and disease diagnostics	Figure 6	☒	☐	☒	☐	
Clinical utility							
A05	Train, test and validate predictive models against the selected cohort data.	Figure 7	☒	☐	☒	☐	
A05	Compare the predicted label to the current diagnostic label	Figure 8	☒	☐	☒	☐	
Model Validation Across Hospitals							
A06	Apply the selected model to the data of the other hospitals.	Figure 9	☒	☐	☒	☐	
Publish Results							
A07	Save the results and output of the model (graph, table).	Figure 9	☒	☐	☒	☐	
A07	Model is available for use by other users.	Figure 10	☒	☐	☒	☐	

Table 27 – CHUV Lausanne Clinical Validation Scenario 2 – Acceptance Criteria Test Matrix

SYSTEM VALIDATION TEST CASE: CLINICAL UTILITY OF CSF MARKERS FOR ALZHEIMER'S DISEASE: TOTAL AND PHOSPHORYLATED TAU, ABETA42							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
Data Preparation							
A01	Variables cerebrospinal fluid markers and diagnostic are selected.	Figure 1	☒	☐	☒	☐	
A01	Population of interest (within one hospitals and across) defined and described.	Figure 2	☒	☐	☒	☐	
A01	Model of interest defined and built.	Figure 3	☒	☐	☒	☐	
Analytical validity and data quality							
A02	Compare the variables against reference value	Figure 4	☒	☐	☒	☐	
A03	Compare the variables against reference values assess interaction between disease diagnostics	Figure 5	☒	☐	☒	☐	
Clinical Validity							
A04	Test significance of the association between variable of interest and disease diagnostics	Figure 6	☒	☐	☒	☐	
Clinical utility							
A05	Train, test and validate predictive models against the selected cohort data.	Figure 7	☒	☐	☒	☐	
A05	Compare the predicted label to the current diagnostic label	Figure 8	☒	☐	☒	☐	
A06	Compare CSF Model to MTL model	Figure 9	☒	☐	☒	☐	
Model Validation Across Hospitals							
A06	Apply the selected model to the data of the other hospitals.	Figure 9	☐	☐	☐	☐	Lack of data other than CLM
Publish Results							
A07	Save the results and output of the model (graph, table).	Figure 9	☒	☐	☒	☐	
A07	Model is available for use by other users.	Figure 10	☒	☐	☒	☐	

Table 28 – CHUV Lausanne Clinical Validation Scenario 3 – Acceptance Criteria Test Matrix

SYSTEM VALIDATION TEST CASE: DIFFERENTIAL DIAGNOSTIC BETWEEN FRONTO-TEMPORAL DEMENTIA AND ALZHEIMER'S DISEASE							
ID	Acceptance Criterion Description	Results	Critical		Test Results Accepted		Comments
			Yes	No	Yes	No	
Data Preparation							
A01	Variables all brain features and diagnostic are selected.	Figure 1	☒	☐	☒	☐	
A01	Population of interest (within one hospitals and across) defined and described.	Figure 2	☒	☐	☒	☐	
A01	Model of interest defined and built.	Figure 3	☒	☐	☒	☐	
Clinical utility							
A05	Train, test and validate predictive models against the selected cohort data.	Figure 4	☐	☐	☐	☐	Not done
Model Validation Across Hospitals							
A06	Apply the selected model to the data of the other hospitals.	Figure 9	☐	☐	☐	☐	Not done
Publish Results							
A07	Save the results and output of the model (graph, table).	Figure 9	☐	☐	☐	☐	Not done
A07	Model is available for use by other users.	Figure 10	☐	☐	☐	☐	Not done

Table 29 – CHUV Lausanne Clinical Benefits – Acceptance Criteria Test Matrix

Did the systems meet the clinical objectives ?				
Id	Description	Yes	No	
Primary Benefits				
1	Clinicians can explore own variable dataset in a well-structured interface (MIP EE) and can run data-mining algorithms on their own datasets	☒	☐	
2	Clinicians can compare specific patients and their measured variables against the whole cohort of the node, observe disease severity and therefore help them in their decision-making processes.	☒	☐	
3	Clinicians can visualize and interpret the quantitative measurements of the MRIs (outputted by the Data Factory) and further link these measures to diagnostic, behaviour and clinical measurements.	☒	☐	
4	As data will be extracted with benchmarked industry tools and standards (within the Data Factory), the results are ready to be published in journals.	☐	☒	Meeting to harmonize clinical criteria and diagnosis model before publishing
Secondary Benefits				
5	Models, articles and data mining experiments may be shared within the users of the node.	☒	☐	

6	The hospitals can explore the MIP software, its functionality, its potential and its technology before deciding to upgrade to the MIP Federation.	☒	☐	

Table 30 – CHUV Lausanne System Validation Survey

Possible Responses: Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
Login to the Medical Informatics Platform			
1	I experienced no issues with accessing the platform	Neutral	
2	Graphical user interface upon logging in is easy-to-understand to start using the platform	Neutral	
Data inspection and selection			
3	The functions available for inspecting the data are appropriate, given the constraints imposed by the data privacy by design (no inspection of individual data is allowed).	Neutral	
4	Graphical user interface is easy-to-use for inspecting the available data	Agree	
5	Graphical user interface is time-efficient for inspecting the available data	Agree	
6	The functions available for selecting the data are appropriate	Neutral	
7	Graphical user interface is easy-to-use for selecting the data of interest	Agree	
8	Graphical user interface is time-efficient for selecting the data of interest	Disagree	
Data analytics			
9	The analytical methods available fulfil our need to analyse the MIP datasets	Disagree	
10	Graphical user interface is easy-to-use for selecting and executing the data analysis methods	Neutral	
11	Graphical user interface is time-efficient for selecting and executing the data analysis methods	Disagree	
12	The time required for processing data analysis is appropriate	Disagree	
13	The results of the data analysis are presented in an informative and easy-to-understand manner	Neutral	
14	The functions available to store, share and retrieve previously made analysis are appropriate	Neutral	
General assessment			
15	I experienced issues related to the usage or performance of the system if you experienced issues, please provide a short description	Neutral	
UAT credibility			
16	Time spent on the UAT (in the format HH:MM)	30.00	
17	Test scenarios conducted during the UAT were representative of the data analytics experiments my institution will perform on a recurrent basis	Agree	

Possible Responses: Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
18	The questions raised during testing were appropriate	Agree	
19	The questions raised during testing covered all my concerns	Neutral	
20	The testing was rigorously performed, allowing me to fully express my views and check for their appropriate retranscription	Agree	
Clinical research needs			
21	I understand the conceptual framework, functionalities, and research applications of the MIP local	Agree	
22	The MIP local is providing useful tools complementary to those currently available in my research environment for analysing my data	Agree	
23	I plan to execute further studies using MIP local on patient data from my hospital/institution	Agree	
24	I understand the conceptual framework, functionalities, and research applications of the MIP federate	Agree	
25	The MIP federate is providing useful tools complementary to those currently available in my research environment for analysing my data	Agree	
26	I plan to execute further studies using MIP federate using the available open research cohort datasets	Agree	
27	I plan to execute further studies using MIP federate using data from other hospitals available in the MIP community ecosystem	Agree	
Final remarks			
28	Please include any other comments you wish to share with the Medical Informatics Platform project team		

Table 31 - CHUV Lausanne System Validation Survey

Possible Responses: Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
Login to the Medical Informatics Platform			
1	I experienced no issues with accessing the platform	Disagree	
2	Graphical user interface upon logging in is easy-to-understand to start using the platform	Agree	
Data inspection and selection			
3	The functions available for inspecting the data are appropriate, given the constraints imposed by the data privacy by design (no inspection of individual data is allowed).	Neutral	I would prefer to have tree-view and drop-down selection of variables
4	Graphical user interface is easy-to-use for inspecting the available data	Disagree	I would prefer to have tree-view and drop-down selection of variables
5	Graphical user interface is time-efficient for inspecting the available data	Disagree	I would prefer to have tree-view and drop-down selection of variables

Possible Responses: Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
6	The functions available for selecting the data are appropriate	Disagree	I would prefer to have tree-view and drop-down selection of variables
7	Graphical user interface is easy-to-use for selecting the data of interest	Disagree	I would prefer to have tree-view and drop-down selection of variables
8	Graphical user interface is time-efficient for selecting the data of interest	Disagree	I would prefer to have tree-view and drop-down selection of variables
Data analytics			
9	The analytical methods available fulfil our need to analyse the MIP datasets	Agree	
10	Graphical user interface is easy-to-use for selecting and executing the data analysis methods	Agree	
11	Graphical user interface is time-efficient for selecting and executing the data analysis methods	Agree	
12	The time required for processing data analysis is appropriate	Neutral	
13	The results of the data analysis are presented in an informative and easy-to-understand manner	Agree	
14	The functions available to store, share and retrieve previously made analysis are appropriate	Agree	
General assessment			
15	I experienced issues related to the usage or performance of the system if you experienced issues, please provide a short description	Disagree	
UAT credibility			
16	Time spent on the UAT (in the format HH:MM)	1:30	
17	Test scenarios conducted during the UAT were representative of the data analytics experiments my institution will perform on a recurrent basis	Neutral	
18	The questions raised during testing were appropriate	Agree	
19	The questions raised during testing covered all my concerns	Agree	
20	The testing was rigorously performed, allowing me to fully express my views and check for their appropriate retranscription	Agree	
Clinical research needs			
21	I understand the conceptual framework, functionalities, and research applications of the MIP local	Agree	
22	The MIP local is providing useful tools complementary to those currently available in my research environment for analysing my data	Strongly Agree	
23	I plan to execute further studies using MIP local on patient data from my hospital/institution	Strongly Agree	

Possible Responses: Strongly Disagree / Disagree / Neutral / Agree / Strongly Agree			
Id	Description	Response	
24	I understand the conceptual framework, functionalities, and research applications of the MIP federate	Agree	But need to harmonise diagnostic methods and clinical criteria to compare each data set
25	The MIP federate is providing useful tools complementary to those currently available in my research environment for analysing my data	Agree	
26	I plan to execute further studies using MIP federate using the available open research cohort datasets	Agree	
27	I plan to execute further studies using MIP federate using data from other hospitals available in the MIP community ecosystem	Agree	
Final remarks			
28	Please include any other comments you wish to share with the Medical Informatics Platform project team		

3.4 System Validation Test Case – Platform Deployment Scenario

This section provides a summary of the results of the MIP Platform Deployment system validation scenario, including the feedback from five participating hospitals:

- University Hospital Centre in Lausanne, Switzerland (Centre Hopitalier Universitaire Vaudois – CHUV)
- Regional University Hospital Centre in Lille, France (Centre Hopitalier Régional Universitaire de Lille – CHRU Lille)
- Research and Healthcare Institute in Brescia, Italy (Instituto di Ricovero e Cura a Carattere Scientifico, Centro San Giovanni di Dio – Fatebenefratelli, Brescia)
- General Hospital and Care Centres in Niguarda, Italy (ASST Grande Ospedale Metropolitano Niguarda)
- University Clinic in Freiburg, Germany (Universitätsklinikum Freiburg)

Table 32 – The MIP Deployment Scenario

System Validation Test Case:	Medical Informatics Platform Deployment
Validation Objectives	**1.** Hospital's data centre has a centralised platform for processing, storing and analysing de-identified and harmonised neuroimaging, neuropsychological, biological and demographic data of its patient population
	2. Efficient, configurable and automated end-to-end software installation, unifying operation system configuration, middleware installation and microservice building minimises the IT efforts to keep the focus on using the MIP platform for the scientific and clinical activities
	3. Harmonisation of the full set of Medical Informatics Platform's patient's biomedical and other health-related features enables large multi-centre, multi-data source studies, increasing the accuracy of the analysis methods and probability for new scientific discoveries
	4. Extraction and harmonisation of patients' biomedical and other health-related features from the source patient's data is a first step in the process of creating the data model for comprehensive molecular-level analysis of both individual patients and populations. Unification of biomedical and other health-related data provides the best opportunity to discover new biological signatures of diseases, improve taxonomy of diseases, develop preventive strategies, and improve medical treatment
Validation Actors	Neurologist (CLR), Neuroscientist (RES), Clinical Data Manager (CDM), Hospital Ethics Committee (HEC), Hospital IT Engineer (HIT), MIP Deployment Engineer (MIT), MIP Data Governance and Data Selection Committee (DGDS), SP8 Representative (SPR), Hospital Management (HMG)
Pre-conditions	Hospitals selected for the evaluation of Medical Informatics Platform (users acceptance test) agreed to participate in systems validation activities

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
A01	SPR	Project presentation / Item = N/A	User assessment positive	Project presentations were done for all concerned hospitals, the user assessment is positive, as witnesses by the signatures of five MoUs in the initial phase, and the MIP Deployment and Evaluation Agreements later for 8 hospitals now.	CLM: The project presentations were delivered by R. Frackowiak and F. Kherif to the memory clinic CLM (Centre Leenards de la Mémoire) in the CHUV. BRESCIA: The presentation to the Scientific director was done and well received, MoU was signed. NIGUARDA: The presentation was positive and interesting. The platform was fully explained. FREIBURG: Done, OK. By R. Frackowiak, and F. Kherif, several Zoom meetings for presentations. LILLE: Done, by R. Frackowiak, and F. Kherif, also to F. Pasquier.
A02	SPR, HMG	Adapt and sign MIP Deployment and Evaluation Agreement / Item = MIP Deployment and Evaluation Agreement	Signed MIP Deployment and Evaluation Agreement	Among the 9 hospitals that have signed the Deployment and Evaluation agreement until now (the agreements themselves are provided in EMDESK), the following ones have been chosen as example to go through the System Validation checklist. They are: - CLM CHUV Lausanne - IRCCS FBF Brescia - CHRU Lille - Niguarda Ospedale Milan - Universitätsklinikum Freiburg The signature of a formal agreement can take quite a long time administratively because many exchanges are necessary for various subjects discussed individually with respect to the standard agreement, such as : place	CLM: CHUV being a HBP Partner, the Internal Data Sharing agreement was signed with the CLM. BRESCIA: The agreement was signed NIGUARDA: The Agreement was signed. FREIBURG: Agreement is signed, the standard text required some adaptations, some discussions with the lawyers were necessary. LILLE: Agreement is signed.

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
				of jurisdiction; contracting party for the evaluation which may be different from the hospital itself (like an affiliated institution or a fund); financing and payment details in case of EU financial support.	
A03	CDM, DGDS	Gather meta-data, including data acquisition protocol identification / Item = Data Element Specification	Metadata Registry, component of Web sub-system successfully updated with new data elements	The taxonomy of variables that were provided by hospitals are documented in chapter 2.2. The final lists of variables that are provided by a hospital often evolve as the hospitals clinical research augment the knowledge of the data. The meaning and usage of Common Data Elements need often additional explanations. Some hospitals used this experience to launch the initiative to improve the availability of the scientific data from the technical point of view, e.g. data from neuropsychological tests. LESSONS LEARNED: Additional documentation for this phase is being written.	CLM: Variables of interest were chosen between the memory clinic data variables BRESCIA: Metadata of the ARWIBO project (the Brescia clinical cohort) was already available and is currently used in Brescia MIP-Local. NIGUARDA: ICT worked with clinicians, there are different data sources. Most data were available from Data Warehouse, but others required working with clinicians, e.g. diagnoses were not codified in the Data Warehouse, other data was in departmental systems. FREIBURG: Uniklinik chose their variables of interest. Diagnostics broad categories have been provided. Acquisition protocol - was discussed between K. Egger and CHUV. LILLE: CHRU provided data schemas coming from the source systems.
A04	HIT	Prepare data centre for installing and configuring new MIP servers, storage and network / Item = Deployment Specification	New MIP servers and storage systems can be installed in the data centre. The requirements are compliant with data centre electricity consumption requirements. MIP TCP/UDP port whitelist is compliant with the data	The specifications used for this step are provided in https://github.com/HBPMedical/mip-federation/blob/master/Documentation/: MIP_Federation_specifications.md; MIP_Local_deployment.md; Firewall_configuration.md. LESSONS LEARNED: More precise documentation on networking requirement is being written.	CLM: Several VMs were provided and configured by the IT department of the CHUV, including the Ubuntu OS, according to the standard procedures. BRESCIA: The MIP server was provisioned in the virtualised infrastructure of FBF hospital by HIT according to the specification.

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
			centre security requirements		NIGUARDA: No specific preparation was necessary. All infrastructure is virtual, the servers and storage were provisioned on the virtualized infrastructure. The Knowledge Extraction server required a different administrative approach as it is provided by cloud infrastructure provides. FREIBURG: The VM was provided, everything was easily deployed, good concept, the IT department could use the standard procedures, it was easy for HIT. LILLE: VM corresponding to the specification was made available in the CHRU data centre.
A05	HIT	HIT Install MIP all-in-one server or separate servers: a. Data capture and de-identification server b. Pre-processing server c. Knowledge extraction and web server / Item = MIP Server installed in hospital's execution environment	MIP server(s) and storage systems powered on, ready for software installation	The requested resources were provided by HIT. The virtual machines with the following number of CPUs and storage were provided by the HIT: 1. CLM 4CPU / 32 GB RAM / GB storage 2. Brescia 4CPU / 16 GB RAM / GB storage 3. Lille 8CPU/16GB RAM / 250 GB storage 4. NIguarda 4CPU / 16 GB RAM / GB storage 5. Freiburg 4CPU / 16 GB RAM / GB storage 6. Plovdiv 4CPU / 16 GB RAM / GB storage At Niguarda, after provisioning an ALL-IN-ONE server, also two more servers were provided for Federation installation, one for De-identification, inside the clinical network, the other for Pre-processing and Knowledge extraction outside of the clinical network. Sometimes the resources provisioned by HIT do not correspond to the specification and need to be	CLM: See above BRESCIA: See above NIGUARDA: See above FREIBURG: See above LILLE: See above

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
				augmented. The number of CPU may be too low, or not enough RAM or storage may be provided. Even though technically provisioning of additional resources is not complicated in virtualized environments, such requests add to the workload of the IT staff and therefore may take additional time. Therefore in the future we will stress the importance of the conformance to the MIP specification and ask for its explicit check by HIT. LESSONS LEARNED : A checklist to be filled in by the HIT is being added to the documentation, in order to avoid that the MIP team detects inconformity to the specification only later in the process,	
A06	HIT	Install operating system on MIP servers according to the Deployment Specification / Item = Operating systems installed on MIP servers, MIP file systems mounted on MIP servers	Operating systems successfully installed on MIP servers. Storage successfully configured with adequate file system type. MIP file systems mounted on MIP servers.	The servers provided by the hospitals were installed by HIT with Ubuntu Linux OS, with the exception for Niguarda, where local standard, RedHat Linux OS was installed. In some cases, depending on the technology used in the hospital environment, the CHUV IT has provided OS images specifically adapted to hospital's virtualisation technology (like VMWare, Hyper-V, ..)	CLM: See above BRESCIA: The Ubuntu OS was installed by HIT according to the specification NIGUARDA: Red Hat (Not Ubuntu) is the Niguarda standard, the OS installation is a standard procedure. FREIBURG: See above LILLE: CHRU HIT planned to make a OS master image, but finally the installation on VMWare was done manually.
A07	HIT	Configure IPv4/IPv6 settings for each MIP server / Item = Deployment Specification	TCP/IP configuration successfully executed on MIP servers. Routing tables of hospital LAN/WAN routers/firewalls updated for the traffic from new MIP nodes	The network cards of the MIP servers were configured by HIT. LESSONS LEARNED: Check whether the deployment scripts correctly change the hostname of the machine, because this might cause problems depending on the hospital infrastructure, and should not be unilaterally executed.	CLM: See above BRESCIA: It was done by HIT without problems, using static IP address. The network setup has allowed to detect some issues thus contributing to improve the security settings at FBF. NIGUARDA: Done by HIT according to the Niguarda security policy FREIBURG: See above

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
					LILLE: CHRU HIT has opened the routes and ports, the MIP-specific network configuration was done by MIP team.
A08	HIT, MIT	Provide remote access Configure SSH VPN tunnelling for remote connection with the MIP deployment team's environment: Configure TCP port 443 for egress HTTPS traffic on MIP servers and open port in firewall(s) for: a. Software package repositories (Ubuntu, Mesosphere, PyPI) b. Source code repositories (GitHub, Bitbucket, Launchpad, CHUV git) c. Docker registries (Docker Hub, CHUV private Docker registry) / Item = MIP server in hospital's execution environment remotely accessible	Remote SSH access through port 22 and HTTPS access through port 443 are successfully tested and access rights provided to MIP IT engineer	In the MIP-Locals for all concerned hospitals, the SSH access is available. The MIP team members can connect to the MIP-Local of the hospital via SSH. There is a variety of VPN client software that should be used depending on the accessed hospital. The access to the server itself is managed by the MIP team, attributing accounts on as needed basis. The future tool for managing the MIP infrastructure should manage the remote access information. LESSONS LEARNED: Make a distinction between the requirements for access from local VPN / Internal Network, and from Internet.	CLM: The MIP VM being in the same IT network as the MIP team, no remote access provision was necessary. BRESCIA: It was done by HIT, SSH connection is working for the ports requested. NIGUARDA: Followed the specification. Followed Niguarda security requirements. FREIBURG: Followed standard Uniklink procedure. Need to be personalized due to the German data protection law and renewal of token due to the change of personnel. LILLE: Open SSH server was installed by MIP team, firewall traffic was enabled by CHRU HIT.
A09	DGDS, CDM	Data selection – variables of interest based on hypothesis/questions /	The list of variables selected for capturing by MIP is agreed with Clinical Data Manager	Partly done before in step A03. When applicable, also a request was made to obtain additional CDE variables corresponding to Diagnostic Broad categories, where a	CLM: See A03. BRESCIA: It is based on the ARWIBO project, see above. The project uses over 220 variables, including the neuroimaging,

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
		Item = Data Element Specification		mapping from local diagnostics is possible to these CDE Diagnostic Broad categories This validation point is partly redundant with A03. LESSONS LEARNED: Propose a documentation platform common with the hospitals in order to share reference information, and thus simplify access to it.	clinical, neuropsychological, genetic variables. NIGUARDA: See A03 above. FREIBURG: See A03. LILLE: See A03.
A10	CLR, RES, HEC	Checking whether ethics approval applies for using MIP / Item = N/A	Hospital's Ethics Committee clearance applies to MIP platform	For SGA1, Hospitals did get clearance based on the requirements of the MIP Deployment and Evaluation agreement. The MIP Deployment and Evaluation agreement specifies in Chapter 5 'DATA PROTECTION' the compliance requirements with applicable national laws and European guidelines	CLM: CHUV obtained the Ethics clearance for its participation the HBP Project as an HBP Partner. BRESCIA: The ARWIBO project is public and has the ethics committee approvals. NIGUARDA: The hospital ethics committee gave the approval at the start of the project. For the Federation phase the Data Sharing Agreement will be signed. FREIBURG: Uniklinik obtained the Ethics clearance, for the Local MIP, will be necessary to renew for the MIP-Federated with the Data Sharing Agreement. LILLE: CHRU obtained the Ethics clearance, for the Local MIP, it will be renewed for the MIP-Federated with the Data Sharing Agreement.
A11	CLR, RES, CDM, DGDS	Variable harmonisation and structuring / Item = UC_DFY_06 Data Mapping and Transformation Specification	Analysing a request to capture the new dataset and enclosed Data Element Specification to cross-compare new data elements with MIP Common Data Element database schema structure and MIP data	Harmonisation process is executed as described in Table 4. The results for the CLM, IRCCS Brescia and CHRU Lille are presented in chapter 2.2.	CLM: Performed by the MIP team. BRESCIA: It was done by CDM according to the CDE specification. NIGUARDA: Done by MIP team. FREIBURG: Performed by the MIP team. LILLE : Performed by the MIP team.

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
			ontology to determine data mapping rules. Updating Data Mapping and Transformation Specification document with new data mapping rules		
A12	HIT, MIT	Installation of MIP software package / Item = UC_ITL_01, Deployment components (Docker images), MIP Installation and Configuration Script	MIP software is installed on all servers with all processes up and running. Confirm that all the processes are up and running from Marathon administrator's dashboard	The MIP software is installed in concerned hospitals and the MIP-Local is accessible in the hospitals where the process is advanced to this stage. The installation work requires adaptations to local environments, like manual adaptations of resources allocation depending on the local resources. LESSONS LEARNED: The documentation will be mode explicit with respect to the requirement for MATLAB installation and its version.	CLM: Performed by the MIP team. BRESCIA: The HIT has run the MIP installation scripts, including MatLab installation. NIGUARDA: Done by MIP team. FREIBURG: Performed by the MIP team. LILLE: Performed by the MIP team.
A13	MIT	Backup the installation and configuration scripts on external server: • MIP team uses a private storage space on Bitbucket.org • Using the private repository, it is possible to safely and securely backup work, share it with other members of MIP for code review and receive upgrades of the	MIP Installation and Configuration scripts customised for the hospital's execution environment archived on a private MIP storage space on the Bickbucket.org external server	The configurations for the hospitals installations are stored on the Bitbucket. LESSONS LEARNED: The management of encryption keys requires additional work and it can be improved. The future tool for managing the MIP infrastructure should allow to manage this data. Both Bitbucket and Gitlab are used. See example documentation is provided in the ADDITIONAL INFORMATION column.	CLM: Performed by the MIP team. BRESCIA: It was done by the MIP team. NIGUARDA: Done by the MIP team. FREIBURG: Performed by the MIP team. LILLE: Performed by the MIP team.

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
		platform / Item = UC_ITL_01, MIP Installation and Configuration Script			
A14	MIT	Configure MIP backup for each MIP server in standard data centre backup environment / Item = UC_ITL_01, MIP Installation and Configuration Script	Standard hospital's data centre backup environment configured for MIP server(s) and data backup	The backup configuration is not executed by the MIP personnel, but provisioned mostly by the HIT using their virtualized infrastructure. This validation point can often be combined with point A05, when it is executed by the HIT personnel using their virtualized infrastructure.	CLM: IT of the CHUV uses virtualised backup BRESCIA: The backup of the MIP server needs be setup by the HIT. NIGUARDA: See A04 FREIBURG: HIT uses the VEAM technology LILLE: Standard Backup is configured in CHRU virtual environment
A15	CDM, HIT, MIT	Installation/configuration/running of non-automated imaging capture Manual inspection of the captured new dataset file content: • DICOM headers have specific, non-standard content in each PACS system because different hospitals have different data acquisition protocols etc. / Item = UC_DFY_01, Data Factory sub-system,	Captured patient's data is de-identified and stored in De-identified data storage in Data Factory sub-system	According to the current agreements, data anonymisation or de-identification is the responsibility of the hospitals. MIP provides help to install, configure and run the dedication anonymisation software Gnubila FedEHR. Most hospitals provided already de-identified data (with the hospital retaining the re-identification information according to their own processes). It is the case for Brescia, CLM, Freiburg. At Niguarda and at Lille the imaging data was de-identified using the Gnubila EHR software. The MIP specification is being updated with the requirement to provide only primary DICOM images, as the secondary images may contain tags with patient data and are more complex to de-identify, because these tags are not standard. See anonymisation /de-identification strategy description can be consulted under	CLM: The IT contact of CLM has provided imaging data. BRESCIA: The anonymized imaging data was already available in the ARWIBO project. NIGUARDA: Patients were selected by clinicians based on diagnostics. ICT has extracted the DICOM files from the PACS. The radiologists only provided information of protocols used. ICT has no knowledge on anonymization, so the MIP team has performed this task. Work was performed together to establish the anonymisation protocol suitable to Niguard requirements (like clinical episode identifiers, sequence number, etc.) FREIBURG: HIP has provided imaging data as anonymised Nifti files. The reason of providing the Nifti files is because the

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
		Data Capture sub-system		https://github.com/HBPMedical/specifications/blob/master/content/data-capture/mip_de_identification_strategy.md. The anonymisation profiles can be provided upon request.	defacing pipeline used in the lab works with Nifti to optimise the storage space. LILLE: CHRU copied to the VM the DICOM files selected from the central PACS for AD diagnosis with T1 acquisition protocol.
A16	MIT	Configuration of image pre-processing Reconfiguring Brain Scan Pre-processing and Brain Morphometric Feature Extraction workflow for processing the new DICOM files / Item = UC_DFY_01, Data Factory sub-system	Brain Scan Pre-processing and Brain Morphometric Feature Extraction workflow is configured for new PACS' brain scan files	The Data Factory pipelines were configured specifically for each concerned hospital for processing of the imaging data. The knowledge of imaging data protocols in advance is very useful. LESSONS LEARNED: A checklist to be filled in by the CDM is being added to the documentation, in order to avoid that the MIP team detects inconformity to the specification only later in the process,	CLM: The configuration was done by the MIP team. The results were also used to improve the Data Factory settings. BRESCIA: The image pre-processing was already performed within the ARWIBO project. NIGUARDA: Done by MIP team. FREIBURG: Remains to be done, due to other SGA1 priorities LILLE: Performed by the MIP team.
A17	MIT	Running of image pre-processing / Item = UC_DFY_03, Data Factory sub-system	All the images are successfully processed with no error reported	The imaging data was processed for the following research datasets (ADNI, EDSD, PPMI), and for the following clinical datasets: CLM, Niguarda, Brescia, and it is being completed now for Lille; Freiburg, Plovdiv. The following number of images have been or are being characterized with the neuromorphic features: 1. CLM – 699 2. Brescia – 1946 3. Lille - in process, ca 700 4. Niguarda – 170 5. Freiburg - in process, 100 6. Plovdiv - in process, 138	CLM: The processing was done by the MIP team. BRESCIA: See above NIGUARDA: Done by MIP team. The various protocols used in the provided images caused additional work in order to filter the right ones. Additional information was exchanged between the CHUV and Niguarda. FREIBURG: Remains to be done, due to other SGA1 priorities LILLE: Performed by the MIP team.

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
A18	MIT	Configuration of brain scan metadata extraction pipeline Reconfiguring Brain Scan Metadata Extraction workflow for processing the new DICOM files / Item = UC_DFY_01, Data Factory sub-system	Brain Scan Metadata Extraction workflow is configured for new PACS' brain scan files	This step is done together with the step A16, in the same pipeline	CLM: The processing was done by the MIP team. BRESCIA: See above NIGUARDA: Done by the MIP team. FREIBURG: Remains to be done, due to other SGA1 priorities LILLE: Performed by the MIP team
A19	MIT	Running of brain scan metadata extraction / Item = UC_DFY_03, Data Factory sub-system	All the images are successfully processed with no error reported	This step is done together with the step A17, in the same pipeline	CLM: The processing was done by the MIP team. BRESCIA: See above NIGUARDA: Done by the MIP team. FREIBURG: Remains to be done, due to other SGA1 priorities LILLE: Performed by the MIP team
A20	CDM, HIT, MIT	Installation/configuration/running of non-automated EHR data capture Manual inspection of the captured new dataset file content: • CSV files with de-identified patient's data are sometimes empty / Item = UC_DFY_01,	Captured patient's data is de-identified and stored in De-identified data storage in Data Factory sub-system	In most cases, the hospital provided already de-identified data (with the hospital retaining the re-identification information according to its own process). This is the case for Brescia, CLM and Freiburg. The EHR data was de-identified using the Gnubila EHR software at Niguarda and Lille. The anonymization profiles can be provided upon request. In some cases, the provided data required additional cleaning, as it used inconsistent formats (e.g. data at YYYY.MM.DD or DD-MMM-YY) or incoherent values (like birth in 2026). The MIP team provides now advice to CDM on data coherence check prior to data delivery. Some hospitals used the experience from the MIP	CLM: The IT contact of CLM has provided anonymized EHR data. BRESCIA: The EHR data from the ARWIBO project was used. NIGUARDA: Done by the MIP team, including the anonymization. FREIBURG: HIT provided the de-identified EHR data for the selected patients. LILLE: CHRU HIT copied onto the MIP VM the data files extracted from source systems.

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
		Data Factory sub-system, Data Capture sub-system		deployment to launch an initiative for improving the technical transfer of data from the clinic. LESSONS LEARNED: Additional documentation is being written with simple advice for CDM and HIT for checking the quality of the data.	
A21	MIT	Configuration of data mapping pipeline Reconfiguring EHR Data Extraction workflow for processing of new EHR files / Item = UC_DFY_01, Data Factory sub-system	Online Data Integration Module is configured with new data mapping rules based on the Data Mapping and Transformation Specification for automatic mapping and loading of new patients' dataset into the permanent storage of harmonised features Updated mapping scenario, an XML configuration file, is updated for automatic transformation of the new dataset to harmonised MIP dataset and its loading into the CDE Database	The mapping tasks were defined using MIPMap tool. Mapping tasks can be provided on request. For the three hospitals participating in the clinical system validation, the datasets were analysed, cleaned – dates and numbers parsed, missing values identified, character encodings corrected, diagnosis codes translated in English, data tidied (see discussion in chapter 2.3) For the data cleaning and data tidying, for the quality control and data provenance tracking, a set of Python tools using PANDAS and NumPy libraries have been used.	CLM: The processing was done by the MIP team. BRESCIA: See above NIGUARDA: Done by the MIP team. FREIBURG: Remains to be done, due to other SGA1 priorities LILLE: Performed by the MIP team.
A22	MIT	Running of data mapping and loading of patients' biomedical and health-related features into the permanent storage of harmonised features / Item = UC_DFY_02, UC_DFY_04,	Monitoring of automatic mapping, transformation and loading of patients' biomedical and other health-related feature datasets into the permanent storage of harmonised features using the Online Data Integration Module. The data mapping is	The MIPMap mapping tasks were executed and the data followed the following path: input EHR data -> non-harmonized i2b2 database -> harmonized i2b database -> flattened CSV file. The clinical data is available in the MIP front end. In the three hospitals participating in the system verification process, the MIPMap has not been used for data cleaning, transformation (tidying) and loading in the permanent storage of harmonised patient features.	CLM: The processing was done by the MIP team. BRESCIA: The loading of the imaging features data and EHR data into the MIP was done by the MIP team. NIGUARDA: Done by the MIP team. FREIBURG: Remains to be done, due to other SGA1 priorities LILLE: Performed by the MIP team.

Description of Validation Actions					
Action ID	**Actor ID**	**What is validated / Item ID or Item Name**	**Validation Criteria / Expected Result**	**Observed result - Evaluation**	**Observed results: from five hospitals**
		Data Factory sub-system	processed with no error reported		
A23	MIT	Data validation: · Check pre-processed images for artefacts and quality metrics · Check data for confound and biases · Check meta-data / Item = UC_DFY_05, Data Factory sub-system, Web sub-system	Check for outliers using web applications then compare the results with high-quality open research dataset available in MIP	The check for outliers was performed using the Web Analytics front end-	CLM: The quality check was done by the MIP team. BRESCIA: The sanity check of the data was done within the ARWIBO project. NIGUARDA: Done by the MIP team. FREIBURG: Remains to be done, due to other SGA1 priorities LILLE: Performed by the MIP team
A24	SPR	Hand-over: · Presentations · Demo · Training / Item = N/A	User assessment positive	Handover sessions were held at the concerned hospitals.	CLM: UAT sessions were held with the CLM clinicians. BRESCIA: The UAT meeting was held between the MIP team and FBF clinicians NIGUARDA: In progress. FREIBURG: Remains to be done, due to other SGA1 priorities. LILLE: Following the necessity to update the workstations for a more recent version of Chrome, the System Validation review was done, with demo of functionalities.

Post-conditions	1. MIP software is installed on all servers with all processes up and running
	2. Harmonised patients' biomedical and other health-related features are permanently stored in Feature Data Store sub-system's Feature Table for multi-centre, multi-dataset clinical studies
Summarised evaluation of the value of the MIP	The MIP system deployment process is seen as a promising development for future efficient, large-scale software installation and data processing technology. Significant added value was recognised by clinical experts in the process of harmonisation of the data -new ideas for harmonising the disease classifications, exchange of experiences with treating the data and testing different expert diagnostic rules-
General remarks and recommendations	Further investment in MIP deployment process and tools to increase their technology readiness level is a prerequisite for achieving the large-scale deployment of the Platform. Collaboration with clinical experts should be on the daily basis to achieve higher-levels of data harmonisation. It needs to be performed by dedicated personnel with rare skills both in IT and biomedical domains.

4. Technology Readiness Level

The Medical Informatics Platform is a sophisticated software system, developed from many individual technologies (i.e., components), and integrated into a complex functional solution for descriptive and predictive analysis of patient datasets, including the combination of data originating from hospital health records and processed brain scans.[6]

4.1 Adaptation of the standard EC TRL scale

The Technology Readiness Level (TRL) scale was originally developed by US National Aeronautics and Space Industry to enable assessment of the maturity of a single particular technology and the consistent comparison of maturity between different types of technology components. The TRL scale originated from the observation that the R&D, operational and planning communities were facing problems in communication and synchronisation of scales during the technology development for complex systems. Various other management tools have been available for the more business-oriented readiness (for example, CMMI), but none of them can be used to assess the stage of the technology development directly.

Today, there is a clear focus on the commercialisation of research results. Therefore, a tool to help to evaluate this process is needed. That fostered the use and further adaptation of the TRL scales by different communities.

Horizon 2020 work programs use TRL scale to (1) make investment decisions, and (2) to evaluate progress and results of the projects. The adapted TRL scale used by the European Commission is provided in the following table:

Table 33 – TRL scale used by Horizon 2020

TRL Level	Description
TRL1	Basic principles observed
TRL2	Technology concept formulated
TRL3	Experimental proof of concept
TRL4	Technological validity in a lab
TRL5	Technology validated in relevant environment
TRL6	Technology demonstrated in relevant environment
TRL7	System prototype demonstration in an operational environment
TRL8	System completed and qualified
TRL9	Actual system proven in operational environment

The standard EC TRLs have been further adapted by Human Brain Project to suit the needs of the twelve subprojects, in general. The Human Brain Project's adaptation of EC's TRL scale is provided in Table 34. Previous versions of that scale have been included in FPA, SGA1 and SGA2 proposals.

Table 34 – HBP adaptation of EC TRL scale

TRL	Expected Properties
TRL 1 Project Initiation	• Project owner identified • Project principles and high-level objectives defined • Use case definitions (includes target users and activities)
TRL 2 Conceptualization	• Analytic study of the problem space • Identify key functions which must be validated in Component Implementation • Formulate validation criteria for critical components

	• Formulate validation criteria of complete prototype system • Prototype Epic planning
TRL 3 Proof of Concept Implementation	• Implementations of key functions • Validation of critical concepts • Identification of additional validation criteria for TRL4
TRL 4 Prototype Component	• Validation of prototype components in Lab • Proof of Concept has become prototype components • System technology selection has been made • Load testing of components under key load criteria • Identification of additional validation criteria for TRL5
TRL 5 Prototype Integration	• Validation of integrated system in a real-world environment • Tested in restricted environment with a small number of real users • Data formats specified • Identification of additional validation criteria for TRL6
TRL 6 Prototype-to-Real-world Integration	• Validation of integrated system in a real-world environment • Load testing of integrated system under expected load • Tested in a real-world environment with a small number of real users • Initial System documentation • Initial User documentation • System monitoring points specified (for services) • Identification of additional validation criteria for TRL7
TRL 7 Operational Integration	• Validation of integrated system in a real-world environment • Tested in a real-world environment with a small number of real users (canary testing for SoA) • System monitoring implemented (for services) • No expected data format or API changes without suitable deprecation period (for services or software components) • Load testing of integrated system under expected load • SLA monitored (for services)
TRL 8 Deployment	• Validation of integrated system in a real-world environment • Tested in a real-world environment with a small number of real users • SLA enforced (for services)
TRL 9 Production	• Validation of integrated system in a real-world environment • Tested in a real-world environment with a target number of real users

HBP adaptations of the source EC TRL scale addresses the aspects of research solutions that will need integration of various technologies, interaction with the users and validation of the systems in the user environments. These adaptations are essential for the comprehensive evaluation of the technological maturity of the Medical Informatics Platform because its technological value and value for users depends on the maturity of the fully integrated and operational system – the platform is a complex solution developed out of a number of individual technologies/components.

The Medical Informatics Platform is a data-intensive analytics solution. It uses available data – patients' biomedical and other health-relevant information from their hospital medical records and neuroimaging data out of their brain scans, to produce more data – results of the descriptive and predictive data analysis. The technological maturity of such a solution, and its value for the users is a function of a quality of the new data (knowledge) production, i.e. it is a function of the quality of the data analysis results. The quality of the data analytics ultimately depends on the type, quality, variability and volume of the analysed data.

Therefore, the technological maturity of the Medical Informatics Platform and its value for the users directly depends on the number and variety of participating hospitals and the number and

type of datasets that are available to the platform for analytics. The number and variety of participating hospitals and research institutes will not only depend on the technological maturity of the platform but equally as much shall financial and organisational aspects determine the success of the widespread deployment of the solution.

For an accurate evaluation of the MIP technological maturity and a precise communication of the technology readiness level in any of the project stages, it is crucially important to take the following aspects into account:

- The TRL setback mechanisms need to be incorporated, as their exclusion would mean that when (not if!) they occur, funding of specific activities would be (temporarily) stopped, leading to the unnecessary destruction of capital. In contrast to the implicit linear character of both EC's TRL scale and its HBP adaptation, the feedback models show that research is needed even at the higher TRL levels, i.e. that an increase in maturity also requires additional R&D. The implication is that in every stage certain kinds of R&D should be incorporated.
- Innovation is usually built up from different technologies. Therefore, the TRL scaling should make a distinction between R&D on individual technologies, integration of those technologies and pilot production. Most of the relevant aspects are provided for in the HBP's adaptation of EC's TRL scale, but the focus of the higher TRLs seem to be on the "small number of users". In the case of the Medical Informatics Platform, the TRL scaling should account for the wide deployment and the maturity of the corresponding technologies. The software "manufacturing" technologies needed (CI/CD, system monitoring, O&M tools, version control, operation processes, etc.), can be seen as just another set of technologies.
- Innovation is not about technology (product and process) alone. Financial and organisational activities can be crucial to commercial success. Both EC's TRL scale and its HBP adaptation are clearly about product oriented technologies. Their focus is apparently on product development, but very little on the ability of the production on a broader scale and no explicit mentioning of the organisational requirements. Non-technological aspects, the readiness of an organisation to implement the innovation, for example, should be incorporated into the TRL definitions. For example, the development of accompanying services, including tools, processes and organisation is just one example that is crucially important in case of the Medical Informatics Platform, as it determines the success and sustainability of the wide-spread platform deployment.

An integrative TRL assessment approach, combining different technologies and addressing market and organisational issues, is recommended for assessing and communicating the MIP technology readiness level. We have decided to adopt the recommendation of European Association of Research and Technology Organisations (EARTO)[8] for its close compliance to the needs of the SP8's strategic objectives and with the nature of the platform. The different maturity stages are summarised in Figure 12 and details provided in Table 35.

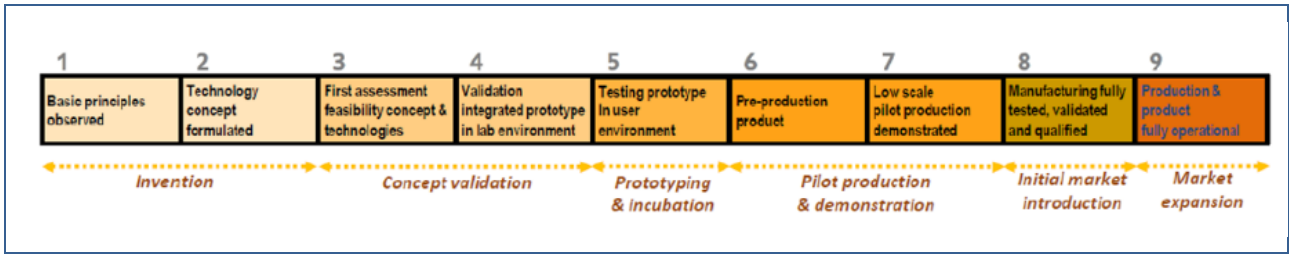

Figure 12 – The adaptation of HBP TRL scale to the SP8-MIP needs

Finally, interaction between disciplines, trans-disciplinary and user-centric approach is needed to solve societal challenges by binding various technologies together, connecting one technology to multiple applications, connecting technologies to non-technological disciplines allowing to take users perspective into account as well as look at solutions bridging commercial interests and society needs. These aspects are all relevant and essential criteria for assessment of a complex data intensive solution, such as the Medical Informatics Platform.

Furthermore, the successful wide-scale use of the new technologies inevitably changes the perceptions and needs of the users and society as a whole. As a consequence of the ever-lasting evolution of the user needs, the organisations need to provide for the sustainable phased development of the solutions. In a typical mature R&D organisation, while the phase N of the complex solution is deployed and in operation (TRL9 level), product phase N+1 is in the development stages on TR levels 5-7, phase N+2 is in the conceptualisation and prototyping stage on TR levels 2-4, and product phase N+3 can be in the early research stage on TRL1 level.

Table 35 – MIP TRL definition overview table

Cluster	TRL	HBP Terminology	MIP/EARTO Reading[8]	MIP Definition and Description[8]
Invention	TRL1	Project Initiation	Basic principles observed	Basic scientific research is translated into potential new basic principles that can be used in news technologies
	TRL2	Conceptualisation	Technology concept formulated	Potential application of the basic (technological) principles is identified, including their technological concept. Also, the first wide-scale software deployment principles are exploited, as well as possible markets identified. A small research team is established to facilitate assessment of technological feasibility
Concept validation	TRL3	Proof of Concept Implementation	First assessment of feasibility of the concept and technologies	Based on the preliminary study, analysis is conducted to assess technical and market feasibility of the concept. This includes active R&D on a laboratory scale and first discussions with potential clients from major European university hospitals. The research team is further expanded and an early market feasibility assessed
	TRL4	Prototype Component	Validation of integrated prototype in a laboratory	Basic technological components are integrated to assess early feasibility by testing in a laboratory environment. Wide-scale software deployment is actively researched and analysed, identifying main production principles. Lead hospitals and institutes are engaged to ensure connection with demand. Organisation is prepared to enter into scale up, possible services prepared and full market analysis conducted
Prototyping and incubation	TRL5	Prototype Integration	Testing of the prototype in a user environment	The system is tested in a user environment, connected to the broader technological infrastructure. Actual use is tested and validated. Wide-scale deployment is prepared and tested in a laboratory environment and lead hospitals and institutes can test pre-production products. First activities within the organisation are established to further scale up to pilot production and marketing
Pilot production and demonstration	TRL6	Prototype-to-Real-world Integration	Pre-production of the product, including testing in a user environment	Product and manufacturing technologies are now fully integrated in a pilot line or pilot plant (low-rate software deployment). The interaction between the product and wide-scale software deployment technologies are assessed and fine-tuned, including additional R&D. Lead hospitals and institutes test the early products and wide-scale software deployment process and the organisation of production is made operational (including marketing, logistics, production and others)
	TRL7	Operational Integration	Low-scale pilot production demonstrated	Wide-scale software deployment process is now fully operational at a low-rate, producing actual final developed products. Lead hospitals and institutes test these final products and organisational implementation is finalised (full marketing established, as well as all other production activities fully organised). The product is formally launched into first early adopter hospitals and institutes

Cluster	TRL	HBP Terminology	MIP/EARTO Reading[8]	MIP Definition and Description[8]
Initial market introduction	TRL8	Deployment	Wide-scale software deployment process fully tested, validated and qualified	Wide-scale software deployment of the product and the product final version are now full established, as well as the organisation of production and marketing. Full-launch of the product is now established in European markets
Market expansion	TRL9	Production	Production and product fully operational and competitive	Full production is sustained, product expanded to worldwide markets and incremental changes of the product create new versions. Wide-scale software deployment and overall production is optimised by continuous incremental innovations to the process. Worldwide markets are fully addressed

4.2 Integrated system technology readiness level assessment

As discussed in the previous sub-chapter, for the precise assessment of the MIP's TRL at the end of SGA1 project phase, and for full compliance with the plans for the technology maturation as defined in SP8's SGA2 proposal, we decided to adopt EARTO's adaptation of EC's TRL definitions (see Table 35 on the previous page).

The MIP is a data-intensive solution. A MIP with a higher level of technological maturity requires access to big data for technologically more advanced ways to discover the biological signatures of diseases by applying predictive machine learning and deep learning algorithms. The emphasis is therefore also on the development of a mature wide-scale production technology of the Platform, corresponding process and organisational aspects as prerequisites for its wide-scale deployment to get access to larger patient datasets.

Table 36 – Technology readiness level assessment of the key technologies / components

ID	Component Name	TRL	Component Type	Description
2938	Algorithm Orchestrator	TRL5	SOFTWARE	The component is integrated into the MIP ecosystem and tested in user environment.
647	Algorithm Repository	TRL5	SOFTWARE	The component is integrated into the MIP ecosystem and tested in user environment
645	Model Benchmark and Validation	TRL5	SOFTWARE	The component is integrated into the MIP ecosystem and tested in user environment
646	Predictive Disease Models	TRL5	SOFTWARE	The component is integrated into the MIP ecosystem and tested in user environment
633	Portal DB (Articles, Experiments, Models)	TRL5	SOFTWARE	The component is integrated into the MIP ecosystem and tested in user environment
1595	Distributed Query Processing Engine – Master	TRL4	SOFTWARE	The component is integrated into the MIP ecosystem to assess early feasibility by testing in a laboratory environment
1596	Distributed Query Processing Engine – Worker	TRL4	SOFTWARE	The component is integrated into the MIP ecosystem to assess early feasibility by testing in a laboratory environment
638	Query Engine	TRL4	SOFTWARE	The component is integrated into the MIP ecosystem to assess early feasibility by testing in a laboratory environment
687	Data Governance Methodology	TRL3	SERVICE	Based on the preliminary study, technical and market feasibility of the concept is analysed and discussed with potential clients from major European hospitals
587	Data Mapping and Transformation Specification	TRL3	DATA	Based on the preliminary study, technical and market feasibility of the concept is analysed and discussed with potential clients from major European hospitals and tested in one hospital (CHRU Lille)

ID	Component Name	TRL	Component Type	Description
1580	Online Data Integration Module	TRL4	SOFTWARE	The component is integrated into the MIP ecosystem to assess early feasibility by testing in a laboratory environment
671	Neuromorphometric Processing	TRL7	SOFTWARE	Lead hospitals and institutes are using the solution. The component is formally launched and training is established. The solution is developed and managed in academic organisation. Product manufacturing and marketing organisation needed for TRL8 categorisation is not established
664	Airflow DAGs	TRL4	SOFTWARE	The component is integrated into the MIP ecosystem and tested in a laboratory environment. It is based on the TRL8/9 categorised Apache Airflow solution
2927	Data Catalogue	TRL4	SOFTWARE	The component is integrated into the MIP ecosystem and tested in a laboratory environment. It is based on the TRL9 PostgreSQL DBMS
2926	Data Capture Database	TRL4	SOFTWARE	The component is integrated into the MIP ecosystem and tested in a laboratory environment. It is based on the TRL9 PostgreSQL DBMS and the star database schema is compatible with TRL7 I2B2 solution
669	Common Data Elements Database	TRL4	SOFTWARE	The component is integrated into the MIP ecosystem and tested in a laboratory environment. It is based on the TRL9 PostgreSQL DBMS and the star database schema is compatible with TRL7 I2B2 solution
102	MIP Microservice Infrastructure	TRL5	SOFTWARE	The component is integrated into the MIP ecosystem and tested in user environment
2940	Data De-identifier	TRL5	SOFTWARE	The component is integrated into the MIP ecosystem and tested in user environment.
2936	MIP De-identification Profiles	TRL5	MODEL	The component is integrated into the MIP ecosystem and tested in user environment.
2935	MIP De-identification Strategy	TRL5	REPORT	The component is integrated into the MIP ecosystem and tested in user environment.

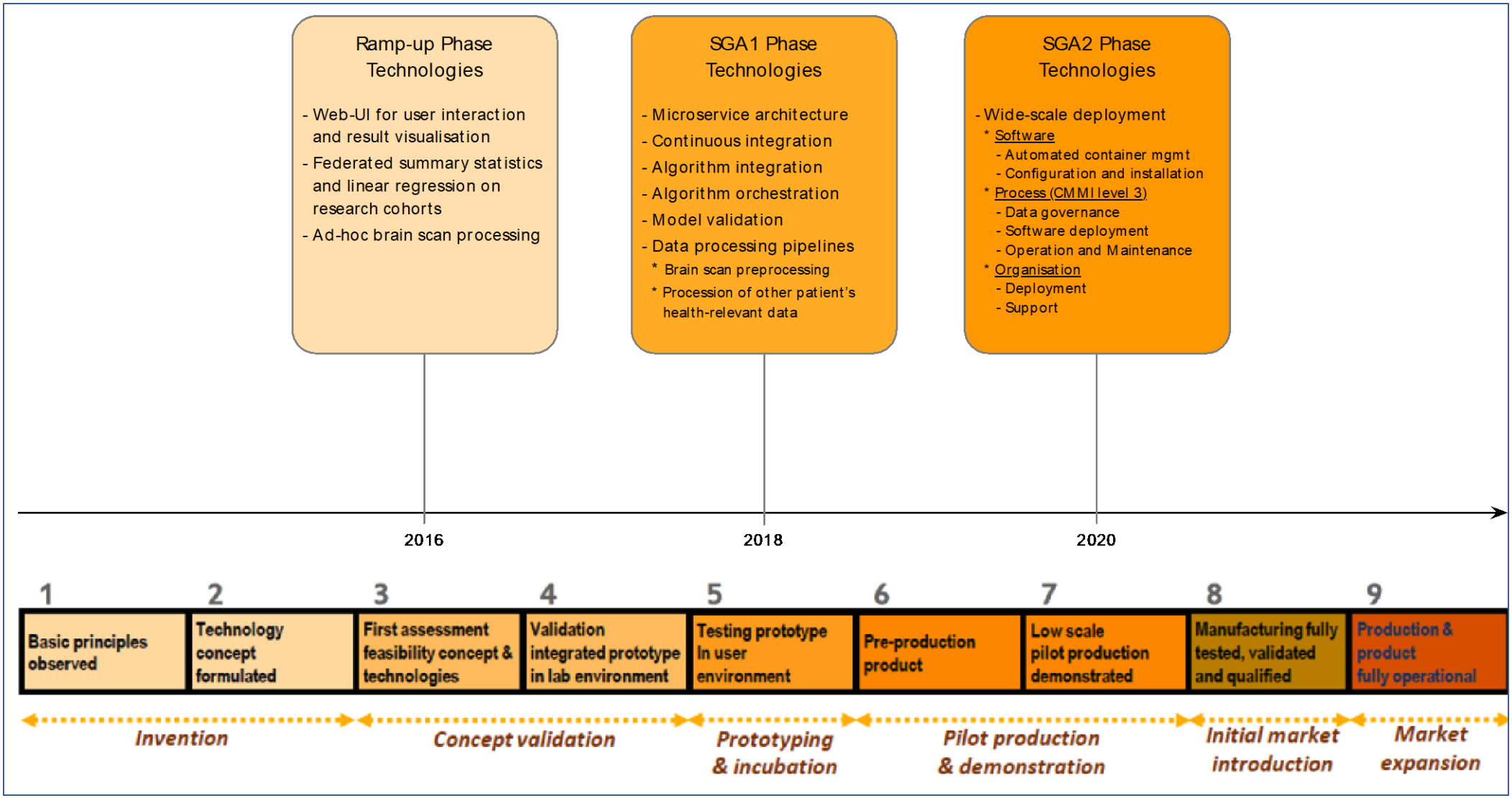

Figure 13 – Transition of MIP technology readiness level and future roadmap

5. Conclusion and Outlook

During the 2-year SGA1 funding period, from April 2016 to April 2018, the Human Brain Project's SP8 has evolved the Medical Informatics Platform technology from the TRL 3 (First assessment of feasibility of the concept and technologies) at the end of the preceding Ramp-Up Phase funding period to the current TRL 5 (Testing of the prototype in a user environment).

By the end of the Ramp-Up Phase, the first version of the Platform had been developed on a laboratory scale and first discussions with potential clients from major European university hospitals had been held. The research team was further expanded and an early market feasibility was assessed. The key features supported by the Platform were (Figure 13):

- Interactive web user interface, including data visualisations
- Federated summary statistics and linear regression on research cohort datasets
- Ad-hoc brain scan processing

During SGA1, the Platform's system technology level evolved towards integrating components into a microservice architecture based on Docker. Technology supporting wide-scale deployment was actively researched and main production principles supporting agile continuous integration / continuous deployment were defined. Selected hospitals and institutes were engaged, by signing deployment and evaluation agreements.

By the end of SGA1, the system had been tested in a user environment, connected to the broader technological infrastructure. Wide-scale deployment was prepared and tested in a laboratory environment and participating hospitals and institutes were able to test pre-production products. Preliminary activities within the organisation were established to further scale up to pilot production and marketing. The Platform is now ready for testing of its clinical applications in a user environment.

In addition to the features developed during the Ramp-Up Phase, the new ones supported by the Platform at the end of SGA1 are (Figure 13):

- Microservice architecture (Docker technology)
- Continuous integration
- Algorithm integration
- Model validation
- Data processing pipelines
  - Brain scan pre-processing
  - Processing of other patients' health-relevant data

The supported features of the Platform at the end of SGA1 provided functional and software engineering prerequisites for a real clinical application of the MIP. The supported clinical applications of the Platform are:

- Measurement of a biomarker's clinical utility
- Improvement/fine tuning of the disease classification
- Improvement of the diagnostic models
- Improvement of the prognostic models
- Exploration and comparison of patient population data
- Harmonisation of biomarkers across the different centres
- Building a diagnostic aid using pathologically proven data

Engagement with clinical experts in the Data Governance and Data Selection Committee - and corresponding processes of data selection, data harmonisation and data processing - triggered discussions between experts from different centres, about harmonisation of disease classifications and neuropsychological tests (Chapter 2.2). The Medical Informatics Platform's metamodel currently contains around 300 harmonised data elements from ADNI, EDSD, PPMI, CHUV/CLM Lausanne, IRCCS Brescia and CHRU Lille (see Chapter 2.2 for details).

5.1 Key Lessons Learned

- Engagement of clinical expert resulted in knowledge and best practice exchange in the domains of diagnostic, disease classification and data harmonisation, in general. To achieve success, the proactive involvement of a person with both IT and biomedical profiles is required
- Software integration and deployment technology, including tools and processes, enabled distributed roll out of the Platform in private hospital execution environments and the integration of these "private" MIPs with the MIP software deployed in a community ("federated") execution environment. These technologies require further development and maturation to scale-up to support wider MIP deployment

5.2 Strategic Plan

During the next 12-month period, platform and deployment technologies should be fully integrated in a pilot line or pilot plant (low-rate software deployment). The interaction between the product and wide-scale software deployment technologies should assessed and fine-tuned, which may require additional R&D. Lead hospitals and institutes shall test the early products and wide-scale software deployment process. The production organisation shall be established and made operational (including market analysis, logistics, production and others). The Platform's target technology readiness level for the end of the 12-month period should be TRL 6 (Pre-production of the product, including testing in a user environment).

The new MIP features that would support the strategic 12-month plan to establish a wide-scale deployment technology and organisation are (Figure 13):

- Software
  - Automated Docker container management
  - Configuration and installation technology maturation
- Process (CMMI level 3 – managed process)
  - Data governance actively engaging clinical and research experts
  - Managed software deployment
  - Managed operation and maintenance
- Organisational
  - Establishment of a deployment organisation
  - Establishment of a support organisation

This 12-month strategic plan is a prerequisite for a large-scale software deployment process that is fully operational at a low-rate, producing actual final developed products at the end of the 24-month SGA2 period. At that point, the lead hospitals and institutes should have installed these final products, organisational implementation would be finalised (full marketing established and all other production activities fully organised), the product should be formally launched into first early adopter hospitals and institutes, and the MIP platform should have reached TRL 7 (Low-scale pilot production demonstrated).

6. Acronyms and Abbreviations

Abbreviation	Meaning
AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ANOVA	ANalysis Of Variance
CHRU	Centre Hospitalier Régional Universitaire (French regional university hospital)
CHUV	Centre Hospitalier Universitaire Vaudois (University hospital in Lausanne, Canton Vaud)
CI/CD	Continuous Integration / Continuous Deployment
CMMI	Capability Maturity Model Integration
CMMI	Capability Maturity Model Integration
CN	Cognitive Normal
DoA	Description of Actions
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	European Commission
EDSD	European Diffusion tensor imaging Study in Dementia
EPFL	École Polytechnique Fédérale de Lausanne (Swiss federal institute of technology in Lausanne)
FBF	Fatebenefratelli (Hospitallers order of the Brothers of Saint John of God)
FPA	Framework Partnership Agreement
HBP	Human Brain Project
IRCCS	Istituto di Ricovero e Cura a Carattere Scientifico (Italian institute for research and healthcare)
M24	24th Month of a project phase
MCI	Mild Cognitive Impairment
MIP	Medical Informatics Platform
MoU	Memorandum of understanding
N/A	Not Available
O&M	Operation and Maintenance
PPMI	Parkinson Progression Marker Initiative
R&D	Research and Development
SGA1	Specific Grant Agreement, phase 1
SP8	Sub-Project 8
UHEI	Universität Heidelberg
WHO	World Health Organisation
WP	Work Package
OLAP	On Line Analytical Processing
TRL	Technology Readiness Level
TRA	Technology Readiness level Assessment
KNN	K-Nearest Neighbours
CSF	CerebroSpinal Fluid
CLM	Centre Leenaards de la Mémoire
PET	Positron Emission Tomography

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Appendix 1 – The MIP SGA1 Software Version

```
---


mip_version: "2.8.5"


java_version: 8
docker_version: "{% if ansible_os_family == 'RedHat' %}17.03.2{% else %}18.03.0{% endif %}"
docker_debian_package_version: "ce-0"
docker_redhat_package_version: "ce"
docker_registry_version: "2.3.1"


zookeeper_version: "{% if ansible_os_family == 'RedHat' %}3.4.10{% else %}3.4.8{% endif %}"
zookeeper_debian_package_version: "1"
mesos_version: "1.5.0"
mesos_package_version: "2.0.1"
mesos_ui_version: "standalone-0.1.4"
marathon_version: "1.6.352"
chronos_version: "3.0.2-5"
caddy_version: "0.10.10-5"


airflow_version: '1.9.0'
airflow_db_image: "postgres"
airflow_db_version: "{{ postgres_version }}"
mri_db_image: "postgres"
mri_db_version: "{{ postgres_version }}"


postgres_version: "9.6.5-alpine"
postgres_jdbc_driver: postgresql-9.3-1103.jdbc41.jar
ldsm_db_version: 'v1.3'
postgresraw_ui_version: 'v1.5'


# Use latest NGinx from official repo
nginx_official_repo: True


# Versions of our Docker containers
```

```
portal_frontend_version: "2.12.0"
portal_backend_version: "2.8.5"
woken_version: "2.8.1"
# Do not override versions of algorithms, they are already defined in Woken
woken_algorithms: []

woken_validation_version: "2.5.3"
woken_db_setup_version: '1.2.1'

# Reference data

mip_cde_meta_db_setup_version: '1.3.1'

adni_merge_db_setup_version: '1.5.5'
edsd_data_db_setup_version: '1.4.4'
ppmi_data_db_setup_version: '1.1.4'

sample_meta_db_setup_version: '0.6.0'
sample_data_db_setup_version: '0.6.1'

# Data factory

matlab_version: "R2016b"
spm_version: 12
spm_revision: r6906
spm_mri_templates_version: '20050329'
spm_mri_tpm_version: '20151218'
data_tracking_version: '1.7.2'
data_catalog_db_setup_version: '1.6.0'
mri_preprocessing_pipeline_version: '1.3.4'
i2b2_import_version: '1.6.3'
i2b2_capture_db_setup_version: '1.5.2'
i2b2_mip_db_setup_version: '{{ i2b2_capture_db_setup_version }}'
slackclient_py_version: '1.0.5'
docker_py_version: '1.10.6'
hierarchizer_version: '1.3.6'
```

```
airflow_imaging_plugins_version: '2.4.3'
data_factory_airflow_dags_version: '0.9.11'
map_ehr_to_i2b2_version: '0.2.0'

# QA environment

gitlab_version: "8.13.3-ce.0"
sonarqube_version: "6.0-alpine"

# For development

ansible_cmdb_version: 1.17

maven_version: "3.5.2"

nodejs_version: "4.6"

captain_version: "1.1.2"
docker_compose_version: "1.18.0"

virtualbox_version: "5.2"
vagrant_version: "2.0.2"

# IDEs
sublimetext_build: "3114"
intellij_version: "2017.3.3"
yed_version: "3.16.2.1"
soapui_version: "5.2.1"
atom_ver: '1.17.2'
```

Appendix 2 – User Acceptance Test Hospital Sign-Off Forms

CHRU, Lille, France

CHUV, Lausanne, Switzerland

IRCCS, Brescia, Italy

These are confidential documents that were removed from the Public Deliverable to comply with the provisions of the EU General Data Protection Regulation (GDPR).