Paper TT07

Open-Source Protocol Automation with the OpenStudyBuilder

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ABSTRACT

The OpenStudyBuilder is a powerful tool designed to streamline the end-to-end process of clinical trials. With its innovative protocol automation capabilities, the OpenStudyBuilder simplifies the management of protocol information, allowing for the easy creation and maintenance of protocol content. Through standard interfaces (APIs), a Word addon can be used to fill structural parts of the protocol, including complex parts like the schedule of activity flowchart. In this presentation, we will demonstrate how the OpenStudyBuilder can be used to facilitate efficient protocol automation and how this is related to the ICH M11 guideline for clinical study protocols.

INTRODUCTION

To enable to vision of end-to-end automations from the CDISC 360° project, the OpenStudyBuilder project was created to implement this vision. This open-source solution is continuously enhanced to support and streamline the processes. A very first part of the processes of conducting studies is the setup of the protocol. As the OpenStudyBuilder started to implement the processes from start, the protocol automation part is well worked out and has currently a business go-live within Novo Nordisk.

But what is the OpenStudyBuilder? What do we need for protocol automation and why do we need protocol automation at all?

The OpenStudyBuilder is a new approach to study specifications including compliance with external and internal standards, build to facilitate automation and content reuse and to ensure a higher degree of end-to-end consistency.

There are three core elements of the OpenStudyBuilder:

- Clinical Metadata Repository (clinical MDR)
  (central repository for all study specification data – a graph database)
- OpenStudyBuilder application / Web UI
- API layer
  (allowing interoperability with other applications)
  (DDF API Adaptor – enabling DDF SDR Compatibility)

The solution contains two major areas where the content is maintained, the studies area maintaining the study specifications and protocol information and the library parts where all standards are maintained including standard templates for objectives, endpoints and much more.

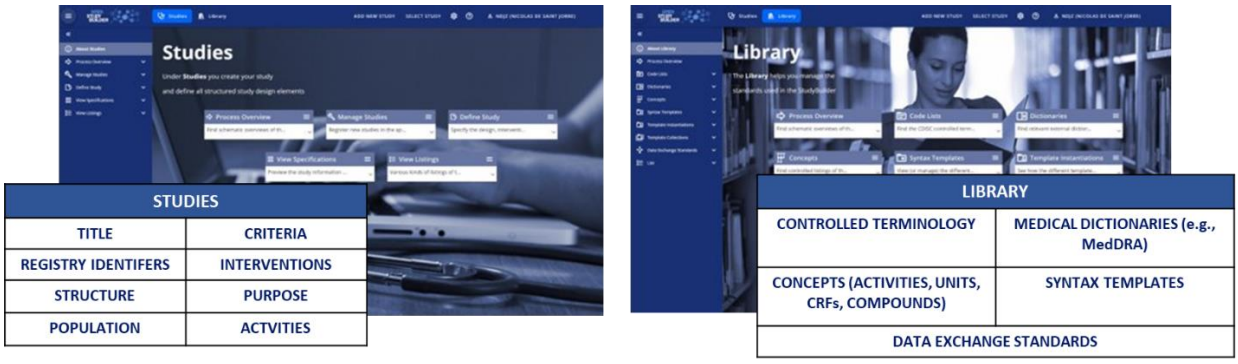

Figure 1: OpenStudyBuilder – Studies and Library part

To automate and harmonize the protocol it is of crucial importance to not only allow entering study protocol metadata into a system, but to embed all information in our standard landscape additionally to use standard texts.

The study protocol drives all study related processes from the Case Report Form generation, the planning of activities, the generation of the define.xml and many more. How many times have information from the protocol be

typed into another tool? Traditionally the protocol is a word or PDF document which makes it very difficult to automate processes from such a file. We need structured and reusable protocol information.

STANDARDS WITHIN THE OPENSTUDYBUILDER

To support the generation of the structured protocol parts, the OpenStudyBuilder team uses industry and sponsor specific controlled terminology as well as additional standard elements. When the protocol information is entered through the OpenStudyBuilder, the terminology is applied where only valid terms can be selected. Additionally, we have created templates to standardize:

- Objectives
- Endpoints
- Time Frames
- Criteria (Inclusion & Exclusion)
- Activities

These templates contain placeholders for specific items. For example, we can use a generic text with placeholders with “Compound”, “Comparator” and “ActivityIncance”. This can then be used with concrete values and then used by studies.

	Indication or disorder	Parent template
⋮	Not Applicable	To assess the effect of Compound and Compound or Compound and Compound combination in biliary tract cancer patients who have failed to 1st-line chemotherapy
⋮	Not Applicable	To assess the safety of Compound and Compound combination or Compound and Compound combination in biliary tract cancer patients
⋮	Heart failure	To compare the effect of Compound relative to Comparator on ActivityInstance

Figure 2: Example Objective Templates

This kind of standardization has the advantage that the protocol for similar studies use the same sentence and additionally we can search for studies using a specific compound within their objectives. As our underlying database is a graph model, such connections can easily be found.

ENTER STUDY PROTOCOL CONTENT

Expecting that all standards are set up, the protocol information is entered in the study area. In the study properties we set type information which are mainly driven by CDISC controlled terminology. We enter the study type, trial type, phase, design and additional information into the screen.

Below study attributes, additional information like intervention type, control type, randomization information and much more can be entered.

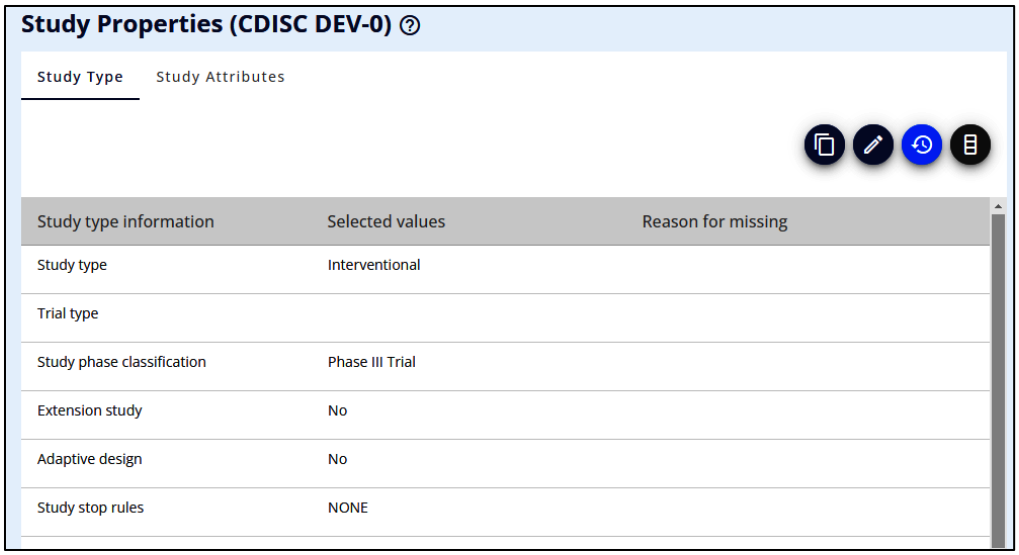

Figure 3: Setup Study Properties

Everything what is entered into the database with the graphical user interface can also be programmed using the Application Programming Interface (API). For this information can be brought into the system if available somewhere else.

Another important part for the protocol is the “Study Structure” area, where study arms, branches, cohorts, epochs, elements and visits can be entered. Additionally, to the content, design specifications can be done within this tool as graphics for the protocol are automatically generated for re-use.

A major advantage of the OpenStudyBuilder tool is the excellent management of activities. These can be defined on a very granular level and easily be assigned to visits.

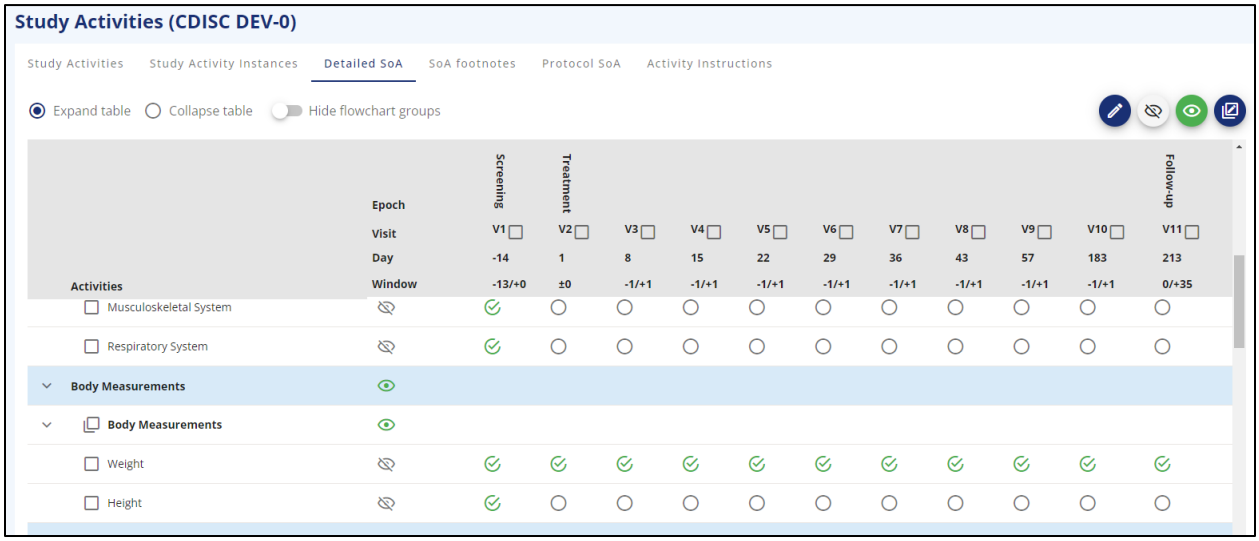

Figure 4: Definition of the Schedule of Activities

The schedule of activities can be used for multiple purposes. There can be a reduced and summarized view used for protocol itself, but by having more details in this can be used to generate the corresponding Case Report Form content for the specific visits.

VIEW PROTOCOL CONTENT

Finally, here is a nice overview to see all the required protocol elements for the study including next to the protocol schedule of activities the study design.

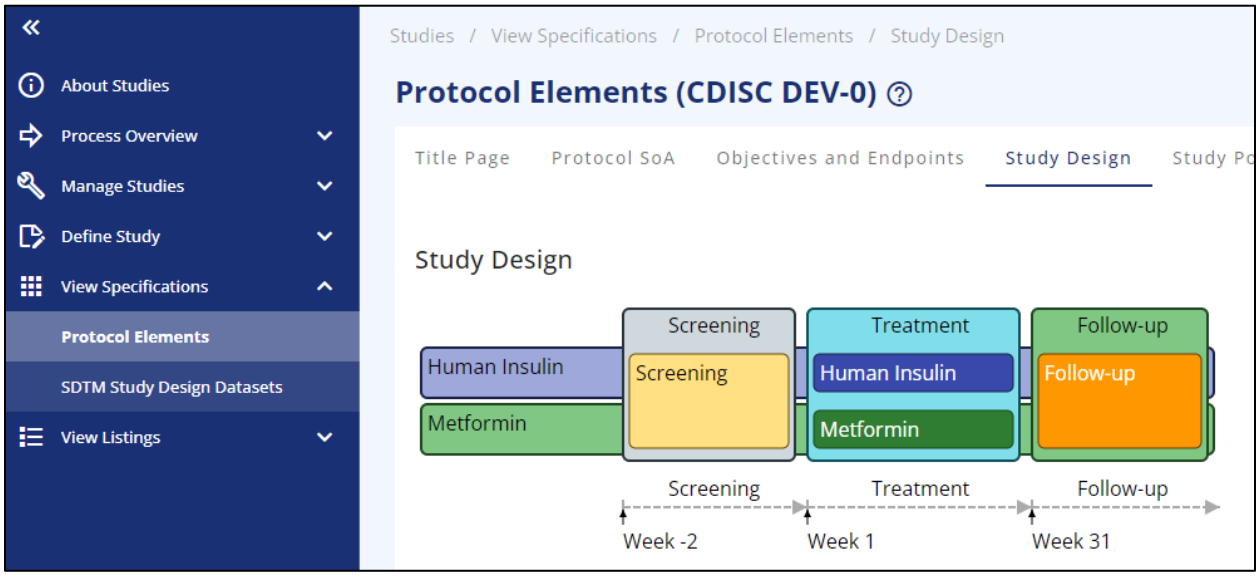

Figure 5: View protocol content

This content can either be copied or exported for example into a word file, or we can use the programming interface to automatically grab the content.

PROTOCOL AUTOMATION – WORD ADD-IN

Novo Nordisk is using a Word Add-In to automate the protocol generation. It is planned that this Add-In will be released as open-source tool as well. Processing wise, structured protocol information are added into the OpenStudyBuilder. Then the Medical Writer opens a word template using specific placeholder blocks where the information is automatically been loaded into. The Medical Writer can log into a specific study, choose which information to update and start the update process.

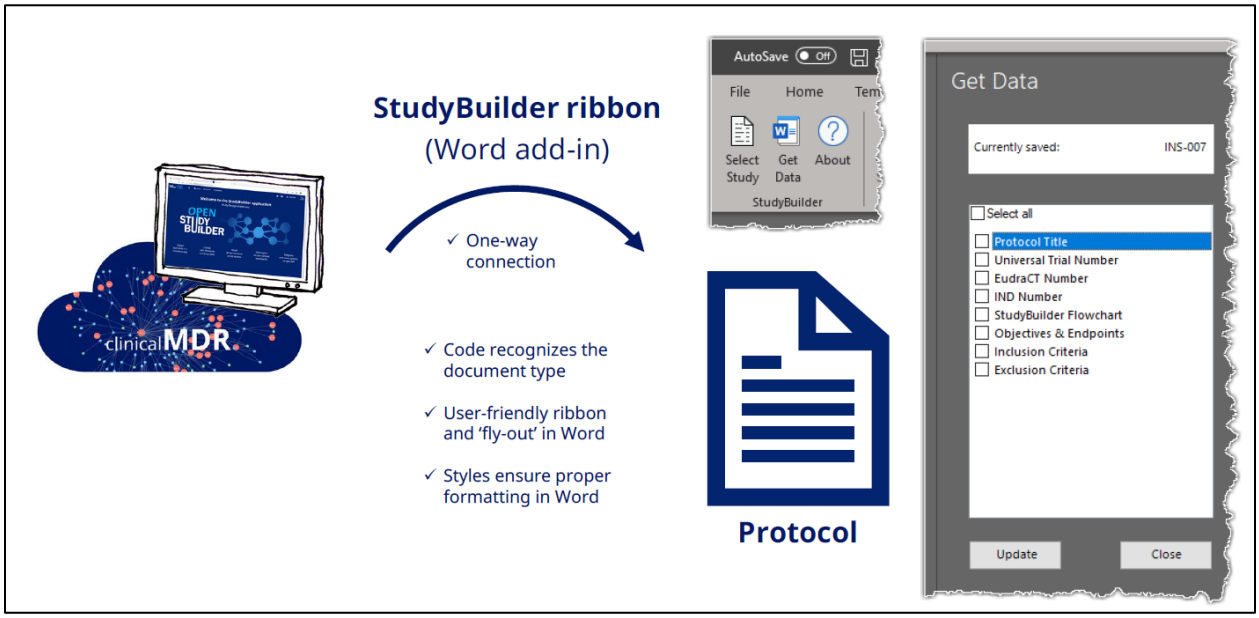

Figure 6: Protocol automation in Word

The placeholder blocks will be kept in the protocol. For this when there are updates in the data, for example a new activity is planned, then the word protocol can easily be updated and will automatically contain the new flowchart for schedule of activities for example.

The Figure 7 displays an example protocol and the data within this protocol which could be automatically loaded. This is the title, short title, substance, various trial numbers, the Schedule of Activity (SoA) flowchart, a table containing objectives and endpoints and the inclusion/exclusion criteria.

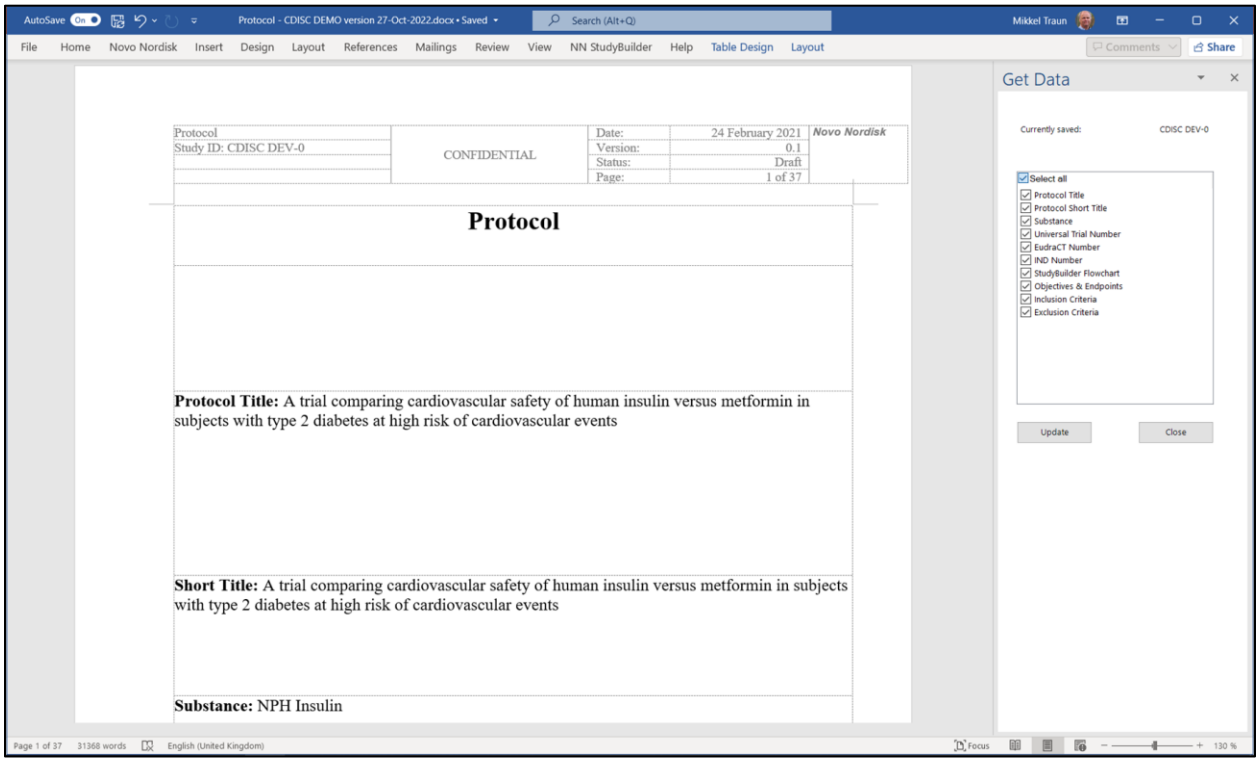

Figure 7: Example protocol including add-in data selection

TRIAL DOMAINS – SIDE ARTIFACT

By having all structured protocol information available, the content of the trial domains is available and can directly be created. For this the trial domain generation is a nice side effect. The trial domains can be viewed in the OpenStudyBuilder via “View-Specifications” and then the “SDTM Study Design Datasets”. Figure 8 shows an example for the “Trial Summary” domain. Additionally, we can use the API interface to receive the trial domains in other tools, like in R or SAS to have them as datasets available.

SDTM Study Design Datasets

Trial Arm | Trial Elements | Trial Visits | Trial Inclusion/Exclusion Criteria | Trial Disease Milestone | Trial Summary

Select rows | Column labels | Column names

Filtering currently not activated

Study Identifier	Domain Abbreviation	Trial Summary Parameter Short Name	Trial Summary Parameter	Parameter Value	Parameter Value Code	Name of the Refe
CDISC DEV-0	TS	ADAPT	Adaptive Design	N	C49487	CDISC
CDISC DEV-0	TS	AGEMAX	Planned Maximum Age of Subjects	P64Y		ISO8601
CDISC DEV-0	TS	AGEMIN	Planned Minimum Age of Subjects	P18Y		ISO8601
CDISC DEV-0	TS	COMPTRT	Comparative Treatment Name	METFORMIN	9100L32L2N	UNII
CDISC DEV-0	TS	CRMDUR	Confirmed Response Minimum Duration			ISO8601
CDISC DEV-0	TS	EXTTIND	Extension Trial Indicator	N	C49487	CDISC

Figure 8: Example trial summary domain

UPDATEPROTOCOL, ICH M11 AND OTHER PROTOCOL STANDARDS

The protocol is not completely automated, as every study has some specialty. Medical Writing prefers to use Word as tool for the protocol development and for this the approach was developed. When additional information can be standardized and driven by metadata, then this will likely be added to the OpenStudyBuilder.

Apart from following initiatives in CDISC and TransCelerate, the OpenStudyBuilder project is additionally looking into other initiatives which support standardization. The EMA had been working on a guideline:

> *The purpose of this new harmonized 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 harmonized data exchange format acceptable to the regulatory authorities. The ICH M11 Clinical Electronic Structured Harmonized 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[1].*

This new guideline provides a template and specification supporting a “CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL (CESHARP)”. The OpenStudyBuilder team is reviewing the guideline closely and will likely provide some support around M11 in the future.

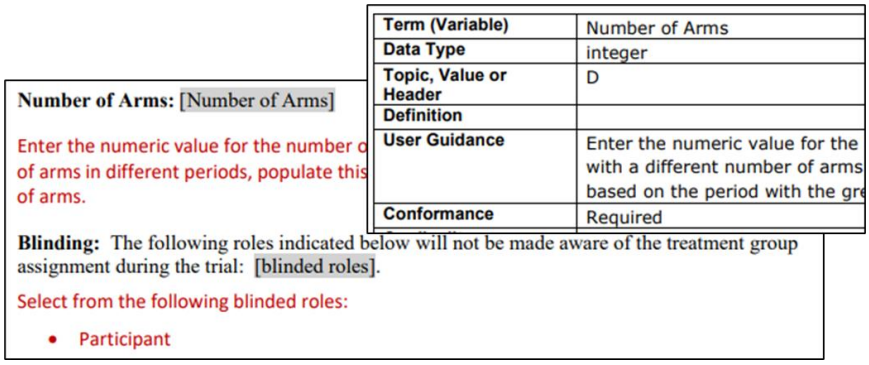

Figure 9: ICH M11 extract

When we are looking into the different standard protocol initiatives, we have the TransCelerate Common Protocol Template (CPT), the USDM model and the ICH M11 guideline. Somehow the basis for the used terminology is not identical. Every standard uses their own terminology. In the OpenStudyBuilder project we are looking into the difference and create a mapping as displayed in Figure 10.

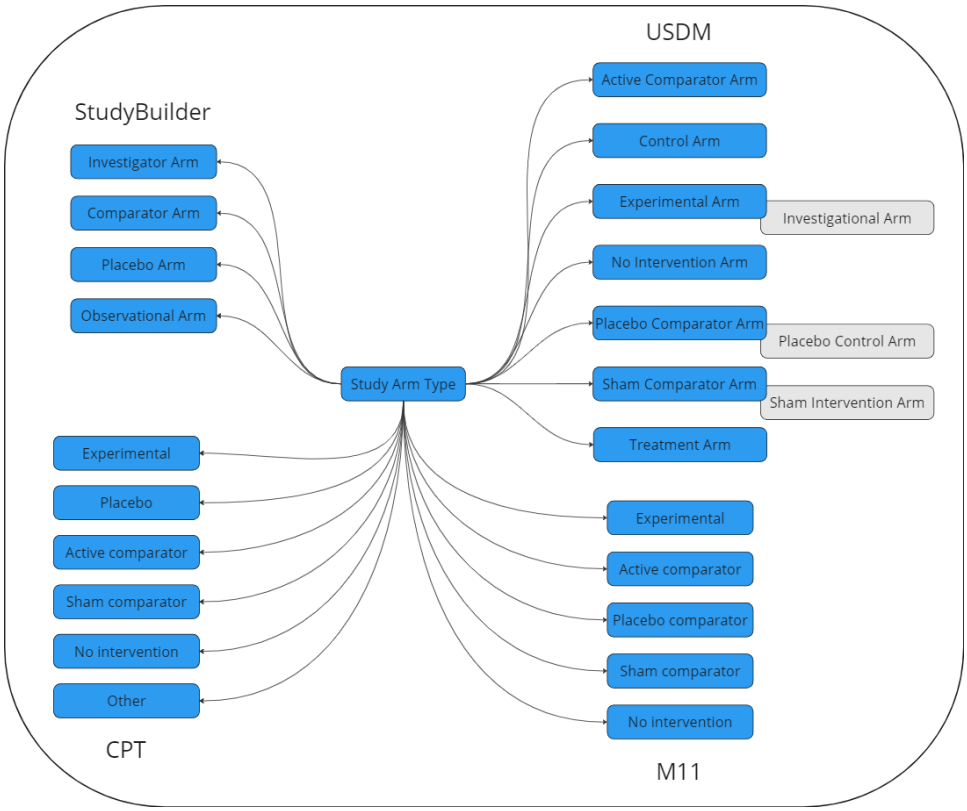

Figure 10: Terminology mapping for “Study Arm Type”

Finally, we plan to comply with these standards by providing mapping in JSON format for the USDM model and the Novo Nordisk Template – which is filles through this JSON with the Microsoft Word Add-In. For CPT and ICH M11 we plan a PDF export.

CONCLUSION

When we discuss protocol automation, we need to consider protocol standardization. Having a metadata repository available maintaining next to typical clinical standards like controlled terminology and dictionaries additionally protocol standards like templates for objectives and endpoints is very valuable.

Additionally, the protocol information needs to be entered in a simple way and required graphics (for example the protocol flowchart) and complex tables (for example the schedule of activities) should ideally be created automatically and enable a fluent process when updates are done.

The final protocol can hardly be fully automized. Considering the colleagues who are responsible for this document, it might be a good idea to keep the traditional Word as tool to finalize the protocol. Combining this tool with an add-in to allow automatic loading and updates of the structured protocol information helps to ensure consistency and allows the information flow to following processes.

The open-source OpenStudyBuilder repository is specifically developed to support the protocol automation in this context. The OpenStudyBuilder is much more and finally aims for fully end-to-end support. The protocol automation part is fully working, and the corresponding Word add-in will likely be released as an open-source tool soon.

By joining an OpenStudyBuilder collaboration, we would be able not to only optimize the processes within Novo Nordisk, but within our complete industry by realizing the vision of CDISC 360°. A main factor is the flexibility and powerful interface to allow any tool and system to communicate with the repository to enable a flexible open and generic landscape of connected solutions.

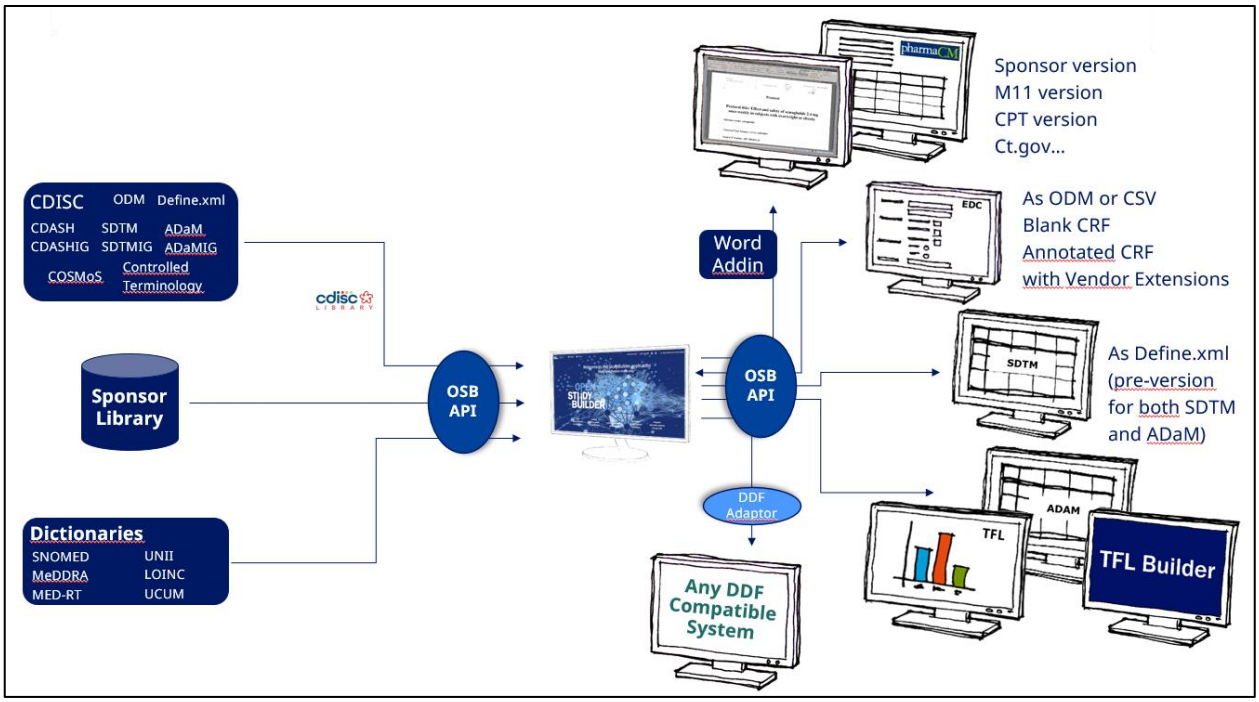

Figure 10: Generic system landscape

REFERENCES

[1] ICH M11 Guideline, Information by EMA, accessed on 10.10.2023 https://www.ema.europa.eu/en/ich-m11-guideline-clinical-study-protocol-template-technical-specifications-scientific-guideline

ACKNOWLEDGMENTS

We would like to thank Novo Nordisk to share this project as open-source solution. Additionally, we would like to thank the complete OpenStudyBuilder team which is a squad of around 30 highly skilled professionals who work together in a dynamic environment to deliver and enhance the amazing OpenStudyBuilder solution.

We are looking forward to collaborations, so if you are interested in joining the OpenStudyBuilder project, please reach out to us.

Figure 11: OpenStudyBuilder team

RECOMMENDED READING

[1] Project Homepage, detailed project information, guides and more is available on the OpenStudyBuilder homepage: https://openstudybuilder.com/

[2] Project Resources, if you would like to see various information resources available, you can check out the resource-list: https://openstudybuilder.com/info_resources/

[3] OpenStudyBuilder demonstration video, we have a 30' demonstration video available showing the functionality of the OpenStudyBuilder in version 0.4: https://www.youtube.com/watch?v=dL5CY0BwfEs

[4] GitLab repository, the complete solution is available in GitLab. A docker setup is available as well: https://gitlab.com/Novo-Nordisk/nn-public/openstudybuilder/OpenStudyBuilder-Solution/

[5] Newsletter, our newsletter is getting out through linkedIn: https://www.linkedin.com/newsletters/openstudybuilder-6990328054849916928/

[6] Slack channel, we do have a slack space available where you can ask any question: https://join.slack.com/t/openstudybuilder/shared_invite/zt-19mtauzic-Jvrhtmy7hGstgyiIvB1Wsw

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