

Responsible AI in Protocol Design



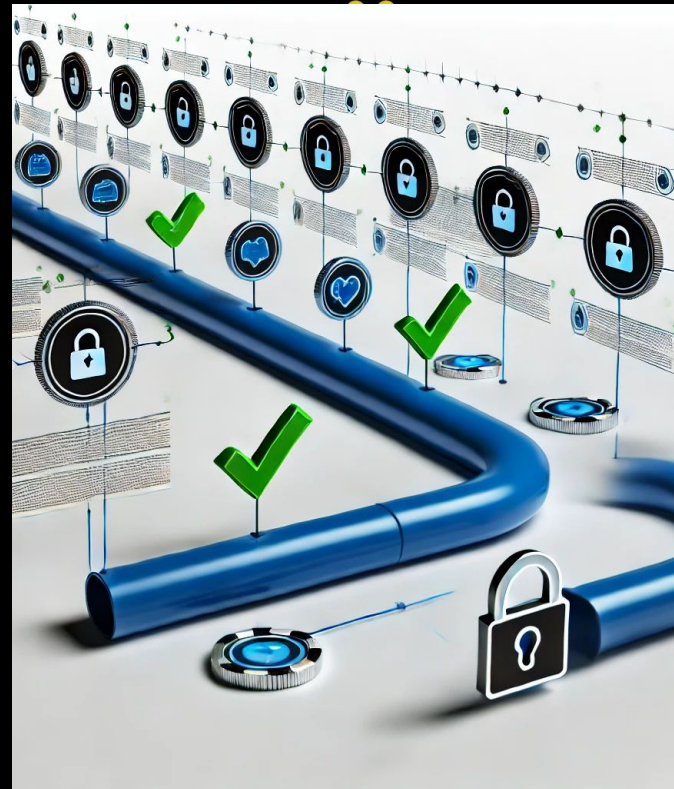
RISKCLICK⁺



EOTY⁺ LIFE
SCIENCES

Content

- Introduction
- What is Responsible AI?
- Reliability and Traceability using cryptography
- Protocol AI
- USDM Content
- Step by Step: FHIR to SDTM
- Conclusions



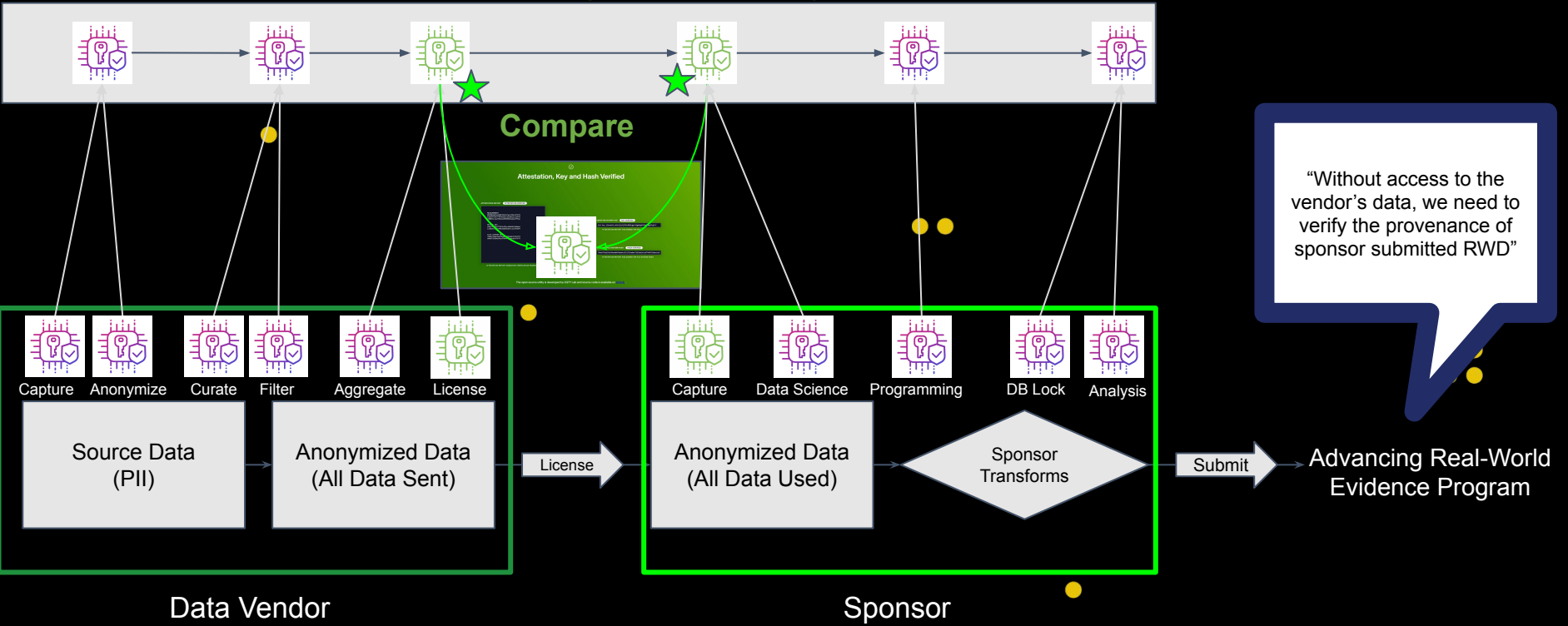
Responsible AI

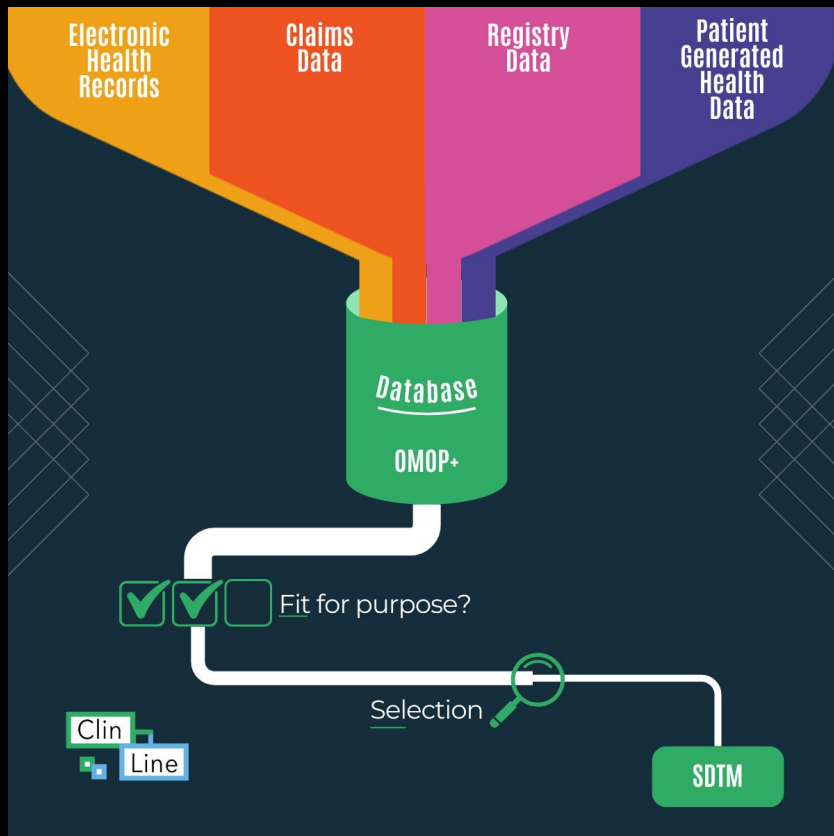


Reliability and Traceability

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.

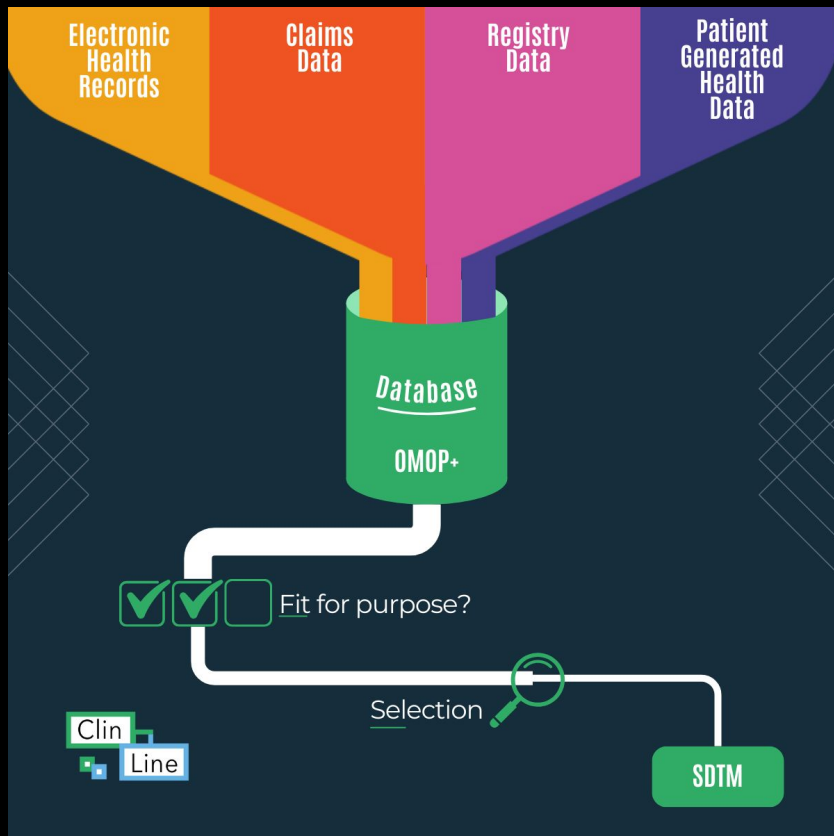
Complete Lineage & Traceability





Digital Data Flow - Proof of Concept

- Protocol AI Study Design →
- LZZT study protocol (Alzheimer indication)
- Select Synthetic data 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



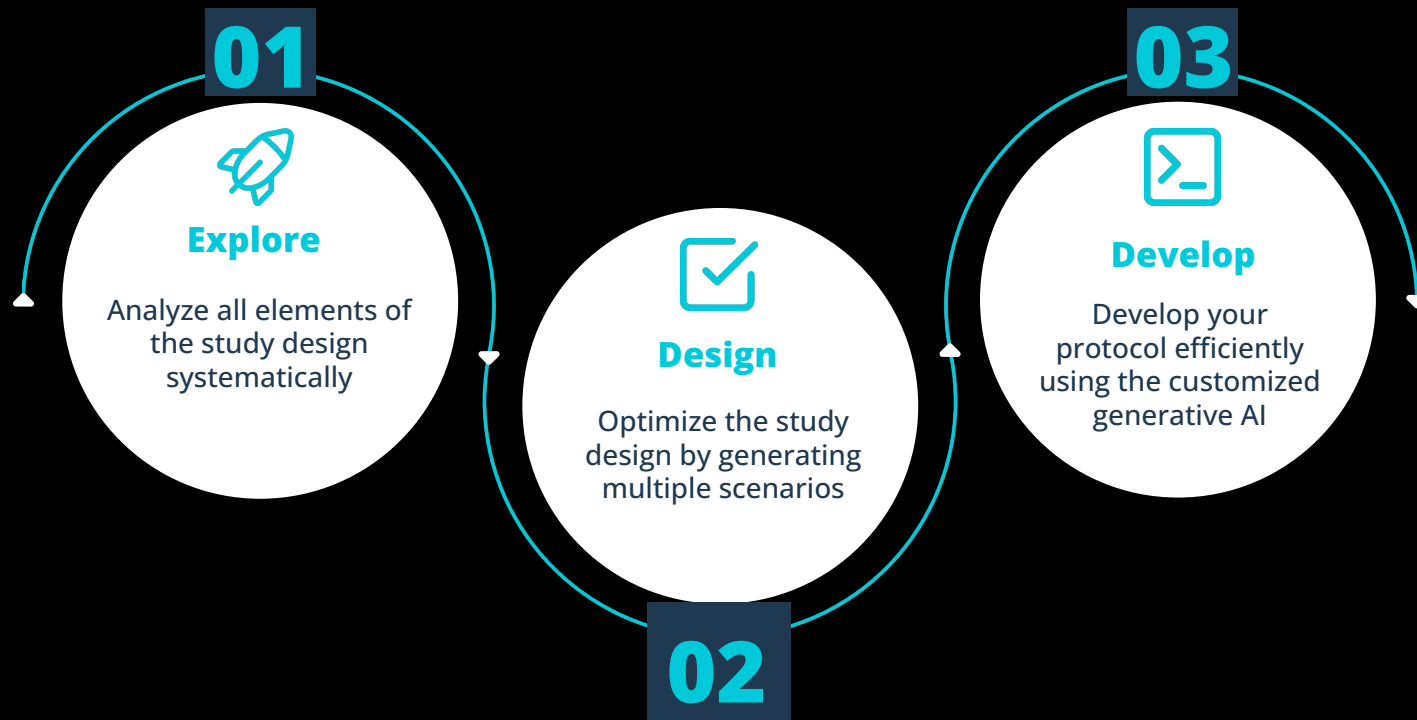
Digital Data Flow - Proof of Concept

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- Select from FHIR source
(Synthea: <https://synthea.mitre.org/>)
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Requirements

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

Develop an evidence-based, digital protocol



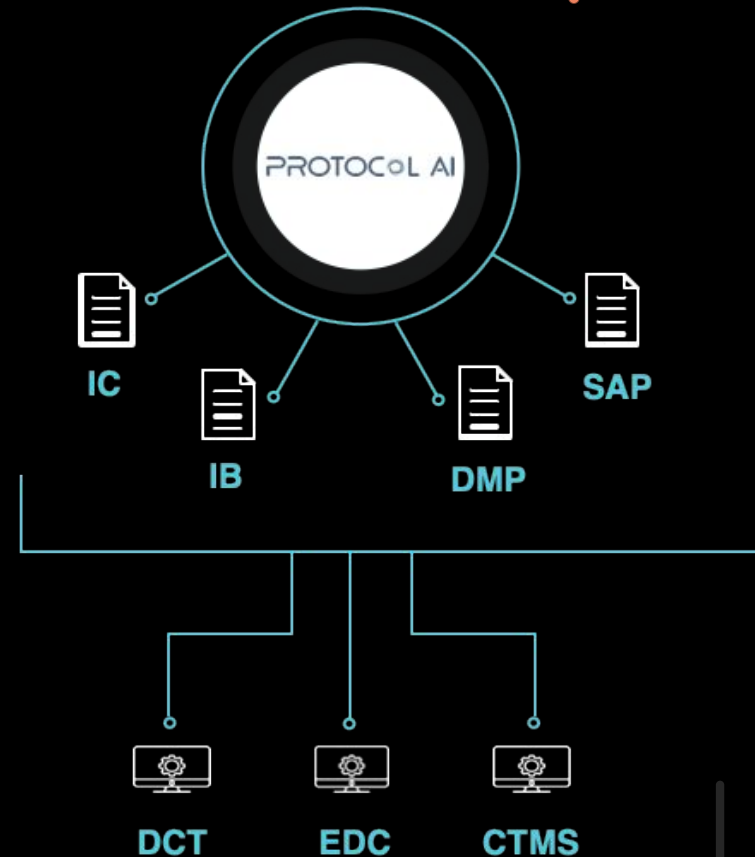
The Power of Digital Protocols

Connecting to trial
electronic systems

Protocol content
standardization

Connecting to other
study documents

Transparent and
traceable

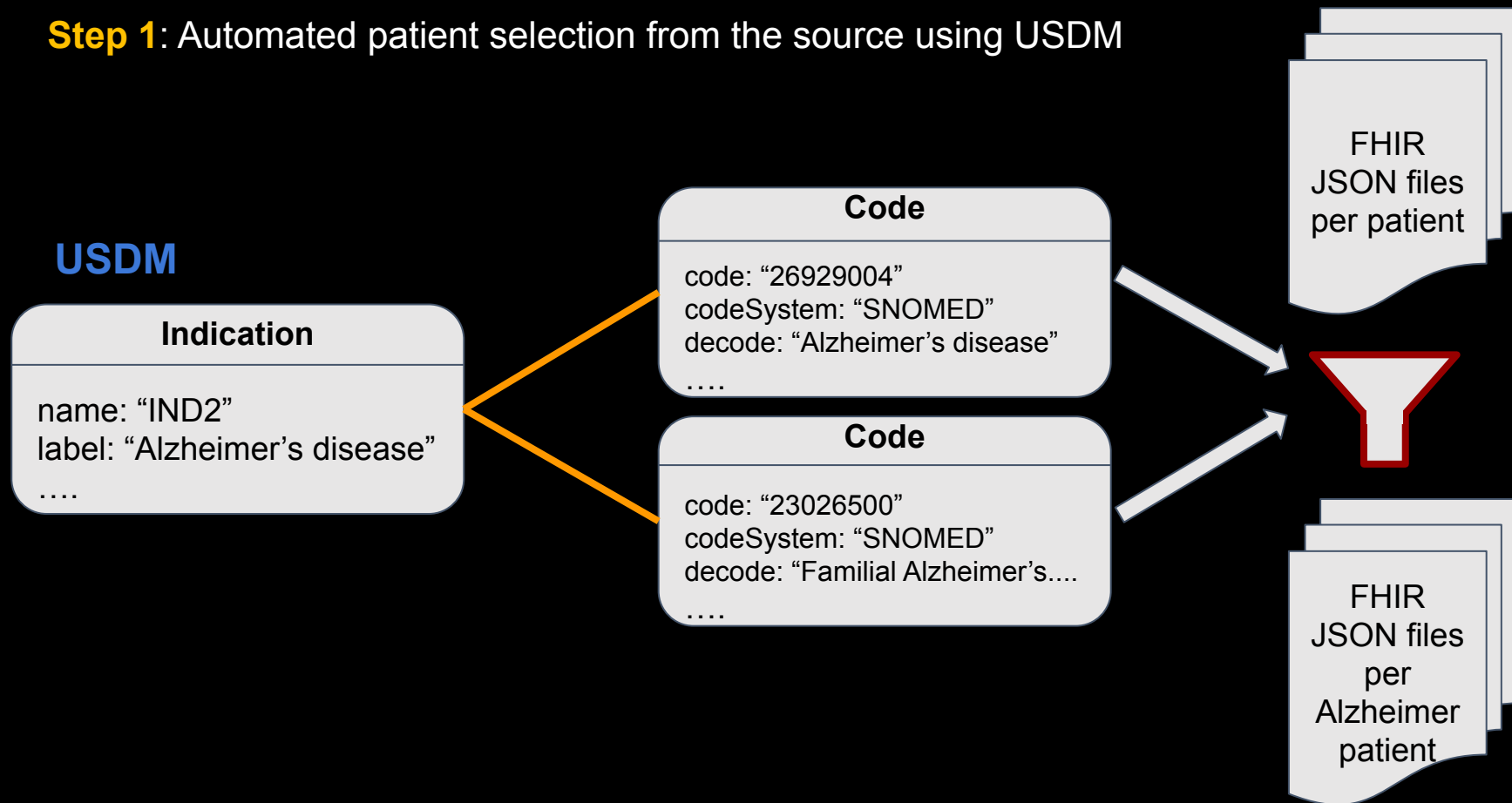


- Eligibility criteria with
 - ◆ tags to USDM attributes:
 - History timeline
 - Biomedical Concepts
 - Population characteristics
 - Indications
 - ◆ tags to external repositories:
 - Contra-Indications
 - Contra-Medications
- Timelines with corresponding windows
- CDISC Biomedical concepts
- Study 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 ≤BC2_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

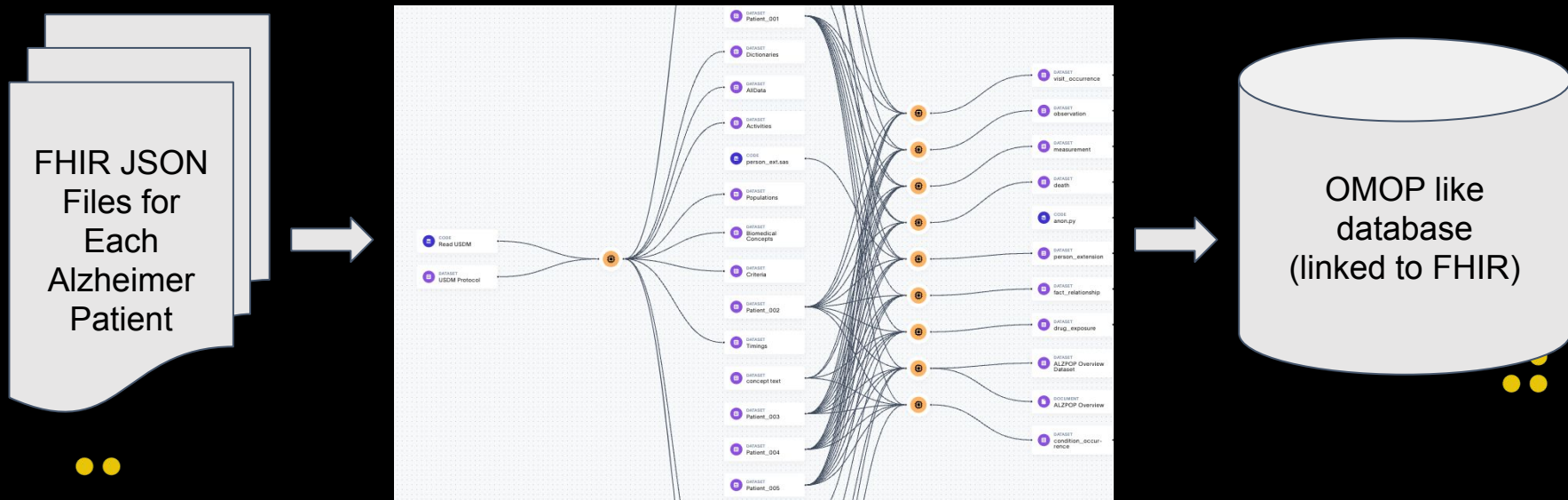
FHIR JSON
Files for
Each
Alzheimer
Patient

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				
Observation				
Observation	32817	code.coding.display	valueQuantity.value	
Observation				
Observation	32817	component.code.coding.display	component.valueQuantity.value	

Codelist	Synthesia / FHIR	Code	OMOP	Code	Name	Vocabulary	CDISC	Codelist code	CT
gender	female		8532	F	Gender	Sex	C66731	F	
gender	male		8507	M	Gender	Sex	C66731	M	
gender	F		8532	F	Gender	Sex	C66731	F	
gender	M		8507	M	Gender	Sex	C66731	M	
gender	missing		45882933	LA14698-7	LOINC	Sex	C66731	U	
Race	White	2106-3	8527	5	White	Race	C74457	WHITE	
Race	African - Black		8516	3	Black or African American	Race	C74457	BLACK OR AFRICAN AM	
Race	African - North		8516	5	White	Race	C74457	WHITE	
Race	Asian - West		8515	2	Asian	Race	C74457	ASIAN	
Race	Asian - East		8515	2	Asian	Race	C74457	ASIAN	
Race	mixed		85882622	LA11110-8	mixed	LOINC	C74457	OTHER	

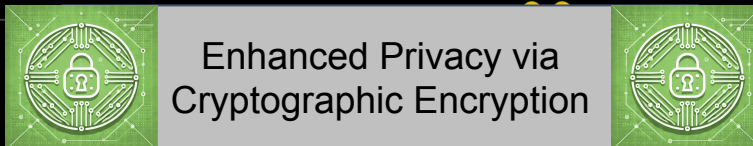
OMOP like
database
(linked to FHIR)

Step 2: Read and Standardize FHIR JSON Data.



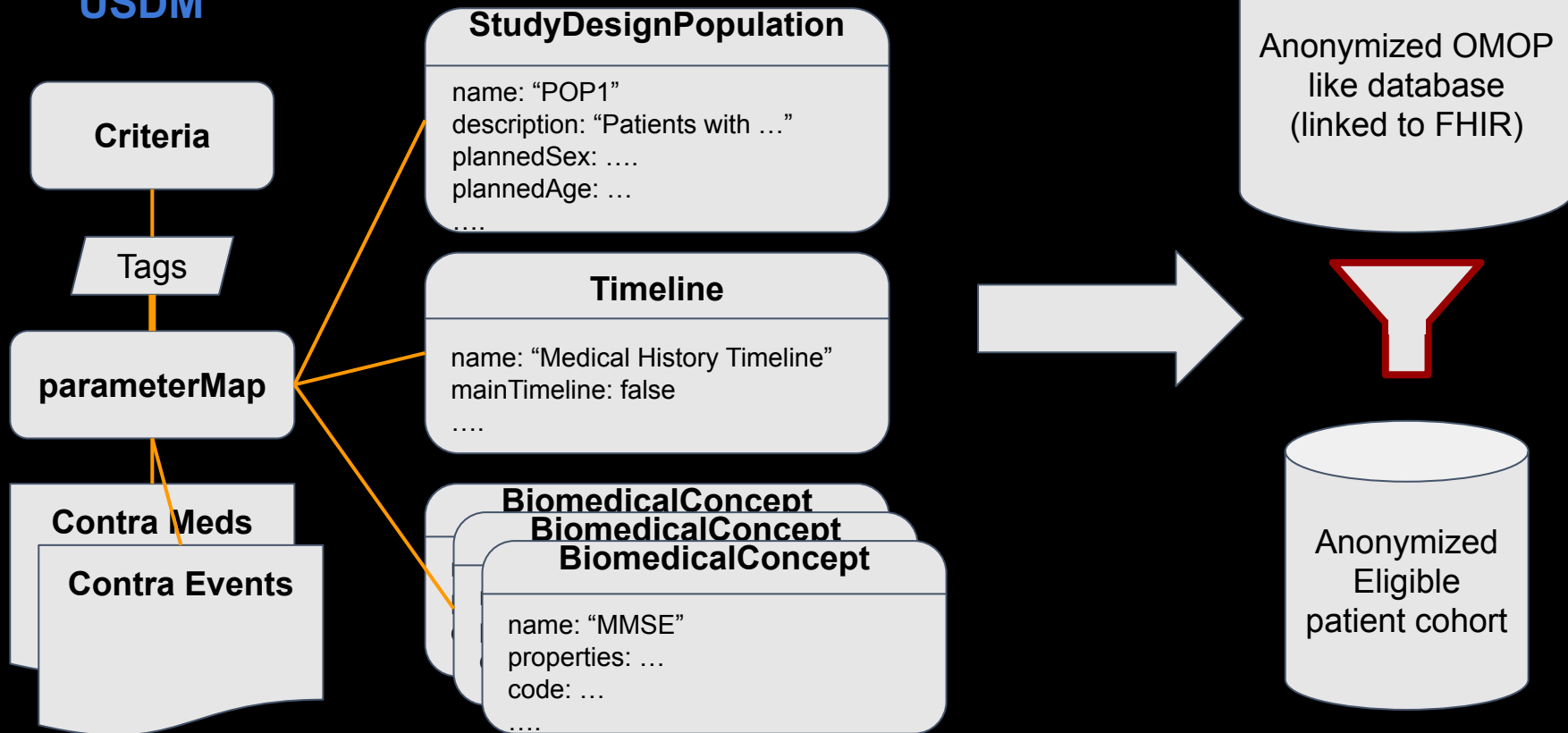
Lineage & Traceability

Step 3: Anonymization



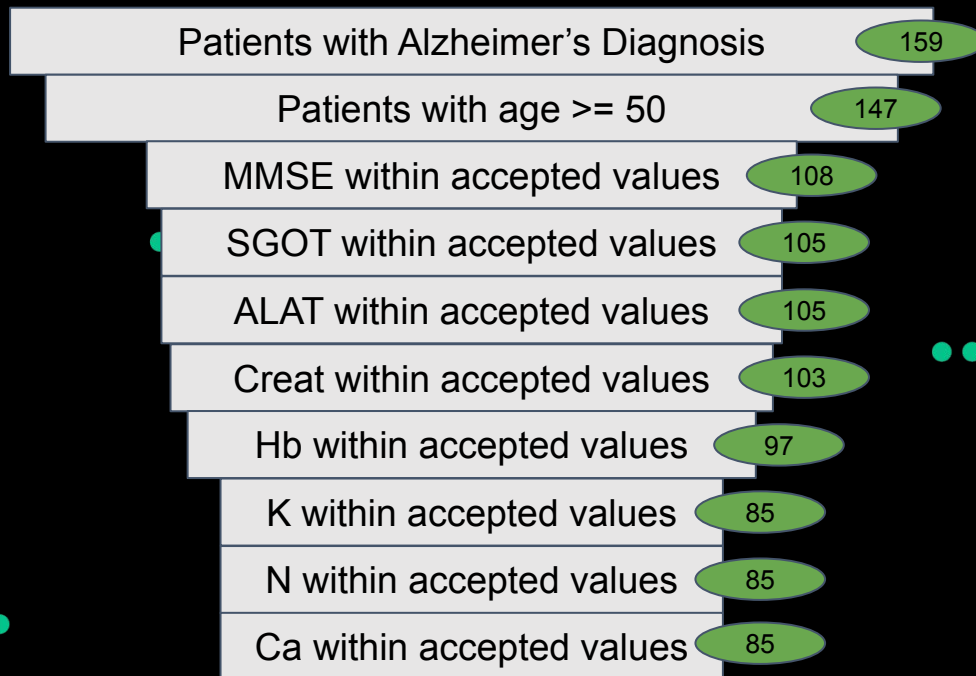
Step 4: Automated Selection of Eligible Patients

USDM



Step 4: Automated Selection of Eligible Patients

Attrition Diagram

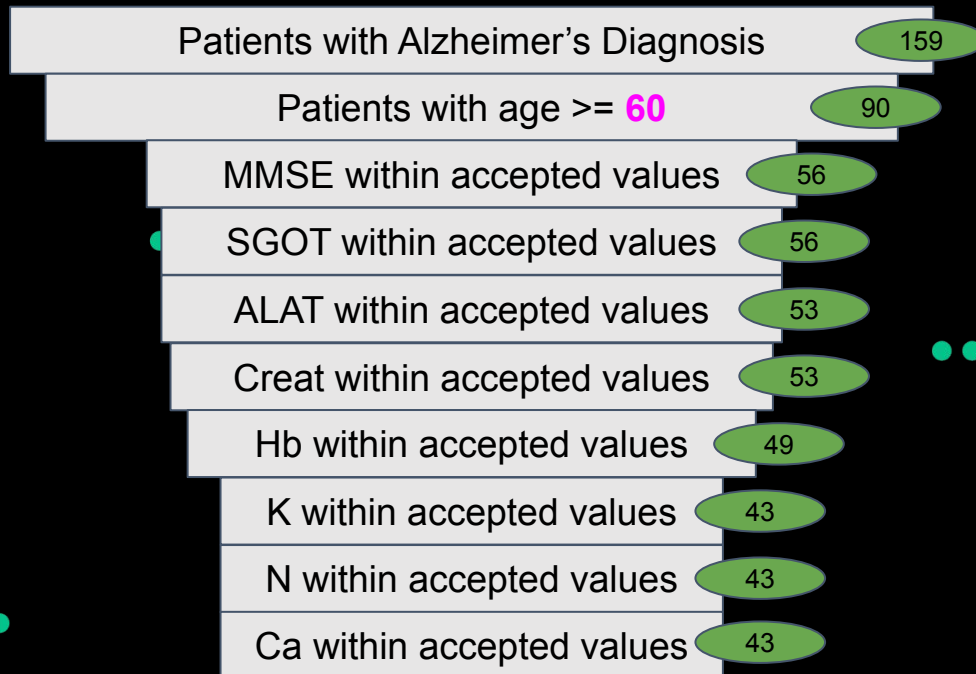


Summary for Attrition Report (Page 1 of 1)

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 in design

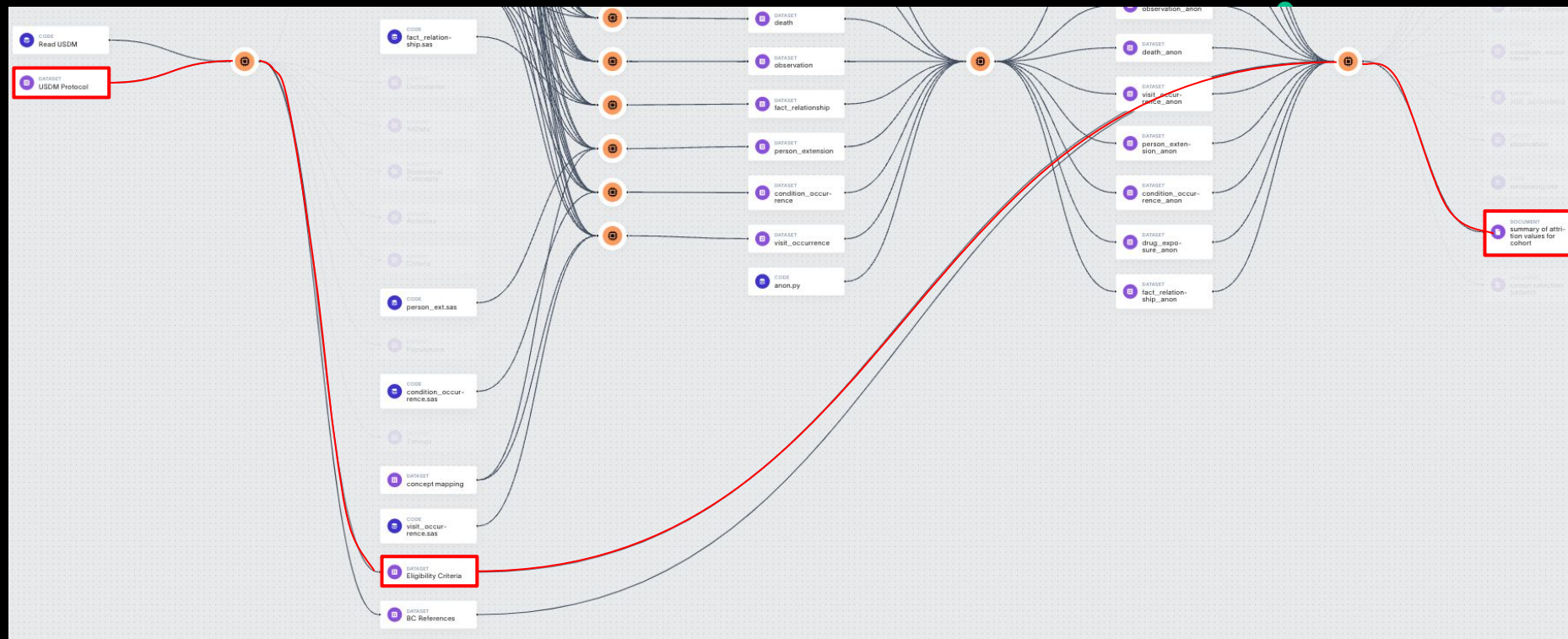


Summary for Attrition Report (Page 1 of 1)

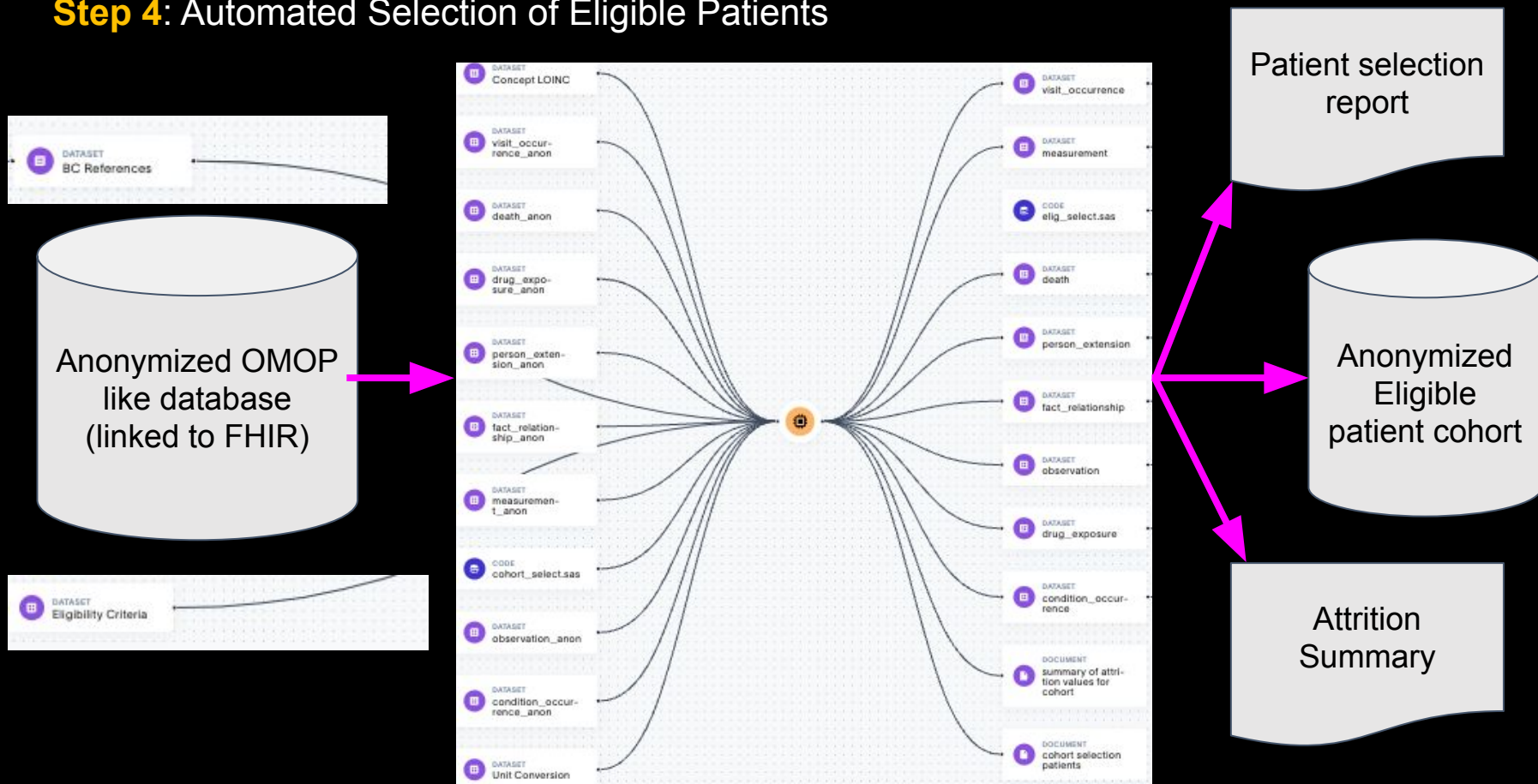
Category	Criteria	Number of Patients
Inclusion	Patients with Alzheimer's Diagnosis	159
Inclusion	Patients with Age ≥ 60	90
Inclusion	Patients with MMSE within accepted values (inclusion criteria)	56
Exclusion	Patients with SGOT not outside accepted values (exclusion criteria, Female specific)	56
Exclusion	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.

Downstream Impacts



Step 4: Automated Selection of Eligible Patients



Step 5: Fit for Purpose Assessment

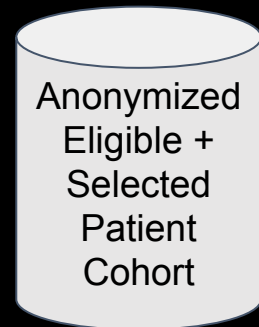
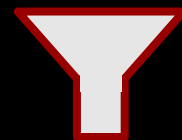
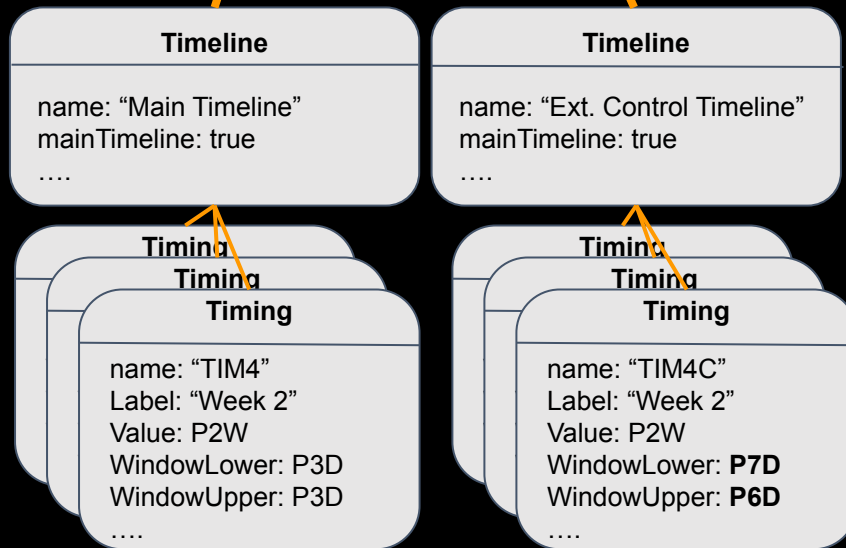
Windowing for RWD

- 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

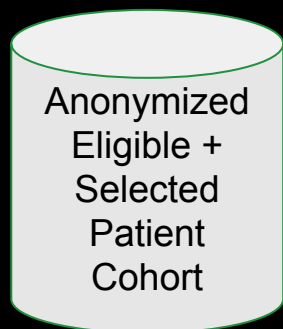
Interventional trial arm			Real-world control arm	
Visit	Week	Planned visit Day	WindowLower Day	WindowUpper Day
1	-2	-14	-180	-1
2	-0.3	-2	DO NOT INCLUDE	
3	0	0	INDEX DATE	7
4	2	14	7	20
5	4	28	21	34
7	6	42	35	48
8	8	56	49	69
9	12	84	70	97
10	16	112	98	125
11	20	140	126	153
12	24	168	154	174
13	26	182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



Step 6: SDTM Mapping

Standardized Mapping

Data source	only include WHERE	additional actions 1	Dataset DM	STUDYID	DOMAIN	USUBJID	SUBJID	RFSTDTCD	RFENDTCD
Person	only include WHERE	eligibility criteria are met	Dataset SC	STUDYID	DOMAIN	USUBJID	SCSEQ	SCTESTCD	
observation	observation_concept_id = 42528763		POC_LZZT_001 SC	SUBJID_studyid	autonumber within subject	"EDULEVEL"			
Data source	only include WHERE	additional actions 1	Dataset QS	STUDYID	DOMAIN	USUBJID	QSSEQ	QSTESTCD	
observation	observation_concept_id = 42528763		POC_LZZT_001 SC	SUBJID_studyid	autonumber within subject	"MMS112"			



Codelist	Synthes / FHIR	Code	OMOP concept_id	Code Name	Vocabulary	Codelist	Codelist code	CT
gender	female		8532	F	Gender	Sex	C66731	F
gender	male		8507	M	Gender	Sex	C66731	M
gender	F		8532	F	Gender	Sex	C66731	F
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Race	Asian - East		8515	2 Asian	Race	Race	C74457	ASIAN



Alternative Route



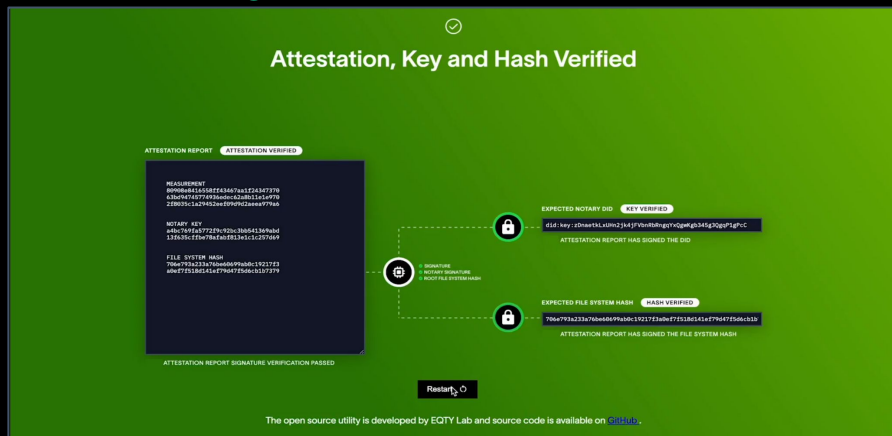
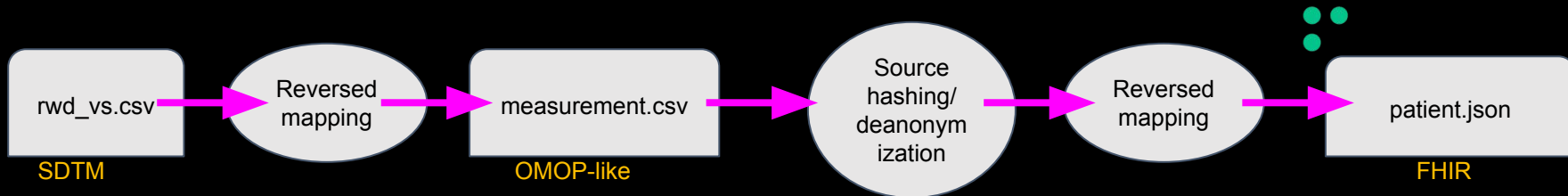
Trial Design Input

BC mapping

SV mapping

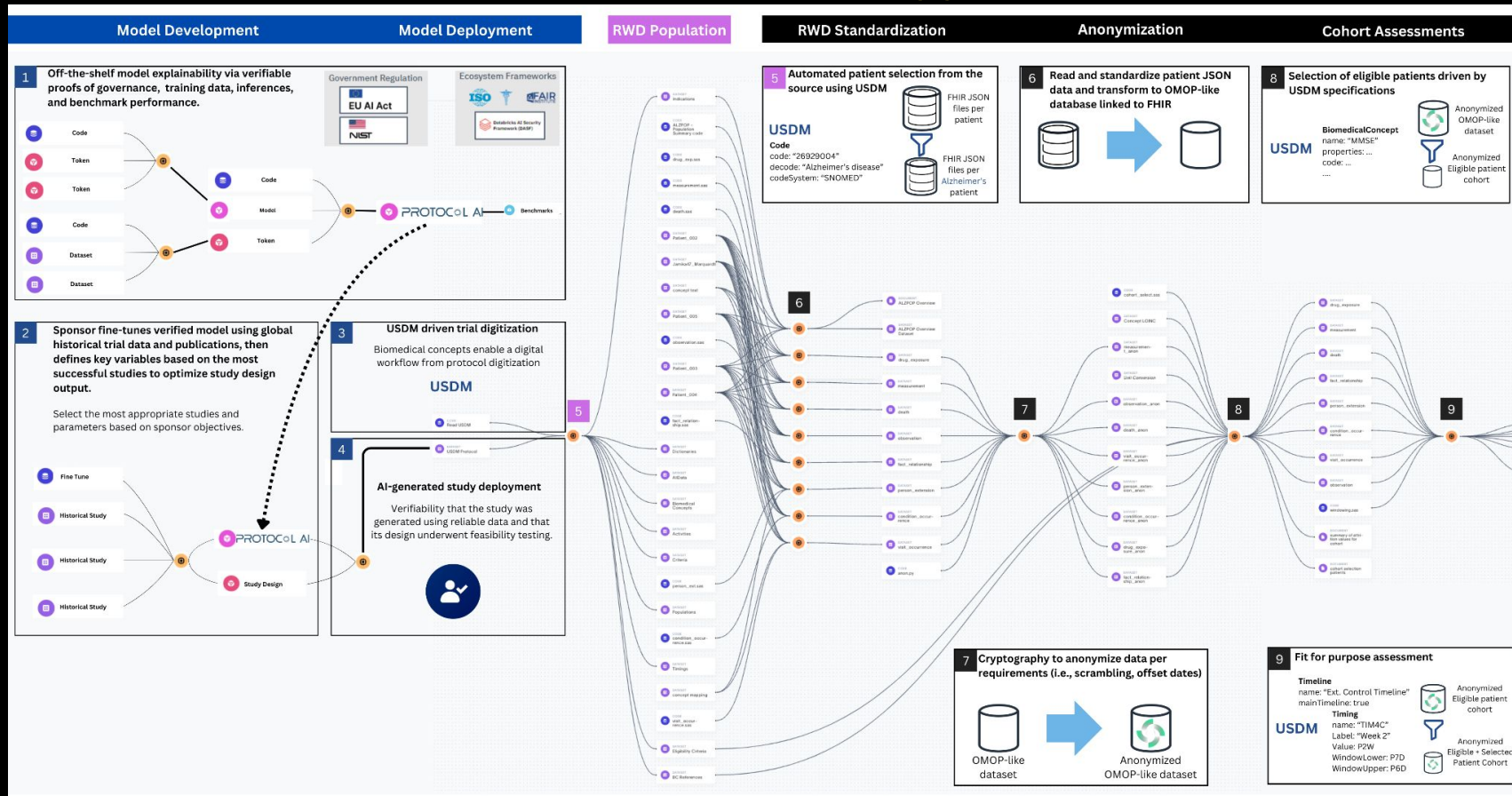


Step 7: Auditable Traceability

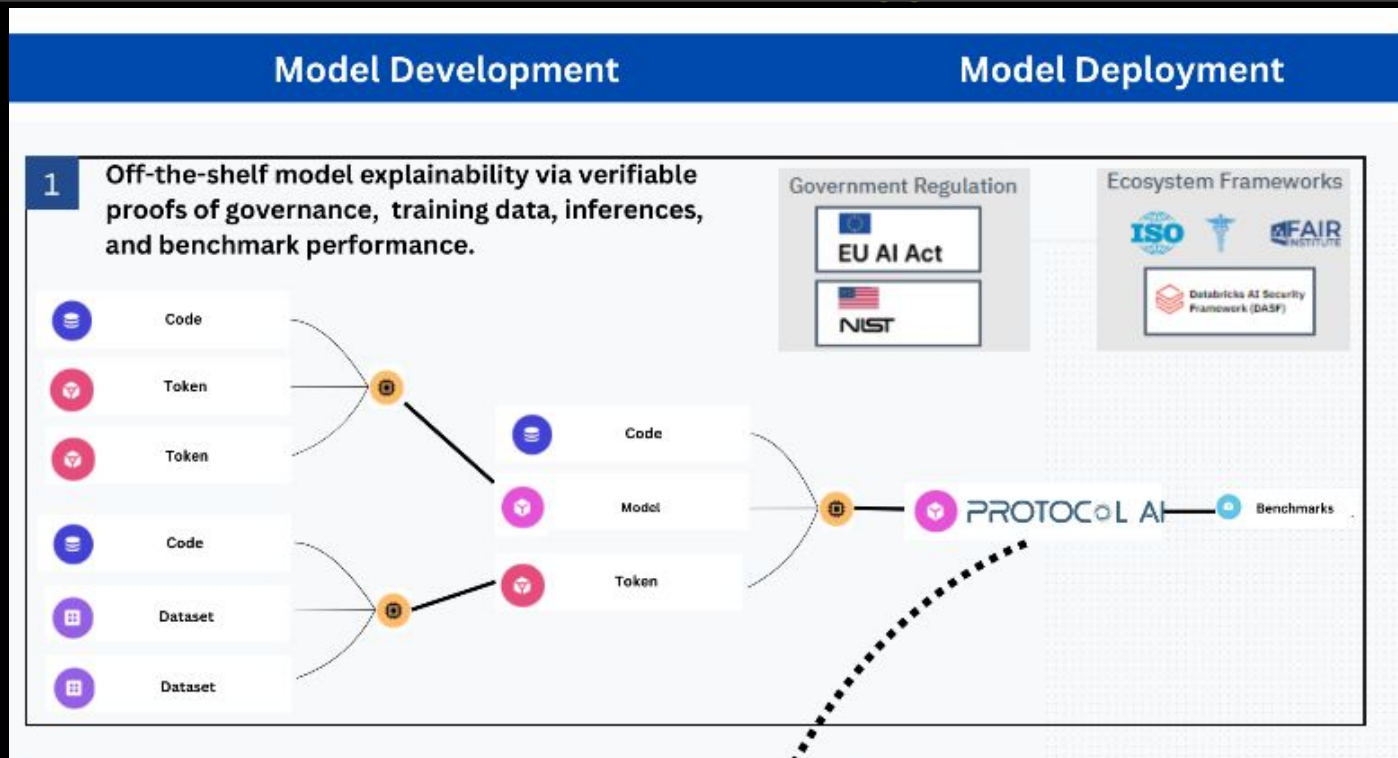


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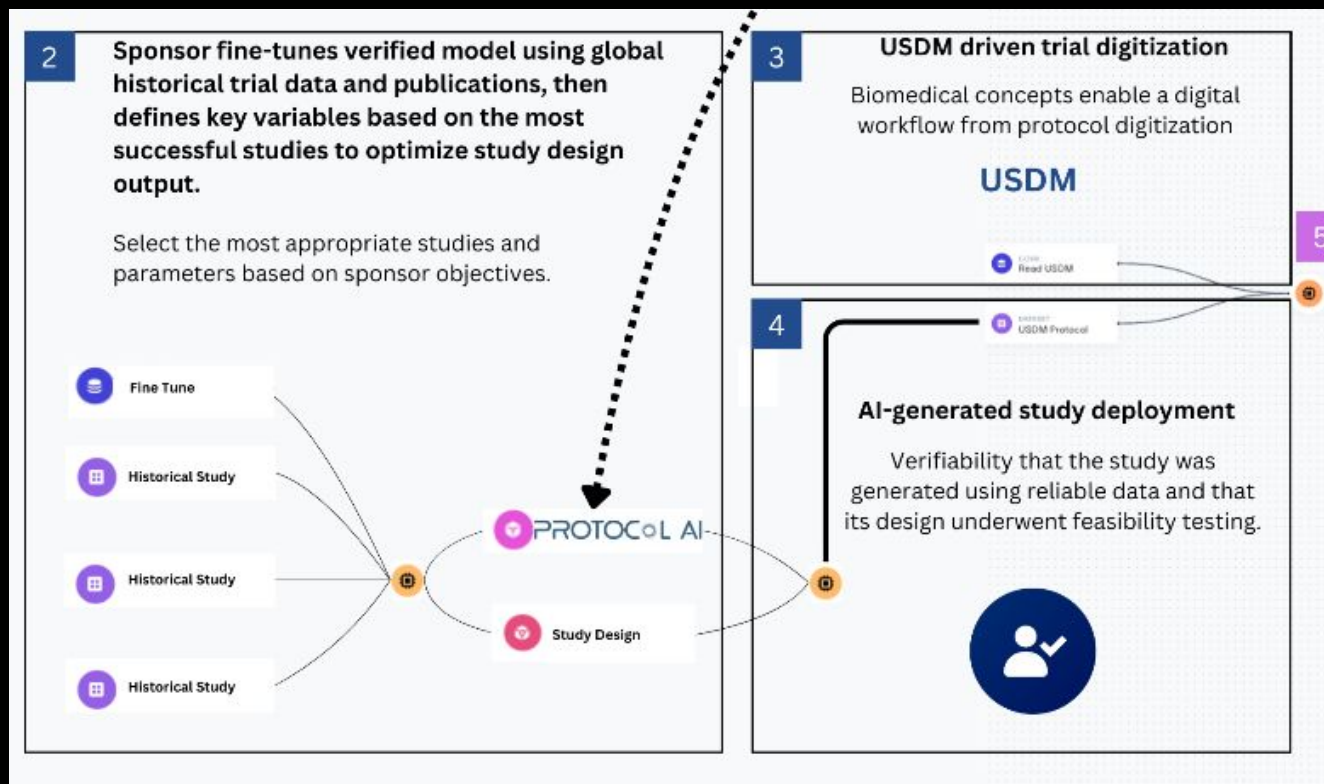
EOTY LIFE SCIENCES



Verifiable AI in Study Design for USDM Driven Feasibility Assessments



Verifiable AI in Study Design for USDM Driven Feasibility Assessments



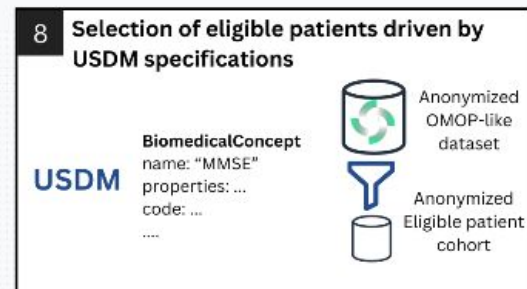
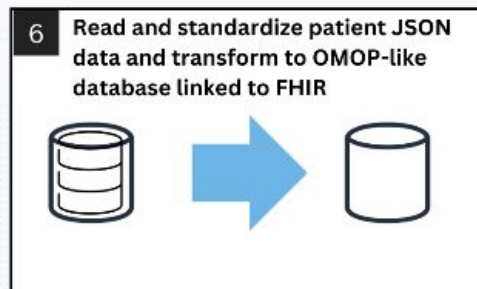
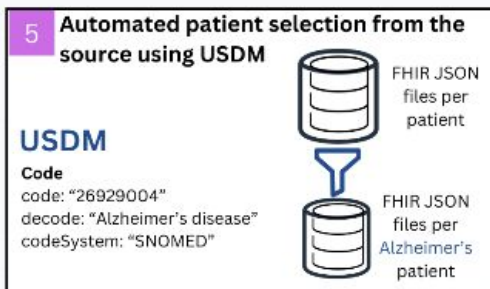
Verifiable AI in Study Design for USDM Driven Feasibility Assessments

RWD Population

RWD Standardization

Anonymization

Cohort Assessments



Challenges in Model Explainability and Compliance

→ Challenges

- ◆ Data Quality
- ◆ Resource-Intensive Verification
- ◆ Complex Buying Cycles
- ◆ Explainability Issues

→ Solution

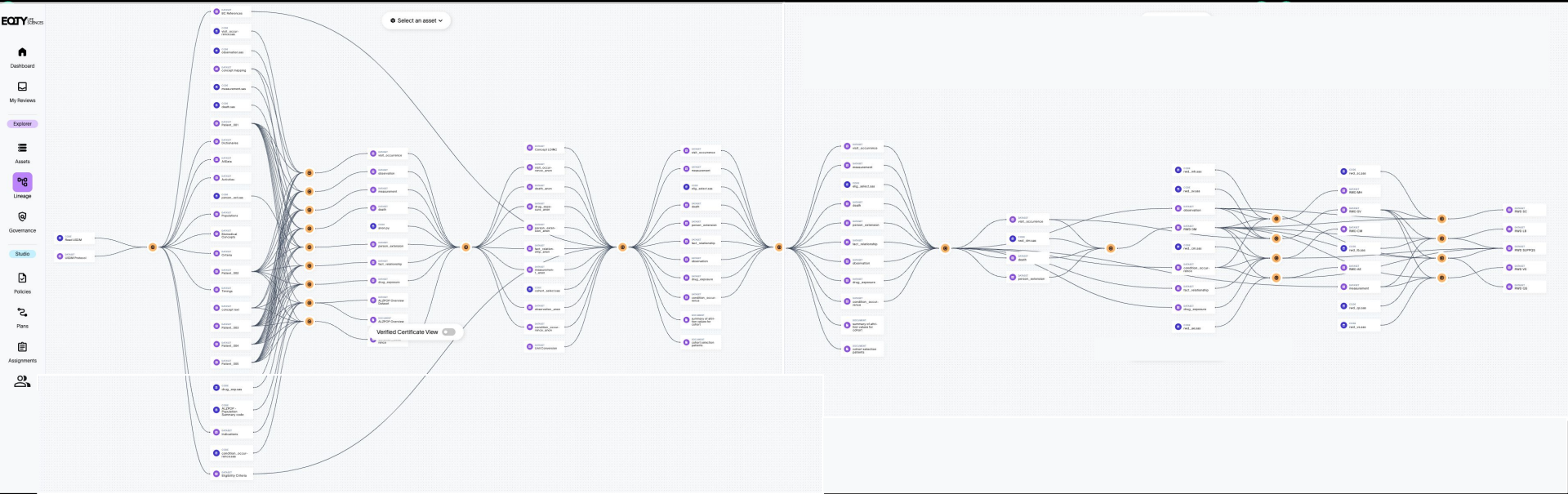
- ◆ Cryptographic Certification
- ◆ Enhanced Model Cards
- ◆ Data and Code Protection

Protocol AI, 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**



Step 7: Auditable Traceability.



Protocol AI
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