



PONTE Presentation

Efficient Patient Recruitment for
Innovative Clinical Trials of
Existing Drugs to other Indications

www.ponte-project.eu

<http://cordis.europa.eu/fp7/ict/>
http://ec.europa.eu/information_society

CETIC

Philippe Massonet

EU Open Day, Cambridge, 31/01/2012

PONTE Description

- Efficient **P**atient Recruitment for Inn**o**vative Clinical **T**rials of **E**xisting Drugs to other Indications
- Start Date: 01/03/2010
- Duration: 36 months
- Budget:
 - Commission contribution: 2 495 024 euros
 - Total budget: 3 276 699 euros
- Partners: 9



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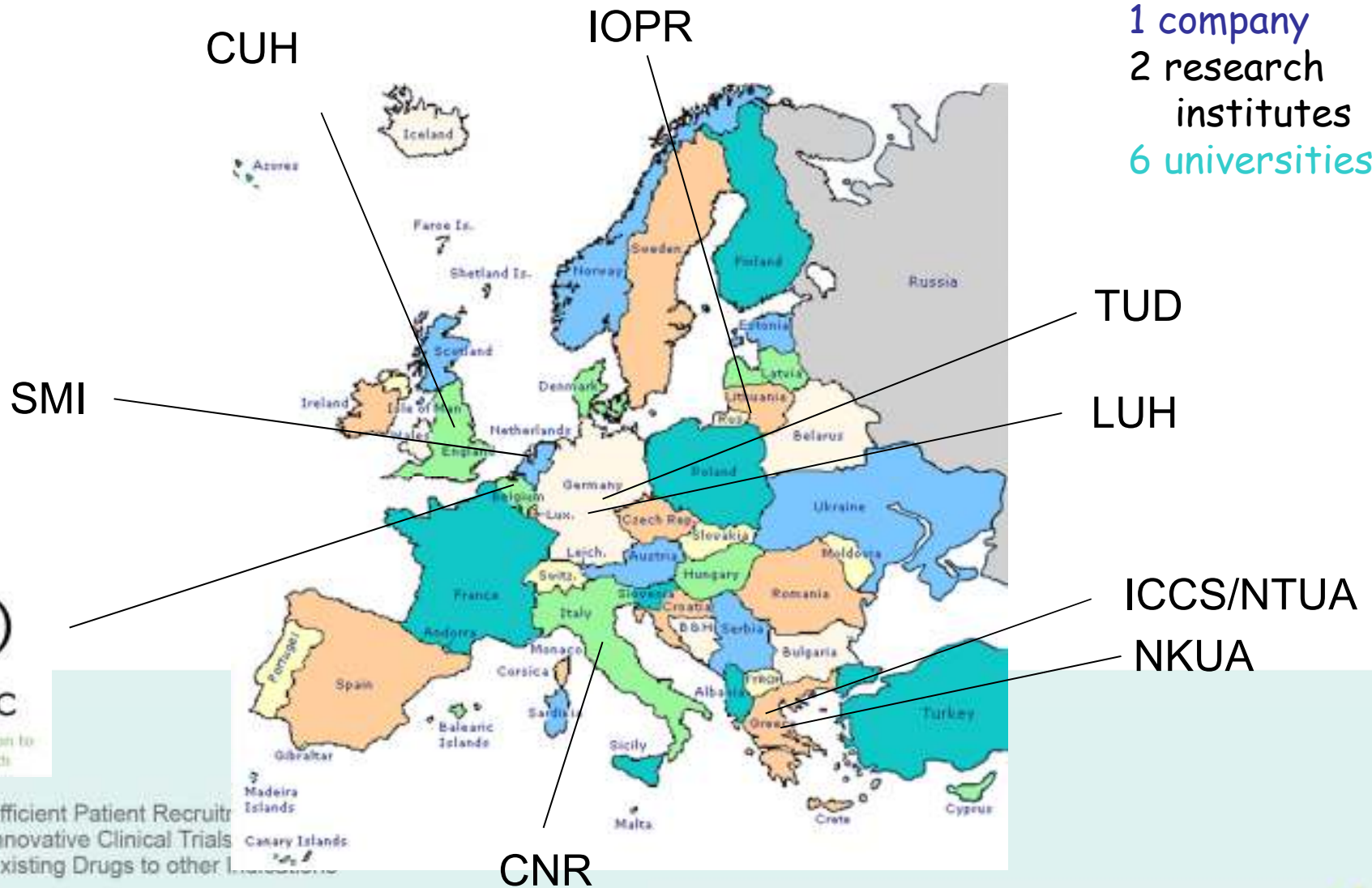
This project is partially funded by the European Commission under the 7th Framework Programme



European Commission
Information Society and Media

PONTE Consortium

7 countries
1 company
2 research
institutes
6 universities



Efficient Patient Recruitment
Innovative Clinical Trials
Existing Drugs to other
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Introduction

- Average Drug Development **cost** is € 500-700 million per drug candidate and **timeline** more than 10 years.
- Tremendous reduction in **new active ingredients** reaching the market yearly:
 - ~ 60/year (late 1980s), 52 (1991), 31 (2001), 20-25 (currently)
- Clinical trials :
 - ~ 1/3 of the costs of drug development half of which depends on duration
 - Low recruitment rates – Long recruitment periods
 - Subjects recruited represent only partially the target patient population
 - Mortality rates in clinical study findings vs real life
 - 1 out of 5000 new drug candidates reach the market
- **Drug repositioning trend** and Complex tests of hypothesis: testing new treatments of existing drugs on patients suffering from another disorder
- **Adaptive** trial trend
- **Humans' high variability** in response to a drug treatment requires **large-scale clinical trial conduction** for ensuring that the investigational treatment is **safe** and **effective**



The PONTE Solution

- A platform designed for the easy and efficient
 - definition, design and adaptation CT protocols
 - patients recruitment
- **Inter linking** of a huge amount of **data** from various, dispersed data sources
 - Intelligent queries
 - Advanced semantic data mining services
- Provision of **decision-support** services for CTP design and patient selection (CTP validation and parameter suggestion)

→ Bridging the gap between **healthcare** (especially EHRs) and **clinical research** will improve the design of CTs (more accurate, scientifically correct eligibility criteria) is a necessary condition to reduce patients' **recruitment time**, improve **safety** and **efficacy**, and reduce **cost** of CT.



PONTE Research and ICT Objectives

TO1. Specification language describing at a high level of abstraction domains' data, patients' profiles and their relationship with the CT

TO2. Core ontology-driven scheme incorporating existing clinical data standards

TO3. Semantic representations for describing the evolution of the patient symptoms in coherence with the evolution of the treatment

TO4. Advanced ontology-based data mining techniques on distributed data sources

TO5. Advanced security mechanisms

TO6. Intelligent advanced decision support mechanisms with focus on patient safety, study efficacy and cost

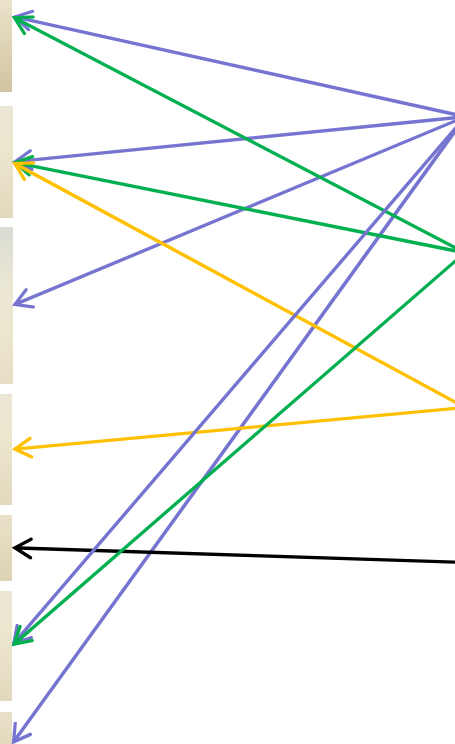
TO7. Semantic interlinking of heterogeneous databases

C1. EHR and clinical study data interlinking

C2. Clinical research data modeling

C3. Interlinking with data sources on clinical and non-clinical information

C4. Privacy-preserving secondary use of EHRs

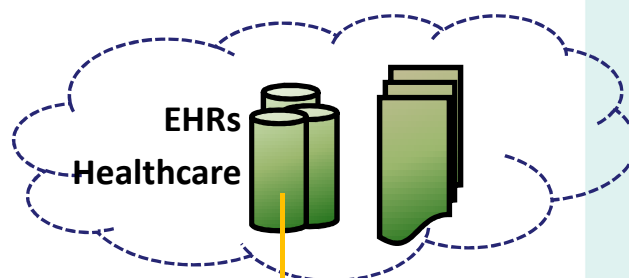
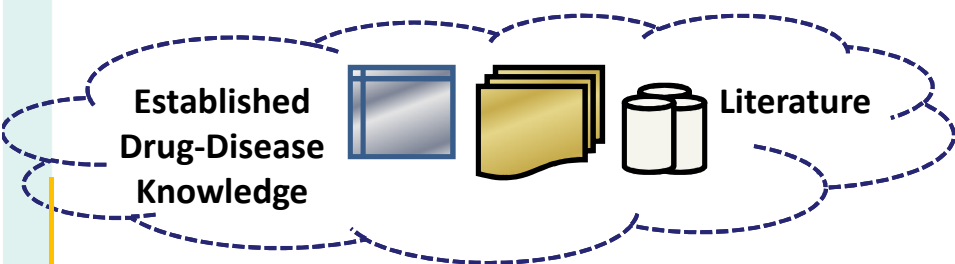


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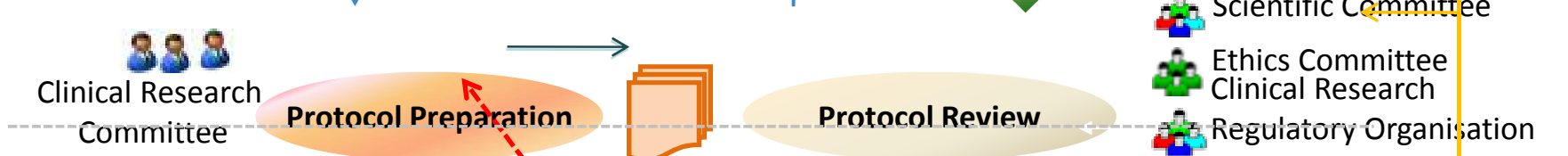
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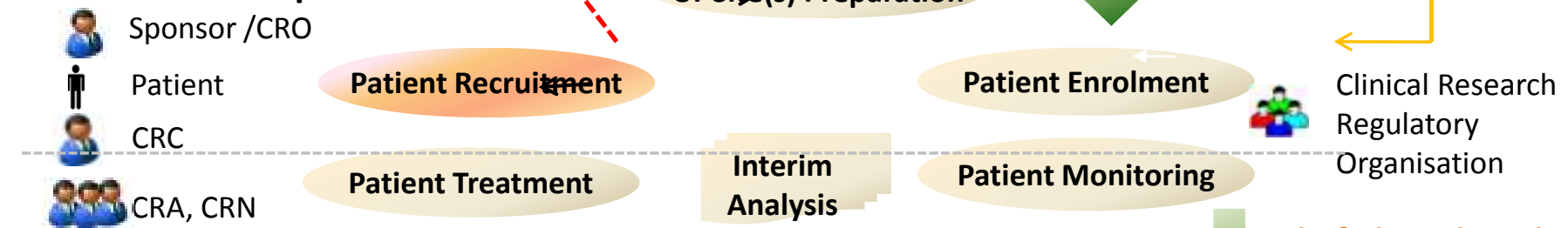
Test of Hypothesis Validation



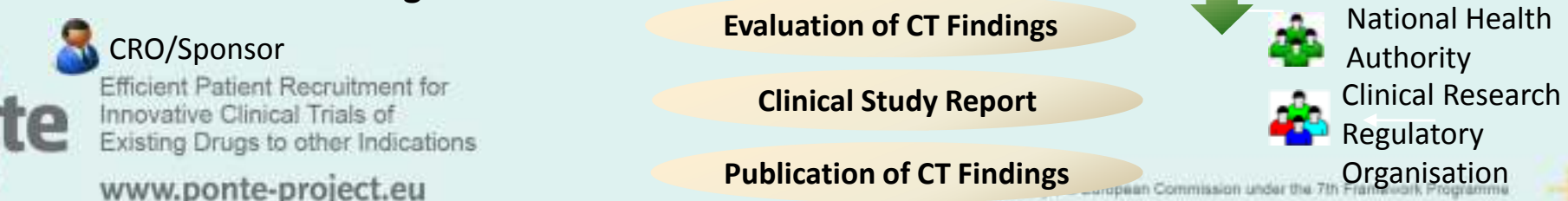
Clinical Trial Design and Planning



Clinical Trial Implementation



CT Evaluation - Findings Dissemination



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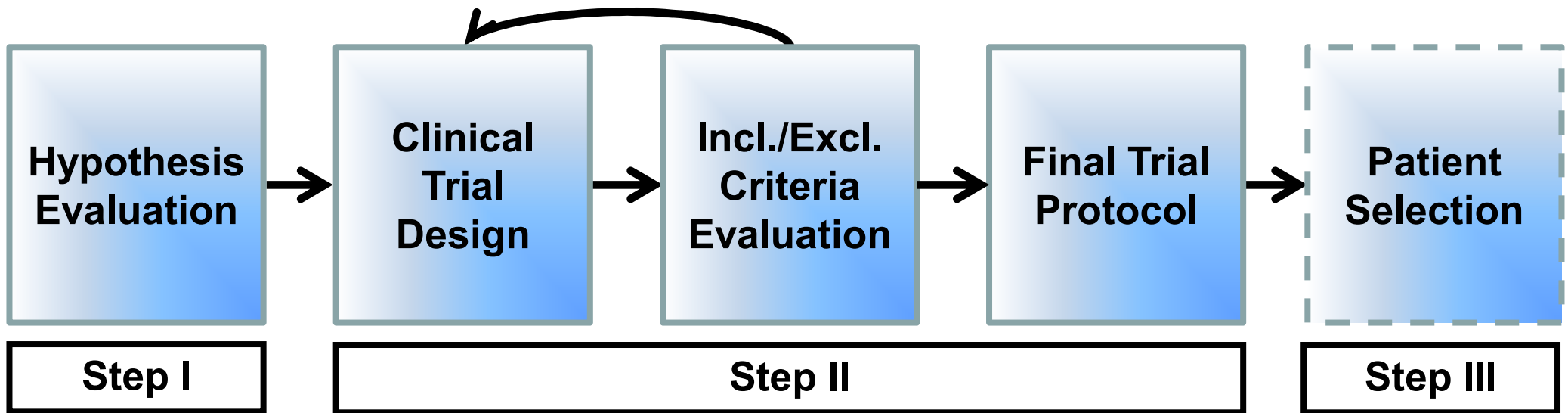


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From Hypothesis to Patient Selection



Drug

- Structure, homologues
- Metabolism
- Pharmacokinetics
- Route of administration

Disease

- Prognosis
- Disease stratification
- Co-morbidities
- Diagnosis, symptoms

Target

- Sensitivity
- Selectivity
- Expression: genes
- Expression: proteins
- Mutations



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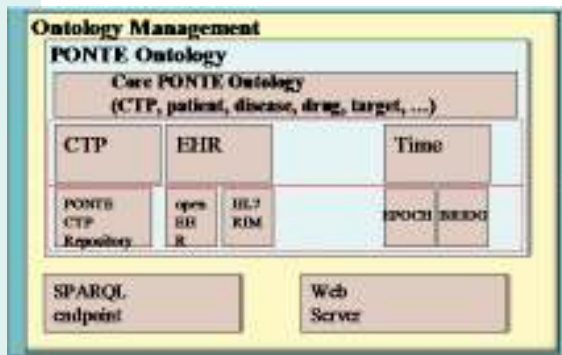


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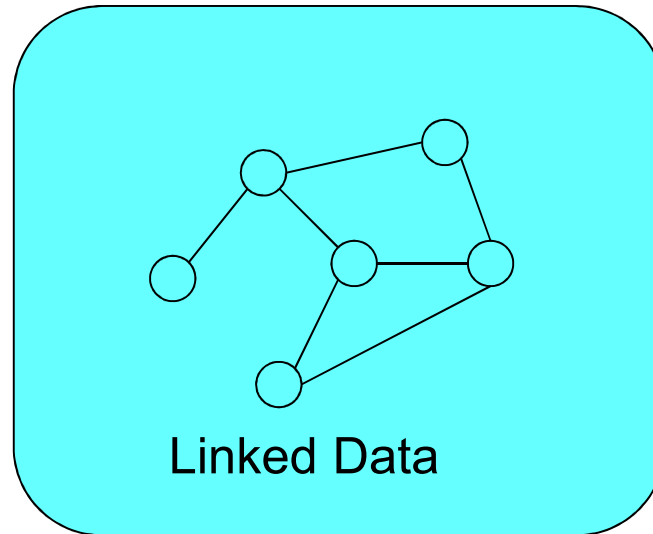


Semantic Interoperability

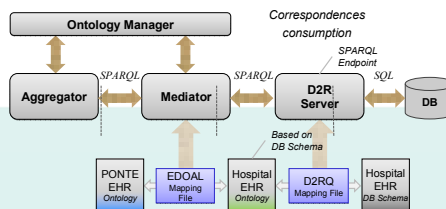
CT Questions



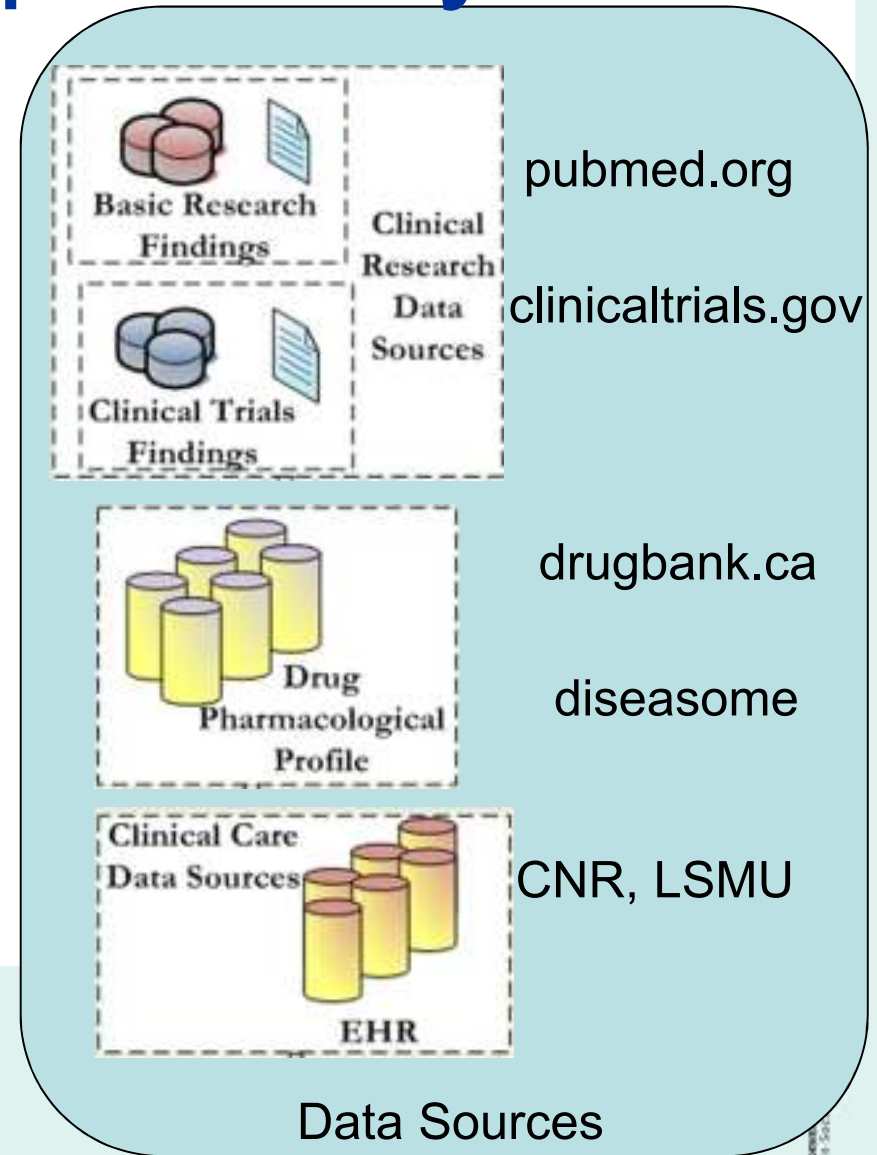
PONTE Ontology



Linked Data



Semantic Mapper

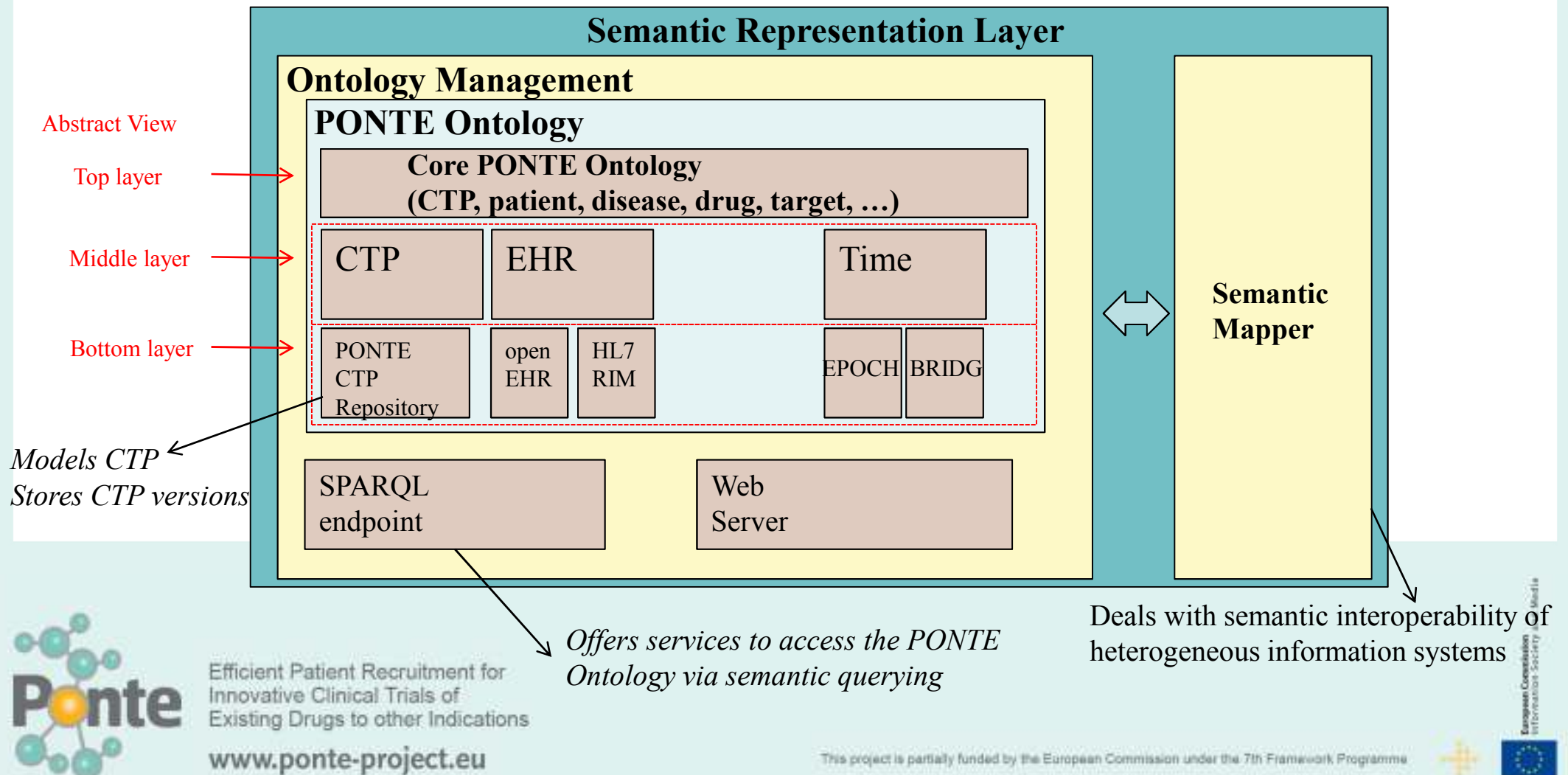


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PONTE Ontology and Standards

- Development of the PONTE ontology based on existing standards in the domain of Health Care



Main Use Cases

- UC1: Login
- UC2: User Management
- UC3: Role Management
- UC4: Set Test of Hypothesis
- UC5: Validation of “Test of Hypothesis”
- UC6: Select Cooperating Hospitals
- UC7: Set Clinical Trial Protocol Parameters
- UC8: Estimate Number of Eligible Patients
- UC9: Perform pre-defined queries
- UC10: Perform Free-Text Intelligent Search
- UC11: Save Search Results
- UC12: View Saved Search Results
- UC13: View Clinical Trial Protocol
- UC14: Save Intermediate Version of Clinical Trial Protocol
- UC15: Validate CTP Parameters
- UC16: Update Clinical Trial Protocol
- UC17: Submit Clinical Trial Protocol
- UC18: Update CTP Status after review
- UC19: Request for Patient Selection
- UC20: View List of Selected Patients
- UC21: Define CTP Parameters for Adaptation

User Case ID	UC5
User Case Name	Perform Intelligent Search
Purpose	The objective of this use case is to allow the authorized user to perform sub-optimal keyword searches which have failed related to drug, disease, topic, patient, trial, hospital, drug, trial, or patient with POC [patient]
Initiator	Pharmaceutical Clinical Staff, Pharmaceutical Sales Representative
Primary Actor	Pharmaceutical Clinical Staff, Pharmaceutical Sales Representative
Additional Actors	
Description	The user sets their query and submits it. They may also be unable to submit their query based on pre-defined categories and file.
Pre-conditions	The user has logged in and the test of hypothesis has been set.
Post-conditions	The user has information results for their query.
	Use Case Priority
Sequence	<ol style="list-style-type: none"> 1. Set Query 2. Optional Set Query parameters 3. Submit the Query 4. View Results for the Query 5. Optional Provide Results per pre-defined categories 6. Population profile, counts, per patient search terms

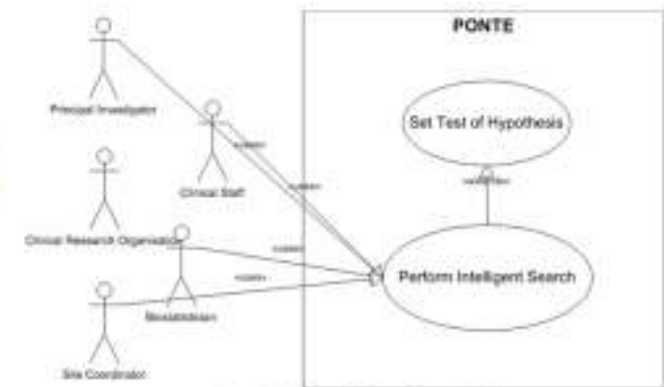


Figure 6 Perform Intelligent Search Use Case



Ontology Based Search Engine

The screenshot displays a search engine interface with an 'Ontology filter' sidebar on the left. The sidebar lists various categories such as 'Diseases (472)', 'Named Groups (476)', and 'Techniques and Equipment (473)'. The main search area shows a search bar with the query 'site:www.ncbi.nlm.nih.gov heart failure' and a 'find it' button. Below the search bar, the results are displayed as a list of documents. The first result is titled '1: Heart failure - Cardiology Explained' and includes a snippet: 'Furthermore, the prognosis for chronic heart failure (CHF) is poor; a patient admitted to ... Heart failure patients with diastolic dysfunction (more common in the elderly) have ...'. Other results include '3: [heart failure]. It seems that the causes of the insomnia are dyspnea and apnea (CSA) and a Cheyne-Stokes respiration (CSR), and' and '4: Cancer drug may cause heart failure'. The interface also shows a search bar with the query 'site:www.ncbi.nlm.nih.gov heart failure' and a 'find it' button. Below the search bar, the results are displayed as a list of documents. The first result is titled '1: Heart failure - Cardiology Explained' and includes a snippet: 'Furthermore, the prognosis for chronic heart failure (CHF) is poor; a patient admitted to ... Heart failure patients with diastolic dysfunction (more common in the elderly) have ...'. Other results include '3: [heart failure]. It seems that the causes of the insomnia are dyspnea and apnea (CSA) and a Cheyne-Stokes respiration (CSR), and' and '4: Cancer drug may cause heart failure'.

Search for 'heart failure'

Semantic filtering, e.g., Diseases, Patients, Chemicals ..

85,000 results from PubMed documents, Go, Mesh terms highlighted.



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Linked Data Application

2: Acute Myocardial Infarction [2010-12-18]

Acute Myocardial Infarction. Clinical Application of Technetium 99m Sulfuric Pyrophosphate Infarct Scintigraphy. Jeffrey A. Werner, MD, Elias H. Botvinick, MD, David M. Shames, MD, and William W. Parmley, MD ... Acute myocardial infarction is being recognized as a spectrum of clinical subsets...

www.ncbi.nlm.nih.gov Description Synonyms Tree **Linked Data**

3: Experimenter Myocardial Infarction [2010-12-21]

Use of digitalis in Links to Linked Data: Myocardial Infarction increased by 28%. Left ventricular end-diastolic pressure increased from 7 to ...

www.ncbi.nlm.nih.gov/pmc/articles/PMC322477

Extend Search in Linked Data

4: Emergency management of acute myocardial infarction [2011-01-08]

Among its various manifestations, acute myocardial infarction continues to present a particular challenge to

Select

Trusted Sources Only

Heart Disease

Myocardial infarction

Expansion

- associatedGene
- possibleDrug
- sameAs
- none

Drug

Human tumor necrosis factor receptor fusion protein

+ Etanercept

T3 thyroid hormone

+ Liothyronine

Target

Gene

Myocardial infarction

Resource URI: <http://www4.wiwiss.fu-berlin.de/diseasome/resource/diseases/797>

Property	Value
diseasome:associatedGene	<ACE>
diseasome:associatedGene	<ALOX5AP>
diseasome:class	<Cardiovascular>
diseasome:classDegree	7 (xsd:int)
diseasome:degree	10 (xsd:int)
is diseasome:diseaseSubtypeOf of	<Myocardial infarction, decreased susceptibility to>
is diseasome:diseaseSubtypeOf of	<Myocardial infarction susceptibility>
rdfs:label	Myocardial infarction
diseasome:name	Myocardial infarction
diseasome:possibleDrug	<Etanercept>
diseasome:possibleDrug	<Coagulation factor VIIa>
diseasome:possibleDrug	<Perindopril>
diseasome:possibleDrug	<Quinapril>
owl:sameAs	< http://data.linkedct.org/resource/condition/8483 >
owl:sameAs	< http://purl.org/net/tcm/tcm.lifescience.ntu.edu.tw/id/disease/Myocardial_Infarction >
owl:sameAs	< http://www.dbpedia.org/resource/Myocardial_infarction >
owl:sameAs	< http://www4.wiwiss.fu-berlin.de/sider/resource/side_effects/C0027051 >
diseasome:size	10 (xsd:int)
rdf:type	diseasome:diseases



Query Expansion across heterogeneous but linked Datasources



Linked Data Application



PONTE Ontology Concepts

Disease

- Heart Disease
 - Myocardial infarction

Expansion
 - associatedGene
 - possibleDrug
 - sameAs
 - none

Drug

- Human tumor necrosis factor receptor fusion protein
 - + [Etanercept](#)
- T3 thyroid hormone
 - + [Liothyronine](#)

Target

- Gene
 - + [ACE](#)

Show Properties:

possibleDrug

Etanercept
Dimeric fusion protein consisting of a dimer of the extracellular CH2 domain, the C1 domain, and a dimer of the extracellular domain of the TNF receptor type I. It is a recombinant DNA derived protein consisting of amino acids.

Menadione
A synthetic naphthoquinone derivative, a form of vitamin K2, menaquinone.

L-Glutamic Acid
A peptide that is a component of the glutamate neurotransmitter.

Drotrecogin alfa
Human Protein C derivative. Drotrecogin alfa (a) is a recombinant protein consisting of a heavy chain and a light chain.

PRINIVIL (Tablets)
PRINIVIL(Lisinopril) is a renin inhibitor. It is a synthetic peptide derivative.

Powered by YLIB

Linked Data Sources

Filter by Properties:

Etanercept

Resource URI: <http://www4.wiwiw.fu-berlin.de/drugbank/resource/drugs/DB000005>

Home | All drugs

Property	Value
drugbank:affectedOrganism	Humans and other mammals
drugbank:ahfsCode	92:00.00
drugbank:atcCode	
drugbank:brandName	
drugbank:brandName	etps
drugbank:casRegistryNumber	
drugbank:chemicalFormula	
drugbank:chemicalIupacName	etps
drugbank:chemicalStructure	
drugbank:contraindicationInsert	

Filter by Properties:

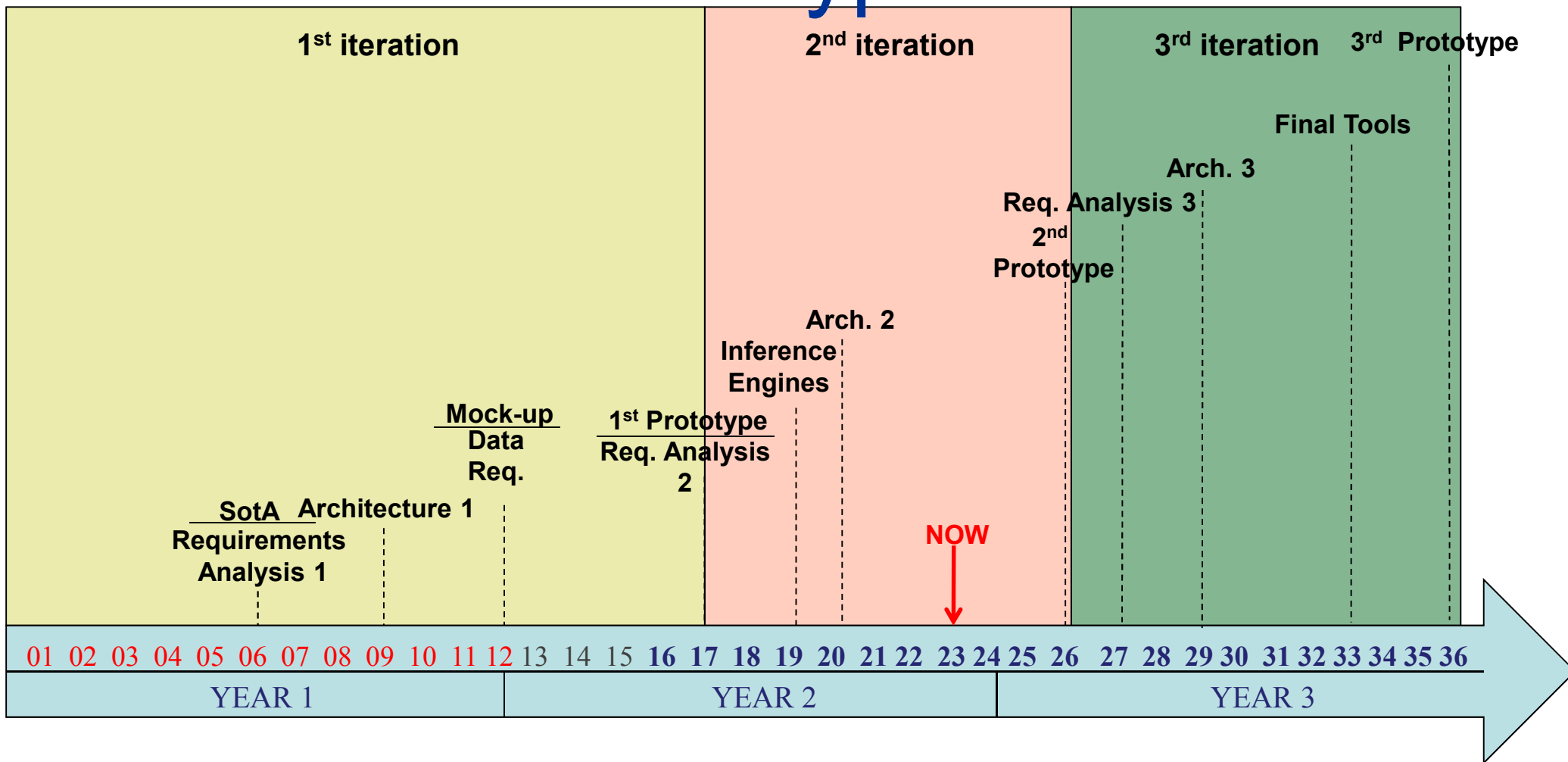
Phase	Phase 2
Start date	December 1999
Has expanded access	No
Suspense descr:	
Detailed description	<p>OBJECTIVES: - Determine the frequency of hematologic responses in patients with myelodysplastic syndrome treated with anti-thymocyte globulin and tumor necrosis factor receptor IgG chimera. - Correlate phenotypic, cytogenetic, and functional disease characteristics with treatment responses in these patients. - Determine the safety of this treatment regimen in this patient population. OUTLINE: Patients receive anti-thymocyte globulin IV over 8 hours daily for 4 days followed by tumor necrosis factor receptor IgG chimera subcutaneously twice weekly for 16 weeks. Patients are followed at 8, 16, and 20 weeks. PROJECTED ACCRUAL: A total of 13 patients will be accrued for this study.</p>



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PONTE Prototype Iterations



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Conclusions and outlook

- Designing Drug Repositioning Clinical Trials
 - Improving safety
 - Improving efficacy
 - Reducing cost
- Approach
 - Integrating clinical research and healthcare (EHR) data sources
- Results
 - Advanced clinical trial design prototype





*Thank you for your
Attention*

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PONTE Rationale

- Clinical trials are most often based on inadequate inclusion of critical study populations due to:
 - *focus on single interventions*
 - *lack of access to and linking with important data (patient pool, other clinical research findings)*resulting in results of **low external validity**:
 - great deviation between real world and clinical trials results
 - inability to predict off-target effects and potential at-risk populations which seriously affect patients' safety.
- Almost half of the delays in clinical trials are due to patient recruitment problems
- Drug repositioning trend
- Reduction in the allocation of funds for new research in pharmaceutical sector due to the world economy shrinking



PONTE Platform Objectives

- A platform designed for the easy and efficient
 - definition, design and adaptation CT protocols
 - Patients recruitment
- **Inter linking** of a huge amount of data from various, dispersed data sources
 - Intelligent queries
 - Advanced semantic data mining services
- Provision of interactive **decision-support** services for CTP design and patient selection (CTP validation and parameter suggestion)
- Automatic selection of eligible patients from **cooperating hospitals (pre consented patient pool)**
- Privacy compliant solution



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The PONTE Solution

- Objectives and innovation
 - Development of a research question into a Clinical Trial
 - Clinical Trial design management
 - Effective decision support (*patient selection*)
 - Efficient navigation capabilities

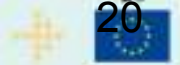


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The PONTE Platform

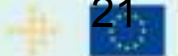
- Hypothesis Evaluation
- Clinical Trial Protocol Authoring Tool
- Intelligent search of data sources through the platform (PubMed, ClinicalTrials.org, drug/disease data, etc.)
- Guidance in every section of the Clinical Trial Protocol through available pre-defined queries



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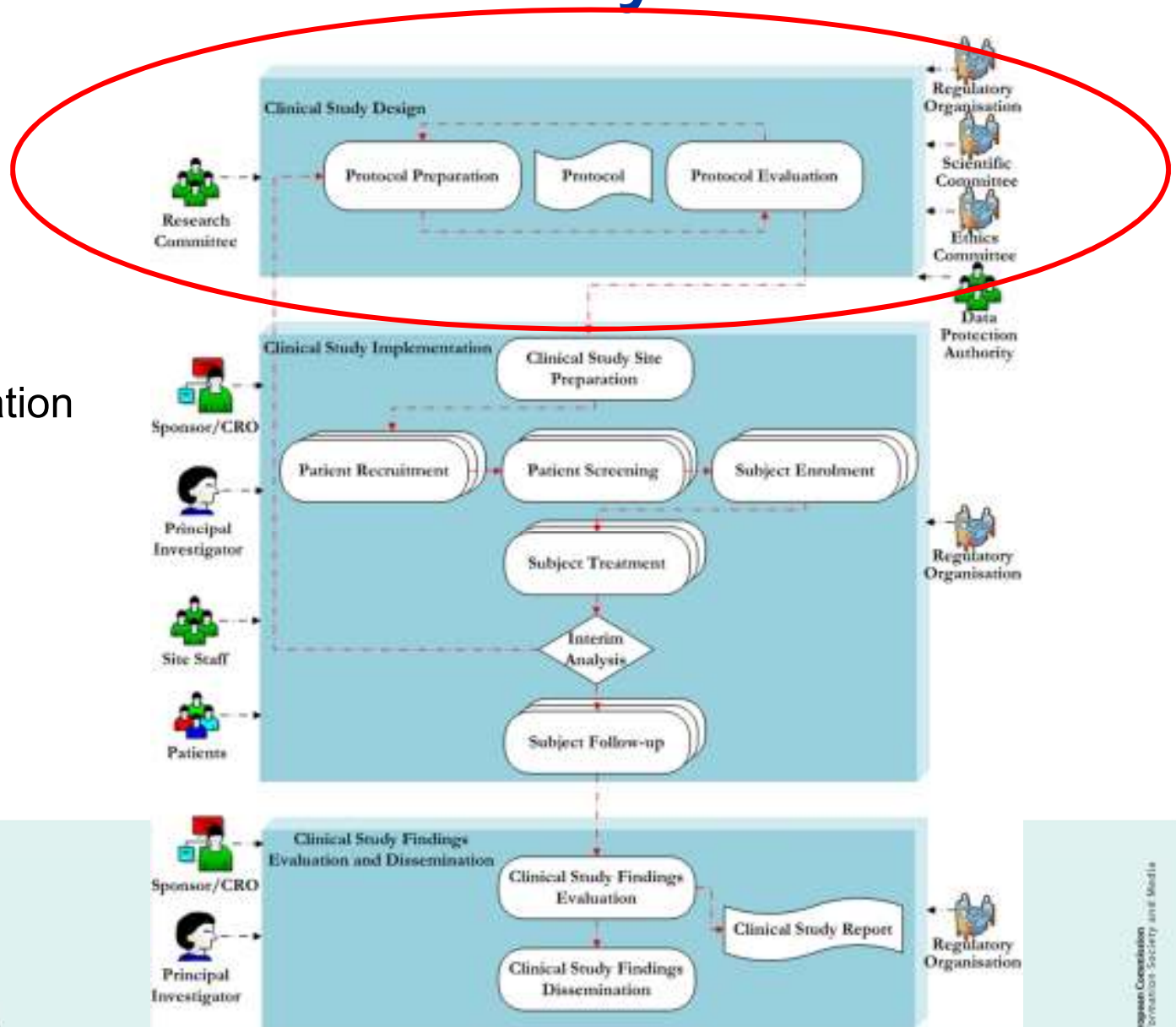
Project Context, Objectives

- *Drug repositioning* trend and *Complex tests of hypothesis*: testing new treatments of existing drugs on patients suffering from another disorder
- *Humans' high variability in response* to a drug treatment requires *large-scale clinical trial conduction* for ensuring that the investigational treatment is *safe* and *effective*
- Repositioning and *Adaptive* CT gain ground

→ Bridging the gap between healthcare (especially EHRs) and clinical research will improve the design of CTs (more accurate, scientifically correct eligibility criteria) and will reduce patients' recruitment time



Clinical Trial Lifecycle



Clinical Study Design
Clinical Study Implementation
Clinical Study Findings Evaluation
and Dissemination



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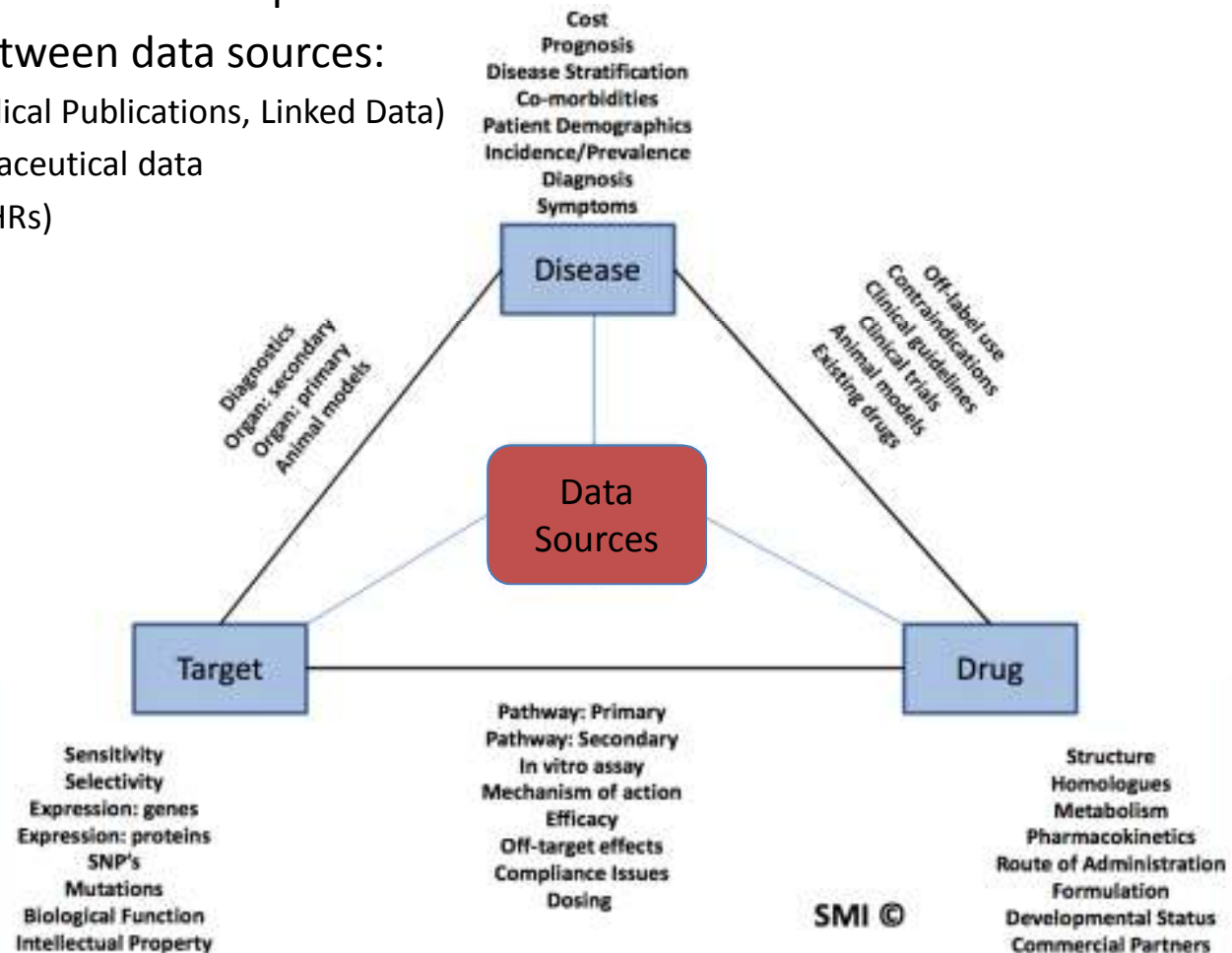
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Clinical Hypothesis Investigation Ontology

- User enters the problem from one of the main perspectives
 - Ontology bridges across these primary concepts/perspectives
 - Assists formulation of research question
 - Semantic Links between data sources:
 - Public data (Medical Publications, Linked Data)
 - Validated Pharmaceutical data
 - Hospital data (EHRs)



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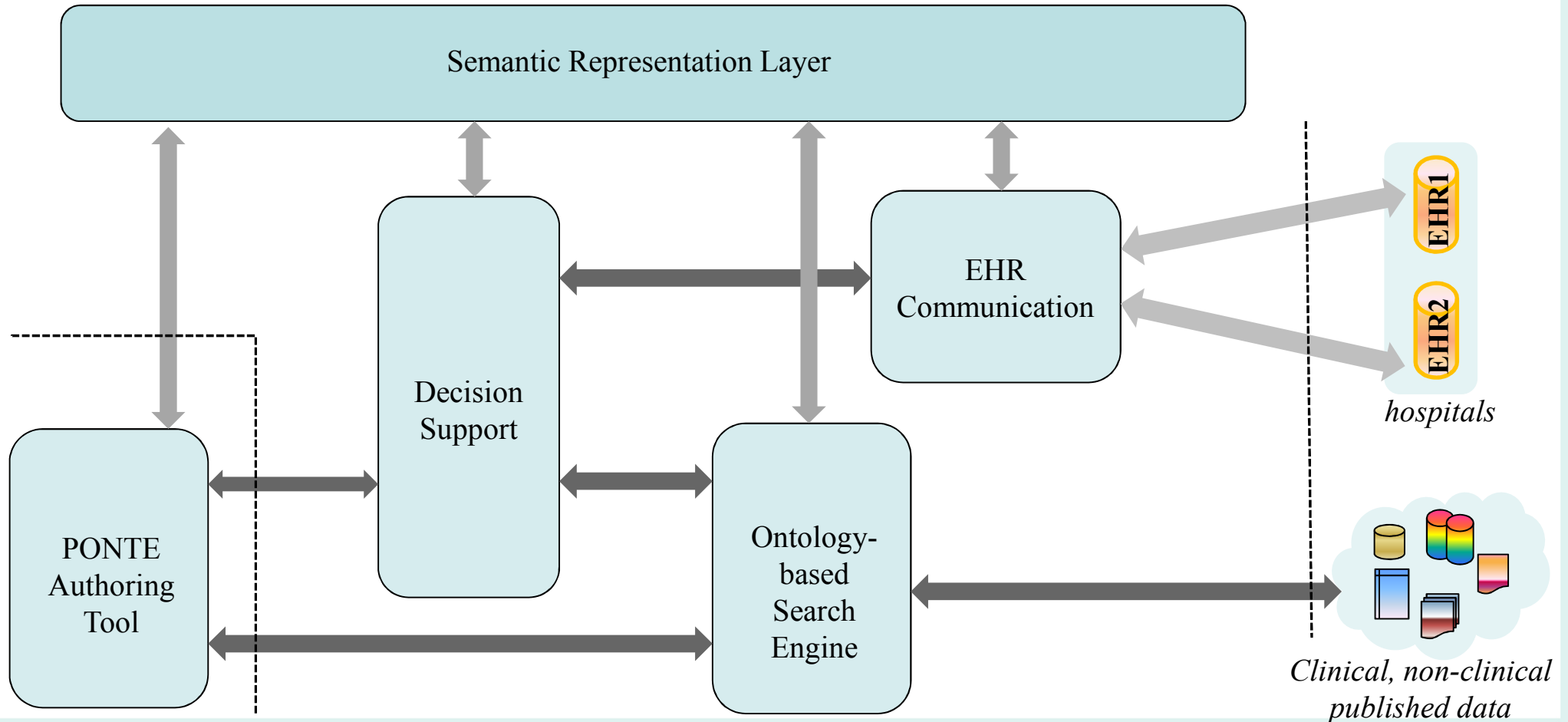
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PONTE Overall Architecture



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