



Machine Learning, AI and Large Language Models (ML)

Development of USDM through translation of human-readable protocols

Jasmine Kestemont,

Head of Data Acquisition (argenx) & Managing Partner (Innovion)

Stijn Rogiers,

Head of Data Integration & Standards (argenx)

12 Nov 2024



Meet The Speakers



Jasmine Kestemont

Title: Head of Data Acquisition & Managing Partner

Organization: argenx / Innovion

Jasmine Kestemont is an entrepreneurial business leader with significant experience in both Sponsor and services organizations. After a few years of global work experience, she has returned to the area she is most passionate about, data and project management, with a special interest in data standardization and regulatory submissions. Jasmine is Head of Data Acquisition at argenx.

[Jasmine Kestemont | LinkedIn](#)



Stijn Rogiers

Title: Head Data Integration & Standards

Organization: argenx

Stijn joined argenx in June 2022 as Head Data Integrations and Standards (Data Acquisition). Argenx is a fast-moving and growing Biotech company. Stijn has 20+ years of experience both at CRO, Pharma industry and Technology. He worked 5 years at SGS Life Sciences (CRO), 10 years within Janssen (Johnson & Johnson) and 7 years at SAS Institute (analytics leader) before moving to argenx. Stijn is also a member of the European CDISC Coordinating Committee (E3C).

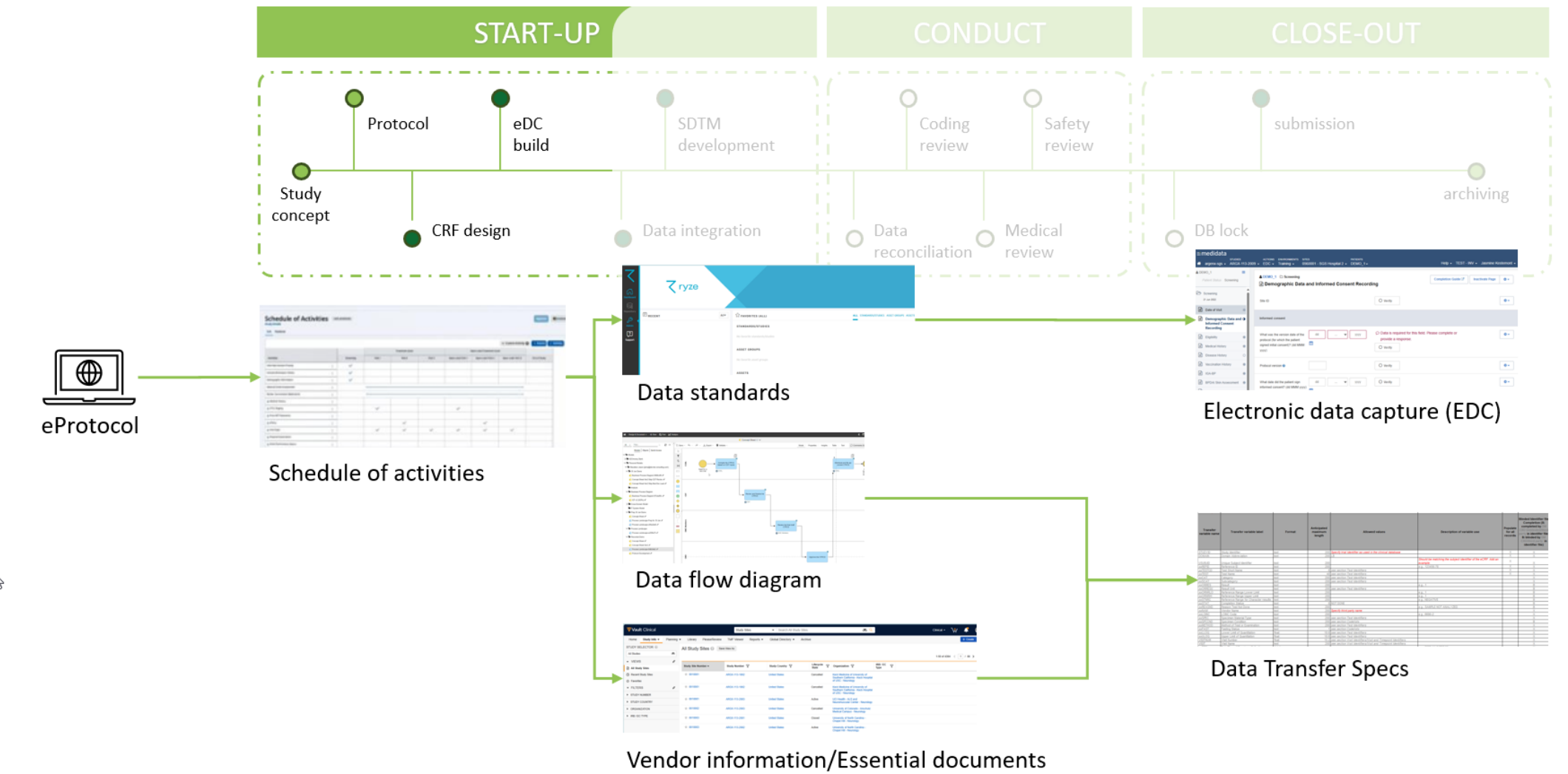
[Stijn Rogiers | LinkedIn](#)



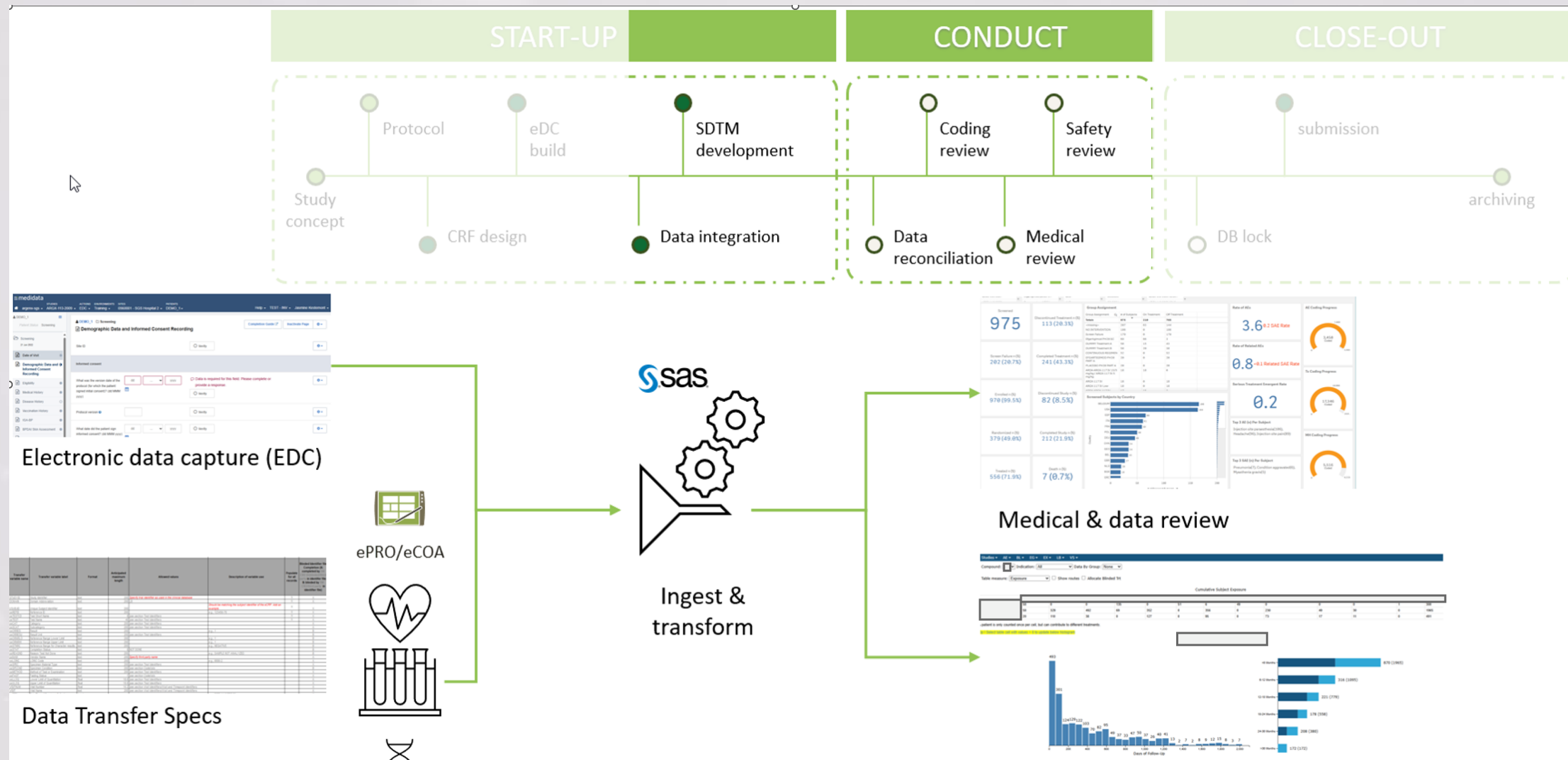
Agenda

- **1. Background to the project**
- 2. The initial Journey
- 3. POC 2.0
- 4. Financial Considerations
- 5. The Journey continues... ?

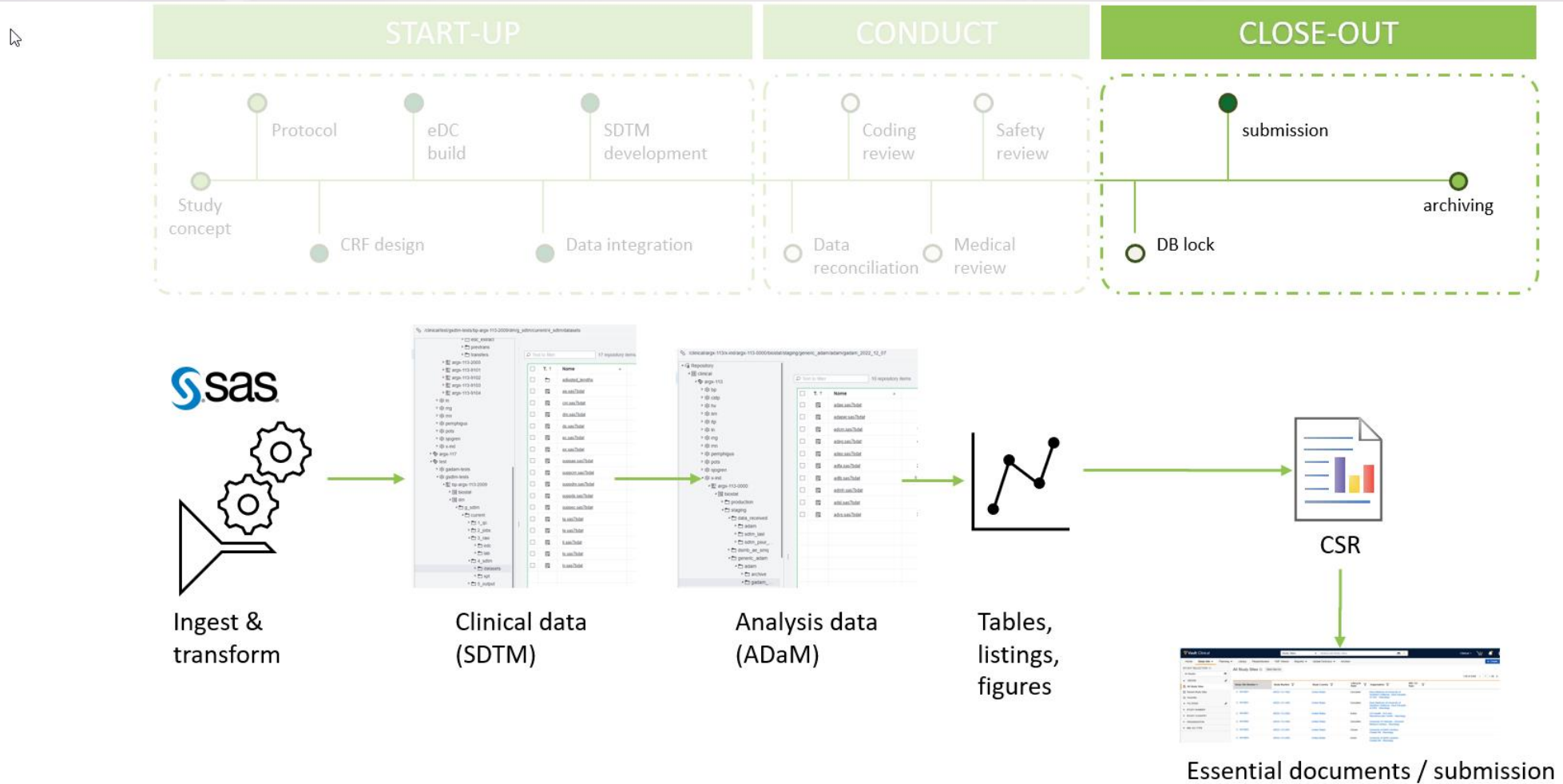
Our ambition ...



... End-to-end integration...



... from protocol authoring to submissions



How did we get here?

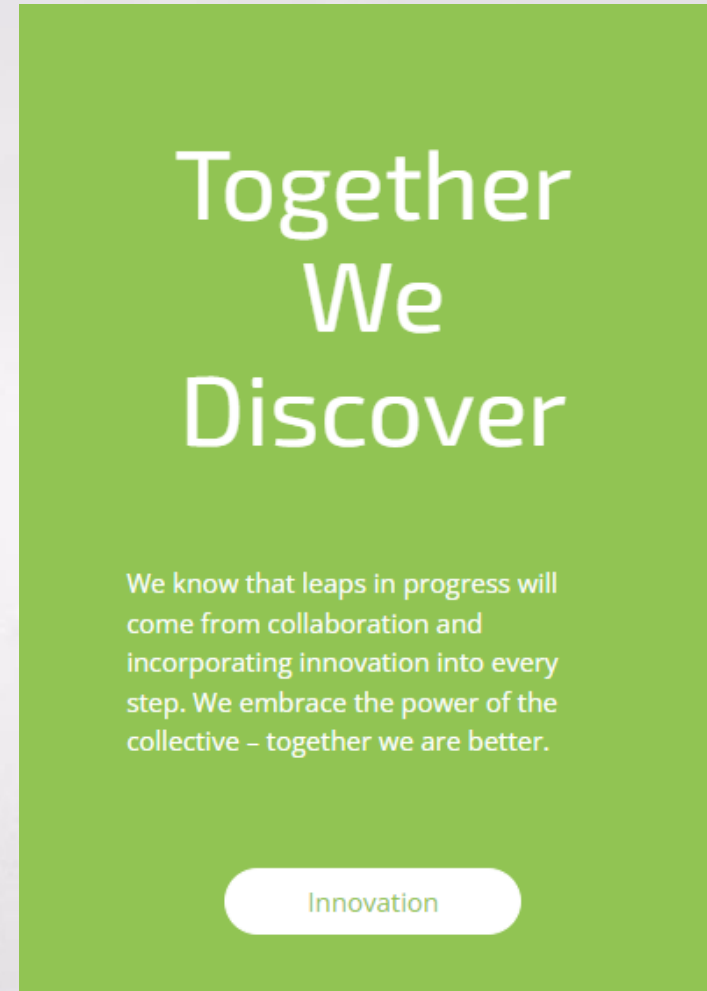
Workshop CDISC

[PHUSE EU Connect 2023 - DDF Workshop - PUBLIC - Wiki \(cdisc.org\)](#)

Need to standardize protocols

[ICH M11 guideline, clinical study protocol template and technical specifications - Scientific guideline | European Medicines Agency \(europa.eu\)](#)

Explore new technology



Phuse EU Connect 2023 – DDF workshop (Birmingham UK)

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PHUSE EU Connect 2023 - DDF Workshop

Created by John Owen, last modified on Nov 28, 2023

Pre EU Connect 2023 Information 27 Oct 2023	Listen to the preparation Webinar and review the preparation webinar slides
Pre-Reads for EU Connect 2023	Pre-Reads (<i>Materials to look at prior to the workshop if you wish to. NOT compulsory!</i>) <i>A the time of the workshop this was version 2.5, since the workshop this now points to the latest versions of the USDM</i> - Model (UML) - Controlled Terminology (XLSX) - Implementation Guide (PDF) - Informative Diagram (PNG) - Miro Board (Web) (P: CDISC-DDF-SME) (or if you prefer you can download a PDF of the Miroboard)
Web tools	Web Tools (<i>no need to install - these will run from a web browser</i>) - Excel To JSON Tool (U: PHUSE - P: learning_usdm) - Excel to JSON Tool readme - Excel to JSON Tool Infographic - JSON Comparison
Example files for EU Connect 2023 Workshop 05 Nov 2023	CDISC_Pilot_Study_Baseline.xlsx Example Protocol SoA Pages.jpeg SoA.png
Slides from EU Connect 2023 workshop 05 Nov 2023	Slides presented at the workshop on 05 Nov 2023
CDISC DDF EU Connect 2023 workshop 07 Nov 2023	2023 11 07 PHUSE Peter VR DS01 M11 - PHUSE EU Connect v0.5.pdf 2023 11 07 PHUSE DAVE IH DS02 V3.pdf
EU Connect 2023 Follow-up Webinar 28 Nov 2023	Listen to the Webinar and review the webinar slides Example files Demography - Adding BCs Vital signs - Adding timeline (demo'd at the follow-up webinar)
Link to DDF Orientation page on the CDISC WIKI	Digital Data Flow (DDF) Team Home/Orientation (CDISC Wiki account required)

argenx

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ICH M11 guideline



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ICH M11 guideline, clinical study protocol template and technical specifications - Scientific guideline

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The purpose of this new harmonised guideline is to introduce the clinical protocol template and the technical specification to ensure that protocols are prepared in a consistent fashion and provided in a harmonised data exchange format acceptable to the regulatory authorities. The ICH M11 Clinical Electronic Structured Harmonised Protocol Template provides comprehensive clinical protocol organization with standardized content with both required and optional components. The Technical Specification that are acceptable to all regulatory authorities of the ICH regions presents the conformance, cardinality, and other technical attributes that enable the interoperable electronic exchange of protocol content with a view to develop an open, non-proprietary standard to enable electronic exchange of clinical protocol information.

Keywords: protocol, harmonised template, interventional clinical trials, technical specification, data exchange, non proprietary standard

Ambition

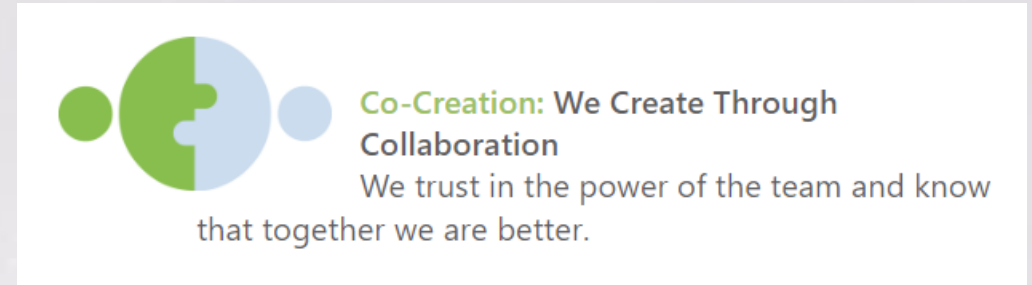
- **Historical protocols – machine readable – searchable library**
 - Secondary goal: prove machine readable to human readable via existing protocol
 - Existing protocol → USDM → human readable
- **Future protocols**
 - Schedule of Assessments (SoA) :
 - Determine:
 - cost of study (cost grid of assessments)
 - duration of visit (patient feasibility)
 - Drive:
 - protocol consistency (quality and speed)
 - CRF design
 - facilitate pooling of data
 - issue tracking and risk mitigation

POC Scope

- Do **contextual information extraction** from 2 argenx clinical trial protocols (early and late phase) and **store the relevant info** into the USDM (excel) workbook ... **in the right place** (in the right field).
- **Scalability:** Make sure the contextual information extraction is generic enough such that the text model used works on as many protocols as possible (including those never seen during training).
- Timelines: Start mid Feb > ready by Wk Apr 22

CDISC EU Connect 2024 – Digital Data Flow stream presentation

Co-Creation



- Team members

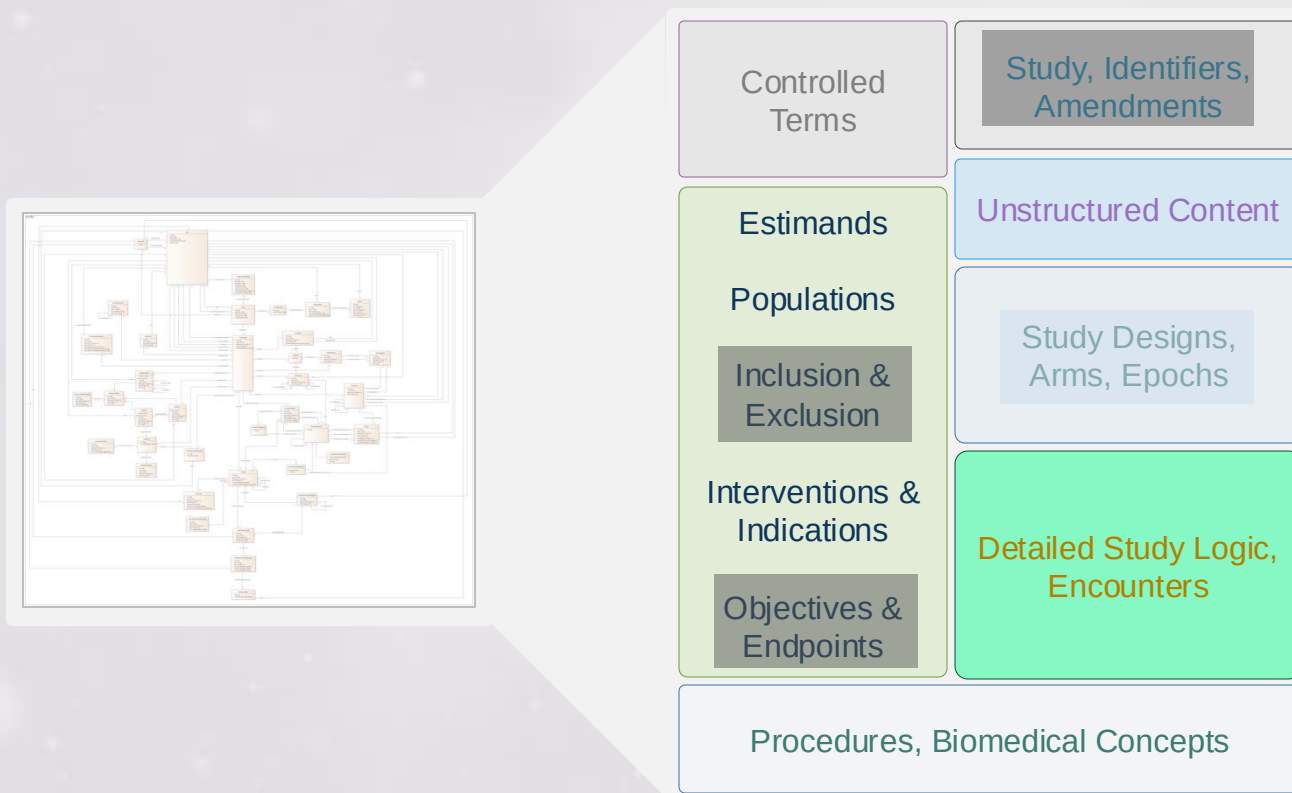
SAS:	Koen Knapen Rens Feenstra Jean-Charles Haillus Fadi Glor	(Principal Analytical Consultant , SAS), (Principal Technology Solution Consultant , SAS), (Senior Project Manager, SAS), (Senior Account Executive , SAS)
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argenx:	Jasmine Kestemont + Stijn Rogiers Sandeep Juneja	(see Bio) (Clinical Solutions, DML, argenx)
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- Semi-weekly meetings + sprint cycles
- Need for both technical expertise and content expertise

Behind the scenes additional domain experts consulted (LLM, Python, ...)

USDM Content



Focus for PoC

1. Study Overview (Text)
Study & StudyIdentifiers
2. Inclusion & Exclusion (Text)
StudyDesignEligibilityCriteria
3. Study Objectives & Endpoints (Text)
studyDesignOE
4. Investigational Plan:
 - 4.1 Study Design (Text + Image)
studyDesign
 - 4.2 SoA (Table)
mainTimeline
 - 4.3 Arms (Text)
studyDesignArms

USDM excel

study Sheet

	A	B	C	D	E	F	G
1	name	SCOPE1					
2	studyTitle	Simple Test 1					
3	studyVersion	1					
4	studyType	Interventional Study					
5	studyPhase	C15602					
6	studyAcronym	SIMPLE					
7	studyRationale	A simple test					
8	businessTherapeuticAreas	SPONSOR: VAC=Vacines Group, SPONSOR: REG=Regulatory					
9	briefTitle	Something Brief					
10	officialTitle	Something Very Official					
11	publicTitle	Something Public					
12	scientificTitle	Something Clever But New					
13	protocolVersion	1					
14	protocolStatus	draft					
15							
16	category	name	description	label	type	date	scopes
17	study_version	Approval	Design approval date	Design Approval	Sponsor Approval Date	01/01/2023	country : GBR, country:FRA, region:ASIA, country :USA
18	protocol_document	Approval	Protocol document approval date	Protocol Approval	Protocol Effective Date	01/01/2023	Global
19	protocol_document	Approval	Protocol document approval date	Protocol Approval	Protocol Effective Date	01/02/2023	region:asia

USDM Excel Sheet Formats & Links Infographic

17th January 2024, USDM Package v0.43

Details the excel workbook format as used by the **USDM** python package.

Details of the package can be found at <https://github.com/data4knowledge/usdm>.
Details for using the package and the sheet formats are detailed within the
readme file within the repository.

studyIdentifiers Sheet

	A	B	C	D	E	F
1	organisationIdentifierScheme	organisationIdentifier	organisationName	organisationType	studyIdentifier	organisationAddress
2	USGOV	CT-GOV	ClinicalTrials.gov	Study Registry	NCT12345678	line city district state postal_code GBR
3	DUNS	123456789	ACME Pharma	Clinical Study Sponsor	AP1234	Somewhere In a City In a District In a big state 12345 FRA

studyDesignEligibilityCriteria Sheet

	A	B	C	D	E	F	G
1	category	identifier	name	description	label	text	dictionary
2	Inclusion	01	Age Criteria	The study age criterion		Subjects shall be between [min_age] and [max_age]	IE_Dict
3	Inclusion	02	Age Criteria Error	The study age criterion with error		Subjects shall be between [min_age] and [max_agexxx]	IE_Dict

USDM Excel (Cont'd)

studyDesignOE Sheet													
	A	B	C	D	E	F	G	H	I	J	K	L	M
1	objectiveName	objectiveDescription	objectiveLabel	objectiveText	objectiveLevel	objectiveDictionary	endpointName	endpointDescription	endpointLabel	endpointText	endpointPurpose	endpointLevel	endpointDictionary
	OB1	Primary		The primary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of severe COVID-19 pneumonia	Study Primary Objective		END1	Day 28, 7 category scale		Clinical status assessed using a 7-category ordinal scale at Day 28		Primary Endpoint	
2	OB2	Secondary		The secondary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of severe COVID-19 pneumonia over the age of [min_age]	Study Secondary Objective	OE_Dict	END2	TTCI		Time to clinical improvement (TTCI) defined as a National Early Warning Score 2 (NEWS2) of <=2 maintained for 24 hours		Secondary Endpoint	
3							END3	Time to improvement		Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status		Secondary Endpoint	
4													

USDM Excel Sheet Formats & Links Infographic
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studyDesignElements Sheet				
1	A	B	C	D
2	name	studyElementDescription	Label	transitionStartRule
3	EL1	Screening Element	Screening	Study Start
4	EL2	Baseline Element	Baseline	Screened
5	EL3	Treatment Element 1	Treatment 1	Radomized
6	EL4	Follow Up Element	Follow Up	Treated
7	EL5	Treatment Element 2	Treatment 2	Radomized

studyDesignArms Sheet					
1	A	B	C	D	E
2	name	description	label	type	dataOriginDescription
3	Active	Active Substance	Active Substance	Active Comparator Arm	Data collected from subjects
4	Placebo	Placebo	Placebo	Placebo Comparator Arm	Data collected from subjects

studyDesign Sheet				
1	A	B	C	D
2	studyDesignName	Study Design 1		
3	studyDesignDescription	The main design for the study		
4	therapeuticAreas	SPONSOR:T2_DIABETES=Type 2 diabetes, SNOMED: 73211009=Diabetes mellitus (disorder)		
5	studyDesignRationale	Basic study		
6	studyDesignBlindingScheme	OPEN LABEL		
7	trialIntentTypes	BASIC SCIENCE, DEVICE FEASIBILITY		
8	trialTypes	Efficacy Study		
9	interventionModel	C82639		
10	mainTimeline	mainTimeline		
11	otherTimelines			
12	Epoch/Arms	Screening	Baseline	Treatment
13	Active	EL1	EL2	EL3, EL5
14	Placebo	EL1	EL2	EL4, EL3

Timeline Name Sheet									
1	A	B	C	D	E	F	G	H	I
2	Name	Main Timeline	name	SCREEN	PRE DOSE	DOSE	D14	PROG	D28
3	Description	This is the main timeline for the study design.	description	Screening	Pre Dose	Dosing	Day 14	Check Opt In	Day 28
4	Condition	Potential subject identified	label	Screen	Baseline	Treatment	Day 14	Check opt in by subject	Day 28
5			type	Activity	Activity	Activity	Activity	Decision	Activity
6			default	PRE DOSE	DOSE	D14	PROG	D28	FU
7			condition					FU: if opted out	Activity (EXIT)
8			epoch	Screening	Baseline	Treatment	Treatment		Treatment
9	Parent Activity	Child Activity	BC/Procedure/Timeline	E1	E2	E3	E4	E5	Follow-Up
10	-	Demographics	BC:Age, BC:Sex, BC:Race, BC:Body Weight	X					
11	-	Procedures	PR: PR1, PR: PR2	X	X	X	X		X
12	-	Optional Weight	BC:Weight	X			X		
13	-	Optional	BC:SYSBP, BC:DIABP					X	



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POC approach

1) Usage of LITI rules for contextual information extraction

LITI = Language Interpretation for Textual Information

LITI is proprietary syntax from SAS

LITI includes concept rule types as well as fact rule types.

2) Usage of LLM (RAG-for-LLMs) for contextual information extraction

RAG = Retrieval-Augmented Generation

3) PDF Table Extractor(s)

4) PDF Image Extractor(s)

5) Load from SAS tables into Excel and Word in an automated way

*while retaining the link i.e. if the info in the SAS table changes, then you can just refresh the *.xlsx or *.docx file to see that new info reflected.*

Comparison of 2 ways for information retrieval / contextual extraction

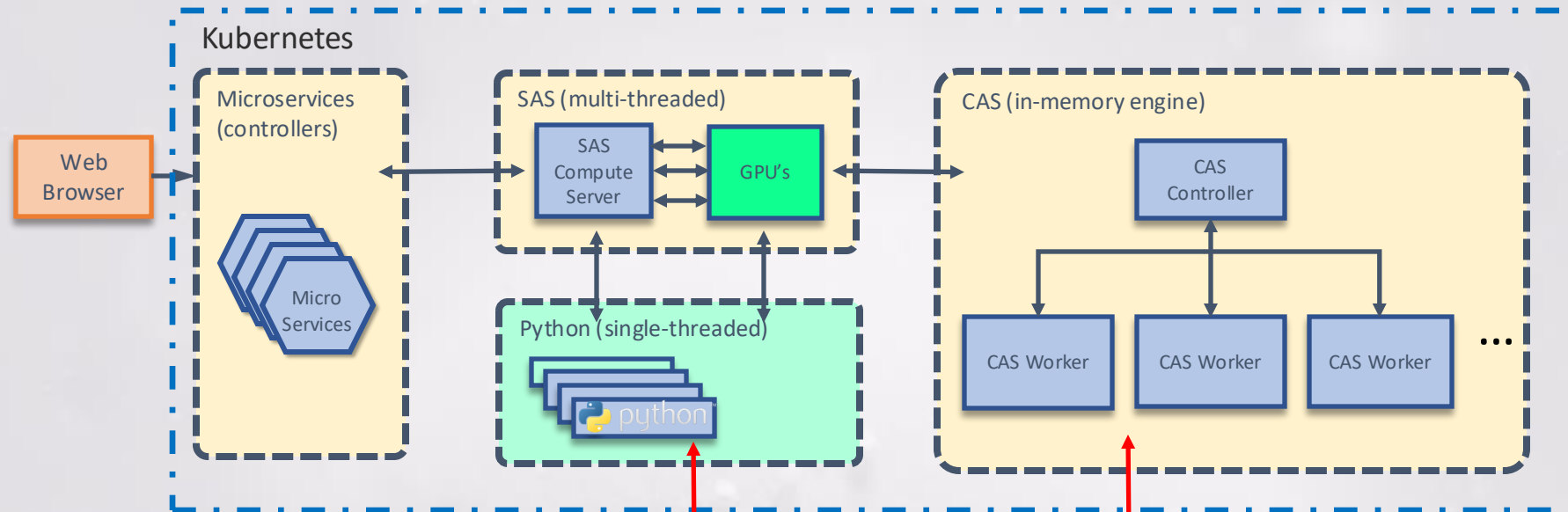
LITI – rules (SAS VTA)

- It's "Regular Expressions on steroids".
- Knowledge (and effort) required to write linguistic rules with correct syntax.
- Some patterns are hard to come by (because they are complicated, non-standard, with a lot of variety in the language ...).
- You need some preliminary knowledge on the topic at hand and on what you want to catch!
- Rules are easily overfit (too specific) if n° of training docs is low.
- Library of LITI-rules can / should grow very big to guarantee a high hit rate.
- Results are "proven", non-debatable (there's a clear match in the text).
- Relatively light in terms of resource usage (and cost).
- page breaks and headers and footers are no gift.
- special and non-printable characters pose no problem.

RAG – LLM (Open Source / Commercial Models)

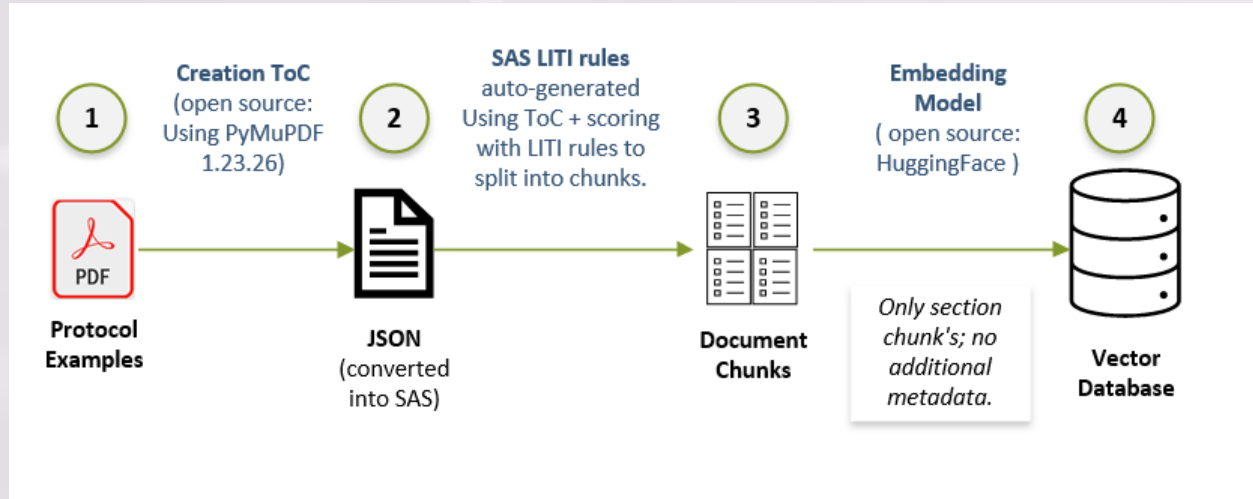
- It's generative AI.
- Knowledge required to do proper prompt engineering (designing the user query). But much less effort required. It's just an API-call to a pre-trained model.
- If the context around a particular topic can vary widely from document to document, there is a clear advantage.
- It's generative AI, so some of the info returned can be made up (hallucination).
- Implementing offline models (internalization) and maintaining them is labor-intensive.
- Heavy and intensive in terms of resource usage (even for one or a few documents). Often, several GPUs are needed, and run-time is considerable.
- Scaling (expand the scope) is easier here.
- page breaks and headers and footers are no gift.
- special and non-printable characters pose no problem.

The environment: SAS Viya & Open Source



Code	Log	Code	Log
<pre>74 model_name = 'meta-llama/llama-2-7b-hf' #@param 75 llm = HuggingFaceLLM(76 context_window=context_window, 77 max_new_tokens=2048, 78 generate_kwargs={"temperature": temperature, "d 79 #system_prompt=system_prompt, 80 query_wrapper_prompt=query_wrapper_prompt, 81 tokenizer_name=model_name, 82 model_name=model_name, 83 device_map="auto", 84 # uncomment this if using CUDA to reduce memory 85 model_kwargs={"torch_dtype": torch.float16, "to 86 tokenizer_kwargs={"token": token}, #"load_in_8bit 87)</pre>	<pre>1 /* region: Generated preamble */ 79 proc python; 81 submit NOTE: Python initialized. Python 3.9.12 (main, Apr 5 2022, 06:56:58) [GCC 7.5.0] :: Anaconda, Inc. on linux Type "help", "copyright", "credits" or "license" for more >>> NOTE: PROCEDURE PYTHON used (Total process time): real time 16:05.37 cpu time 1.08 seconds</pre>	<pre>1 proc cas; 2 session CAArgenX; 3 builtins.loadActionSet / actionSet="textRuleDevelo 4 builtins.loadActionSet / actionSet="textRuleScore" 5 6 textRuleScore.applyConcept / 7 casOut =(caslib="CASUSER", name="out_conc 8 docId="IndexDocNR" 9 factOut =(caslib="CASUSER", name="out_fact 10 matchType="ALL" /* matchType="ALL" 11 model=(name="outli") 12 language="ENGLISH" 13 ruleMatchOut={caslib="CASUSER", name="out_rule 14 table={caslib="PUBLIC" name="PROTOCOL_13FEB202 15 textVar="content"; 16 17 ; 18 run; 19 quit;</pre>	<pre>1 /* region: Generated preamble */ 9 proc cas; 10 session CAArgenX; 11 builtins.loadActionSet / actionSet="textRuleDevelop"; 12 builtins.loadActionSet / actionSet="textRuleScore"; 13 14 textRuleScore.applyConcept / 15 casOut =(caslib="CASUSER", name="out_conce 16 docId="IndexDocNR" 17 18 quit; NOTE: The PROCEDURE CAS printed page 4. NOTE: PROCEDURE CAS used (Total process time): real time 0.32 seconds cpu time 0.02 seconds 19 20 /* end of program */ 21 action applyconcept; 22 param</pre>

Pre-Processing to Overcome challenges

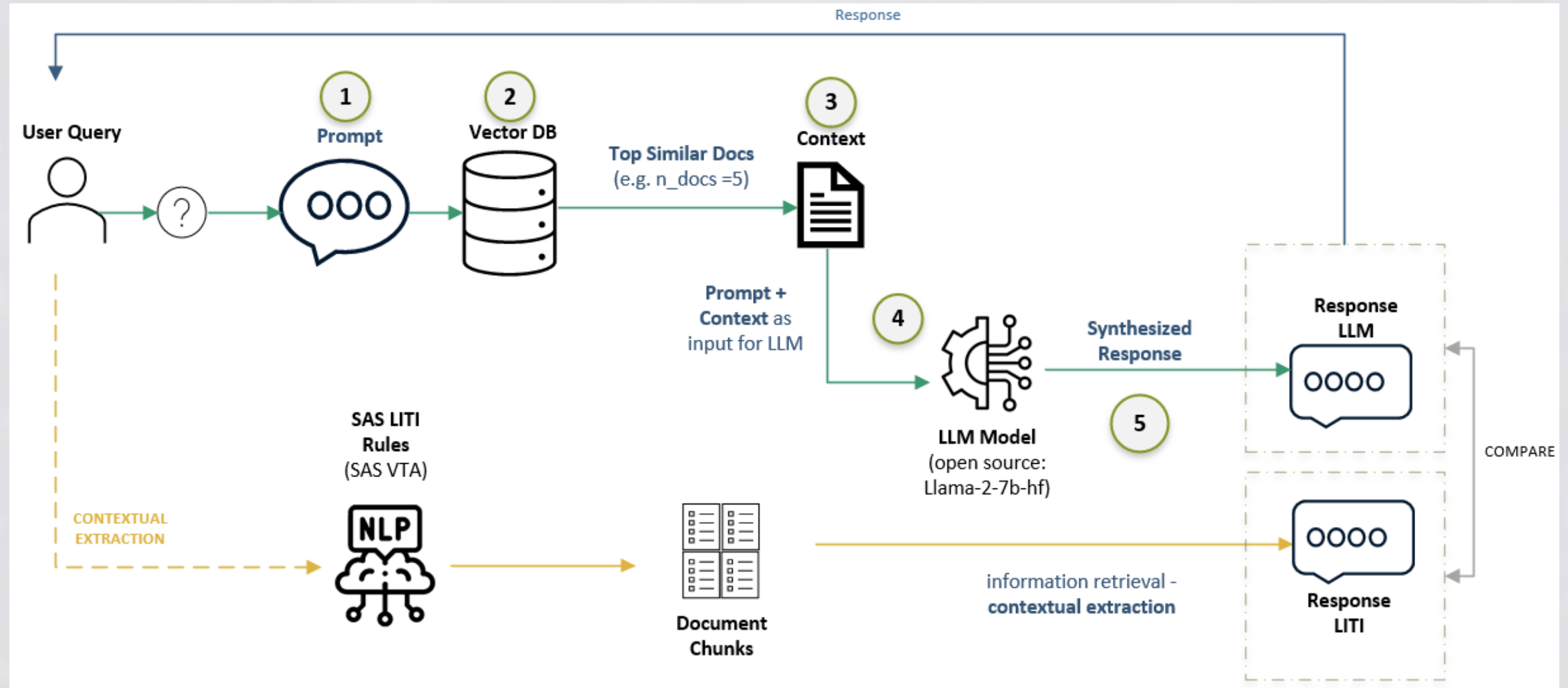


Log Output Data (1)

TOC Table rows: 113 Columns: 3 of 3 Rows 1 to 113

	toc	@ page	chapter
20	[3, '6.2.1. Primary Endpoint', 19]	19	6.2.1. Primary Endpoint
21	[3, '6.2.2. Secondary Endpoints', 19]	19	6.2.2. Secondary Endpoints
22	[1, '7. Investigational Plan', 20]	20	7. Investigational Plan
23	[2, '7.1. Overall Study Design', 20]	20	7.1. Overall Study Design
24	[2, '7.2. Number of Subjects', 20]	20	7.2. Number of Subjects
25	[2, '7.3. Treatment Assignment', 20]	20	7.3. Treatment Assignment
26	[2, '7.4. Dose Adjustment Criteria', 21]	21	7.4. Dose Adjustment Criteria
27	[2, '7.5. Criteria for Termination of Study', 21]	21	7.5. Criteria for Termination of Study
28	[1, '8. Selection and Withdrawal of subjects', 27]	27	8. Selection and Withdrawal of subjects
29	[2, '8.1. Inclusion Criteria', 27]	27	8.1. Inclusion Criteria
30	[2, '8.2. Exclusion Criteria', 28]	28	8.2. Exclusion Criteria
31	[2, '8.3. Subject Withdrawal Criteria', 30]	30	8.3. Subject Withdrawal Criteria
32	[1, '9. Treatment of Subjects', 31]	31	9. Treatment of Subjects
33	[2, '9.1. Description of IMP', 31]	31	9.1. Description of IMP
34	[2, '9.2. Restrictions', 31]	31	9.2. Restrictions
35	[3, '9.2.1. Concomitant Medication/Procedure(s)', 31]	31	9.2.1. Concomitant Medication/Procedure(s)
36	[3, '9.2.2. Alcohol', 32]	32	9.2.2. Alcohol
37	[3, '9.2.3. Physical Activities', 32]	32	9.2.3. Physical Activities
38	[3, '9.2.4. Dietary Aspects', 32]	32	9.2.4. Dietary Aspects
39	[3, '9.2.5. Smoking', 32]	32	9.2.5. Smoking

SAS LITI (NLP) + LLM



Results after pre-/processing

(example IN/EXCLUSION criteria)

Legend :

perfect
> 75 % hit rate
between 60% and 75 % hit rate
< 60% hit rate

Documents (clinical trial protocols)	document partitioning (training / validation / test)	INCLUSION CRITERIA			EXCLUSION CRITERIA		
		Number	Number Captured With LIT	Number Captured with LLM	Number	Number Captured With LIT	Number Captured with LLM
Protocol - 13 Feb 2020.pdf	TRAINING	15	15	12*	22	22	19
Protocol_22Jul2020.pdf	TEST	7	7	6	20	20	34*
EliLilly_NCT03421379_Diabetes.pdf		10	10	10	26	26	26
Roche_NCT04320615_COVID.pdf		7	7	7	12	12	12
CDISC_Pilot_Study.pdf		8	8	8	23	23	23

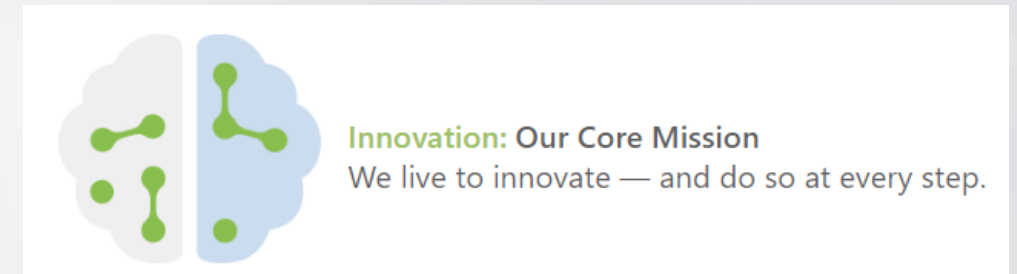
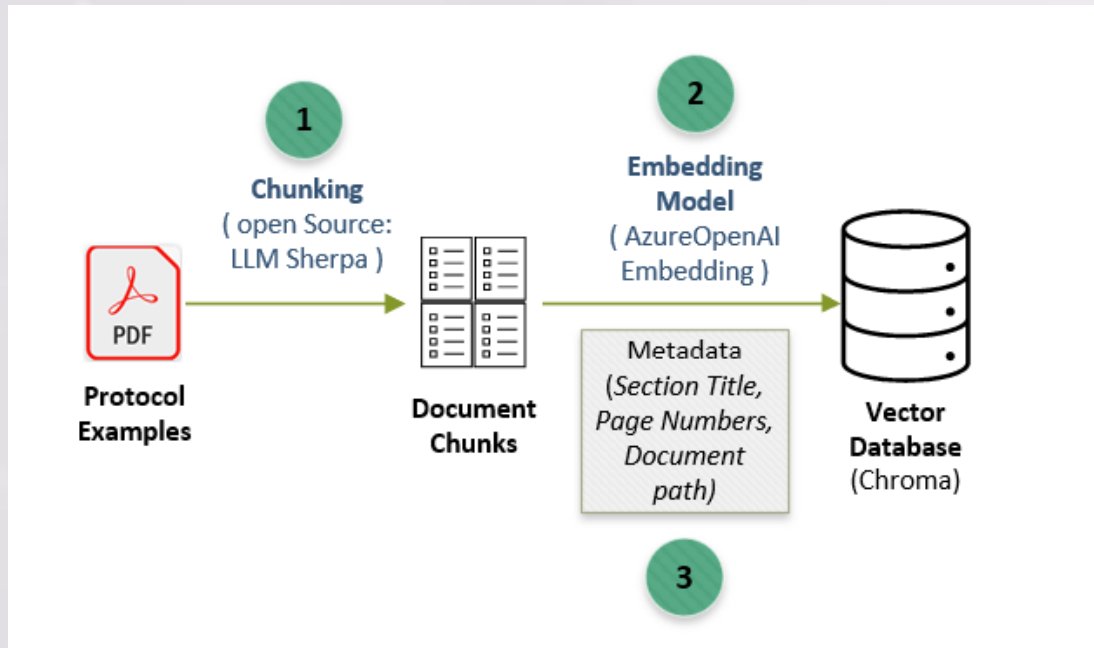


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POC 2.0 - Accuracy Enhancements

Pre-Processing

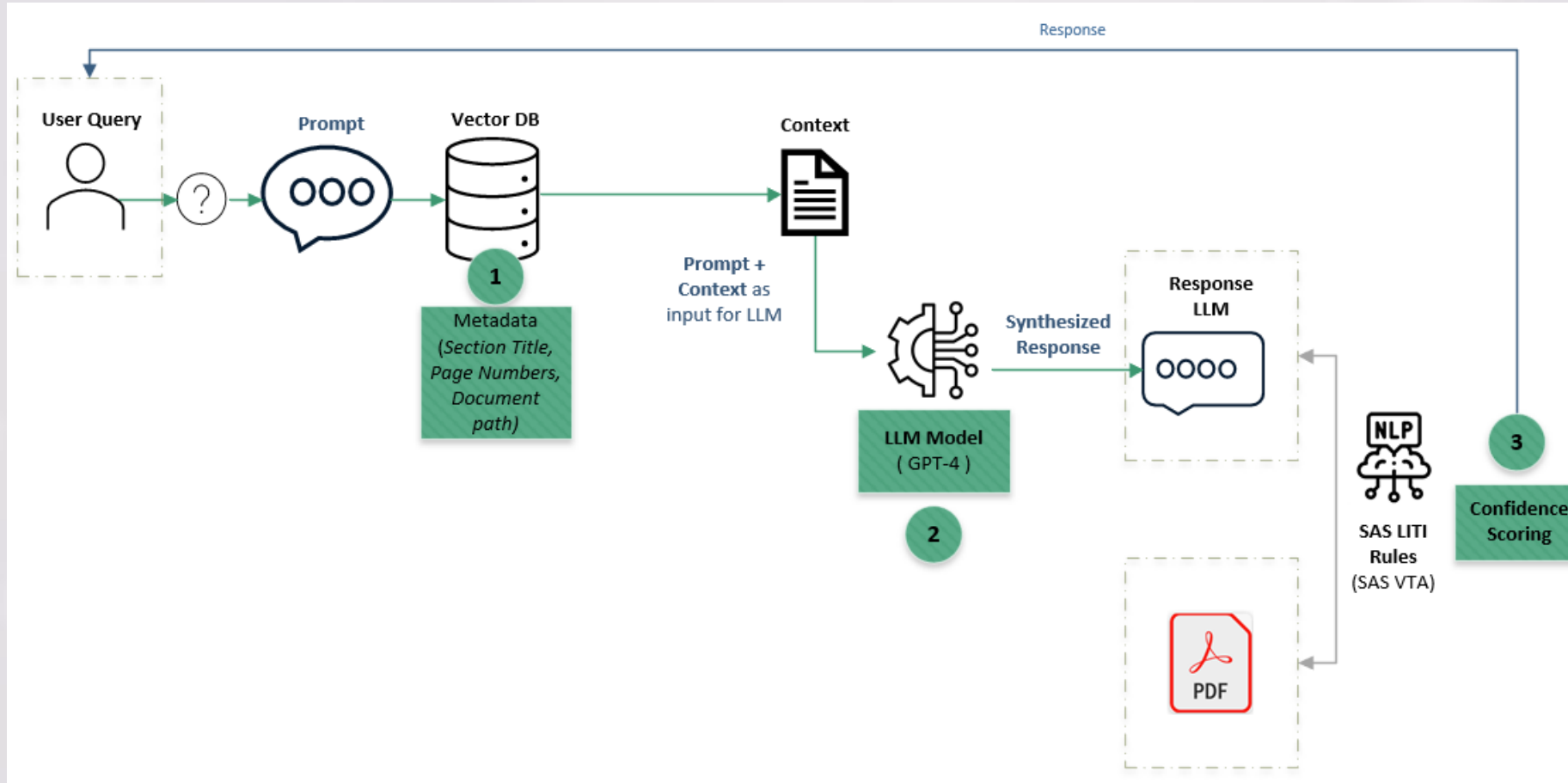


```
56 os.environ["EMBED_MODEL"] = "text-embedding-ada-002-endpoint"  
57  
58 embedding_model_deployment = SAS.symget("embeddingModelDeployment")
```

LLM Sherpa → https://github.com/nlmatics/nlm-ingestor/blob/main/notebooks/test_llmsherpa_api.ipynb

POC 2.0 - Accuracy Enhancements

LLM (Open AI) + SAS LITI (NLP + Confidence Scoring)



```
54 os.environ["AZURE_OPENAI_API_VERSION"] = "2024-02-01"  
55 os.environ["CHATGPT_MODEL"] = "gpt-4-endpoint"
```

POC 2.0 - Accuracy Enhancements

Result

Example << primary / secondary endpoint >>

Endpoints

6.2.1. Primary Endpoint

- Percentage reduction in total IgG levels, compared to baseline, at day 29 (week 4), 7 days after the fourth IV or SC administration of efgartigimod

6.2.2. Secondary Endpoints

- Percentage reduction in total IgG levels at all other assessment timepoints as of week 4
- Percentage reduction in levels of IgG subtypes (IgG1, IgG2, IgG3, and IgG4) at all assessment timepoints
- Absolute values and changes from baseline in total IgG levels and levels of IgG subtypes (IgG1, IgG2, IgG3, and IgG4) at all assessment timepoints
- AUEC for percentage reduction in total IgG levels and for each subtype per weekly interval after each dose (week 1, week 2, week 3, and week 4), over the interval week 1 to week 4, and over the entire study period (week 1 to week 11)
- Serum levels of efgartigimod and derived PK parameters
- Clinical laboratory evaluations, vital sign measurements, ECG recordings, and incidence and characterization of TEAEs

```
query_text = "List all Primary and Secondary endpoints of the study"
```

```
context = retriever.get_relevant_documents(query_text)
prompt = prompt_template.format(context=context, question=query_text)
```

```
with get_openai_callback() as cb:
    response = llm.invoke(prompt)
    print(f"Total Cost (USD): ${format(cb.total_cost, '.6f')}")
    print(f"Model: {response.response_metadata['model_name']}, Response Metadata: {response.response_metadata['token_usage']}")
    print(response.content)
# print(response)
```

Total Cost (USD): \$1.602420

Model: gpt-4, Response Metadata: {'completion_tokens': 256, 'prompt_tokens': 52902, 'total_tokens': 53158}

Primary Endpoint:

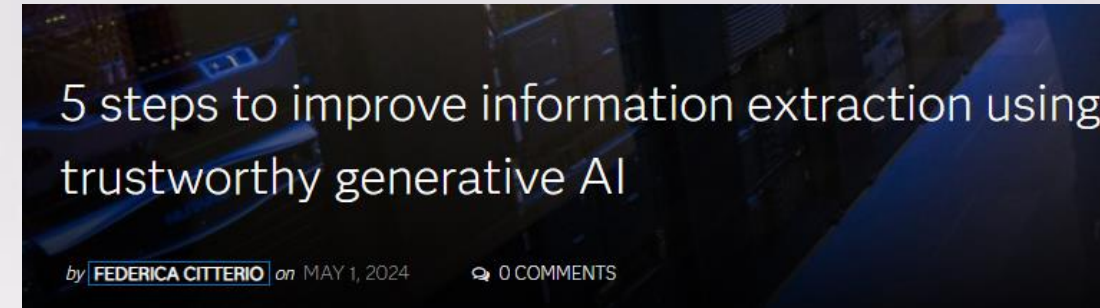
- Percentage reduction in total IgG levels, compared to baseline, at day 29 (week 4), 7 days after the fourth IV or SC administration of efgartigimod.

Secondary Endpoints:

- Percentage reduction in total IgG levels at all other assessment timepoints as of week 4.
- Percentage reduction in levels of IgG subtypes (IgG1, IgG2, IgG3, and IgG4) at all assessment timepoints.
- Absolute values and changes from baseline in total IgG levels and levels of IgG subtypes (IgG1, IgG2, IgG3, and IgG4) at all assessment timepoints.
- Area under the effect curve (AUEC) for percentage reduction in total IgG levels and for each subtype per weekly interval after each dose (week 1, week 2, week 3, and week 4), over the interval week 1 to week 4, and over the entire study period (week 1 to week 11).
- Serum levels of efgartigimod and derived PK parameters.
- Clinical laboratory evaluations, vital sign measurements, ECG recordings, and incidence and characterization of TEAEs.

POC 2.0 - Accuracy Enhancements

Confidence Scoring (SAS Viya VTA – LITI)



“Step 5: Rule inference and confidence score calculation”

...the same corpus that was used to extract information with the LLM can be scored against the LITI rule to check if the information is actually present. A confidence score is calculated based on the number of relevant terms matched by the rule.

- Confidence is a number between 0 and 1, where a higher value indicates a better quality of the extraction.
- The confidence score decreases if the LLM model hallucinates undesirable effects that were not present in the input document.

As a result, this methodology can also be used to evaluate different LLM models or different prompts by providing a quantifiable and robust metric of accuracy.

<https://blogs.sas.com/content/subconsciousmusings/2024/05/01/five-steps-to-improve-information-extraction-using-trustworthy-generative-ai/>

POC 2.0 - Accuracy Enhancements

Confidence Scoring (SAS Viya VTA – LITI)

Query Text (user-query):

Based on study design, what are different treatment assignments and how many subjects are enrolled per treatment group?

Total Cost (USD): \$0.021900

Model: gpt-4, Response Metadata: {'completion_tokens': 100, 'prompt_tokens': 530, 'total_tokens': 630}

Answer by gpt-4 (LLM extraction):

Based on the provided context, the different treatment assignments in the study are:

1. 10 mg/kg xxxxxxxxxxxx IV administered as a 1-hour IV infusion.
2. 1000 mg xxxxxxxxxxxx SC xxxx administered as a single SC injection.

Up to 54 subjects are planned to be enrolled to ensure 23 subjects per treatment group complete the study.

Subjects will be randomized in a 1:1 ratio to receive one of the two treatments.

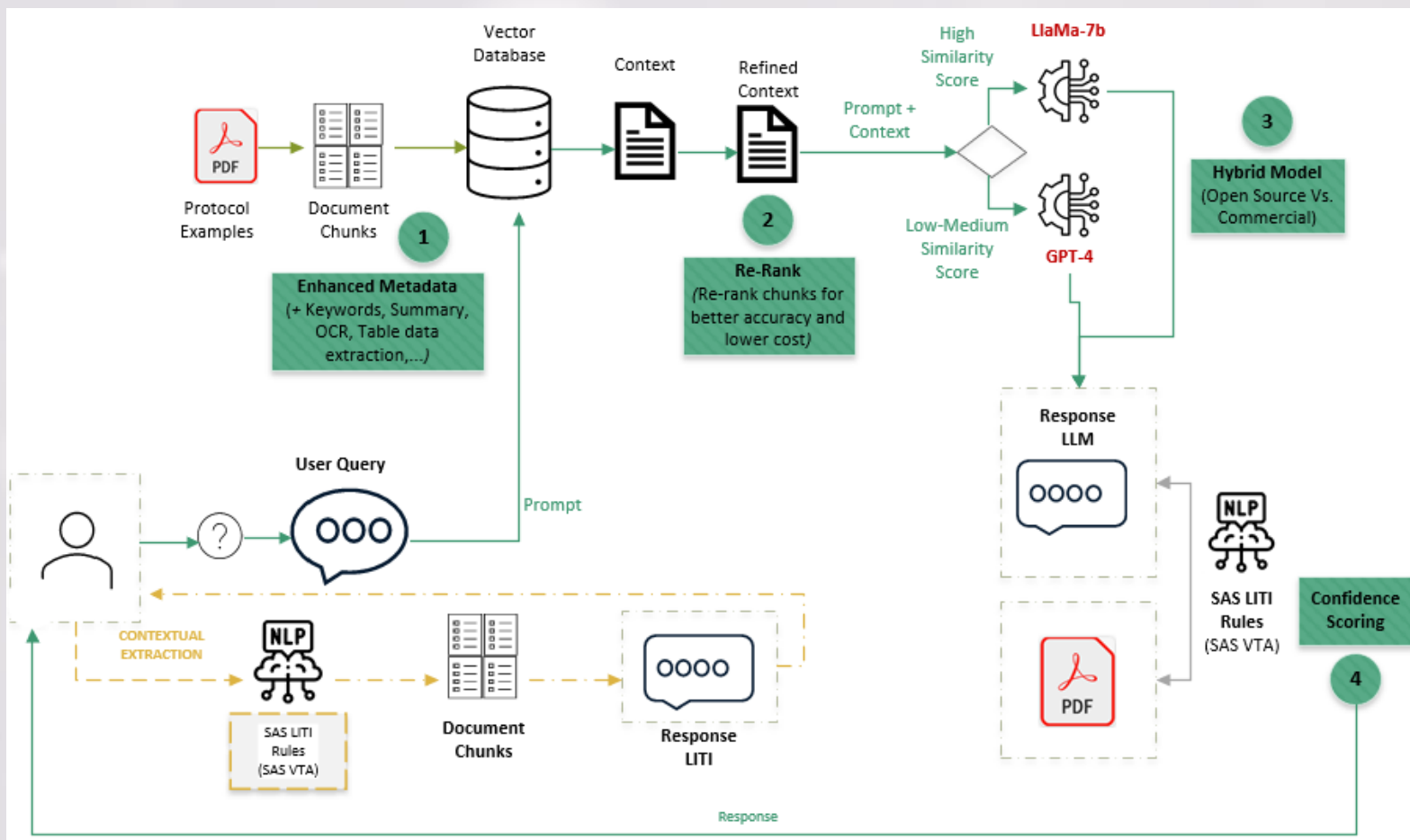
- The above LLM-extraction (with the real compound name instead of xxxxxxxxxxxx) has a confidence score of 1 (max.)!
- Inserting the string “**ABCDEFGHIJKLM**” somewhere in the response (faking a hallucination) makes the confidence score go down to 0.96 (given the sensitivity set).



Agenda

- 1. Background to the project
- 2. The initial Journey
- 3. POC 2.0
- **4. Financial Considerations**
- 5. The Journey continues... ?

Financial Considerations - Accuracy Enhancements & Cost Optimizations

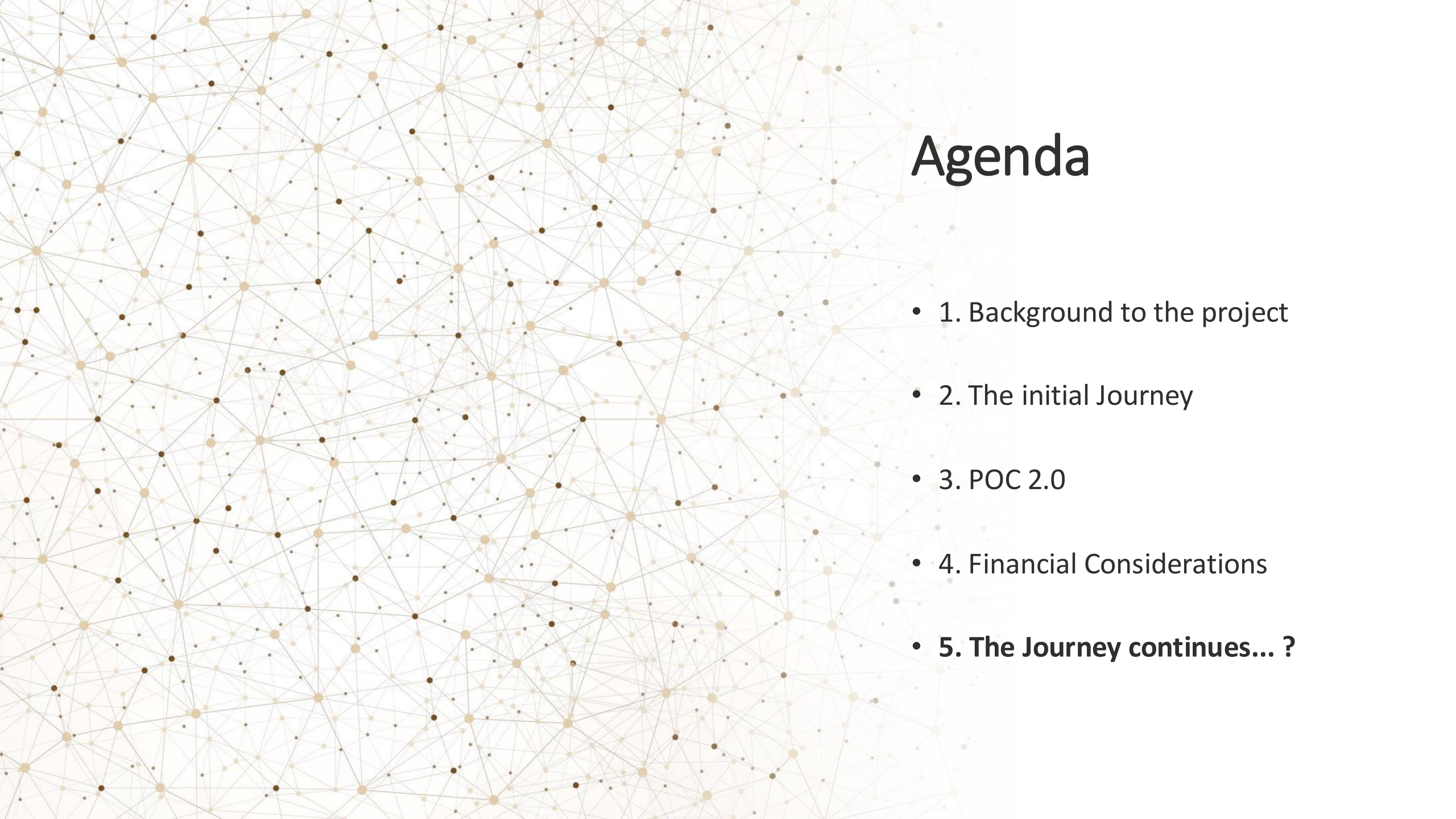


```
query_text = "List all Primary and Secondary endpoints of the study"

context = retriever.get_relevant_documents(query_text)
prompt = prompt_template.format(context=context, question=query_text)

with get_openai_callback() as cb:
    response = llm.invoke(prompt)
    print(f"Total Cost (USD): ${format(cb.total_cost, '.6f')}")
    print(f"Model: {response.response_metadata['model_name']}, Response Metadata: {response.response_metadata['token_usage']}")
    print(response.content)
# print(response)

Total Cost (USD): $1.602420
Model: gpt-4, Response Metadata: {'completion_tokens': 256, 'prompt_tokens': 52902, 'total_tokens': 53158}
```



Agenda

- 1. Background to the project
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- 4. Financial Considerations
- **5. The Journey continues... ?**

End Result (SoA)

Clinical Study Protocol														
Table 3: Schedule of Assessments														
Study Period	Screening ^a	-1	Treatment Period											
Study Day	-28 to -2		1	2	7	8	14	21	28	35	42	49	56	63
Informed consent	X													
In-/exclusion criteria	X	X	X ^c											
Virology screen	X													
Medical history	X													
Demographic data	X													
Pregnancy test ^d		X												
Urine drug screen & alcohol urine test ^e	X	X												
Height	X													
Physical examination	X	X												
Weight ^f (+ BMI) ^g	X ^{f,g}	X ^f			X ^f		X							
Vital signs ^h	X	X	X ^h				X ^h							
Triplicate 12-lead ECG ⁱ	X	X												
Urinalysis ^j	X	X												
Clinical laboratory tests ^j	X	X					X ^c							
Blood sampling: • PKI		X ^a	X ⁱ				X ⁱ							
• PD ^m		X ^a	X ⁱ				X ⁱ							
• ADA ^a		X ^a	X ^c											
Randomization			X ^c											
IMP administration ^o			X				X							
Ambulant visits	X													

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Enter expression

	Study Period	Screen ing ^a	-1	Treatment Period	Treatment Period_1
1	Study Day	-28 to -2	-28 to -2	1	2
2	Informed consent	X			
3	In-/exclusion criteria	X	X	X ^c	
4	Virology screen	X			
5	Medical history	X			
6	Demographic data	X			
7	Pregnancy test ^d		X		
8	Urine drug screen & alcohol urine teste	X	X		
9	Height	X			
10	Physical examination	X	X		
11	Weight ^f (+ BMI) ^g	X ^{f,g}	X ^f		
12	Vital signsh	X	X	X ^h	
13	Triplicate 12-lead ECGi	X	X		
14	Urinalysise	X	X		
15	Clinical laboratory testsj	X	X		
16	Blood sampling: • PKI • PDm • ADA ^a		X ^k X ^k X ^k	X ^l X ^l X ^c	
17	Randomization			X ^c	
18	IMP administrationo			X	
19	Ambulant visits	X			

X X X X X

From USDM to Protocol

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SAS (engage)

Glucagon (LY900018)

Eli Lilly Japan K.K

Japan

26 October 2017

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

6.1.2. Secondary Objectives

Fact Rule = '1.b. ObjectivesSecondary'

Match Text	Fact Rule
* To compare the safety and tolerability of 3 mg LY900018 with 1 mg IMG * To characterize the PK profile of 3 mg LY900018 compared to 1 mg IMG * To characterize the PD profile of 3 mg LY900018 compared to 1 mg IMG	1.b. ObjectivesSecondary

SAS

HomeReportsResults

Eli_Lilly_CDISC_Protocol_ObjectivesEndpoints

1.a. ObjectivesPrimary1.b. ObjectivesSecondary1.c. ObjectivesExploratory2.a. EndpointsPrimary

Match Text	Fact Rule
To demonstrate that 3 mg LY900018 is non-inferior to 1 mg IMG for the proportion of patients achieving treatment success from insulin-induced hypoglycemia using a non-inferiority margin of 10%	1.a. ObjectivesPrimary
* To compare the safety and tolerability of 3 mg LY900018 with 1 mg IMG * To characterize the PK profile of 3 mg LY900018 compared to 1 mg IMG * To characterize the PD profile of 3 mg LY900018 compared to 1 mg IMG	1.b. ObjectivesSecondary
* Explore the formation of anti-glucagon antibodies to glucagon * To evaluate the recovery from clinical symptoms of hypoglycemia	1.c. ObjectivesExploratory
The proportion of patients achieving treatment success defined as the minimum PG value at the following glucagon administration	2.a. EndpointsPrimary

Next Steps

- **Short term (Q2-Q4)**
 - Leverage Open AI service (commercial models) instead of LLAMA-V2 7B model as prep finalization internal business case.
 - Reflect on POC and Define Next Steps (Q4 2024)
- **Mid term (2025)**
 - focus on CTPS (concept sheet)
 - Schedule of Assessments (SoA)
- **Longer term - protocol builds**
 - Cost
 - Technology (no off-the shelf available yet?), we are biotech ... not software builders
 - Change management
 - New roles

Thank You