

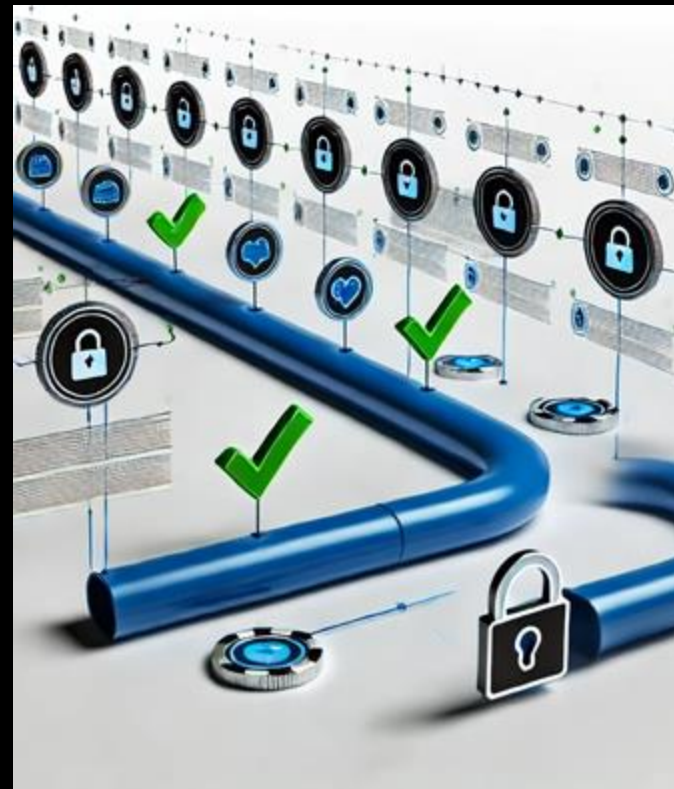


Using USDM to Drive Real World Data



EQTY LIFE
SCIENCES

- Introduction
- Reliability and Traceability using cryptography
- USDM Content
- Step by Step: FHIR to SDTM
- Full Lineage & Governance
 - ◆ Data Lineage
 - ◆ Process Traceability
 - ◆ Governance Control
- Conclusions



Real World Evidence

Project:
Quality and reusability
of Real-World Data

This poster summarizes the RWE working group discussions from the recent 2023 PHUSE CSS. At the event, sponsors, vendors and regulators evaluated recent regulatory guidance, created definitions, and identified gaps for sponsors to utilize Real-world data (RWD) to generation Fit For Purpose Real-World-Evidence (RWE).

How did we define data quality?



Key dimensions of fit for purpose:

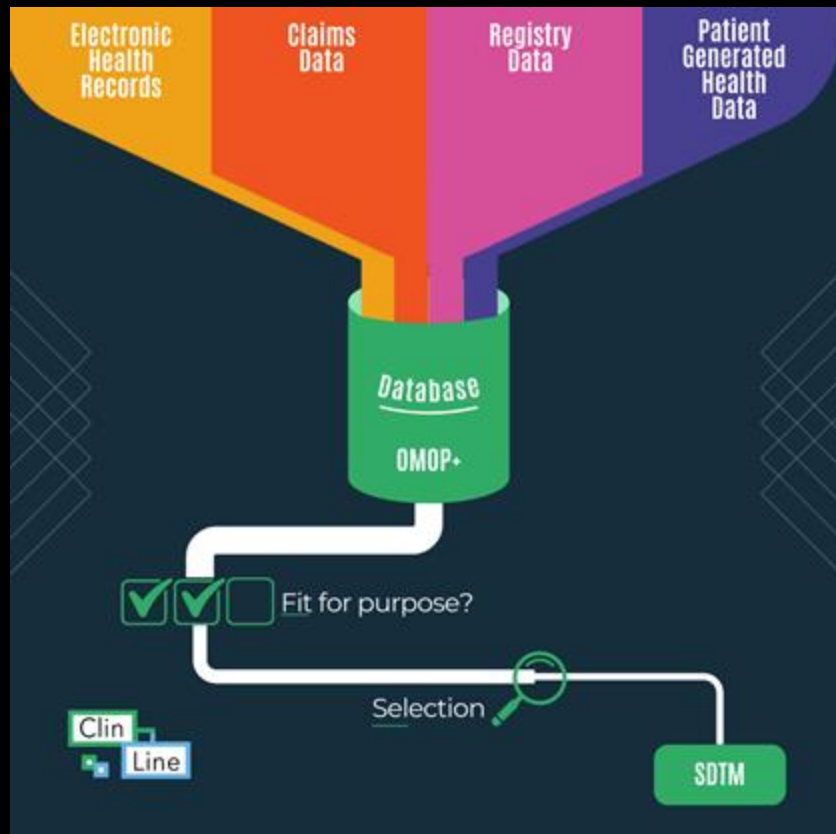
	FDA ¹	EMA ²
Relevance	• Availability	• Representativeness • Timeliness
Reliability	• Data accuracy • Completeness • Provenance • Traceability	• Precision • Accuracy • Plausibility • Extensiveness • Coherence

1. US Food and Drug Administration. Framework for FDA's Real-World Evidence Program. US Department of Health & Human Services; December 2018.



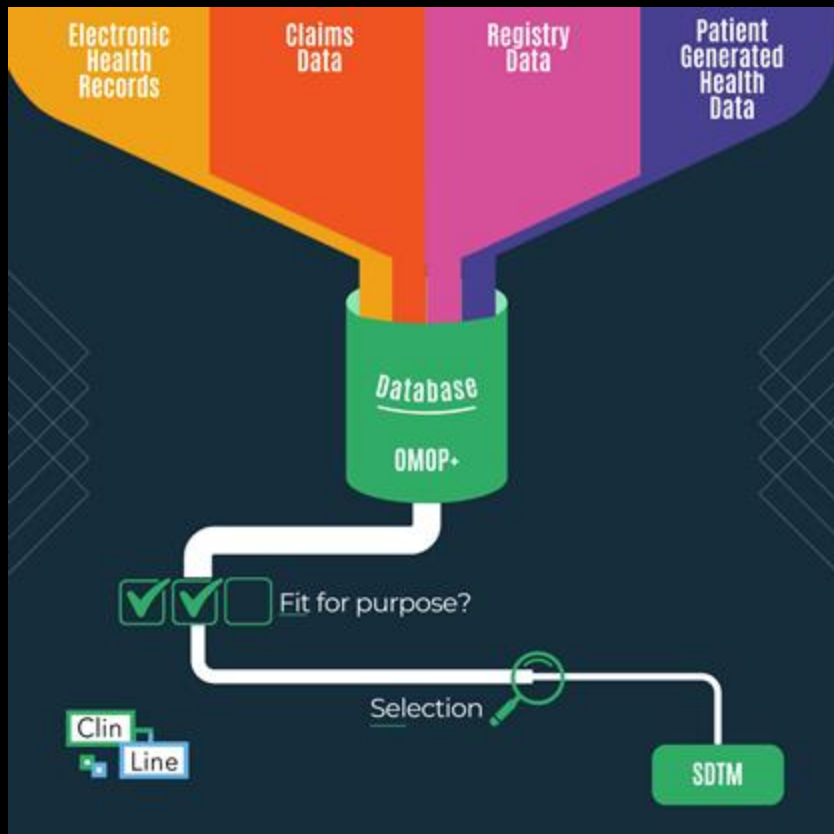
Working Group Poster

US Connect 2024



Digital Data Flow - Proof of Concept

- LZZT study (Alzheimer indication)
- Select from FHIR source
(Synthea: <https://synthea.mitre.org/>)
- Transform to observational standard
- Anonymization
- Select patient cohort
 - ◆ Eligibility
- Assess fit for purpose
 - ◆ Matching, windowing, data availability
- Transform to SDTM



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Requirements

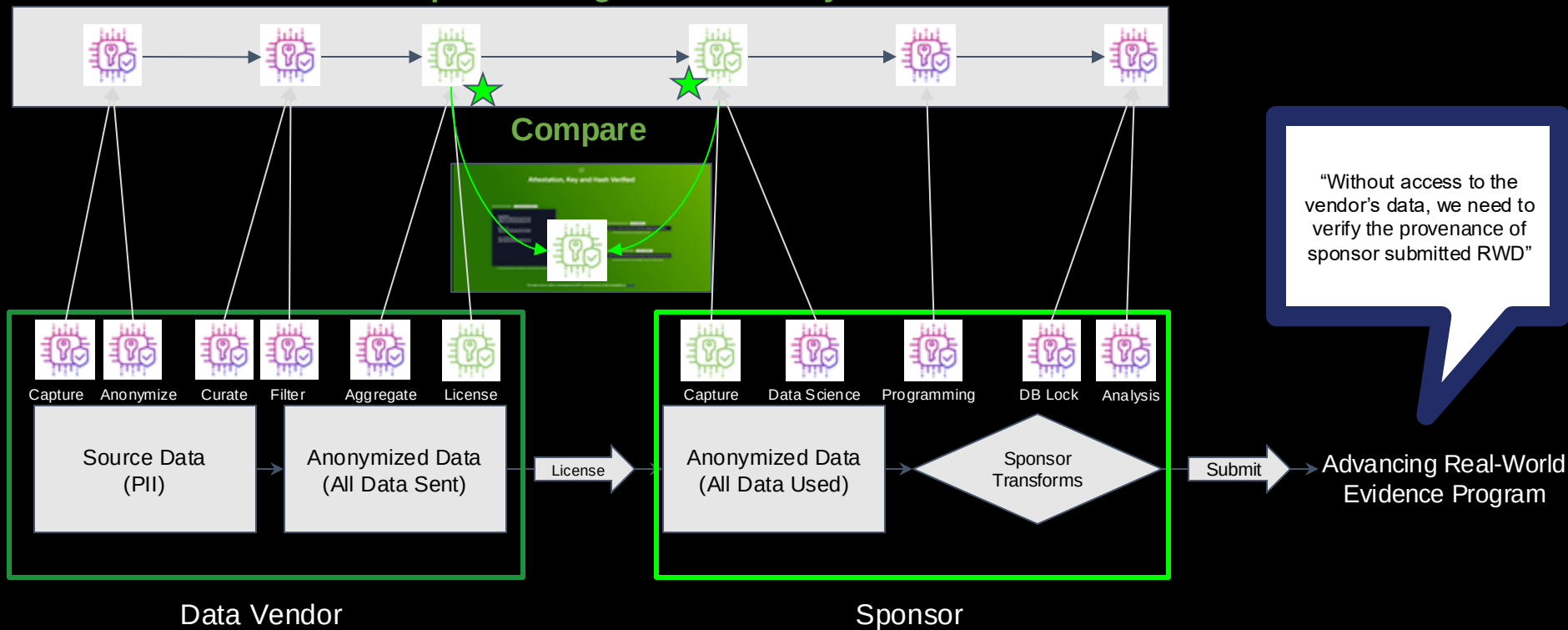
- Standardization
- Anonymization
- Fit for purpose Assessments
- Lineage, Traceability and Governance

Reliability and Traceability



Cryptographic certificates provide tamper-proof verification, creating a trusted chain of custody. Comparing hashes from the Data Vendor and Sponsor verifies the data's integrity and any transformation, negating the need to access the underlying data from the vendor.

Complete Lineage & Traceability



- Eligibility criteria with
 - ◆ tags to USDM attributes:
 - History timeline
 - Biomedical Concepts
 - Population characteristics
 - Indications
 - ◆ tags to external repositories:
 - Contra-Indications
 - Contra-Medications
- Timelines with corresponding windows
- CDISC Biomedical concepts
- Study design elements

3.4.2.1. Inclusion Criteria

Patients may be included in the study only if they meet **all** the following criteria:

- [1] Males and postmenopausal females at least 50 years of age.
- [2] Diagnosis of probable AD as defined by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) guidelines (Attachment LZZT.7).
- [3] MMSE score of 10 to 23.
- [4] Hachinski Ischemic Scale score of ≤ 4 (Attachment LZZT.8).
- [5] CNS imaging (CT scan or MRI of brain) compatible with AD within past 1 year.

- Eligibility criteria with
 - ◆ tags to USDM attributes:
 - History timeline
 - Biomedical Concepts
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- Study design elements

category	Identifier	Eligibility Criteria with resolved tags (categorized)
Inclusion Criteria	01	Males and postmenopausal females at least 50.0 Year of age.
Inclusion Criteria	02	Alzheimer's disease as defined by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) guidelines (Attachment LZZT.7).
Inclusion Criteria	03	MMSE score of 10 to 23.
Inclusion Criteria	04	Hachinski Ischemic Scale score of ≤4 (Attachment LZZT.8).
Inclusion Criteria	05	CNS imaging (CT scan or MRI of brain) compatible with AD within within the past 1 year. The following findings are incompatible with AD: a. Large vessel stroke - Any definite area of encephalomalacia consistent with ischemic necrosis in any cerebral artery territory. - Large, confluent areas of encephalomalacia in parieto-occipital or frontal regions consistent with watershed infarcts. The above are exclusionary. Exceptions are made for small areas of cortical asymmetry which may represent a small cortical stroke or a focal area of atrophy provided there is no abnormal signal intensity in the immediately underlying parenchyma. Only one such questionable area allowed per scan, and size is restricted to ≤1cm in frontal/parietal/temporal cortices and ≤2 cm in occipital cortex.

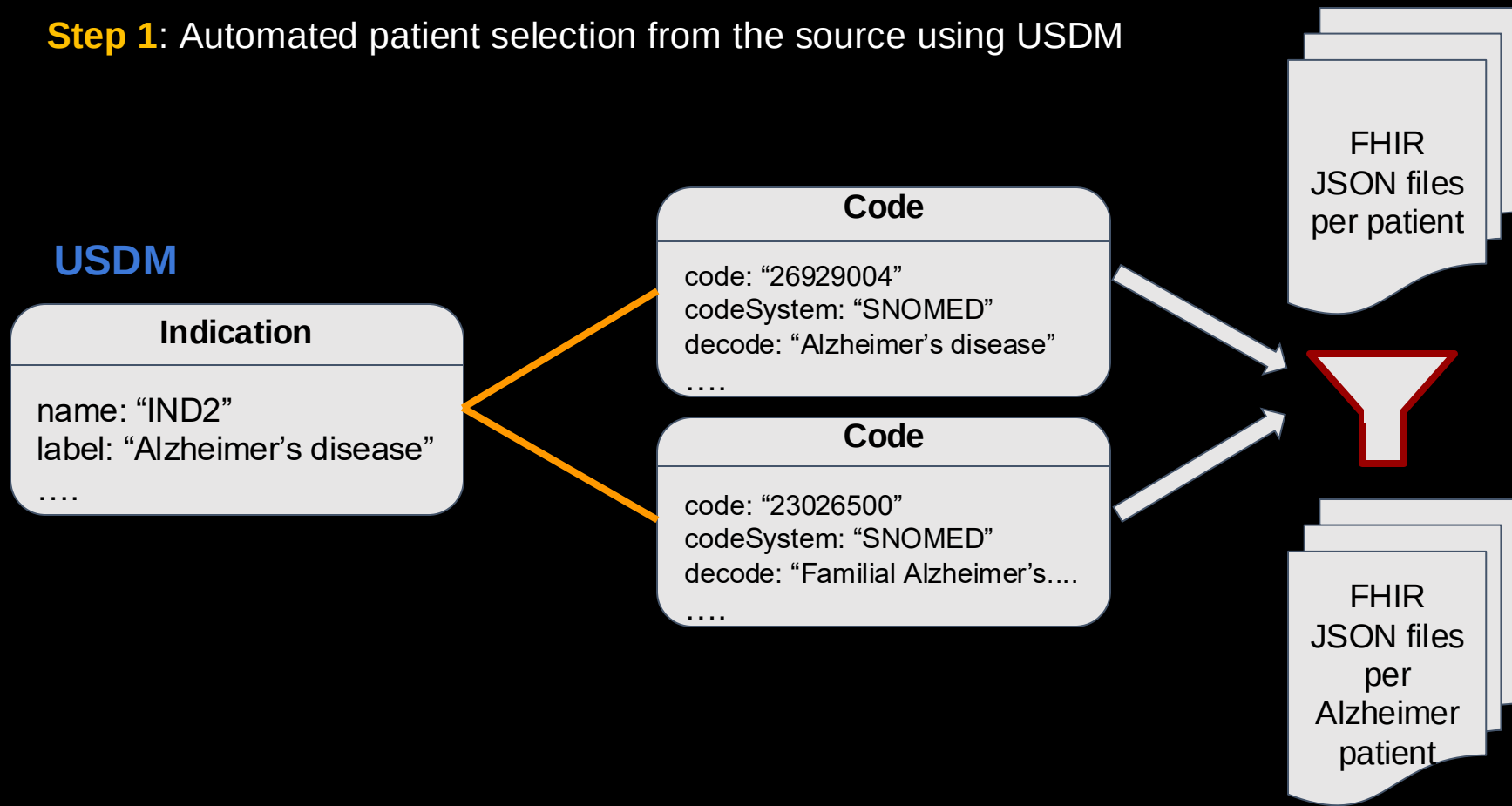
Information transformed to USDM based on USDM v3.0 test data output
 LZZT Protocol: H2Q-MC-LZZT (2006) provided as example study

- Eligibility criteria with
 - ◆ tags to USDM attributes:
 - History timeline
 - Biomedical Concepts
 - Population characteristics
 - Indications
 - ◆ tags to external repositories:
 - Contra-Indications
 - Contra-Medications
- Timelines with corresponding windows
- CDISC Biomedical concepts
- Study design elements

category	Identifier	Eligibility Criteria with tag names
Inclusion Criteria	01	Males and postmenopausal females at least Age_minVal Age_Unit of age.
Inclusion Criteria	02	StudyIndication as defined by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRD) guidelines (Attachment LZTZ.7).
Inclusion Criteria	03	BC1 score of BC1_minVal to BC1_maxVal.
Inclusion Criteria	04	BC2 score of sBC2_minVal (Attachment LZTZ.8).
Inclusion Criteria	05	CNS imaging (CT scan or MRI of brain) compatible with AD within Event1_Timing. The following findings are incompatible with AD: a. Event1_Sub1 - Any definite area of encephalomalacia consistent with ischemic necrosis in any cerebral artery territory. - Large, confluent areas of encephalomalacia in parieto-occipital or frontal regions consistent with watershed infarcts. The above are exclusionary. Exceptions are made for small areas of cortical asymmetry which may represent a small cortical stroke or a focal area of atrophy provided there is no abnormal signal intensity in the immediately underlying parenchyma. Only one such questionable area allowed per scan, and size is restricted to ≤1cm in frontal/parietal/temporal cortices and ≤2 cm in occipital cortex.

Information transformed to USDM based on USDM v3.0 test data output
 LZTZ Protocol: H2Q-MC-LZTZ (2006) provided as example study

Step 1: Automated patient selection from the source using USDM



Step 2: Read and Standardize FHIR JSON Data



Standardized Mapping

FHIR JSON
Files for
Each
Alzheimer
Patient



ResourceType	measurement_type_concept_id	measurement_source_value	value_source_value	operator_concept_id
ResourceType	measurement_type_concept_id	measurement_source_value	value_source_value	operator_concept_id
Observation				
Observation	32017	code coding display	valueQuantity value	
Observation	32017	component code coding display	component valueQuantity value	

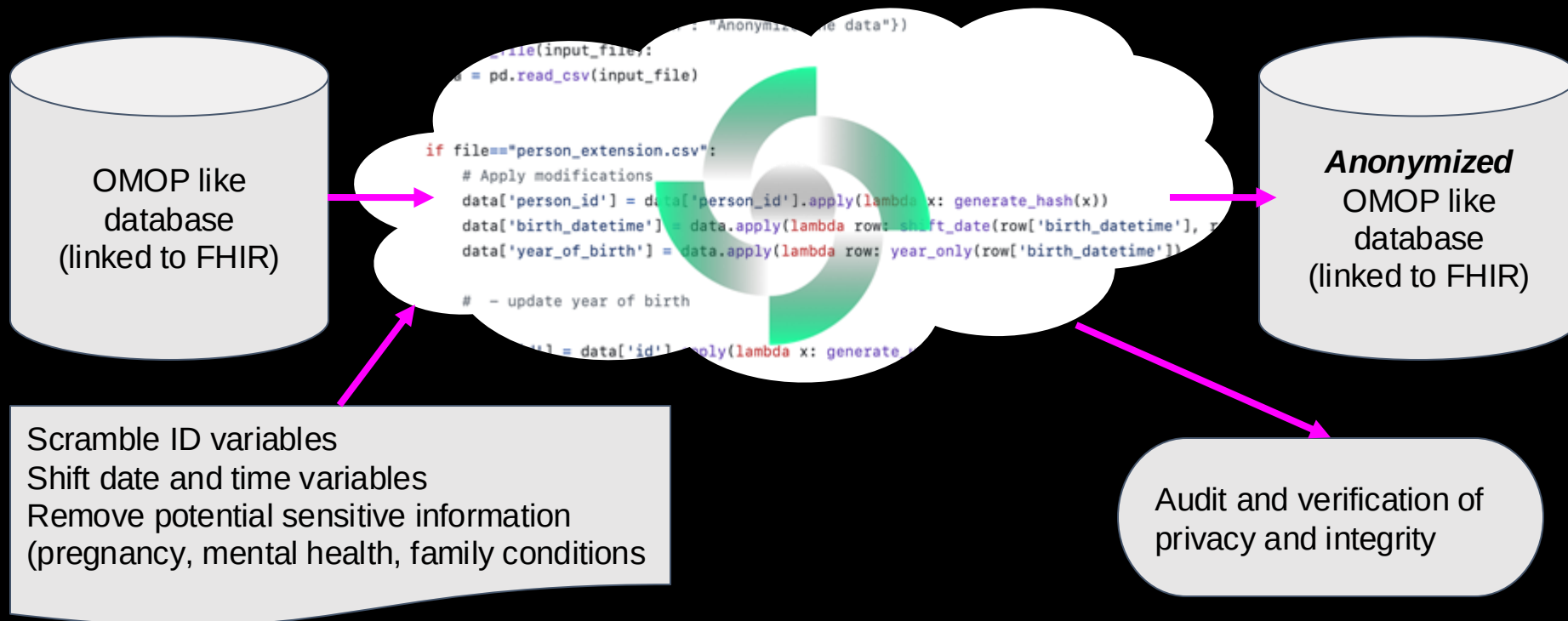
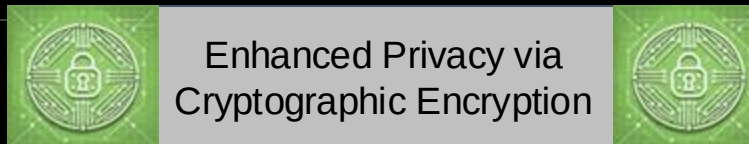
Codelist	Value	Code	OMOP	Code name	Vocabulary	Codelist code	CT
gender	female		8532	F	Gender	Sex	086791
gender	male		8537	M	Gender	Sex	086791
gender	F		8532	F	Gender	Sex	086791
gender	M		8537	M	Gender	Sex	086791
gender	missing		45802913	U	UONC	Sex	086791
Race	White	2206-8	8527	3 White	Race	Race	074637
Race	African - Black		8528	3 Black or African American	Race	Race	074637
Race	African - North		8528	3 White	Race	Race	074637
Race	Asian - West		8528	3 Asian	Race	Race	074637
Race	Asian - East		8528	2 Asian	Race	Race	074637



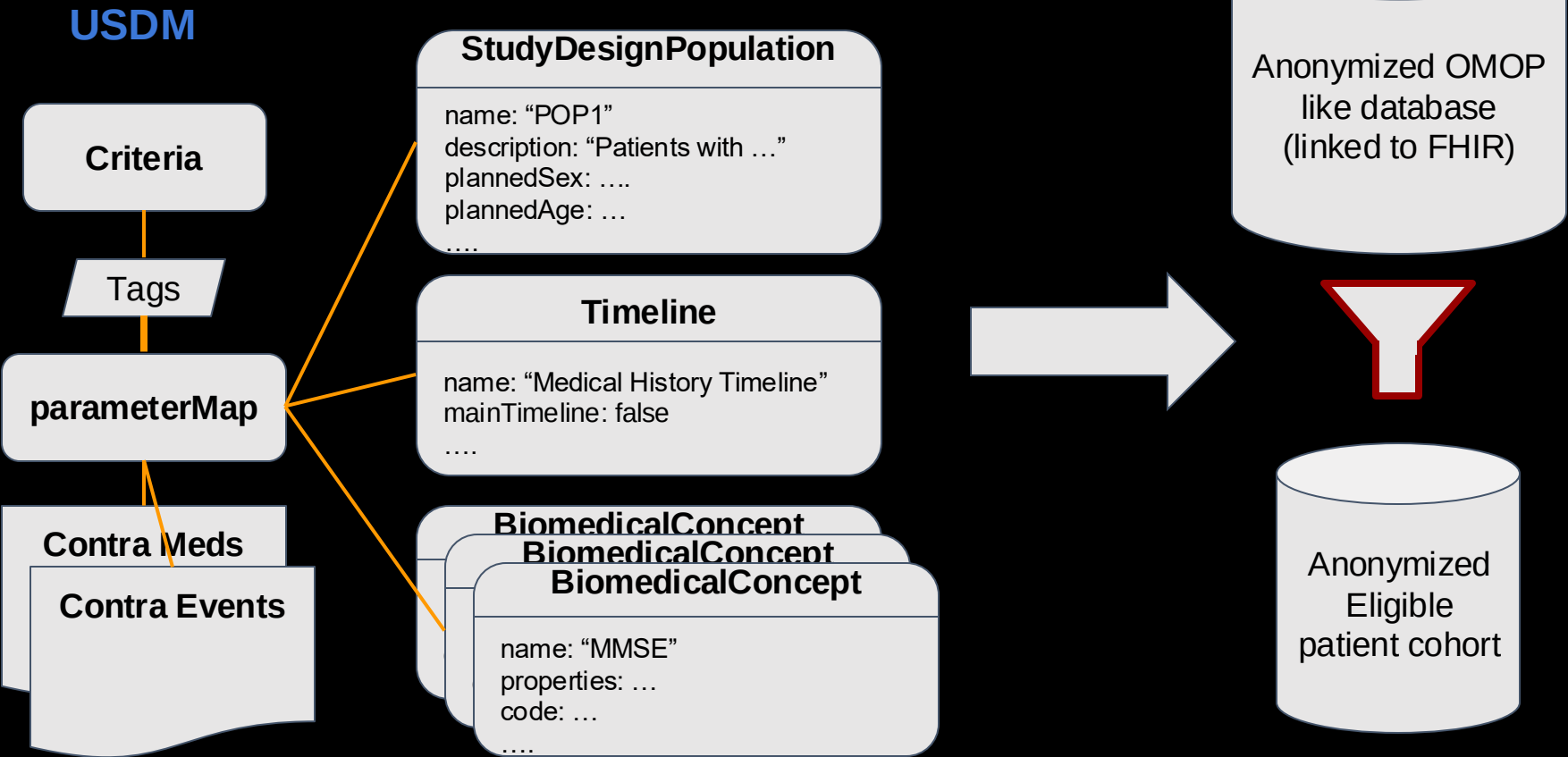
OMOP like
database
(linked to FHIR)



Step 3: Anonymization



Step 4: Automated Selection of Eligible Patients



Step 4: Automated Selection of Eligible Patients



USDM: Biomedical Concepts Referenced in Criteria

bcNo	Biomedical concept	Maximum Value	Minimum Value	Unit	Maximum Value Females	Maximum Value Males	Minimum Value Females	Minimum Value Males
1	MMSE	23	10					
2	Hachinski Ischemic Scale		4					
3	SGOT			Microkatal per Liter	0.75	0.92		
4	Alanine Aminotransferase Concentration in Serum/Plasma			Microkatal per Liter	0.84	1.17		
5	Creatinine			Micromole per Liter	97.2	114.9		
6	hemoglobin			Millimole per Liter	10	11	7.5	8.5
7	potassium	144	133	Millimole per Liter				
8	sodium	5.3	3.4	Millimole per Liter				
9	calcium	2.6	1.9	Millimole per Liter				

Step 4: Automated Selection of Eligible Patients



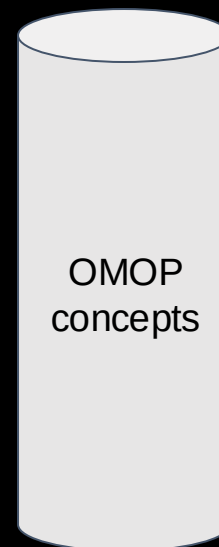
USDM: Specified Biomedical Concepts and Aliases

Transformation

Table rows: 20 | Columns: 19

expression

tag	BCId	AliasId	code	codeSyst...	codeSystemVersion	decode	instanceType
BC1	BiomedicalConcept_x001	Code_x003	273617000	SNOMED	2023-07-31	Mini-mental state examination	Code
BC1	BiomedicalConcept_x001	Code_x004	72107-6	LOINC	2.76	Mini-mental state examination [MMSE]	Code
BC1	BiomedicalConcept_x001	Code_x091	273619002	SNOMED	2023-07-31	Mini-mental state examination	Code
BC1	BiomedicalConcept_x001	Code_x092	72106-8	LOINC	2.76	Total score [MMSE]	Code
BC3	BiomedicalConcept_29	Code_x008	45896001	SNOMED	2023-07-31	Aspartate aminotransferase measurement	Code
BC3	BiomedicalConcept_29	Code_x009	1920-8	LOINC	2.76	Aspartate aminotransferase [Enzymatic ...	Code
BC4	BiomedicalConcept_8	Code_x011	34608000	SNOMED	2023-07-31	Alanine aminotransferase measurement	Code
BC4	BiomedicalConcept_8	Code_x012	1742-6	LOINC	2.76	Unit of Catalytic Activity Concentration	Code
BC5	BiomedicalConcept_30	Code_x013	70901006	SNOMED	2023-07-31	Creatinine measurement	Code
BC5	BiomedicalConcept_30	Code_x014	14682-9	LOINC	2.76	Creatinine [Moles/volume] in Serum or ...	Code
BC5	BiomedicalConcept_30	Code_x097	38483-4	LOINC	2.76	Creatinine [Moles/volume] in Blood	Code
BC6	BiomedicalConcept_x002	Code_x016	441689006	SNOMED	2023-07-31	Measurement of total hemoglobin conc...	Code
BC6	BiomedicalConcept_x002	Code_x017	718-7	LOINC	2.76	Hemoglobin [Mass/volume] in Blood	Code
BC7	BiomedicalConcept_31	Code_x013	59573005	SNOMED	2023-07-31	Potassium measurement	Code



<https://athena.ohdsi.org/>

Step 4: Automated Selection of Eligible Patients



Automated Selection BC Data from Anonymized Source

Based On

- Source codes and corresponding code system used
- Defined alias codes aligning with source code system used

Note: code children can be used to extend the selection for more complete data.

Automated Criteria Evaluation

Based On:

- Available measurements
- Last value carried forward
- Min and max values
- Units and unit conversion
- Gender

```
selectFromSource;

do i=1 %to &totBCs;
  ** Get list of related concept Ids ;
  Data MySelBC;
    Set MyBcs;
    WHERE bcnun=&i;
    call symput ("Name",Substr(bc,1,6));
  Run;

  %Put NOTE: dataset name will be &name;

  proc SQL;
    Create Table MyCConcepts as Select a.*, b.tag from OMOP_concepts as a
      INNER join MySelBC as b on
        lowercase(left(trim(a.vocabulary_id))) = lowercase(left(trim(b.codeSystem))) a
  quit;

  Proc Sql;
    Create Table &Name as Select observation_date,e860lda.) as datec from anonomop.ob
      b.concept_id;
```



Step 4: Automated Selection of Eligible Patients



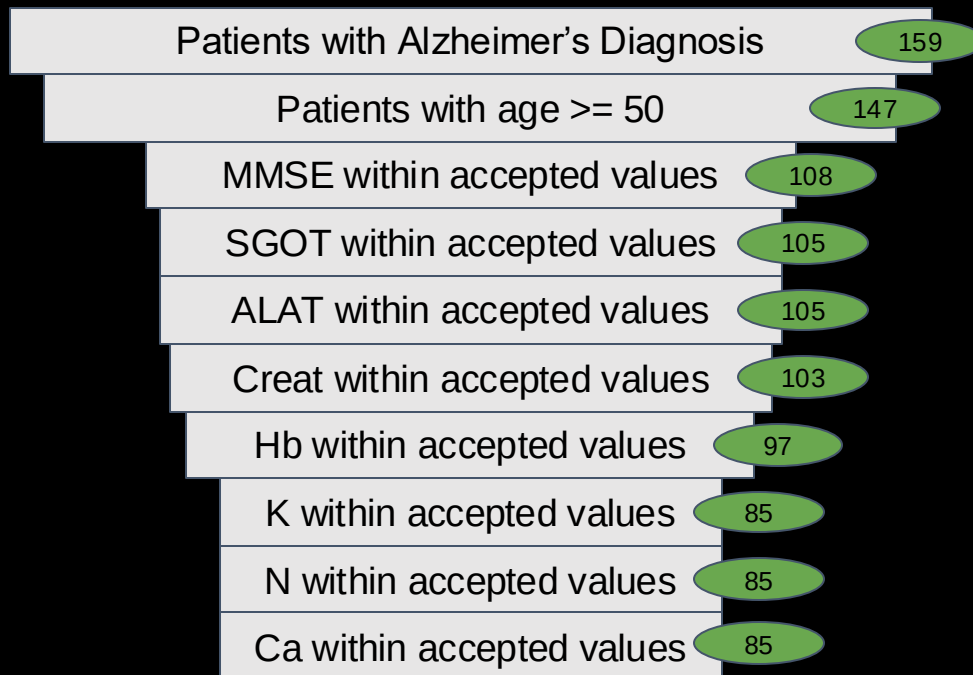
ALLSHELLM Table rows: 18614 Columns: 21 of 26 Rows 18401 to 18600

Enter expression

	@_	@_	@_new_patno	@_date	@_source_value	@_value_...	@_unit_sourc...	@_Age1	@_BCEvalUnit	@_BC1	@_BC2	@_BC3	@_BC4	@_BC5
18552	49	F	2159	2018-03-25	Creatinine [Mass/volum...	3.1037	mg/dL	0	Micromole per Liter	.	1	.	0	.
18553	49	F	2159	2018-03-25	Calcium [Mass/volume] i...	9.37	mg/dL	0	Millimole per Liter	.	1	.	0	.
18554	49	F	2159	2018-08-04	Familial Alzheimer's dis...	.		0		.	1	.	0	.
18555	49	F	2159	2018-08-04	Total score [MMSE]	24.716		0		0	1	.	0	.
18556	49	F	2159	2018-08-04	Creatinine [Mass/volum...	1.14	mg/dL	0	Micromole per Liter	0	1	.	0	.
18557	49	F	2159	2018-08-04	Calcium [Mass/volume] i...	8.88	mg/dL	0	Millimole per Liter	0	1	.	0	.
18558	50	F	2159	2019-02-02	Creatinine [Mass/volum...	0.82	mg/dL	1	Micromole per Liter	0	1	.	0	.
18559	50	F	2159	2019-02-02	Calcium [Mass/volume] i...	9.79	mg/dL	1	Millimole per Liter	0	1	.	0	.
18560	50	F	2159	2019-03-25	Aspartate aminotransfer...	35.592	U/L	1	Microkatal per Liter	0	1	.	0	.
18561	50	F	2159	2019-03-25	Alanine aminotransferas...	20.573	U/L	1	Microkatal per Liter	0	1	.	1	.
18562	50	F	2159	2019-03-25	Creatinine [Mass/volum...	2.8363	mg/dL	1	Micromole per Liter	0	1	.	1	.
18563	50	F	2159	2019-03-25	Calcium [Mass/volume] i...	8.9	mg/dL	1	Millimole per Liter	0	1	.	1	.
18564	50	F	2159	2019-06-24	Total score [MMSE]	15.634		1		1	1	.	1	.
18565	51	F	2159	2020-02-08	Creatinine [Mass/volum...	0.81	mg/dL	1	Micromole per Liter	1	1	.	1	.
18566	51	F	2159	2020-02-08	Calcium [Mass/volume] i...	9.71	mg/dL	1	Millimole per Liter	1	1	.	1	.
18567	51	F	2159	2020-03-24	Aspartate aminotransfer...	9.5298	U/L	1	Microkatal per Liter	1	1	.	1	.
18568	51	F	2159	2020-03-24	Alanine aminotransferas...	28.77	U/L	1	Microkatal per Liter	1	1	.	1	.
18569	51	F	2159	2020-03-24	Creatinine [Mass/volum...	3.1922	mg/dL	1	Micromole per Liter	1	1	.	1	.
18570	51	F	2159	2020-03-24	Calcium [Mass/volume] i...	9.02	mg/dL	1	Millimole per Liter	1	1	.	1	.
18571	51	F	2159	2020-05-01	Aspartate aminotransfer...	26.252	U/L	1	Microkatal per Liter	1	1	.	1	.
18572	51	F	2159	2020-05-01	Alanine aminotransferas...	49.013	U/L	1	Microkatal per Liter	1	1	.	1	.

Step 4: Automated Selection of Eligible Patients

Attrition Diagram

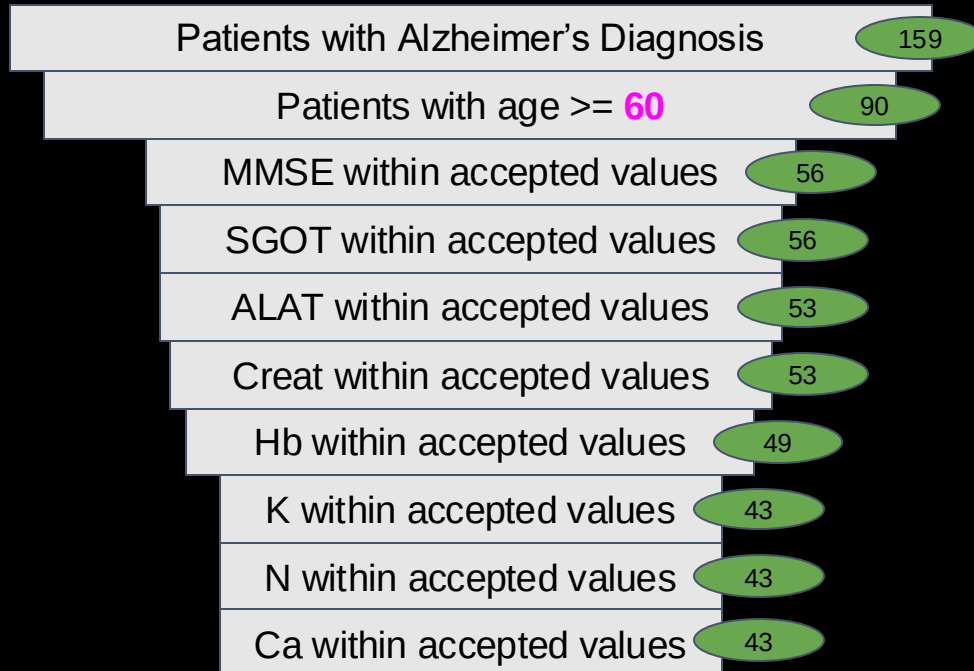


Summary for Attrition Report (Page 1 of 1)

Category	Criteria	Number of Patients
Inclusion	Patients with Alzheimer's Diagnosis	159
Inclusion	Patients with Age ≥ 50	147
Inclusion	Patients with MMSE within accepted values (inclusion criteria)	108
Exclusion	Patients with SGOT not outside accepted values (exclusion criteria, Female specific)	108
Exclusion	Patients with SGOT not outside accepted values (exclusion criteria, Male specific)	108
Exclusion	Patients with Alanine Aminotransferase Concentration in Serum/Plasma not outside accepted values (exclusion criteria, Female specific)	105
Exclusion	Patients with Alanine Aminotransferase Concentration in Serum/Plasma not outside accepted values (exclusion criteria, Male specific)	105
Exclusion	Patients with Creatinine not outside accepted values (exclusion criteria, Female specific)	105
Exclusion	Patients with Creatinine not outside accepted values (exclusion criteria, Male specific)	105
Exclusion	Patients with hemoglobin not outside accepted values (exclusion criteria, Female specific)	103
Exclusion	Patients with hemoglobin not outside accepted values (exclusion criteria, Male specific)	97
Exclusion	Patients with potassium not outside accepted values (exclusion criteria)	85
Exclusion	Patients with sodium not outside accepted values (exclusion criteria)	85
Exclusion	Patients with calcium not outside accepted values (exclusion criteria)	85
	Total patients Eligible	85

Step 4: Automated Selection of Eligible Patients

Attrition Diagram - Changed Eligibility Criteria

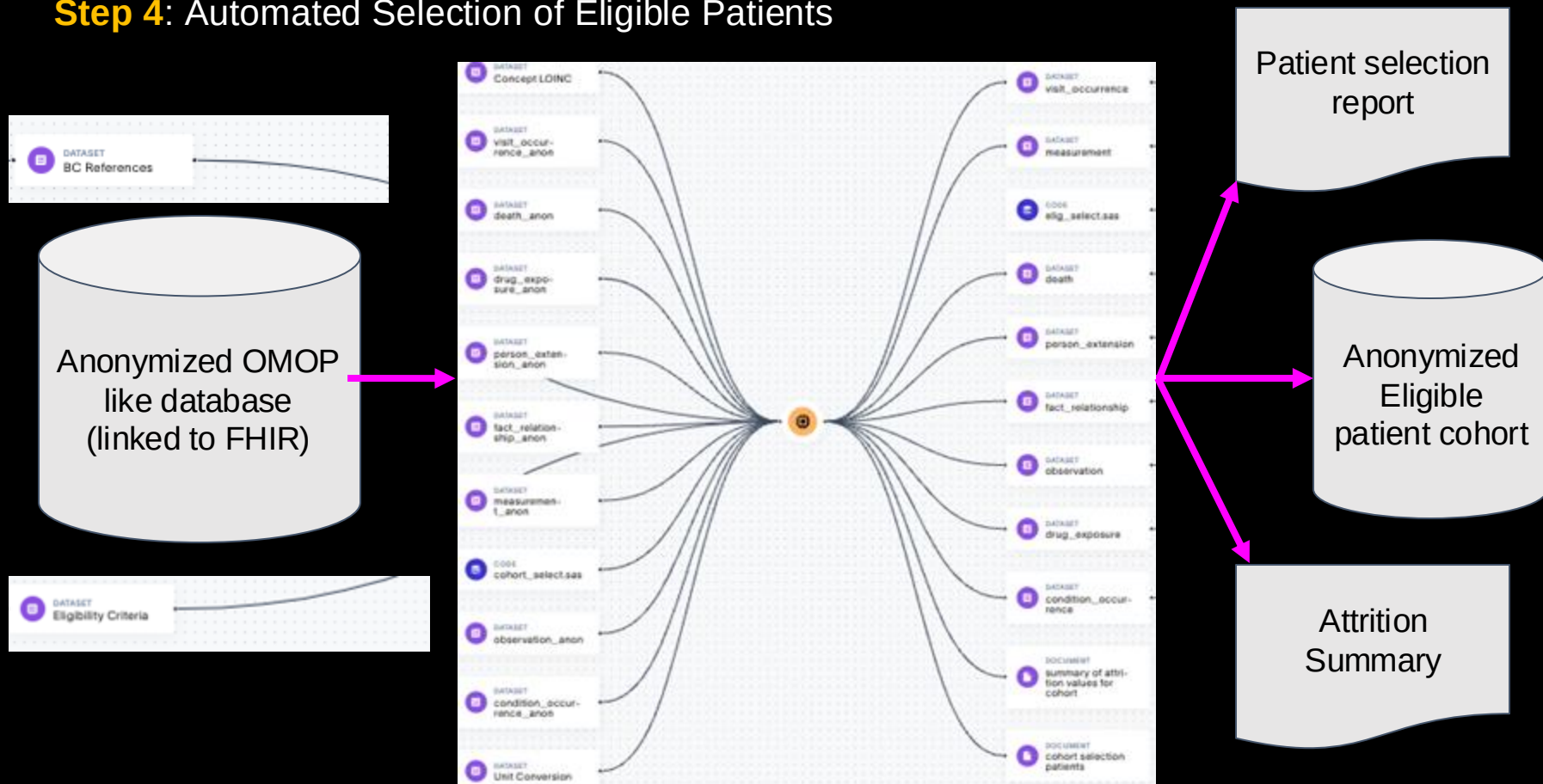


Summary for Attrition Report (Page 1 of 1)

Category	Criteria	Number of Patients
Inclusion	Patients with Alzheimer's Diagnosis	159
Inclusion	Patients with Age ≥ 60	90
Inclusion	Patients with MMSE within accepted values (inclusion criteria)	56
Exclusion	Patients with SGOT not outside accepted values (exclusion criteria, Female specific)	56
Exclusion	Patients with SGOT not outside accepted values (exclusion criteria, Male specific)	56
Exclusion	Patients with Alanine Aminotransferase Concentration in Serum/Plasma not outside accepted values (exclusion criteria, Female specific)	53
Exclusion	Patients with Alanine Aminotransferase Concentration in Serum/Plasma not outside accepted values (exclusion criteria, Male specific)	53
Exclusion	Patients with Creatinine not outside accepted values (exclusion criteria, Female specific)	53
Exclusion	Patients with Creatinine not outside accepted values (exclusion criteria, Male specific)	53
Exclusion	Patients with Hemoglobin not outside accepted values (exclusion criteria, Female specific)	53
Exclusion	Patients with Hemoglobin not outside accepted values (exclusion criteria, Male specific)	49
Exclusion	Patients with potassium not outside accepted values (exclusion criteria)	43
Exclusion	Patients with sodium not outside accepted values (exclusion criteria)	43
Exclusion	Patients with calcium not outside accepted values (exclusion criteria)	43
	Total patients Eligible	43

category	Identifier	Eligibility Criteria with resolved tags
Inclusion Criteria	01	Males and postmenopausal females at least 60.0 Year of age.

Step 4: Automated Selection of Eligible Patients



Step 5: Fit for Purpose Assessment

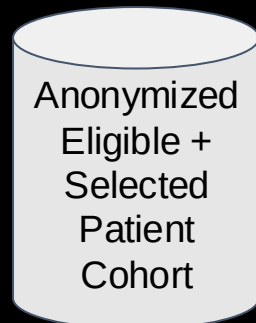
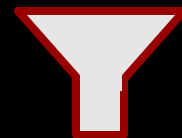
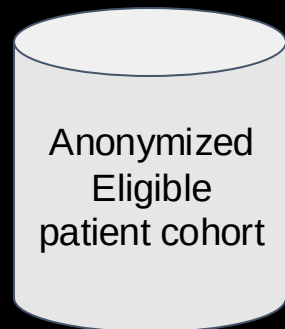
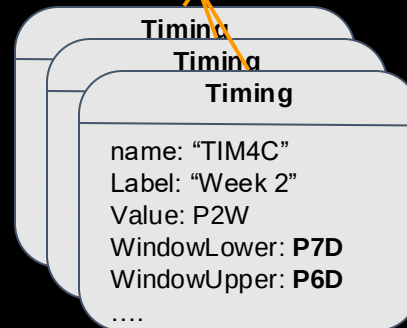
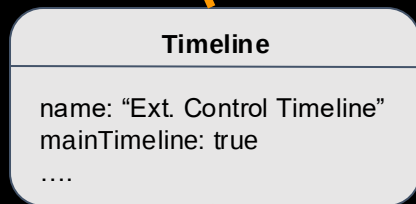
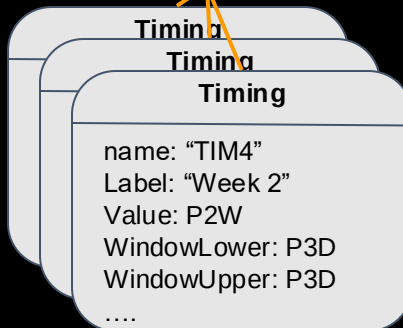
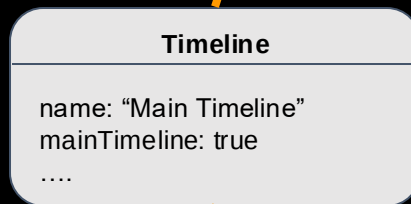
Windowing for RWD

- Limit gaps between timings
- Rules in case of more visits within window
- Define minimum of available data required
 - ◆ Minimum 6 months data after index date
 - ◆ Available endpoint data for visit 8-13

Other

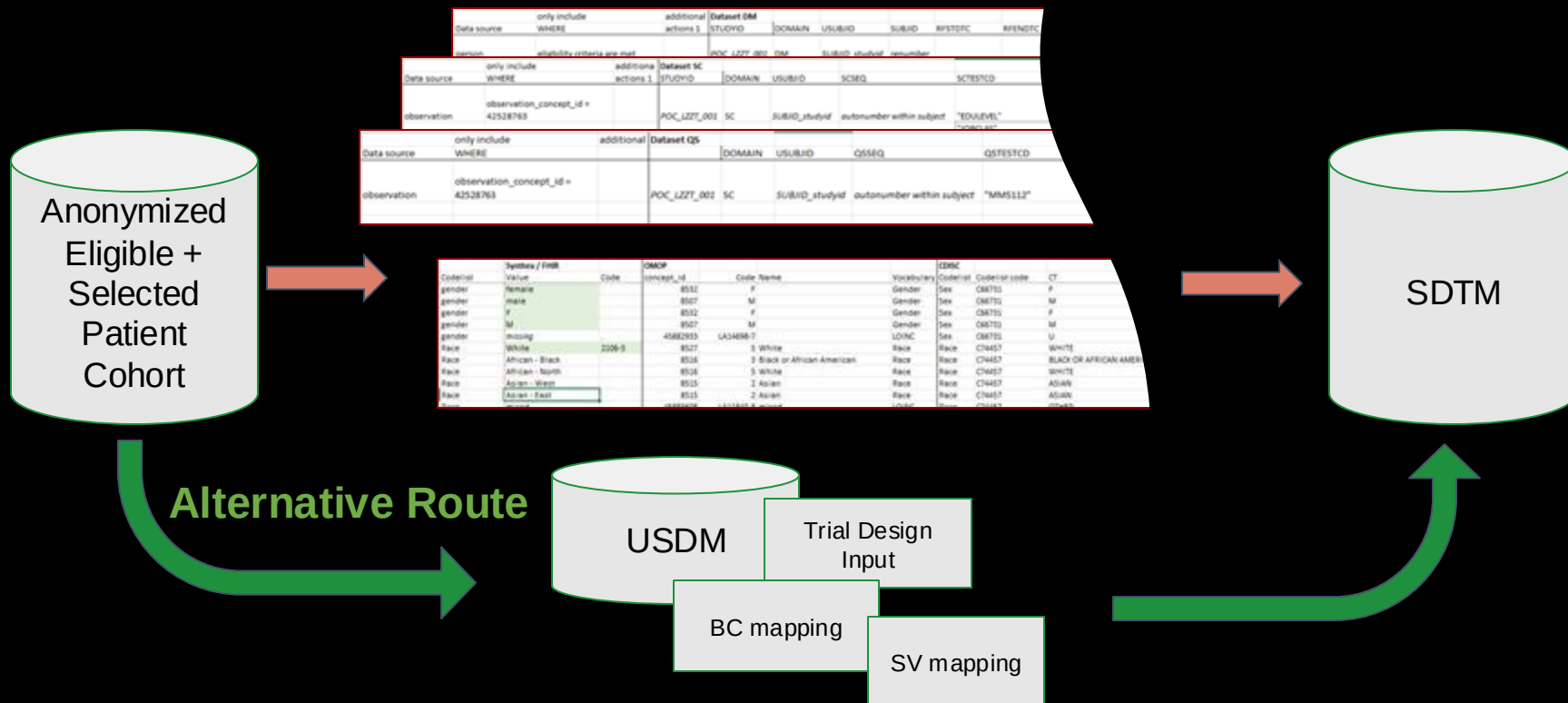
- Data validation
- Bias assessments
- Missingness imputations
- Matching

Interventional trial arm			Real-world control arm	
Visit	Week	Planned visit Day	<u>WindowLower Day</u>	<u>WindowUpper Day</u>
1	-2	-14	-180	-1
2	-0.3	-2	DO NOT INCLUDE	
3	0	0	INDEX DATE	7
4	2	14	7	20
5	4	28	21	34
7	6	42	35	48
8	8	56	49	69
9	12	84	70	97
10	16	112	98	125
11	20	140	126	153
12	24	168	154	174
13	26	182	175	188

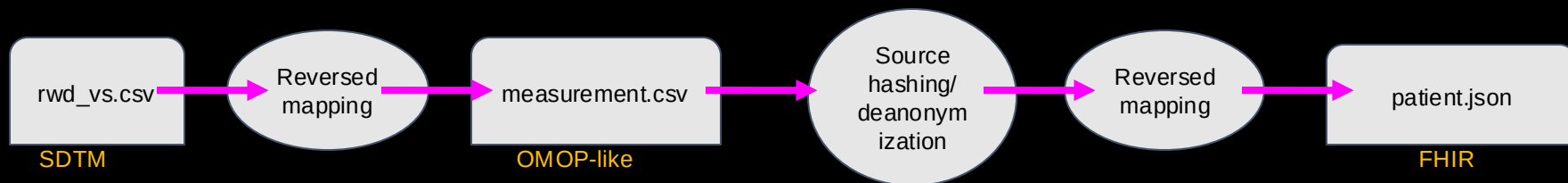


Step 6: SDTM Mapping

Standardized Mapping

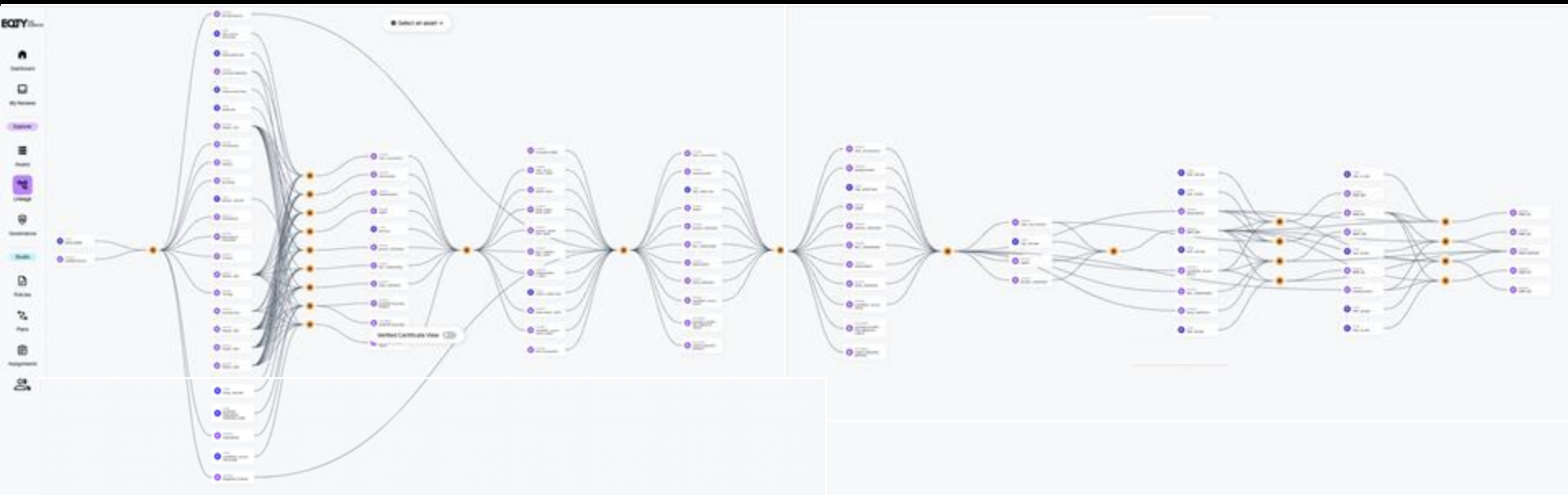


Step 7: Auditable Traceability



```
{
  "coding": [ {
    "system": "http://terminology.hl7.org/CodeSystem/observation-
category",
    "code": "vital-signs",|
    "display": "Vital signs"
  } ]
},
{
  "code": {
    "coding": [ {
      "system": "http://loinc.org",
      "code": "39156-5",
      "display": "Body mass index (BMI) [Ratio]"
    } ],
    "text": "Body mass index (BMI) [Ratio]"
  },
  "subject": {
    "reference": "urn:uuid:ad4c1e30-ddd7-5a4b-6af1-efcb19d8d96d"
  },
  "encounter": {
    "reference": "urn:uuid:110a54bd-0ef2-1d33-9a4d-acf6cd109be1"
  },
  "effectiveDateTime": "2021-08-23T08:19:34+01:00",
  "issued": "2021-08-23T08:19:34.512+01:00",
  "valueQuantity": {
    "value": 29.36,
    "unit": "kg/m2",
  }
}
```

Step 7: Auditable Traceability.



USDM and Cryptography Enable a Trusted Solution

- ◆ Automated Patient Selection from Source
 - ◆ Automated Eligibility / Feasibility Checks
 - ◆ Automated data selection using windowing and BCs
 - ◆ SDTM Mapping
 - ◆ Automated Documentation and Verifiability
- Enables Faster Study Design and SDTM Mapping
- Increases Feasibility Assessment Accuracy
- Cryptographical Automated Lineage, Process Traceability and Governance Controls
- **USDM can inform RWD Fit for Purpose Assessments, ensuring suitability for RWE**





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