Horizon 2020 Project LETHE
"A personalized prediction and intervention model for early detection and reduction of risk factors causing dementia, based on AI and distributed Machine Learning."

Research and Innovation Action
H2020-SC1-DTH-2020-1
GA 101017405

Duration: 48 months from 01/01/2021
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Deliverable ID.:	**D2.5**	
Deliverable title:	**LETHE Interoperability Framework**	
Planned delivery date:	23/12/2021 (M12)	
Actual delivery date:	31/12/2021 (M12)	
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Dissemination Level:	**X**	PU = Public;
		CO = Confidential
Type:	Report	

Document information and history

Deliverable description (from DoA)
This deliverable defines the interoperability frameworks and provides possible modules or interfaces needed (FHIR API e.g.)

Please refer to the Project Quality Handbook for guidance on the review process and the release numbering scheme to be used in the project.

Release number	Release date	Author [Person and Organisation]	Milestone*	Release description /changes made
V. 0.1	27/05/2021	Carina Seerainer, Bianca Schnalzer (FHJ)	ToC	
V0.2	12/10/2021	Carina Seerainer, Bianca Schnalzer (FHJ)	Intermediate	
V0.3	16/12/2021	Carina Seerainer, Bianca Schnalzer Hannes Hilberger Philipp Grieshofer, Jacqueline Kuch (FHJ)	Proposed	
V0.4	22/12/2021	Carina Seerainer, Bianca Schnalzer Hannes Hilberger Philipp Grieshofer, Jacqueline Kuch (FHJ)	Revised	Included review recommendations
V0.5	22/12/2021		Approved	
V1.0	23/12/2021		ER	

The project uses a multi-stage internal review and release process, with defined milestones. Milestone names include abbreviations/terms as follows:

- *TOC = "Table of Contents" (describes planned contents of different sections);*
- *Intermediate: Document is approximately 50% complete – review checkpoint;*
- *ER = "External Release" (i.e. to commission and reviewers);*
- *Proposed: document authors submit for internal review;*

- *Revised: document authors produce new version in response to internal reviewer comments*
- *Approved: Internal project reviewers accept the document.*

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1   Executive Summary

This document gives a guidance for data flow as well as the possible standards which could be used in LETHE project. The deliverable D2.5 provides a guideline for technical implementation and gives an overview about the retro – and prospective data collection as well as the visualization through dashboards and reports. First, a definition of entities and modules is provided, followed by a more detailed description of use cases and data flow. Afterwards, a guideline for technical implementation is presented. This guideline includes the definitions and requirements of interoperability frameworks as well as standards and profiles for semantic interoperability. In aforementioned section, a deeper insight to collected data, more precisely retro- and prospective data of several LETHE components, is given. For each data feature, a standardization format is proposed. Before showing the future reuse of LETHE model, a technique for harmonizing new collected features within LETHE is given.

2   About this Document

This document gives a brief overview of all recommendations of interoperability aspects within the LETHE project phase I as well as LETHE project phase II. Commonly known standards should be used to set up the LETHE project in an interoperable way.

2.1   Role of deliverable

The deliverable builds the basis (from the interoperability aspect) for further technical implementation of the LETHE architecture with all LETHE modules and data collection.

Nevertheless, this document can at the current stage be seen as a "snapshot" version of the interoperability framework, whereby most of the variables/features and digital biomarkers are selected and described, but this set may not be a final selection at the stage of deliverable publication.

Further continuous improvement of digital biomarker selection can be identified as valuable, as the final LETHE trial protocol and the AI module task are still ongoing tasks.

2.2   Relationship to other LETHE deliverables

The following relationships to other LETHE deliverables and tasks were identified:

- Task 2.1 Data Harmonization: retrospective joint master data set as basis for interoperability recommendations
- Task 2.2 LETHE System Architecture: Decisions on Use Cases, Middleware, Platforms
- WP4: Digital Biomarkers Data Set as basis for interoperability recommendations
- Task 4.4 LETHE sensing ecosystem: decisions on the use of RADAR-base etc.
- WP5: Setup of LETHE big data infrastructure where all retrospective and prospective data will be inter-connected and commonly presented

2.3   Structure of the document

The document provides information on the following:

1) Which systems and components will be necessary to be integrated
2) Which information will be necessary to be exchanged
3) Where and how the information will be generated/recorded

Therefore Chapter 3 provides information and references to describe the use cases of data collection within the LETHE project including relevant entities and the basic data flow. Additionally, relevant eHealth standards and terminologies are mentioned in chapter 3.5.

Chapter 4 includes interoperability recommendations, mainly specifications on how to map retrospective and prospective data sets to FHIR resources. Besides the choice of FHIR resources, codes and data types, chapter 4 includes recommendations for value sets based on international terminologies.

Chapter 5 provides a short summary, including a discussion of open issues.

2.4   List of abbreviations

Relevant abbreviations are listed in the following section:

Abbreviation	Explanation
AD	Alzheimer Disease
AI	Artificial Intelligence
CDISC	Clinical Data Interchange Standards Consortium
CN	Cognitive Normal
DICOM	Digital Imaging and Communications in Medicine
DT	Data Type
ETL	Extract Transform Load
FHIR	Fast Healthcare Interoperability Resources
HDFS	Hadoop Distributed File System
HTTP	Hypertext Transfer Protocol
IoT	Internet of Things
JDBC	Java Database Connectivity
JSON	JavaScript Object Notation
LOINC	Logical Observation Identifiers Names and Codes
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental-State-Examination
MRI	Magnetic Resonance Imaging
REST-API	Representational State Transfer - Application Programming Interface
SNOMED - CT	Systematized Nomenclature of Medicine - Clinical Terms
UCUM	Unified Code for Units of Measure

3   Introduction

The following chapter gives a brief overview of identified entities and modules as well as basic data flow between the different systems, which will be integrated during the LETHE project.

3.1   Identified Entities and Modules

Identified Entities:

Within the LETHE project the following physical entities can be identified:

- Participants
- Study centres/clinicians

Moreover, after the project other health care professionals can add support to provide health care intervention, nevertheless this is not primarily planned within the LETHE project. Researchers can also be identified as entity after the LETHE project duration.

Participants involved in the LETHE project are part of a study with a control and a study group. Detailed information about the study protocol is described in a separate deliverable [14]. Participants who are part of the study group receive additional LETHE intervention and are therefore provided with a technical setup to receive the intervention. This setup includes:

- Smartphone with LETHE app (data collection and intervention)
- Wearables (data collection and intervention)
- Robot (intervention) - some of the study group participants
- Smart glasses (intervention) - some of the study group participants

Identified modules:

The LETHE system architecture modules can be summarized as followed:

- Data Collection and Processing modules
- Data Storing Modules (Structured Datastore/Data Warehouse)
- AI (artificial intelligence) modules
- Data (Re-)Presentation modules

A detailed description of the system architecture and their related modules is described in the deliverable D2.2 [12].

3.2   Use Cases of Data Collection/Basic data flow between systems

The use cases of data collection and basic data flow between systems are described in detail in chapter 7 of the deliverable D2.2 - LETHE architectures and scenarios [12]. The use cases are collected from the point of view of participants (users), healthcare professionals, experts and scientists. LETHE requirement workshops accompanied the definition of use cases.

Additionally (technical) description of use cases will be refined during the ongoing project progress.

3.2.1 Retrospective Clinical Data Collection

The retrospective data collection describes the necessary processing steps in LETHE project phase I. Structure and content of the dataset is described in the deliverable D2.1 [2]. The description includes clinical markers, cognitive test results, demographic data, functional status, health status, lifestyle, mood and quality of life.

Generally, the system architecture of Phase I (Figure 1 - retrospective data collection) is highlighted and described in D2.2 [12] in more detail.
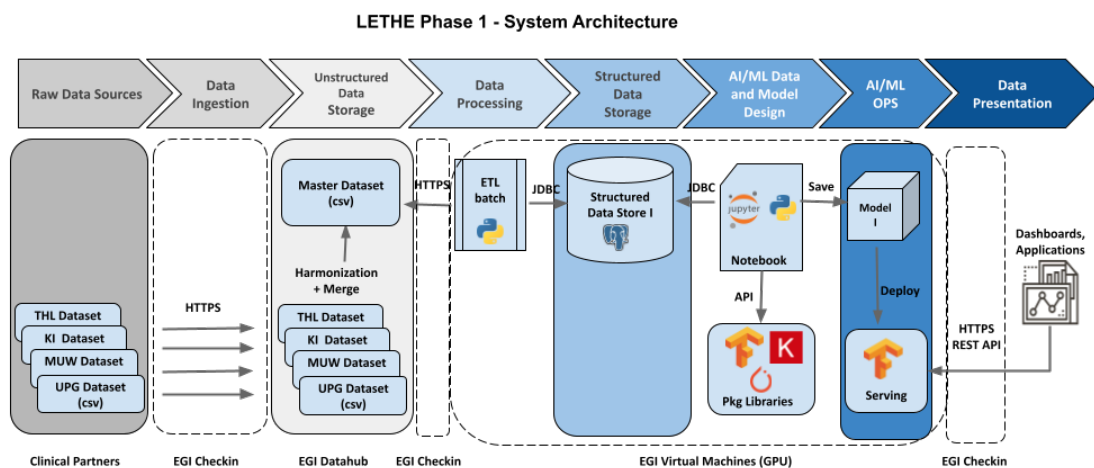
Figure 1: Overview of system architecture and modules of Phase I (retrospective data collection).

For interoperability reasons over all datasets, elements (variables) were defined in a joint master data set. A detailed, standardized description is given in chapter 4.

The joint master data set will be included via ETL process (JDBC) in a structured data store/data warehouse via PostgREST API.

3.2.2 Prospective Data Collection

Prospective data collection within the LETHE project is carried out during phase II.

Generally, the system architecture of Phase II (Figure 2 - prospective data collection) is highlighted and described in D2.2 [12] in more detail.

Data collection in phase II can be split up for two entities:

- Participants (Patient Generated Data Collection)
- Clinicians (Prospective Clinical Data Collection)
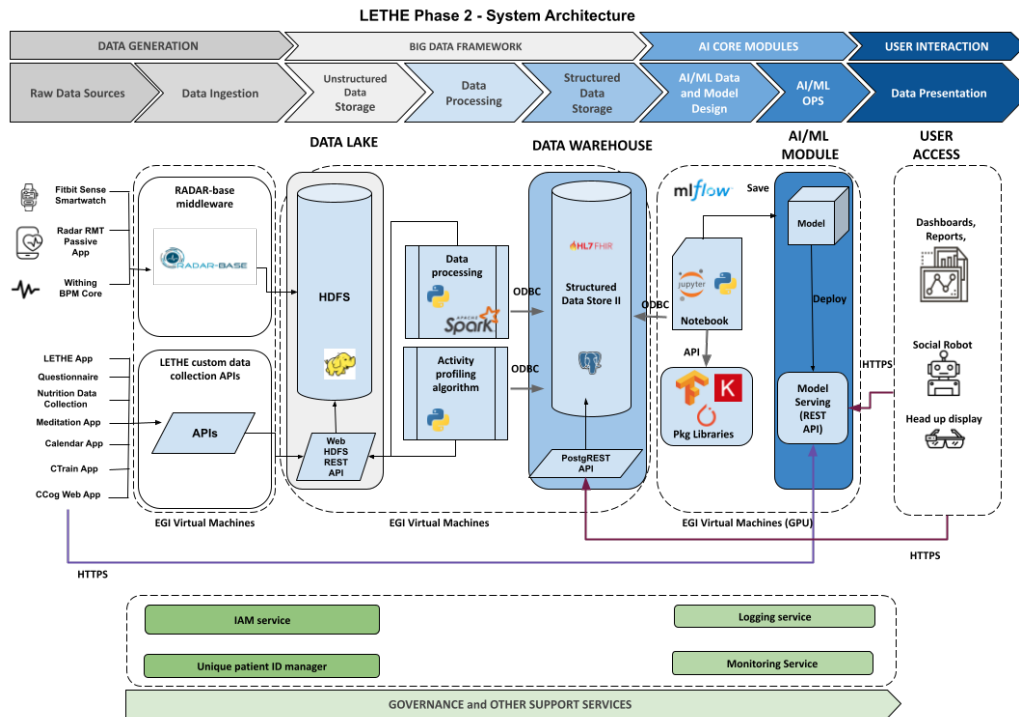
Figure 2: Overview of system architecture and modules of Phase II (prospective data collection).

3.2.2.1 Patient Generated Data Collection (apps, wearables etc)

Generated data from the participant will be collected via various apps and wearables:

- Fitbit Sense (integration via RADAR-base): The Fitbit Sense will be integrated via RADAR-base via Kafka Connector source connector (REST-API). A detailed API description can be found online on GitHub [13].
- Within BPM Core (planned integration via RADAR-base): RADAR-base [3] additionally allows and enables wearable and app integration, which can be implemented through a customized API
- LETHE app (will be developed within the project): The LETHE app collects all passive and active data from the participant in phase II which can not be collected through 3rd party or other integrated apps. The LETHE app uses REST APIs to be connected to the data lake (HDFS).
- 3rd party apps like meditation app, nutrition app, cTRAIN app, cCOG web app: additional apps collecting active data from the participant will be integrated via customized API to the data lake or integrated directly over PostgREST API or SMART on FHIR

A detailed description of all sensors and final selection will be presented in Deliverable D4.3 (LETHE sensing ecosystem) [18].

3.2.2.2 Prospective Clinical Data Collection

Prospective data from the clinical perspective includes data collection from the study centres and will be entered by health care professionals. A detailed description of which clinical data will be collected is described in the LETHE protocol deliverable [14].

3.2.3   Reporting and Dashboards

Dashboards and reports (user interaction/data representation layer) act as representation as well as data collection platforms, where clinical data will be entered via web application and data is integrated into the data warehouse via PostgREST API (see Figure 2).

3.3   Relevant Standards and Terminologies

In order to achieve a maximum of semantic interoperability and interchangeability, the interoperability recommendations are mainly based on HL7 FHIR and international terminologies, in particular SNOMED CT, LOINC and UCUM.

HL7 FHIR (Fast Healthcare Interoperability Resources) is a state-of-the-art standard for health data exchange. FHIR is based on resources to bundle up information, some of the most commonly used resources are Patient, Observation, Medication, Condition. FHIR resources can be handled via RESTful interfaces, applying widely used web technologies like HTTP and JSON. FHIR focuses on easy implementation and adaption for local requirements. Together with the use of web-standards this leads to the fact, that FHIR can be applied in various environment, from healthcare apps to electronic health records [4]. For personal health device communication, a collaboration between the Personal Connected Health Alliance (Continua Alliance) and HL7 FHIR was established, leading to joint specifications like the FHIR Personal Health Device Implementation Guide [5]. To facilitate exchangeability of (personal) healthcare apps, SMART on FHIR offers a standards-based API [6].

Wherever feasible, codes (e.g. for the type of observation or value sets) were taken from the international terminologies LOINC [7], SNOMED CT [8] and UCUM for units of measurements [9]. For the international terminologies, various browsers but also terminology service API are available, like Snowstorm, a SNOMED CT terminology service API based on FHIR [10].

4 Guidelines for Technical Implementation

The following section gives an overview of all relevant interoperability aspects for the technical implementation of the LETHE project. This chapter highlights the recommendations for interoperability.

4.1 Definitions of Interoperability Requirements

In the LETHE project, numerous data elements are collected from different study centres, participants and devices (such as wearables). The premises in data exchange within such a distributed environment should be semantic interoperability, exchangeability and expandability. Furthermore, the LETHE model, that will be set up and trained during the project, should be ready for re-use after the project duration. Ideally, new centres and data sources should be able to use the LETHE model for further research even after the project duration. To ensure sustainability, the definition and use of standards and terminologies is crucial.

The specifications in the following chapters include recommendations on how to store and exchange data collected during the LETHE project in a semantically interoperable and up-to-date way using HL7 FHIR. Retrospective data exchange will be carried out in LETHE project Phase I based on the joint master data set description, which will be described in deliverable D2.1 [2]. The specification for standards and terminologies for retrospective data can be seen as a recommendation and can facilitate the re-use of the LETHE model. For the collection and exchange of prospective data, the use of standards and terminologies should definitely be considered in an earlier step of the project.

The use of widely applied standards and terminologies in combination with standard-based middle ware technologies such as RADAR-base and SMART on FHIR should also facilitate exchangeability of modules/devices/sensors and expandability of the LETHE framework. The overall goal here is to ensure that new wearables, apps, sensors (like IoT sensors) can easily be integrated into the LETHE environment.

4.2 Standards and Profiles for Semantic Interoperability within LETHE

This chapter provides guidelines and recommendation for a semantically interoperable data collection and exchange of retrospective and prospective data (see use cases of data collection in chapter 3.2).

The following tables specify a standard-based structure and terminologies for each data element (e.g. body height or medical history).

Retrospective data elements, descriptions, and units were taken from the deliverable D2.1 [2]. In case the sources had different units, the observation.code is based on the unit taken from the FINGER data set. Notice: A change of the chosen unit of measurement, in particular a switch from e.g. mol/l to g/l, will most likely results in a change of the observation.code. If a conversion from one unit of measurement to another is feasible, the official UCUM unit conversion tool can be used [11].

To represent the data elements using a state-of-the-art standard, HL7 FHIR resources were chosen. For each element the corresponding FHIR resource, code (e.g. observation.code), datatype (e.g. Quantity or CodeableConcept) and recommendation for a value set (wherever needed) are specified.

Beside code and value of a resource (e.g. observation.code and observation.value), FHIR specifies further data elements that can be included as a resource (e.g. observation), like date and performer. These elements are not expressed in the following tables but should definitely be used in the LETHE project, if appropriate.

For examples of FHIR observation resource with different formats/datatypes of the contained value see Figure 3 and Figure 4.

```
<Observation xmlns="http://hl7.org/fhir">          Name of FHIR Resource
  <id value="f004"/>
  <identifier>
    <use value="official"/>
    <system value="http://www.bmc.nl/zorgportal/identifiers/observations"/>
    <value value="6326"/>
  </identifier>
  <status value="final"/>
  <code>
    <coding>                                        Observation.code=
      <system value="http://loinc.org"/>            type of Observation
      <code value="789-8"/>
      <display value="Erythrocytes [#/volume] in Blood by Automated count"/>
    </coding>
  </code>
  <subject>
    <reference value="Patient/f001"/>               Reference to Patient Resource
    <display value="P. van de Heuvel"/>
  </subject>
  <effectivePeriod>
    <start value="2013-04-02T10:30:10+01:00"/>
    <end value="2013-04-05T10:30:10+01:00"/>
  </effectivePeriod>
  <issued value="2013-04-03T15:30:10+01:00"/>
  <performer>
    <reference value="Practitioner/f005"/>
    <display value="A. Langeveld"/>
  </performer>
  <valueQuantity>                                    Value of the Observation, in this
    <value value="4.12"/>                            case a Quantity consisting of
    <unit value="10^12/L"/>                          value and a UCUM unit
    <system value="http://unitsofmeasure.org"/>
    <code value="10*12/L"/>
  </valueQuantity>
  <interpretation>
    <coding>
      <system value="http://terminology.hl7.org/CodeSystem/v3-ObservationInter
      <code value="L"/>
      <display value="Low"/>
    </coding>
  </interpretation>
```

Figure 3: Example of a FHIR Observation Resource (with Datatype Quantity), code snippet taken from https://www.hl7.org/fhir/observation-examples.html

```
<valueCodeableConcept>
    <coding>
        <system value="http://snomed.info/sct"/>
        <code value="35748005"/>
        <display value="Wine (substance)"/>
    </coding>
    <text value="Wine"/>
</valueCodeableConcept>
```

Figure 4: Example of a Value with Datatype CodeableConcept within an Observation Resource, code snippet taken from https://www.hl7.org/fhir/observation-examples.html

4.2.1   Retrospective Data: Demographic Data

To depict retrospective demographic data, the FHIR resource "Patient" is used to a large extent.

The following table shows the interoperability definitions/recommendations for the demographic data set included during the data harmonization task of the retrospective data set.

Mapping from numerical values in retrospective dataset (e.g. marital status, educational level) to FHIR value will be carried out for phase II of the LETHE project when the final variable selection for phase II is done. The current FHIR value sets are including and referenced in the table.

Table 1: Interoperability Recommendations for Demographic Data (Retrospective)

Variable (Label)	Type of data in dataset	Resource.Element	DT (and recommended value set)	unit	FHIR Profile/example Observation, if applicable
Date of birth	Numerical	Patient.birthDate	Date	Not used	https://www.hl7.org/fhir/patient-definitions.html#Patient.birthDate
Age, years	Numerical	Search Parameter using Patient.birthDate			https://www.hl7.org/fhir/patient-extensions-Patient-age.html
Sex	Numerical	Patient.gender	Code ValueSet: AdministrativeGender	Not used	https://www.hl7.org/fhir/patient-definitions.html#Patient.gender
Educational Level	Numerical	New Patient extensions needed: Patient education (combining level and years)	CodeableConcept ValueSet: EducationalLevel	Not used	
Educational Years	Numerical	New Patient extensions needed: Patient education (combining level and years)	Quantity	y	
Marital status	Numerical	Patient.maritalStatus	CodeableConcept ValueSet: Marital Status	Not used	https://www.hl7.org/fhir/patient-definitions.html#Patient.maritalStatus
LivingAlone	Numerical	New Patient extensions needed: PatientLivingArrangement	CodeableConcept ValueSet: LivingArrangement	Not used	

Recommendations for Value Sets for Demographic Data (retrospective):

Marital Status: https://www.hl7.org/fhir/valueset-marital-status.html

Educational Level: https://terminology.hl7.org/1.0.0/ValueSet-v3-EducationLevel.html

LivingArrangement: http://hl7.org/fhir/2020Feb/v3/LivingArrangement/vs.html

Administrative Gender: https://www.hl7.org/fhir/valueset-administrative-gender.html

4.2.2   Retrospective Data: Clinical Data

The following table shows the interoperability definitions/recommendations for the clinical data set included during the data harmonization task of the retrospective data set. For clinical test data, mainly LOINC Codes [7] are used.

Table 2: Interoperability Recommendations for Clinical Data (Retrospective)

Variable	Type of data in dataset	FHIR Observation.code (system;code;display)	FHIR Observation.value DT	FHIR Observation.unit (UCUM)	FHIR Profile/example Observation, if applicable
Height	Numerical	LOINC:8302:body height	Quantity	cm	https://www.hl7.org/fhir/bodyheight.html
Weight	Numerical	LOINC:29463-7:body weight	Quantity	kg	https://www.hl7.org/fhir/bodyweight.html
BMI	Numerical	LOINC:39156-5:body mass index	Quantity	kg/m2	https://www.hl7.org/fhir/bmi.html
DBP	Numerical	Diastolic Blood Pressure Panel (see example observation for data structure): LOINC:8480-6:Systolic blood pressure LOINC:8462-4:Diastolic blood pressure	Quantity	mmHg	https://www.hl7.org/fhir/observation-example-bloodpressure.json.html
SBP	Numerical	Systolic Blood Pressure Panel (see example observation for data structure): LOINC:8480-6:Systolic blood pressure LOINC:8462-4:Diastolic blood pressure	Quantity	mmHg	https://www.hl7.org/fhir/observation-example-bloodpressure.json.html
Cholesterol	Numerical	LOINC:14647-2 Cholesterol [Moles/volume] in Serum or Plasma	Quantity	mmol/l	http://hl7.org/fhir/R4/diagnosticreport-example-lipids.json.html

HDL	Num erical	LOINC Code: 14646-4 Cholesterol in HDL [Moles/volume] in Serum or Plasma	Quantity	mmol /l	
LDL	Num erical	LOINC: 22748-8: Cholesterol in LDL [Moles/volume] in Serum or Plasma	Quantity	mmol /l	
Glucose	Num erical	LOINC:15074-8: Glucose [Moles/volume] in Blood	Quantity	mmol /l	https://www.hl7.org/ fhir/observation-example-f001-glucose.json.html
HbA1C	Num erical	LOINC: 4548-4 Hemoglobin A1c/Hemoglobin.total in Blood	Quantity	%	
Hemoglobin	Num erical	LOINC:718-7:Hemoglobin [Mass/volume] in Blood	Quantity	g/dl	https://www.hl7.org/ fhir/observation-example-f005-hemoglobin.html
Vitamin D	Num erical	LOINC:1649-3: Vit.D, 1,25-Dihydr.-	Quantity	ng/dl	
Vitamin B12	Num erical	LOINC:2132-9:Vitamin B12	Quantity	ng/dl	
Albumine	Num erical	LOINC:1751-7:Albumin	Quantity	g/dl	
Creatinine	Num erical	LOINC:59826-8: Creatinine [Moles/volume] in Blood	Quantity	umol /l	
Calcium	Num erical	LOINC:2000-8:Calcium	Quantity	mmol /l	
TSH	Num erical	LOINC:3016-3:TSH	Quantity	uU/m l	
Folic acid	Num erical	LOINC:2282-2: Folate [Mass/volume] in Blood	Quantity	ng/ml	
Triglycerides	Num erical	LOINC:3043-7:Triglyceride [Mass/volume] in Blood	Quantity	mmol /l	
a-Beta 42	Num erical	LOINC-Code: 33203-1 Amyloid beta 42 peptide [Mass/volume] in Cerebral spinal fluid	Quantity	pg/m L	
pTau	Num erical	LOINC-Code: 72260-3 Phosphorylated tau 181 [Mass/volume] in Cerebral	Quantity	pg/m L	

		spinal fluid by Immunoassay			
totalTau	Num erical	LOINC-Code: 30160-6 Tau protein [Mass/volume] in Cerebral spinal fluid	Quantity	pg/m L	
abeta42pTa u	Num erical	LOINC-Code: 97102-8 Phosphorylated tau 181/Amyloid beta 42 peptide [Ratio] in Cerebral spinal fluid	Quantity	%	
ApoE genotype	Num erical	LOINC: 21619-2: APOE gene mutations found [Identifier] in Blood or Tissue by Molecular genetics method Nominal	CodeableConcept Value Set: LetheApoOEgenotype	Not used	

Recommendations for Value Sets for Clinical Data (Retrospective Data):

LetheAPOEgenotype: LOINC Answer List APOE (https://loinc.org/LL2986-9/)

4.2.3   Retrospective Data: Cognition Data

The following table shows the interoperability definitions/recommendations for the cognition data set included during the data harmonization task of the retrospective data set. Harmonized value sets are given as recommendations.

Table 3: Interoperability Recommendations for Cognitive Data (Retrospective)

Variable	Type of data in datas et	FHIR Observation.code (system;code;display)	FHIR Observation.value DT	FHIR Obser vatio n.unit (UCU M)	FHIR Profile/example Observation, if applicable
Dementia (type)	Num erical	SNOMED: 52448006 | Dementia (disorder)	CodeableConcept ValueSet LetheDementiaType	Not used	
Dementia (binary)	Num erical		CodeableConcept ValueSet:LetheDement iaBinary	Not used	
Clinical dementia rating (CDR) Clinical dementia total rating, first time available at	Num erical	SNOMED: 720204003 |Clinical Dementia Rating score (observable entity)	CodeableConcept ValueSet: LetheClinicalDementia TotalRating	Not used	

2y-visit, completed by the study nurse.					
Digit Symbol (Letter digit substitution test)	Num erical	LetheParameters:LDST:Letter Digit substitution test

273857000 \| Symbol digit modalities test (assessment scale) \| | CodeableConcept

ValueSet: LetheDigitSymbolV1 LetheDigitSymbolV2 | Not used | |
| Digit Span (Wechsler memory scale numbers, digit span) | Num erical | SNOMED: 273921009 \|Wechsler memory scale (assessment scale | CodeableConcept

ValueSet: LeheDigitSpan | Not used | |
| FAS test (verbal fluency by letter) | Num erical | LetheParameters:FluencyLetter: verbal fluency by letter | CodeableConcept ValueSet: LetheFluencyLetter | Not used | |
| Verbal fluency by category | Num erical | LetheParameters:FluencyCategory: verbal fluency by category | CodeableConcept ValueSet: LetheFluencyCategory V1

LetheFluencyCategory V2 | Not used | |
| TMT - A time TMT - B time | Num erical | Panel code: SNOMED: 273882000 \|Trail making test (assessment scale) \|

TMT-A observation code:

LetheParameters:TMT-A:Trail Making Test A

TMT-B observation code: LetheParameters:TMT-B:Trail Making Test B | Quantity (2 observations in panel) | sec | |
| RAVLT | Num erical | | Quantity | [scor e] | |
| Memory Immediate Recall | | SNOMED

311532009 \| Immediate verbal memory (observable entity) \| | CodeableConcept ValueSet: LetheMemImmRecallV 1 | Not used | |

		LetheParameters:MemImmRecall	LetheMemImmRecallV2		
Memory Delated Recall		311533004 | Delayed verbal memory (finding) | LetheParameters:MemoryDelayedRecall	CodeableConcept ValueSet: LetheMemDelRecallV1 LetheMemDelRecallV2	Not used	
Memory Test Story Recall		LetheParameters:MemoryTStoryRecall	CodeableConcept ValueSet: LetheMemStoryRecall	Not used	
MMSE (Mini–Mental State Examination)	Numerical	SNOMED: 447316007 |Mini-mental state examination score (observable entity)	Quantity	[score]	https://hl7.org/implement/standards/fhir/2015Jan/observation-ccda-assessmentscale-ccdaassessmentscaleobservation.html

Recommendations for Value Sets for Cognition Data (Retrospective Data):

LetheDementiaType: 0= no cognitive impairment or dementia, 1= SCI, 2= MCI, 3= Alzheimer's dementia, 4= Frontotemporal dementia, 5= Lewy body dementia, 6= Parkinson-dementia, 7= Vascular dementia, 8= Mixed dementia, 9= other dementia

Alternatively selected child concepts of SNOMED concept 52448006 |Dementia (disorder), see https://browser.ihtsdotools.org/?perspective=full&conceptId1=52448006&edition=MAIN/2021-07-31&release=&languages=en

LetheDementiaBinary: 0=no dementia, 1=dementia (type not specified)

LetheClinicalDementiaTotalRating: Original Values from Data Set: 1=CDR 0; 2=CDR 0.5; 3=CDR 1; 4=CDR 2; 5=CDR 3

*It is **highly recommended** to use **other codes here** (e.g. alphanumerical ones, if value set is used). Otherwise, there is the danger of ambiguities (e.g. between code "1" and score "1").*

LetheDigitSymbolV1: For simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal / mildly below the norm (-1.49 SD or above), 2= markedly below the norm (–1.5 SD to –2.9 SD), 3= very low (-3.0 SD or below)

LetheDigitSymbolV2: For simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal (-0.9 SD or above), 2= impaired (-1.0 SD to –1.9 SD), 3= markedly impaired (-2.0 SD to –2.9 SD), 4= very low (-3.0 SD or below)

LetheDigitSpan: For simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal (-0.9 SD or above), 2= impaired (-1.0 SD to –1.9 SD). 3= markedly impaired (-2.0 SD to –2.9 SD), 4= very low (-3.0 SD or below)

LetheFluencyLetter: for simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set

LetheFluencyCategoryV1: for simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal / mildly below the norm (-1.49 SD or above), 2= markedly below the norm (–1.5 SD to –2.9 SD), 3= very low (-3.0 SD or below)

LetheFluencyCategoryV2: for simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal (-0.9 SD or above), 2= mild impairment (-1.0 SD to –1.49 SD), 3= impaired (-1.5 SD to –1.9 SD), 4= markedly impaired (-2.0 SD to –2.9 SD), 5= very low (-3.0 SD or below)

LetheMemImmRecallV1: for simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal / mildly below the norm (-1.49 SD or above), 2= markedly below the norm (–1.5 SD to –2.9 SD), 3= very low (-3.0 SD or below)

LetheMemImmRecallV2: for simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal (-0.9 SD or above), 2= mild impairment (-1.0 SD to –1.49 SD), 3= impaired (-1.5 SD to –1.9 SD), 4= markedly impaired (-2.0 SD to –2.9 SD), 5= very low (-3.0 SD or below)

LetheMemDelRecallV1: for simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal / mildly below the norm (-1.49 SD or above), 2= markedly below the norm (–1.5 SD to –2.9 SD), 3= very low (-3.0 SD or below)

LetheMemDelRecallV2: for simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal (-0.9 SD or above), 2= mild impairment (-1.0 SD to –1.49 SD), 3= impaired (-1.5 SD to –1.9 SD), 4= markedly impaired (-2.0 SD to –2.9 SD), 5= very low (-3.0 SD or below)

MemoryTStoryRecall: for simple scored results (without categories), DT Quantity and unit {score} can be an alternative to the use of a value set, 1= normal (-0.9 SD or above), 2= impaired (-1.0 SD to –1.9 SD), 3= markedly impaired (-2.0 SD to –2.9 SD), 4= very low (-3.0 SD or below)

LETHEParameters_VS:

Table 4: Value Set LetheParameters_VS

Code	Display	CodeSystem (system)	URL system
LDST	Letter digit substitution test	LETHEParameters	To be registered
FluencyLetter	verbal fluency by letter	LETHEParameters	To be registered
FluencyCategory	verbal fluency by category	LETHEParameters	To be registered
TMT-A	Trail Making Test A	LETHEParameters	To be registered
TMT-B	Trail Making Test B	LETHEParameters	To be registered
MemImmRecall	Memory, immediate recall	LETHEParameters	To be registered
MemDelrecall	Memory, delayed recall	LETHEParameters	To be registered

| MemoryTStoryRecall | Memory test, story recall | LETHEParameters | To be registered |

Table 5: Value Set LetheParameters_VS

4.2.4 Retrospective Data: Functioning/Depression Data

The following table shows the interoperability definitions/recommendations for the functioning and depression data set included during the data harmonization task of the retrospective data set. Harmonized value sets are given as recommendations.

Table 6: Interoperability Recommendations for Functioning/Depression Data (Retrospective)

Variable	Type of data in dataset	FHIR Observation.code (system;code;display)	FHIR Observation.valueDT	FHIR Observation.unit (UCUM)	FHIR Profile/example Observation, if applicable
ADL Basic	Numerical	SNOMED|129025006 |Activity of daily living (observable entity)	Quantity	[score]	
ADL Complex	Numerical	SNOMED|129025006 |Activity of daily living (observable entity)	Quantity	[score]	
SPPB or similar	Numerical	SNOMED|714339007 |Short Physical Performance Battery score (observable entity)	Quantity	[score]	
Balance	Numerical	LOINC Code: 84421-7 Standing Balance Test - unadjusted scale score [NIH Toolbox]	Quantity	[score]	
Chair Stand	Numerical	LOINC Code: 89393-3 Sit to stand - functional ability [CMS Assessment]	CodeableConcept Value Set: LetheChairStand	Not used	
Walk 10 m	Numerical	SNOMED:252480006 | Simple walk test (procedure)	Quantity	m/s	
Grip Strength	Numerical	SNOMED: 75067006 | Manual muscle-testing of hand (procedure) |	Quantity	kg	
Geriatric Depression Scale	Numerical	SNOMED: 273481004 | Geriatric depression scale (assessment scale) |	Quantity	[score]	

| Categorized Depression | | Categorized variable for depression/depressive symptoms | CodeableConcept

Value Set:

LetheDepressionCategorized | | |

Recommendations for Value Sets for Functioning/Depression Data (Retrospective Data):

LetheChairStand: categorical, 1 = average or above, 2 = below average

LetheDepressionCategorized: categorical, 0= no depression/depressive symptoms, 1= depression/depressive symptoms

4.2.5 Retrospective Data: Health Status Data

The following table shows the interoperability definitions/recommendations for the health status data set included during the data harmonization task of the retrospective data set. Harmonized value sets are given as recommendations.

Table 7: Interoperability Recommendations for Health Status Data (Retrospective)

Variable	Type of data in dataset	FHIR Observation.code (system;code;display)	FHIR Observation.valueDT	FHIR Observation.unit (UCUM)	FHIR Profile/example Observation, if applicable
Number of Medication	Numerical			Not used	
Current Medication (ATC code)		Medication.code:atcClass	CodeableConcept Value Set: WHOATC		
Current Medication as ATC Code	Alpha numerical	Resource Medication (MedicationIPS, containing ATC codes)	CodeableConcept Value Set: LetheCurrentMedication		http://hl7.org/fhir/uv/ips/StructureDefinition-Medication-uv-ips.html
Current Medication as ATC Code (selected)		Resource Medication (MedicationIPS, containing ATC codes)	CodeableConcept Value Set: LetheCurrentMedication		
Current Medication		Resource Medication with present status FHIR Medication.code FHIR Medication.status	CodeableConcept Value Set: LetheCurrentMedication		https://www.hl7.org/fhir/medication.html

Medical History (during past year)	Num erical	Ressource <u>Condition</u> Condition.subject = Patient Condition.code	CodeableConcept Value Set: LetheMedicalHistory		
Hospitalizati on within last year	Num erical		CodeableConcept Value Set: LetheHospitalization	Not used	
Falls (in the last year)	Num erical		CodeableConcept Value Set: LetheFallenLastYear	Not used	
Dementia in Family History		FHIR Resource FamilyMemberHistory. condition SNOMED: 429961000	CodeableConcept Value Set: LetheDementiaHistory		https://www.hl7.org/ fhir/familymemberhi story.html

Recommendations for Value Sets for Health Status Data (Retrospective Data):

LetheCurrentMedication: Recommendation for Medication.code - Value Set for the current medication. The use of SNOMED medication codes (existing FHIR value set) is recommended: https://www.hl7.org/fhir/valueset-medication-codes.html

WHOATC: http://hl7.org/fhir/uv/ips/ValueSet-whoatc-uv-ips.html

LetheHospitalization: categorical, 0= no; 1= yes

LetheFallenLastYear: categorical, 0= no; 1= yes

LetheDementiaHistory: categorical, 0= no; 1= yes

Table 8: Recommendation for Condition.code values for the Medical History

429961000	Family history of dementia (situation)	Dementia in family history	SNOMED CT

Recommendations for Supplement CodeSystems:

LETHEParameters: supplement codesystem defined for special project needs, e.g. parameter codes that can't be found in international code systems. Values see ValueSet LETHEParameters_VS above

LetheMedicalHistory: Recommendation for Condition.code values for the Medical History:

Table 9: Interoperability Recommendations - Recommended Codes for LetheMedicalHistory VS

Code	Display	Variable name in joint master data set	System
230690007	Cerebrovascular accident (disorder)	Stroke	SNOMED CT
22298006	Myocardial infarction (disorder)	Myocardial infarction	SNOMED CT

32798002	Parkinsonism (disorder)	Parkinson's disease	SNOMED CT
73211009	Diabetes mellitus (disorder)	Diabetes any	SNOMED CT
46635009	Diabetes mellitus type 1 (disorder)	Diabetes type 1	SNOMED CT
44054006	Diabetes mellitus type 2 (disorder)	Diabetes type 2	SNOMED CT
363346000	Malignant neoplastic disease (disorder)	Cancer	SNOMED CT
55822004	Hyperlipidemia (disorder)	Hyperlipidemia	SNOMED CT
251019006	Coronary bypass graft finding (finding)	Heart bypass	SNOMED CT
35489007	Depressive disorder (disorder)	Depression	SNOMED CT
38341003	Hypertensive disorder, systemic arterial (disorder)	Hypertension	SNOMED CT
82271004	Injury of head (disorder)	Head injury	SNOMED CT
39898005	Sleep disorder (disorder)	Sleep Disorder	SNOMED CT
47505003	Posttraumatic stress disorder (disorder)	PTSD	SNOMED CT
58535001	Physical AND emotional exhaustion state (disorder)	Burnout	SNOMED CT
197480006	Anxiety disorder (disorder)	Anxiety Disorder	SNOMED CT
266257000	Transient ischemic attack (disorder)	TIA	SNOMED CT
14304000	Disorder of thyroid gland (disorder)	Hypothyreosis, hyperthyreosis or other thyroid disease	SNOMED CT
73430006	Sleep apnea (disorder)	Sleep Apnea	SNOMED CT
195967001	Asthma (disorder)	Asthma	SNOMED CT
69896004	Rheumatoid arthritis (disorder)	Rheumatoid Arthritis	SNOMED CT
84757009	Epilepsy (disorder)	Epilepsy	SNOMED CT

4.2.6 Retrospective Data: Lifestyle Data

The following table shows the interoperability definitions/recommendations for the lifestyle data set included during the data harmonization task of the retrospective data set. Harmonized value sets are given as recommendations.

Table 10: Interoperability Recommendations for Lifestyle Data (Retrospective)

Variable	Type of data in dataset	FHIR Observation.code (system;code;display)	FHIR Observation.value DT	FHIR Observation.unit (UCUM)	FHIR Profile/example Observation, if applicable
Sleep time	Numerical	SNOMED| 248263006 |Duration of sleep (observable entity)	Quantity	h	
Sleep difficulties	Numerical	SNOMED| 248254009 |Quality of sleep (observable entity)	CodeableConcept Value Set: LetheSleepQuality	Not used	
Alcohol use	Numerical	LOINC: 74013-4: Alcoholic drinks per day	Quantity	/d	
Smoking	Numerical	SNOMED| 365981007 |Finding of tobacco smoking behavior (finding)|	CodeableConcept ValueSet LetheSmoking: choice of SNOMED CT concepts for Smoker, Ex-Smoker, Never smoked	Not used	

Recommendations for Value Sets for Lifestyle Data (Retrospective Data):

LetheSleepQuality: categorical, 0= no, 1= yes

LetheSmoking: List of 77176002 |Smoker (finding), 8517006 |Ex-smoker (finding)|, 266919005 |Never smoked tobacco (finding)|

4.2.7 Retrospective Data: Neuroimaging Data

The harmonization task for the neuroimaging data is, at the time of deliverable, still an ongoing process. This fact mainly depends on:

- Same MRI parameters have different meanings in different systems (Combinostics [23] vs. FreeSurfer [24])
- Not all selected parameters during the harmonization process are available from all Retrospective Data Sources

For future standardization for neuroimaging data and even neuro MRI images (if applicable) DICOM [16] can be recommended as a standard.

Detailed information about DICOM about the format, media storage and media interchange as well as the services can be found on the DICOM webpage [16].

4.2.8   Prospective Data: Digital Biomarkers (Sensor System)

The digital biomarkers from the LETHE phase II come from various sources.

The data elements included in the following table were taken from WP2 results Biomarkers_Table_Phases (see Annex 2), but final selection still needs to be done depending on the Trial Protocol.

For time-discrete data elements see recommendations for retrospective data above. For all the digital biomarkers the same recommendations will be used.

The measuring devices can be identified and described using the FHIR resource "Device". These resources can then be linked to single measurements within each observation.

Table 11: Interoperability Recommendations for Prospective Data: Digital Biomarkers (Sensor System)

Lifestyle Category	Variable	Data source	FHIR Observation.code	FHIR Observation.value DT	FHIR Observation.unit (UCUM)	FHIR Profile, if applicable
Physical Activity	Heart rate	Sensor	LOINC: 8867-4: heart rate	Quantity	/min	https://www.hl7.org/fhir/observation-example-heart-rate.html
	Exercise/Activity	Sensor	228450008 |Time spent exercising (observable entity)	Quantity	h/d	
	Pulse	Sensor	See line for Heart Rate above			
	SpO2	Sensor	LOINC: 2708-6: Oxygen saturation in Arterial blood	Quantity	%	https://www.hl7.org/fhir/observation-example-satO2.html
	Gait characteristics	Sensor	SNOMED: 363836006 |Gait observable (observable entity)| (more detailed concepts are available as child	To be defined		

			concepts of the above mentioned, e.g. step height, step length, gait type, dynamic gait index score)			
Meditation /Sleep	Sleep quality	Sensor	SNOMED| 248254009 |Quality of sleep (observable entity)	CodeableConcept Value Set: LetheSleepQuality	Not used	
	Sleep Duration	Sensor	SNOMED | 248263006 | Duration of sleep (observable entity)	Quantity	min	
	Sleep Fragmenta tion	Sensor	SNOMED | 404950004 | Sleep behavior (observable entity)	CodeableConcept Value Set: LetheSleepFragmen tation	min	
	Sleep Movement	Sensor		To be defined		

Recommendations for Value Sets for Prospective Data from Sensor System:

LetheSleepQuality: SNOMED answers or LOINC Answer List may be useful (very poor, poor, fair, good, very good): https://loinc.org/LL1023-2/ and should be mapped with sleeping variables of retrospective dataset

LetheSleepFragmentation: SNOMED answers or LOINC codes may be useful (93821-6 Deep sleep duration, 93829-0 REM sleep duration, 93830-8 Light sleep duration)

4.2.9   Prospective Data: Digital Biomarkers (App Systems)

The digital biomarkers from the LETHE phase II come from various sources.

The data elements included in the following table were taken from WP2 results of Digital Biomarkers (see Annex 2), but final selection still needs to be done.

For time-discrete data elements see recommendations for retrospective data above. For all the digital biomarkers the same recommendations will be used.

The measuring devices can be identified and described using the FHIR resource "Device". These resources can then be linked to single measurements within each observation.

Table 12: Interoperability Recommendations for Prospective Data: Digital Biomarkers (App Systems)

Lifestyle Category	Variable	Data source	FHIR Observation.code	FHIR Observation.valueDT	FHIR Observation.unit (UCUM)	FHIR Profile, if applicable
Cardio-vascular risk	Alcohol	App	LOINC: 74013-4: Alcoholic drinks per day	Quantity	/d	
	Smoking		**Option A:** SNOMED CT: 65568007 |Cigarette smoker (finding)| **Option B:** LOINC: 8663-7: Cigarettes smoked current (pack per day) - Reported	**Option A:** CodeableConcept ValueSet: LetheSmokerLevel: Choice of SNOMED CT concepts for Very heavy, Heavy, Moderate, occasional cigarette smoker **Option B** Quantity (Attention: PACK/day)	**Option A.** Not used **Option B:** {#}/d	
Nutrition	Weight	App	LOINC: 29463-7: Body weight	Quantity	kg	https://www.hl7.org/fhir/bodyweight.html
	Meals	App	In case "number of meals" is documented: SNOMED: 1156180009 |Estimated intake of meals in 24 hours (observable entity)|	Quantity	{#}/d	
	Calorie intake	App	SNOMED: 860729008 |Estimated quantity of	Quantity	Cal/d	

			intake of energy in 24 hours (observable entity)|			
	Water intake	App	SNOMED: 789336006 |Estimated quantity of intake of water via oral route in 24 hours (observable entity)|	Quantity	l/d	
Cognition	Cognitive games	App	Specific data elements to be defined			
	Tapping/ typing games	App	Specific data elements to be defined			
	Eye movement	App	SNOMED: 246692008 |Eye movement with both eyes open (observable entity)|	CodeableConcept Value Set: LetheEyeMovement		
	Meditation	App	Specific data elements to be defined			
	Emotion recording	App	SNOMED: 285854004 |Emotion (observable entity)| In case "mood" is more suitable: SNOMED: 1155968006 |Mood (observable entity)|	CodeableConcept Value Set: LetheEmotions		

Recommendations for Value Sets for Prospective Data (App related):

LetheSmokingLevel: Choice of SNOMED CT concepts for Very heavy, Heavy, Moderate, occasional cigarette smoker. Child concepts of 65568007 |Cigarette smoker (finding)|. SNOMED CT defines the values for cigarettes per day for each level (e.g. heavy cigarette smoker = 20-39 cigarettes/day)

LetheEyeMovement: to be harmonized. A selection of descendants of SNOMED CT concept 366079002 |Finding of eye movement (finding)| may be useful (https://browser.ihtsdotools.org/?perspective=full&conceptId1=366079002&edition=MAIN/2021-07-31&release=&languages=en)

LetheEmotions: to be harmonized. A selection of descendants of SNOMED CT concept 106126000 |Emotional state finding (finding)| may be useful (https://browser.ihtsdotools.org/?perspective=full&conceptId1=106126000&edition=MAIN/2021-07-31&release=&languages=en)

4.2.10 Prospective Data: cCOG Features

cCOG [1] is a web-based cognitive test which can be performed at patient's home and will take place every 6 months. It consists of six different tasks:

- Immediate recall
- Reaction time test (2 letters Right/Left)
- Fragmented letters test
- Attention test 1
- Attention test 2
- Delayed recall

It also contains an optional questionnaire for dementia with Lewy bodies [22].

Table 13: Interoperability Recommendations for Prospective Data: cCOG Features

Variable/Feature	Unit	Range	Comment	Possible FHIR Resource => Custom FHIR Questionnaire
Date	date	DD.MM.YYYY	Date when test was performed	https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.date
Immediate recall	# of words	0-36	12 pictures + word below shown three times	Item: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item which is readOnly: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.readOnly with an initial integer value: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.initial.value_x
Delayed recall	# of words	0-12	memorize the 12 pictures shown	Item: https://www.hl7.org/fhir/quest

				ionnaire-definitions.html#Questionnaire.item which is readOnly: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.readOnly with an initial integer value: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.initial.value_x_
Choice reaction time	seconds	0-	standard deviation of the reaction time for L and R letters	Item: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item which is readOnly: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.readOnly with an initial integer value: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.initial.value_x_
Fragmented letters	# of letters	0-20	20 fragmented letters shown	Item: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item which is readOnly: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.readOnly with an initial integer value: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.initial.value_x_
Trail making A	seconds	0-	click numbers 1-24 shown in the order	Item: https://www.hl7.org/fhir/quest

				ionnaire-definitions.html#Questionnaire.item which is readOnly: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.readOnly with an initial integer value: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.initial.value_x_
Trail making B	seconds	0-	click numbers 1-24 as follows: 1 within circle, 2 within square, 3 within circle, …, 24 within square	Item: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item which is readOnly: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.readOnly with an initial integer value: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.initial.value_x_
Global cognitive score	-	0-1	Global score for the six tasks [score]	with an initial float value: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.initial.value_x_
Q - Age	years	0-100	age	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Q - Sex	-	male/female/other	Sex Code ValueSet: AdministrativeGender	Reference choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-reference Answers are defined in: http://hl7.org/fhir/ValueSet/administrative-gender

Q -Education	-	-	choices are country specific, e.g., no education (<8 years), primary school (~8 years), secondary school (~13 years), college or university bachelor (~15 years), university masters (~17 years) CodeableConcept ValueSet: EducationalLevel	Reference choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-reference Answers are defined in: http://www.hl7.org/fhir/v3/EducationLevel/cs.html
Q - Alertness	-	alert/neither alert or tired/tired	the alertness of the user CodeableConcept ValueSet: LetheAlertness	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html
Q - Concentration	-	good/moderate/poor	the concentration level of the user CodeableConcept ValueSet: LetheConcentration	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html
Q - Help obtained	-	yes/no	if help obtained, specify what: 1) typing the words/letters, 2) understanding the instructions, 3) doing the tasks, e.g., received tips about the words to be remembered CodeableConcept ValueSet: LetheHelpObtained	Item: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item from type question: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-question Enable other options if answer is yes with following resource: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.enableWhen If yes, options appear: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice

				Answer codes are defined in: https://www.hl7.org/fhir/value set-questionnaire-answers.html
Q - Distraction	-	yes/no	if distractions during the test, write down what. CodeableConcept ValueSet: LetheDistraction	Item: https://www.hl7.org/fhir/quest ionnaire-definitions.html#Questionnaire. item from type question: https://www.hl7.org/fhir/codes ystem-item-type.html#item-type-question Enable other options if answer is yes with following resource: https://www.hl7.org/fhir/quest ionnaire-definitions.html#Questionnaire. item.enableWhen If yes, text appear: https://www.hl7.org/fhir/codes ystem-item-type.html#item-type-text
Q - Place	-	clinic/home/s omewhere else	place where the test was administered CodeableConcept ValueSet: LethePlace	Type choice: https://www.hl7.org/fhir/codes ystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/value set-questionnaire-answers.html
Q - Pointing device	-	touch screen/laptom mouse/extern al mouse	pointing device used CodeableConcept ValueSet: LethePointingDevice	Type choice: https://www.hl7.org/fhir/codes ystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/value set-questionnaire-answers.html
Q - Keyboard	-	software keyboard on the touch screen / physical keyboard	CodeableConcept ValueSet: LetheKeyboard	Type choice: https://www.hl7.org/fhir/codes ystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/value set-questionnaire-answers.html
Optional				

QDLB - Walking & balance	-	yes/no	CodeableConcept ValueSet: LetheWalkingBalance	Type boolean: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-boolean
QDLB - Hallucinations	-	> once/week, < once/week, no	CodeableConcept ValueSet: LetheHallucinations	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html
QDLB - Constipation	-	never/sometimes/often	CodeableConcept ValueSet: LetheConstipation	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html
QDLB - Orthostatic hypotension	-	never/sometimes/often	CodeableConcept ValueSet: LetheOrthostaticHypotension	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html
QDLB - RBD	-	yes/no if yes, since how long: < 1 year / 1-5 years / 5-10 years / >10 years CodeableConcept ValueSet: LetheRBD	Item: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item from type question: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-question Enable other options if answer is yes with following resource: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.enableWhen If yes, options appear: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/value

				set-questionnaire-answers.html
			if yes, how often: daily / weekly / monthly and how long: >1 hr / 5mins-1hr / <5 mins / seconds CodeableConcept ValueSet: LetheFluctuations	Item: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item from type question: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-question Enable other options if answer is yes with following resource: https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.item.enableWhen If yes, options appear: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html
QDLB - Fluctuations	-	yes/no		
QDLB - Urinary retention	-	never/sometimes/often	CodeableConcept ValueSet: LetheUrinaryRetention	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html

Recommendations for Value Sets for cCOG Features (Prospective Data):

Educational Level: https://terminology.hl7.org/1.0.0/ValueSet-v3-EducationLevel.html

LetheAlertness: alert/neither alert or tired/tired

LetheConcetration: good/moderate/poor

LetheHelpObtained: yes/no

LetheDistraction: yes/no

LethePlace: clinic/home/somewhere else

LethePointingDevice: touch screen/laptom mouse/external mouse

LetheKeyboard: software keyboard on the touch screen / physical keyboard

LetheWalkingBalance: yes/no

LetheHallucination: > once/week, < once/week, no

LetheConstipation: never/sometimes/often

LetheOrthostaticHypotension: never/sometimes/often

LetheRBD: yes/no

LetheFluctuations: yes/no

LetheUrinaryRetention: never/sometimes/often

4.2.11 Prospective Data: cTRAIN Features

cTRAIN [1] is a cognitive training battery similar to the one used in FINGER.

The battery consists of six games covering executive processes, working memory, episodic memory and mental speed. The user is supposed to have training sessions 3 times per week (10-15 mins/session) based on a predefined training program (two games/session).

The following games are covered:

- executive processes
- working memory
- episodic memory
- mental speed

Table 14: Interoperability Recommendations for Prospective Data: cTRAIN Features

Variable/Feature	Unit	Range	Comment	Possible FHIR Resource => Custom FHIR Questionnaire
Date	-	DD.MM.YYYY	Date when training was performed	https://www.hl7.org/fhir/questionnaire-definitions.html#Questionnaire.date
Updating - task	-	number/letter/color/spatial CodeableConcept ValueSet: LetheUpdatingTask	Defines the specific task used	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html
Updating - level	-	low/medium/high CodeableConcept	Length of the list (4-7/6-	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-

			11/5-15)	choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html
Updating - correct sequences	# of sequences	0-	Number of correct recalled 4-item sequences	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Updating - correct items	# of items	0-	Total number of correct recalled items	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Mental set shift - time	seconds	0-	Time for correct choices	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Mental set shift - items	# of items	0-	Number of correct choices	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Working memory - level	-	2-	Length of sequence shown	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Working memory - correct trials	# of trials	0-	Number of correct trials	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Episodic memory relational - level	-	low/medium/high CodeableConcept ValueSet: LetheEpisodicMemoryRelationalLevel	Time the triplets are shown (10 s/8 s/ 6 s)	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-

				questionnaire-answers.html
Episodic memory relational - correct items	-	0-24	Number of correct triplet eithers when a cue is shown (2 x 12 words)	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Episodic memory spatial - level	-	low/medium/high CodeableConcept ValueSet: LetheEpisodicMemorySpatialLevel	Number of pairs (8/10/12)	Type choice: https://www.hl7.org/fhir/codesystem-item-type.html#item-type-choice Answer codes are defined in: https://www.hl7.org/fhir/valueset-questionnaire-answers.html
Episodic memory spatial - time	seconds	0-	Time to find all pairs	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Episodic memory spatial - number of turns	# of turns	16-	Time to find all pairs	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Shape match - time	seconds	0-	Mean reactiontime	Type integer: https://www.hl7.org/fhir/valueset-item-type.html
Shape match - accuracy	%	0-100	Overall accuracy	Type decimal: https://www.hl7.org/fhir/valueset-item-type.html

Recommendations for Value Sets for cTRAIN Features (Prospective Data):

LetheUpdatingTask: number/letter/color/spatial

LetheUpdatingLevel: low/medium/high

LetheEpisodicMemoryRelationalLevel: low/medium/high

LetheEpisodicMemorySpatialLevel: low/medium/high

4.2.12 Prospective Data: LETHE App

The LETHE app consists of several parts, which will now be discussed in more detail.

4.2.12.1 LETHE App - Questionnaire & Calendar

The questionnaire in the LETHE app is mainly mapped via the FHIR resource "Questionnaire" [15]. Following types of questions are planned: (see Annex 1)

- Audio
  - Record audio files from patients
  - Not included in Questionnaire resource. Could be accomplished by a deviation from the standard and send audio recordings as Media resource (https://www.hl7.org/fhir/media.html).
- Checkbox
  - Multiple Selection of predefined items
  - Accomplished by Extension: http://hl7.org/fhir/2016may/extension-questionnaire-itemcontrol.html with following value set: http://hl7.org/fhir/2016may/codesystem-questionnaire-item-control.html#check-box
- Descriptive
  - Display information without input from user
  - https://www.hl7.org/fhir/codesystem-item-type.html#item-type-display
- Info-Screen
  - Display information without input from user
  - https://www.hl7.org/fhir/codesystem-item-type.html#item-type-display
- Radio
  - Buttons for single-selection
  - Accomplished by Extension: http://hl7.org/fhir/2016may/extension-questionnaire-itemcontrol.html with following value set: http://hl7.org/fhir/2016may/codesystem-questionnaire-item-control.html#radio-button
- Range-info
  - Provides information for Range-input
  - https://www.hl7.org/fhir/codesystem-item-type.html#item-type-display
- Range-input
  - Select value from given range
  - Could be accomplished by Extension: http://hl7.org/fhir/2016may/extension-questionnaire-itemcontrol.html with following lower http://hl7.org/fhir/2016may/codesystem-questionnaire-item-control.html#lower and upper http://hl7.org/fhir/2016may/codesystem-questionnaire-item-control.html#upper bound
- Slider
  - Select value from given range
  - Accomplished by Extension: http://hl7.org/fhir/2016may/extension-questionnaire-itemcontrol.html with following value set http://hl7.org/fhir/2016may/codesystem-questionnaire-item-control.html#slider and with step size https://www.hl7.org/fhir/extension-questionnaire-sliderstepvalue.html
- Text
  - Narrative text input
  - http://hl7.org/fhir/2016may/codesystem-item-type.html#text
- Date

- o Input of a date
- o http://hl7.org/fhir/2016may/codesystem-item-type.html#date
- Time
  - o Input of a time
  - o http://hl7.org/fhir/2016may/codesystem-item-type.html#time
- Timed-test
  - o Test with countdown
  - o Timed tests e.g. with a countdown are not supported by FHIR standard. An extension needs to be written on our own with all instructions for the app to fulfil the test.

The exchange of information for the calendar will take place via iCal/JSON. An example could look like this [17]:

```
BEGIN:VCALENDAR

VERSION:2.0

PRODID:-//ZContent.net//Zap Calendar 1.0//EN

CALSCALE:GREGORIAN

METHOD:PUBLISH

BEGIN:VEVENT

SUMMARY:Abraham Lincoln

UID:c7614cff-3549-4a00-9152-d25cc1fe077d

SEQUENCE:0

STATUS:CONFIRMED

TRANSP:TRANSPARENT

RRULE:FREQ=YEARLY;INTERVAL=1;BYMONTH=2;BYMONTHDAY=12

DTSTART:20080212

DTEND:20080213

DTSTAMP:20150421T141403

CATEGORIES:U.S. Presidents,Civil War People

LOCATION:Hodgenville\, Kentucky

GEO:37.5739497;-85.7399606

DESCRIPTION:Born February 12\, 1809\nSixteenth President (1861-1865)\n\n\n

 \nhttp://AmericanHistoryCalendar.com

URL:http://americanhistorycalendar.com/peoplecalendar/1,328-abraham-lincoln
```

END:VEVENT

END:VCALENDAR

4.2.12.2 LETHE App - Personal Goals

Participants should be allowed to set their own goals. This will be realised by the FHIR resource "Questionnaire" [15]. For each of the seven lifestyle categories, the patient can choose an option from a set of values (e.g. steps at physical activity) and afterwards he/she can set a specific target value (e.g. 500). First, seven group items are created which are then filled with further elements representing the choices. As this is a generic solution, the objectives can be extended with further choices per category. Another variant would be to use the resource "Goal" (https://www.hl7.org/fhir/goal.html) or "PlanDefinition" (https://www.hl7.org/fhir/plandefinition.html). When using PlanDefinition, several goals could be defined and also be mapped with a CodeableConcept of categories. The representation of the seven categories will be a new value set which is called **LetheLifeStyle**:

- Physical Activity
- Nutrition
- Cognition
- Meditation & Sleep
- Social
- Cardiology

4.2.12.3 LETHE App - Tasks

The tasks and messages are defined by a physician and should be completed by the patient until a certain time. There are several possibilities to represent the tasks in FHIR. First, PlanDefinition (https://www.hl7.org/fhir/plandefinition.html) could be used, where several goals could be defined. As mentioned in aforementioned section, the categories will be mapped with a new value set: **LetheLifeStyle**. Another representation of the tasks would be possible via resource "Goal" (https://www.hl7.org/fhir/goal.html) or "Task" (https://www.hl7.org/fhir/task.html).

4.2.12.4 LETHE App - Knowledge material

The LETHE app can be used to provide material and information on the LETHE lifestyle sections. This will be mainly carried out by health care professionals via REST-APIs to provide the audio/video/material content.

4.2.13 AI Module Data

There are various predictions that can be made, such as the classification of Cognitive Normal (CN), Mild Cognitive Impairment (MCI) and Alzheimer Disease (AD) or if there is a conversion from MCI to AD. Another possible prediction is the MMSE. As there is no decision on the final forecast type yet, this point remains open.

4.3 Mapping and Harmonization (LETHE project phase I and phase II)

Identified features from the retrospective data set within the LETHE project phase I will also be collected in LETHE phase II. For some features mapping tables will be necessary to harmonize new

collected feature values to use it within the LETHE model and overall architecture. Where necessary, this will be carried out via mapping tables during the technical implementation of the LETHE architecture.

4.4 Platforms, Middleware, Reports, Dashboards

Various platforms and middleware for the sensing system will be described in the deliverable D4.3 [18] and deliverable D2.2 [12] in more detail. During technical setup a customized REST API will be created to integrate various sources into the data lake and respectively into the data warehouse. One possible solution is SMART on FHIR [19]. Final technology selection will be done when the final LETHE trial protocol is developed.

Interoperable dashboards will be forced during the LETHE project. Wherever possible, state-of-art standards for interoperable dashboards will be used. Those include:

- CDISC Standards [20]
- EMA Trial Recommendations [21]

4.5 Prospect: Recommendation for future re-use of LETHE model

The plain model structure without weights as well as the dimensions of training and test data can be publicly available. With this information, other models can be developed by tuning the hyperparameters of given model structure. Another point that would be interesting for other projects would be the construction of the data pipeline, in which the data is extracted from the devices and converted into features.

There are several ways to share the model structure as well as some dummy data and the data pipeline. For example, this information could be hosted on Jupyter Notebooks, Streamlit or Github.

5 Summary/Discussion

The deliverable provides the information as well as the recommendations for the interoperability aspects for the technical LETHE implementation. Whenever possible, state-of-the-art standards for healthcare (FHIR, LOINC, …) were used. Standardized value sets (e.g. FHIR) were collected and will be implemented during the technical setup phase. Especially the recommended standards and value sets within this document enable a re-use of models and interfaces. Moreover, recommended standards aim to speed up the setup of the technical interoperability model.

As the LETHE technical infrastructure and technology landscape is a complex system, it is not possible at the stage of the project to identify all digital biomarkers and features. Hence all modules were identified and an interoperability standard with proposed value sets is given for the certain interoperability problem within each module.

Related to the interoperability framework, mapping tables between LETHE phase I and LETHE phase II value sets are partially an open issue, which will be solved when the final features are selected to be harmonized over the two phases. Moreover, final feature selection and variables from the AI core module needs to be done, which depends on the final selection of the digital biomarkers.

Therefore, tech selection for the interoperability framework in this deliverable is provided in a scalable way, whereby new upcoming features can be easily added and integrated if needed.

6 References

[1] LETHE WP4, Deliverable D4.2 - LETHE brain training app "cTrain tool"

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[4] HL7 FHIR Summary https://hl7.org/FHIR/summary.html

[5] HL7 FHIR Personal Health Device Implementation Guide Home Page http://hl7.org/fhir/uv/phd/2019May/

[6] SMART on FHIR https://smarthealthit.org/

[7] LOINC (Logical Observation Identifiers Names and Codes) https://loinc.org/

[8] SNOMED CT https://www.snomed.org/

[9] UCUM (Unified Codes for Units of Measurement) https://ucum.org

[10] Snowstorm https://github.com/IHTSDO/snowstorm

[11] UCUM Converter web services https://ucum.nlm.nih.gov/ucum-service.html

[12] LETHE WP2, Deliverable D2.2 - LETHE architecture and scenarios (draft)

[13] GitHub, RADAR-base REST connector, https://github.com/RADAR-base/RADAR-REST-connector

[14] LETHE WP7, LETHE Deliverable D7.1 - Study Protocol (draft)

[15] FHIR Questionnaire https://www.hl7.org/fhir/questionnaire.html

[16] DICOM Standard: https://www.dicomstandard.org/

[17] iCalendar Standard https://icalendar.org/

[18] LETHE WP4, Deliverable D4.3 - LETHE sensing ecosystem (draft)

[19] SMART on FHIR, https://smarthealthit.org/

[20] CDISC, https://www.cdisc.org/standards

[21] EMA - Clinical trials in human medicines, https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials-human-medicines

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7 Annex

Research: Types of questions (Radarbase vs. FHIR)

This research is based on all supported types of questions found in the Radarbase documentation [src] and checked against the possibilities provided by FHIR Questionnaire resource [src].

As Radarbase does not stick to any international standard with its own procotol files for defining questions, it's difficult to translate all types of questions 1:1. Providing the same user experience with FHIR as with Radarbase will heavily depend on the used rendering logic in the app. We will likely need to implement our custom rendering logic if special cases like timed tests or media input are needed.

Type of question	Radarbase	FHIR Questionnaire
Audio	✅ Allows participants to record audio files and send them to the Radarbase server [screenshot]	⚠️ Not included in Questionnaire resource. Could be accomplished by a deviation from the standard and send audio recordings as Media resource. Research needs to be done on how to instruct the rendering platform to record something without violating against FHIR rules.
Checkbox	✅ Displays checkboxes for multi-selection [screenshot]	✅ Extension questionnaire-itemControl available for providing UI rendering instructions based on the *questionnaire-item-control valueset* [valueset]
Descriptive	✅ *<Supported by Radarbase according to their Wiki, but no further information on this type nor its representation is provided>*	✅ Allows to display text without capturing an answer [valueset]
Info-Screen	✅ Provide information to the participants [screenshot]	✅ Allows to display text without capturing an answer [valueset]
Matrix-radio	✅ *<Supported by Radarbase according to their Wiki, but no further information on this type nor its representation is provided> [commit on github]*	⚠️ *<As no information is provided by Radarbase, no complement can be looked up in the FHIR standard>*
Radio	✅ Displays radio buttons for single-selection [screenshot]	✅ Extension questionnaire-itemControl available for providing UI rendering instructions based on the *questionnaire-item-control valueset* [valueset]
Range-info	✅ Allows the participant to select a value from a given range with additional information on each value [screenshot]	✅ Providing "display" information along with questions is possible out of the box.
Range-input	✅ Allows the participant to select a value from a given range [screenshot]	⚠️ Upper-bound and Lower-bound can be provided using the questionnaire-itemControl extension and the binded value set
Slider	✅ Provide a slider for selecting a value within a given range [screenshot]	✅ Extension for hinting a step size on siders is available [sliderStepValue]. Rendering instructions for sliders can be passed with the questionnaire-itemControl extension
Text	✅ Allows input of narrative text [screenshot]	✅ Narrative text input is supported [QuestionnaireItemType]
Date	✅ Allows input of a date [screenshot]	✅ Date input is supported [QuestionnaireItemType]
Time	✅ Allows input of a time [screenshot]	✅ Time input is supported [QuestionnaireItemType]
Timed-test	✅ Test with a time countdown to fulfill a given task [screenshot]	⛔ Timed tests e.g. with a countdown are not supported by FHIR standard. An extension needs to be written on our own with all instructions for the app to fulfill the test.

Ad Radarbase: For most types of questions proper documentation is missing *[see RADAR-REDCap-aRMT-Definitions]. Reverse engineering for existing protocols needs to be done.*

Sources
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- https://radar-base.atlassian.net/wiki/spaces/RAD/pages/466878472/RADAR-REDCap-aRMT-Definitions
- https://www.hl7.org/fhir/questionnaire.html
- https://www.hl7.org/fhir/media.html
- https://lhncbc.github.io/lforms/demos.html
- http://hl7.org/fhir/2016may/valueset-item-type.html

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Table 1: Available data for phases I and II of the LETHE project.

	Phase I	Phase II	Acquisition Type	Data source
Clinical Parameter	Body measures	Body measures	time-discrete	
	Blood markers	Blood markers	time-discrete	
	Blood pressure	Blood pressure	time-discrete	
	-	Genetic markers	time-discrete	
Physical Activity and Health	Medication	Medication	time-discrete	
	Heart diseases	Heart diseases	time-discrete	
	Diabetes	Diabetes	time-discrete	
	Injuries	Injuries	time-discrete	
	Family history	Family history	time-discrete	
	Accidents	Accidents	time-discrete	
		Exercise/Activity	continuous	Sensor
		Hear rate	continuous	Sensor
		SpO$_2$	continuous	Sensor
		Gait characteristics	continuous	App
Cardio-vascular risk	Alcohol		time-discrete	
		Alcohol	continuous	App
	Smoking	-	time-discrete	
		Smoking	continuous	App
Social interaction	Marriage status	Marriage status	time-discrete	
	Education level	Education level	time-discrete	
	Occupation	Occupation	time-discrete	
	Living alone	Living alone	time-discrete	
		Location change	continuous	Sensor
		Social Apps	continuous	App
		Time spent outside	continuous	Sensor
		Chatbot	continuous	App
Nutrition	Weight	-	time-discrete	
		Weight	continuous	App
		Meals	continuous	App
		Calorie intake	continuous	App
		Water intake	continuous	App
Cognition	Dementia (type)	Dementia (type)	time-discrete	
	Impairment state	Impairment state	time-discrete	
	Dementia ratings	Dementia ratings	time-discrete	
	MRI	MRI	time-discrete	
	CSF	CSF	time-discrete	
	ApoE	ApoE	time-discrete	
		Cognitive games	continuous	App
		Tapping/typing games	continuous	App
		Eye movement	continuous	App
Meditation and Sleep	Depression/GDS	Depression/GDS	time-discrete	
	Sleep quality	-	time-discrete	
		Sleep quality	continuous	Sensor
		Meditation	continuous	App
		Pulse, HRV	continuous	Sensor
		Emotion recording	continuous	App

HRV: hear rate variability, GDS: global deterioration scale; acquisition type *continuous* is to be understood on a daily/weekly basis and not as permanent acquisition.