

# CDISC Europe Virtual Interchange 2021

## Full paper:

### Automated generation of CDISC Biomedical Concepts Starting from Healthcare Terminologies

Jozef Aerts, XML4Pharma  
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#### Abstract

CDISC Biomedical Concepts (BCs) are being developed as basic protocol building blocks allowing automated generation of CRFs, extracts of Electronic Health Records (EHRs), up to SDTM and ADaM table generation. Similar concepts are already used for a longer time in healthcare, such as "archetypes" (OpenEHR), "profiles" (HL7-FHIR). Also LOINC "panels" look to be very similar to CDISC BCs.

With the new LOINC-to-CDISC mapping (published Spring 2020), and considerably extended by us (also to vital signs and COVID-19 microbiology), it becomes possible to create CDISC-BCs automatically or semi-automatically, starting from LOINC panel codes and codes for individual tests. The software, named "LOINC2CDISCBiomedicalConcepts" and its implications are described in this article. It not only allows to generate BCs with mappings to CDISC SDTM, but also to SNOMED-CT concepts and codes, thus allowing to use the BC for retrieval data from EHRs for clinical research purposes ("Real World Data" usage).

#### Introduction

CDISC Biomedical Concepts (BCs) are regarded as basic protocol building blocks, envisaged to finally realize the long expected start-to-end idea (from protocol to submission) in clinical research [1]. It is expected or hoped, that in future, protocol writers will just assemble major parts of the protocol using BCs. As these already contain the information for and mapping to submission standards, they are expected to be used through the whole process, down to the submission to regulatory authorities.

BCs are however currently developed fully manually [2], and mostly published just as images in CDISC Therapeutic Area User Guides (TAUGs) [3], and thus are limited to human consumption only: they are not at all available in a machine-readable format.

(Bio)medical concepts are however not an invention of CDISC. Similar concepts are already for long time known in healthcare: OpenEHR has its "archetypes" [4] and even developed a language [5] for describing them. HL7-FHIR [6] has its "profiles" [7] with FHIR contributors having developed a "Scenario Builder", named ClinFHIR [8] to assemble the necessary FHIR resources for a given medical scenario.

When one however looks at LOINC panels [9], consisting of logical groups of tests, one sees that these are very similar, with of course, missing the mappings to CDISC submission standards.

In 2019, CDISC published a mapping between the most used LOINC codes for laboratory tests and SDTM and its terminology [10]. This mapping was not only considerably extended by us [11], but also a mapping for vital signs LOINC codes to SDTM was developed [12]. We also developed RESTful web services for these [13], making it much easier to use them in automation than when using the Excel worksheets published by CDISC.

Several RESTful web services for working with LOINC codes already exists, such as from LOINC/FHIR [14] and of the National Library of Medicine NLM [15].

With all these extremely useful resources already available, the question arises whether it is possible to (semi-) automatically generate CDISC-BCs starting from LOINC panel codes, including mappings to CDISC SDTM and to SNOMED-CT for use with RWD.

#### Methods

A locally installed MySQL LOINC database, generated from the LOINC v.2.69 distribution available from the LOINC website was used. This not only involves the "loinc" table, but also additional accessory tables such as "loincanswerlinklist", "answerlist", "panelsandforms" and "parts".

A simple Java program (without graphical user interface) was developed. For execution, it requires Java version 8 or OpenJava version 10 or higher. The program uses the following RESTful web services: for the mappings between LOINC codes and SDTM variables and domains, our own RESTful web service is used, available on a remote, public server [11]. A similar service is used to find CDISC controlled terminology (CDISC-CT) matching the "LOINC answers" for individual LOINC codes [16]. UMLS (Unified Medical Language System) RESTful web services from the National Library of Medicine NLM [17] are used to generate mappings from LOINC answers to SNOMED-CT and to CDISC-CT. Remark that the usage of the UMLS RESTful web service requires an API key, which can be freely obtained from NLM [18].

Mapping between UCUM units to CDISC units was performed from an XML file containing mappings between both

systems. Although we could easily do so, we decided in the past not to make these mappings available as a RESTful web service, as we do not want to encourage people to use CDISC units: CDISC should definitely move away from its own list of units to the UCUM system, which e.g. allows automated unit conversions (CDISC units do not make this possible).

In order to execute the RESTful web services requests, we used the Jersey 2.30 Java libraries [19].

The Biomedical Concepts are generated as graphs and are exported in RDF-Turtle format. This makes it possible to query the BCs (e.g. to generate sub-graphs). The human-readable graphs were then generated using the online program "RDF Grapher" [20]. Any other program to visualize RDF-Turtle can however also be used.

### Program execution

The simple Java program does not have a graphical user interface and is run from the command line. It first asks the user for the LOINC code of a LOINC panel or individual test. The code is then tested against the LOINC database, and if invalid, the program stops. The software then checks whether the code represents a panel or an individual test. In the latter case, it gives a warning that it will create what we called a "mini-BC". In case of a panel, which currently can either be a laboratory panel or a vital signs panel, the panel members are retrieved using the LOINC database table "panelsandforms". Each of them is then further separately. The software also asks whether also mappings to SNOMED-Electronic Health Records (EHRs). Unfortunately, due to a lack of understanding of terminologies used in the medical world in the clinical research community, SNOMED-CT is currently not used within CDISC. We therefore decided that the user can "opt out" for generating SNOMED-CTs in the BCs. Another question asked to the user concerns the splitting between SDTM "--LOC" (body location) and "--LAT" (laterality). Reason is that LOINC answers and also SNOMED-CT codes usually combine body location and laterality. For example, LOINC answer code for "left ankle" is LA18739-5, whereas it is LA18740-3 for "right ankle". CDISC-CT however splits this up in "body location" (--LOC) and in --LAT (laterality). So, for example for a vital sign measurement, the LOINC answer code LA18739-5 will need to generate SDTM VSLOC=C32078 ("ANKLE JOINT") and VSLAT=C25229 ("LEFT").

```
Please provide the LOINC code for the LOINC panel
85354-9
CDISC Domain from LOINC class 'PANEL.VITALS' = VS
Panel member LOINC code = '85354-9' with name = 'BP pnl w all optional'
LOINC code = 85354-9 - long common name = Blood pressure panel with all children optional
LOINC Result Type = -
LOINC name for panel '85354-9' = Blood pressure panel with all children optional
Besides Mapping to CDISC-SDTM, do you also want to add the mapping to SNOMED-CT? (Y/N)
Y
LOINC uses answers like 'Ankle right' for 'body location'
Do you allow the system to attempt to split these into CDISC-CT '--LOC' and '--LAT'? (Y/N)
Y
***** Starting retrieving members of the LOINC panel = *****
Panel member LOINC code = '41904-4' with name = 'BP measurement site'
LOINC code = 41904-4 - long common name = Blood pressure measurement site
LOINC Result Type = Anatomy
Panel member LOINC code = '8357-6' with name = 'BP method'
LOINC code = 8357-6 - long common name = Blood pressure method
LOINC Result Type = Type
Panel member LOINC code = '41901-0' with name = 'BP device Class'
LOINC code = 41901-0 - long common name = Type of Blood pressure device
LOINC Result Type = Type
Panel member LOINC code = '8358-4' with name = 'BP device Cuff size'
LOINC code = 8358-4 - long common name = Blood pressure device Cuff size
UCUM unit = cm
LOINC Result Type = Length
Panel member LOINC code = '8462-4' with name = 'BP dias'
LOINC code = 8462-4 - long common name = Diastolic blood pressure
UCUM unit = mm[Hg]
LOINC Result Type = Pressure
Panel member LOINC code = '8478-0' with name = 'BP mean'
LOINC code = 8478-0 - long common name = Mean blood pressure
UCUM unit = mm[Hg]
LOINC Result Type = Pressure
Panel member LOINC code = '8480-6' with name = 'BP sys'
LOINC code = 8480-6 - long common name = Systolic blood pressure
```

The current LOINC-CDISC mappings [10-12] are limited to those cases where the LOINC code represents a CDISC test that is represented by a --TESTCD (test code). This is however not always the case. For example, the LOINC code 41904-4 "blood pressure measurement site" does not map to a value for VSTESTCD, but maps to VSLOC. In such a case, the software reports to the user that the LOINC code cannot be mapped to a known value for --TESTCD, and asks to which variable it needs to be mapped. In the case of LOINC code 41904-4, the user will then need to enter

"VSLOC".

```
***** No CDISC Mapping found for LOINC code = 41904-4 'BP measurement site' *****
With standardized answers (SNOMED-CT in brackets):
['Biceps left','Biceps right','Wrist left','Wrist right','Thigh left','Thigh right','Ankle left','Ankle right','Finger']

The LOINC code 41904-4 cannot be mapped to a VSTESTCD
Maybe it must be mapped to another SDTM variable (e.g. VSLOC, VSPOS, VSEVLINT, SUPPVS.xxx, ...)
If it must be mapped to an SDTM variable, please enter the name of the SDTM variable
P.S. This can also be 'VSTESTCD'
If the LOINC code must be skipped in the generation of BCs, enter 'NULL'
VSLOC
```

In some cases, there will simply be no SDTM variable to map to, for example for LOINC code 41901-0 (blood pressure device class). In that case, the user can decide to skip that LOINC code (by entering "NULL") or to provide a non-standard variable as a supplemental qualifier, e.g. "SUPPVS.DEVCLASS":

```
***** No CDISC Mapping found for LOINC code = 41901-0 'BP device Class' *****
With standardized answers (SNOMED-CT in brackets):
['Mercury sphygmomanometer','Aneroid (mechanical) sphygmomanometer','Ambulatory oscillometric device','Home oscillometric device','Continuous noninvasive arterial pressure (CNAP) device','Invasive arterial blood pressure device']

The LOINC code 41901-0 cannot be mapped to a VSTESTCD
Maybe it must be mapped to another SDTM variable (e.g. VSLOC, VSPOS, VSEVLINT, SUPPVS.xxx, ...)
If it must be mapped to an SDTM variable, please enter the name of the SDTM variable
P.S. This can also be 'VSTESTCD'
If the LOINC code must be skipped in the generation of BCs, enter 'NULL'
SUPPVS.DEVCLASS
```

For each LOINC code, the software then generates the mappings to both CDISC-CT and to SNOMED-CT (if there was no opt-out for it). If the LOINC code represents a quantitative result, the possible UCUM units are retrieved, and the corresponding CDISC units for them are retrieved. For example, for the LOINC code 8302-2 (Body Height), the associated UCUM units are "[in\_us]", "cm", and "m", which translate to CDISC units "in" (C48500), "cm" (C49668) and "m" (C41139). Remark that unlike for UCUM, for CDISC-CT, there is no machine-readable way to find out that 1 inch = 2.54 cm. The only information that can be found is a textual description "A traditional unit of length equal to 2.54 centimeters. (NCI)", which is not usable by machines.

In case the LOINC code has enumerated possible answers, these "LOINC answers" are retrieved, and an attempt is made to obtain the CDISC equivalents using the above described RESTful web service, searching in the "CDISC terms" and "CDISC synonyms" for the LOINC answer. If no value is found, the UMLS RESTful web service is triggered, and the system tries to obtain a mapping to CDISC-CT from the service.

At the same time, the system also uses the UMLS RESTful web service to obtain a SNOMED-CT code for the LOINC Answer. In some cases, more than one result is obtained. For example, for the LOINC code 41904-4 (Blood pressure measurement site), one of the answers is code LA11862-2 ("Finger"), for which CDISC-CT code C32608 is obtained as well as 2 SNOMED-CT codes 7569003 (Finger structure) and 125685002 (Digit of hand structure):

```
2021-03-21 09:21:26,973 INFO Generating new UMLSMapping for LOINC Answer code = LA11862-2 'Finger'
2021-03-21 09:21:54,193 INFO Maps to CDISC-CT with NCI code = C32608 and term = 'FINGER'
2021-03-21 09:21:54,271 INFO Maps to SNOMED-CT with SNOMED-CT code = 7569003 and term = 'Finger structure'
2021-03-21 09:21:54,271 INFO Maps to SNOMED-CT with SNOMED-CT code = 125685002 and term = 'Digit of hand structure'
```

When all LOINC codes that are members of the LOINC panel are iterated over, the software then analyzes the results and converts this into an internal graph presentation, taking care of result code uniqueness. For example, if two or more tests in the panel have the same CDISC unit, it will appear in the graph only once, but with two or more relations to it (graph edges). The internal graph is then formatted into RDF-Turtle, and the result is displayed on the screen. At the same time, it is also written to file. For example:

```

RDF representation =

@prefix rdf:    <http://www.w3.org/1999/02/22-rdf-syntax-ns#> .
@prefix ln:    <http://prul.bioontology.org/ontology/LNC/> .
@prefix rdfs:  <http://www.w3.org/2000/01/rdf-schema#> .
@prefix sn:    <http://purl.bioontology.org/ontology/SNOMEDCT/> .
@prefix umls:  <http://bioportal.bioontology.org/ontology/UMLS/> .
@prefix cdisc: <http://bioportal.bioontology.org/ontology/CDISC/> .
@prefix ucum:  <http://bioportal.bioontology.org/ontology/UCUM/> .
@prefix x:     <http://xml4pharmaserver.com/WebServices/LOINC2CDISC_webservices/> .

ln:LN85354-9 rdfs:label "Blood pressure panel with all children optional" ;
ln:has_member ln:LN41904-4 ;
ln:has_member ln:8357-6 ;
ln:has_member ln:41901-0 ;
ln:has_member ln:8358-4 ;
ln:has_member ln:LN8462-4 ;
ln:has_member ln:LN8478-0 ;
ln:has_member ln:LN8480-6 ;
.
ln:LN41904-4 rdfs:label "Blood pressure measurement site" ;
ln:has_answer ln:LA11158-5 ;
ln:has_answer ln:LA11159-3 ;
ln:has_answer ln:LA11160-1 ;
ln:has_answer ln:LA11161-9 ;
ln:has_answer ln:LA21901-6 ;
ln:has_answer ln:LA21900-8 ;
ln:has_answer ln:LA21903-2 ;
ln:has_answer ln:LA21902-4 ;
ln:has_answer ln:LA11862-2 ;
x:maps_to cdisc:SDTM:VSLOC ;
x:maps_to cdisc:SDTM:VSLAT ;
.
cdisc:SDTM:VSLOC rdfs:label "VSLOC" ;

```

In the RDF-Turtle output, nodes are represented by the code as much as possible, with `rdf:label` containing the human-readable version of the resource's name.

## Results

With this software, CDISC-BCs (including SNOMED-CT mappings) can be generated from LOINC panel codes in just minutes. The time-limiting step is the use of the NLM UMLS RESTful web service, which is pretty slow (response times of seconds). The RDF-Turtle can then be used to generate a human-readable visualization of the graph.

The thus generated graphs can be found on our website at:

[http://xml4pharma.com/CDISC\\_Biomedical\\_Concepts\\_From\\_LOINC/](http://xml4pharma.com/CDISC_Biomedical_Concepts_From_LOINC/).

At first sight, these graphs may look complicated, but as there is a machine-readable representation, simpler sub-graphs can easily be generated, e.g. leaving out the SNOMED-CT code and the "supplemental qualifier" variables such as for the "Blood pressure device class". Fig. 1 shows a small part of the visualization of the "simplified" version of the BC for LOINC code 85354-9 "Blood pressure panel with all children optional", with SNOMED-CT codes and LOINC codes that would map to SDTM supplemental qualifier variables ("Non-standard variables") left out.

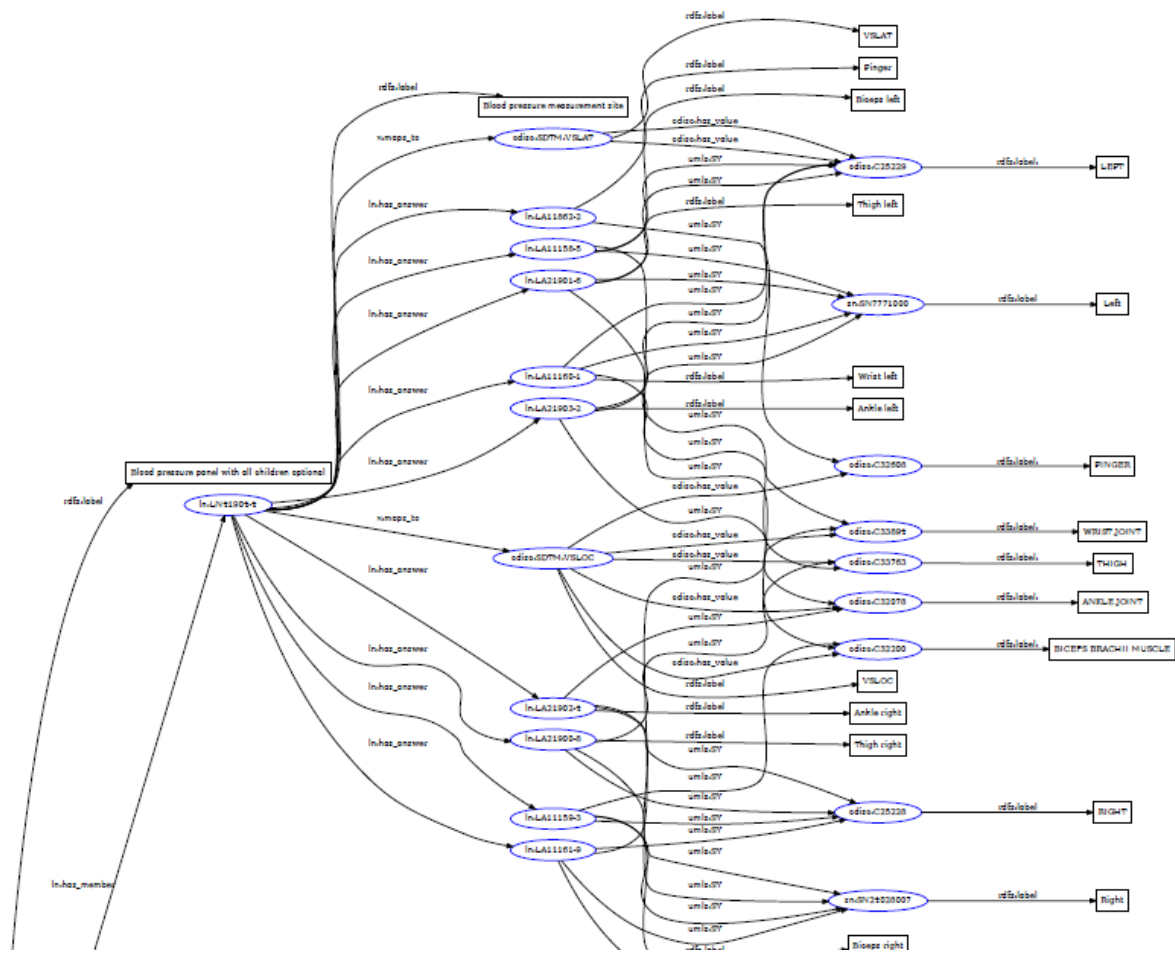


Fig. 1: Visualization of a small part of the "simplified" version of the BC for LOINC code 85354-9 "Blood pressure panel with all children optional". The full zoomable version can be found at: [http://xml4pharma.com/CDISC\\_Biomedical\\_Concepts\\_From\\_LOINC/](http://xml4pharma.com/CDISC_Biomedical_Concepts_From_LOINC/)

As the thus generated BCs have a machine-readable representation, they can also easily be extended to obtain additional information, e.g. comments or test instructions. For this, no tools have been developed yet, but we expect that this will happen once CDISC standardizes the machine-readable representation of the Biomedical Concepts, which has not been done yet.

Results for a number of LOINC panels and individual test codes for laboratory tests, COVID-19 microbiology and vital signs test can be found on our website at [http://xml4pharma.com/CDISC\\_Biomedical\\_Concepts\\_From\\_LOINC/](http://xml4pharma.com/CDISC_Biomedical_Concepts_From_LOINC/). Each result comes at least as a Turtle-RDF file, for machine-consumption, and as a PDF for human inspection.

### Limitations

This semi-automated generation of CDISC-BCs starting from LOINC panel codes and single-test codes is currently limited to cases where the LOINC code for a panel member (or an individual test code) for which there is a LOINC-CDISC-SDTM mapping available. At the moment of writing, this is the case for a large number of laboratory codes (>6000 codes resulting in >9500 mappings), vital signs codes (537 codes resulting in 600 mappings) and COVID-19 microbiology test codes (97 codes resulting in 146 mappings) [11,12].

As can be seen for some of the graphs, there is not always a CDISC-CT mapping for every LOINC answer, even not when there is a mapping for the LOINC code to an SDTM variable. For example, for LOINC code 8357-6 "blood pressure method" mapping to VSMETHOD, for LOINC answer LA24016-0 "Continuous noninvasive arterial pressure" there is no mapping in CDISC-CT "METHOD" (codelist C85492). For another LOINC Answer code :LA24014-5 (Oscillometry) there is however a mapping in CDISC CT to CDISC code C154788. For both LOINC answers however, mappings to SNOMED-CT exist (codes 31813000 and 17146006). The UMLS RESTful web service could however not detect these either. Usually, we find much more mappings to SNOMED-CT codes as we find to CDISC-CT codes. The reason is that CDISC-CT does not aim for completeness. SNOMED-CT does. CDISC-CT is extended only when there is a request from the CDISC community to add an additional term [21], and even then, the request is not always accepted. For example, when developing mappings for ECG tests, we found out that the list in CDISC-EGTESTCD is

very limited, so we did a request for additional 50 test codes, which however was denied, with the argument that these codes mostly represent tests that are "only used in calculations", and/or "would never be submitted to the FDA". Our argument that these codes are needed for the development of BCs and for retrieval of RWD with subsequent automated generation of SDTM datasets was not understood.

Although this would be extremely useful, CDISC-SDTM does not allow yet to populate any of its variables (except very few in the "Trial Summary" (TS) dataset, with SNOMED-CT codes. If this were allowed, regulatory reviewers would have a much easier job comparing results from RWD with SDTM submissions.

## **Discussion**

The idea for using LOINC in biomedical concepts is not entirely new: David Ibersen-Hurst already used LOINC codes in BCs [22]. In his approach, the test code from the BC is translated in a LOINC code to be used for retrieval of FHIR resources from an EHR system. We work the other way around, i.e. use LOINC codes to generate BCs.

Currently, the thus generated BCs are in RDF-Turtle machine-readable format, that can then be used further e.g. for CRF generation in e.g. CDISC-ODM [reference] format. In case of LOINC panels, it is not always necessary to go over BCs, as CRFs in ODM format can also be generated directly from the LOINC code using another, already existing, public RESTful web service [23]. The generated BCs can however already be used as protocol building blocs. As they are machine-readable, they can be used in a sponsor's Metadata Repository system (MDR) for any purpose. In the case they also contain the SNOMED-CT codes, they can be used to automatically retrieve RWD from EHRs, and feed the retrieved Real-World data into EDC systems. As the SDTM information is already in the BC, this then also allows the generation of SDTM records. SDTM datasets can however also be generated directly from EHR systems starting from either LOINC codes for tests or groups of tests, or starting from the SNOMED-CT code for the therapeutic area under investigation, as has been demonstrated before [24]. For example, "retrieve lab data and generate LB-SDTM datasets for all patients with Parkinson disease (SNOMED-CT 49049000). When the EHR system has an HL7-FHIR interface, such queries can now already be combined with statements like "where the patient is involved with study XYZ and has given informed consent to use his/her data in the study", using the FHIR resources "ResearchStudy" [25] and "ResearchSubject" [26]. In view of this, it is remarkable that by CDISC published "Therapeutic Area User Guides" (TAUGs) [3] still do not mention the SNOMED-CT code or codes of the therapeutic area they are about.

Except for when the FDA mandates it, LOINC, UCUM, and SNOMED-CT are not used in most of the CDISC standards. Whether this is due to a lack of knowledge and understanding of these standards in the CDISC community, or due to a "non invented here" attitude, can be discussed. Of course one could start major efforts to develop considerably more mappings from LOINC to CDISC-CT (as we did), and to start developing mappings from SNOMED-CT to CDISC-CT, but this is an enormous task, and probably counter-productive.

## **Conclusions**

It is possible to generate CDISC Biomedical Concepts (BCs), with or without mappings to SNOMED-CT, starting from LOINC codes for panels or for individual tests. The methodology and software that we developed allows to generate such BCs and to store them in a machine-readable format using RDF-Turtle, allowing to use them in applications.

## **Future work**

The RDF-Turtle representation currently uses namespaces and names for the relations (graph edges) that are pretty arbitrary but that are as much reused from other standards and ontologies. These will in future be aligned with those that CDISC selects in their Biomedical Concept work.

It will also be discussed with the CDISC colleagues whether RDF-Turtle is the most suitable format for publishing Biomedical Concepts, and/or that other machine-readable representations such as Define-XML (with "ValueLists") should be added [27]. And last but surely not least, we will align our work with the results of the CDISC project with A3 Informatics for the generation of biomedical concepts that just has started [28].

Once all this is decided on, we plan to make our software available as "open software" with a very liberal license. We are currently also developing mappings for LOINC ECG test codes and panels. Problematic is however that the amount of CDISC-CT is very limited, and that the responsible CDISC-CT team does not want to extend the current codelist for ECG tests with LOINC equivalents.

Work is also planned to investigate whether LOINC codes for questionnaires can be mapped to CDISC-CT.

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