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The Use of RESTful Web Services in Medical Informatics and Clinical Research and Its Implementation in Europe

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Abstract. Background: RESTful web services nowadays are state-of-the-art in business transactions over the internet. They are however not very much used in medical informatics and in clinical research, especially not in Europe. Objectives: To make an inventory of RESTful web services that can be used in medical informatics and clinical research, including those that can help in patient empowerment in the DACH region and in Europe, and to develop some new RESTful web services for use in clinical research and regulatory review. Methods: A literature search on available RESTful web services has been performed and new RESTful web services have been developed on an application server using the Java language. Results: Most of the web services found originate from institutes and organizations in the USA, whereas no similar web services could be found that are made available by European organizations. New RESTful web services have been developed for LOINC codes lookup, for UCUM conversions and for use with CDISC Standards. Discussion: A comparison is made between "top down" and "bottom up" web services, the latter meant to answer concrete questions immediately. The lack of RESTful web services made available by European organizations in healthcare and medical informatics is striking. Conclusion: RESTful web services may in short future play a major role in medical informatics, and when localized for the German language and other European languages, can help to considerably facilitate patient empowerment. This however requires an EU equivalent of the US National Library of Medicine.

Keywords. RESTful web services, medical informatics, clinical research.

1. Introduction

RESTful web services are nowadays very common in machine-to-machine communication, but are not much used yet in medical informatics. For example, the ELGA Terminology Server provides services using the older SOAP method, allowing to retrieve information in the HL7 CLAML format, but does not provide a RESTful web service interface yet [1].

With the rise of the new HL7 FHIR standard, where REST and services are two of the four interoperability paradigms [2,3], the use of RESTful web services in medical informatics is expected to grow considerably.

In clinical research, the use of RESTful web services is extremely rare. Until now, only one electronic data capture (EDC) provider has developed RESTful web services for exchange of clinical research data [4]. CDISC, the Clinical Data Interchange Standards Consortium very recently published its RESTful API [5], but with still limited

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functionality. In the review process for new drug applications and treatments at the regulatory authorities FDA, PMDA and EMA, the use of web services is unknown, although such services could help bringing new treatments to the patients earlier and improve the quality of the review process considerably [6].

2. Methods

2.1. Literature research on existing web services in medical informatics

As we are developing RESTful web services for use in clinical research, we first made an inventory of available web services (based on SOAP as well as on REST) that are publicly available for use in medical informatics and in clinical research. We first performed several searches in PubMed, then extended the search to a classic internet search, as most of these services are described by web pages. As RESTful web services usually are however easier to implement in software [7], and many RESTful web services have support for the JSON notation which is the preferred data format by many mobile application developers [8], we dropped SOAP and further concentrated on RESTful web services in medical informatics and clinical research. The results of our inventory are described in the "Results" section. The scope of our research excludes bioinformatics, for which a large number of web services is available [9].

2.2. Development of new RESTful web services for use in clinical research

As we found that there are almost no public RESTful web services available for use in clinical research, we developed a number of them in the following areas:

- Lookup services for LOINC (Logical Observation Indentifiers Names and Codes) codes
- UCUM (Unified Code for Units of Measure) unit conversion services
- Services for using CDISC controlled terminology
- Services for use with SDTM (Submission Data Tabulation Model) electronic submissions to the FDA and PMDA
- Experimental services for supporting modern "open rule" validations for electronic submissions to the FDA and PMDA

These RESTful web services were developed in the Java language, using the "Jersey" toolkit [10] and deployed as web applications on a Java application server.

2.3. Consumption of RESTful web services in clinical research

A number of CDISC volunteers have developed the "Smart Dataset-XML Viewer" [11], allowing to inspect and work with electronic submissions to the FDA and PMDA that use the "Dataset-XML" format [12]. It has been named "smart" as its features go far beyond what the FDA and PMDA have available for inspecting and validating electronic submissions in SAS-XPT format. This software is written in Java and is freely available as "open source" [11]. Several of the web services that we developed on the server are

being used ("consumed") by the "Smart Dataset-XML Viewer" (as "client"), as will be explained in the "Results" section.

3. Results

3.1. Available public web services for medical informatics

The most interesting publicly available web services (and especially RESTful web services) for use in medical informatics that we found originate from:

- The National Library of Medicine (NLM) with its "MedLinePlus Connect" set of web services [13], allowing client applications to request for information on diagnosis (problem) codes, medications and lab tests. These web services are available as RESTful web services, either returning XML, JSON or JSONP.
- Another set of web services (REST and SOAP) is offered by "RxNav" (also part of NLM) concentrating on drug information [14]. It uses the RxNorm terminology that is specific to the US. It also provides a RESTful web service for drug interactions [15] based on the RxNorm identification number and a LOINC mapping service [16], allowing to find tests that are related.
- HIPAASpace provides a number of web services, with the choice between SOAP and REST, the latter allowing responses in (compressed or non-compressed) JSON or XML [17]. Most of these web services are either in the area of provider insurance, or lookup systems for codes used in health informatics (ICD-x, LOINC, and others). The emphasis is clearly on insurance and reimbursement use cases.
- UMLS offers a number of very interesting RESTful web services, allowing to find relationships between terms in different coding systems [18]. These services are still in beta, but are very promising. For example, it allows client applications to find out relationships between lab tests and diseases. Although the web service requires authentication tokens, we found out that they are pretty easy to implement in client applications.
- OpenFDA offers a number of RESTful web services [19] returning information in JSON format for queries on national drug codes (NDC), structured product labels (SPL), unique ingredient identifiers (UNII), and branded drugs (RxNorm).
- The US National Cancer Institute (NCI) offers a range of RESTful web services for querying the SEER (Surveillance, Epidemiology, and End Results) databases [20]. Responses are formatted as JSON. They require an API key which can be obtained after registration (free of charge)
- NCI also offers other RESTful web services for use in medical research, such as for querying the Genomic Data Commons (GDC) database [21] and for obtaining information on registered clinical trials [22].
- Several RESTful web services are available for lookup of ICD-10 codes [23,24]
- ClinicalTrials.gov, the US registry for clinical trials offers web services which can be regarded as RESTful [25]. They do, however, return zip files containing sets of XML files. These files can, of course, also be consumed by client applications.
- CDISC recently published an API for its SHARE (Shared Health And Research Electronic) library [26] containing all the CDISC standards. The approach can

be regarded as a "top down" approach, as it allows to query for a standard, and from the response than allows to query for a class in that standard, leading to variables, for which the details (such as associated codelists) can then be queried for. This "drilling down" is made possible by "chaining", as each response contains information to start a new query.

- Lablans et al. [27] developed a RESTful web service for pseudonymization in medical research networks.

It was striking that we did not found any web services in the area of medical informatics from organizations in Europe. For example, DIMDI (Deutsches Institut für Medizinische Dokumentation und Information) does not yet make any public web services available [28]. The only RESTful web services we found from a European organization that may somehow be useful in medical informatics, are the web services from Europe PMC [29] for finding articles in the area of life science. Also the EMA (European Medicine Agency) has no equivalent to openFDA [19], and does not allow automated searches for clinical trials in EudraCT, the European clinical trials register [30]. It only allows to search for clinical trials through a browser interface. In the DACH region, we observe that even for very simple things, like looking up a medication ID ("Pharmazentralnummer" in Germany and Austria, "Pharmacode" in Switzerland) no web services are available. Solely, information about approved medications in Switzerland can be obtained in an automated way using a SOAP-based web service [31] by using the GTIN article number of the medication. Also no web services seem to be available for working with ICD-10 GM (Germany) or ICD-10 BMG (Austria) codes.
Of course, the diversity in languages used in the EU and the fragmentation of information over the different member countries does not make it easy to develop web services in the area of healthcare informatics that can be consumed by modern applications. The lack of even the simplest web services in this area may however also have to do with "protectionism on information" i.e. organizations claiming "ownership" of information even when the development or generation of that information was paid by tax money.

3.2. Newly developed RESTful web services developed by the author

We recently developed a number of new RESTful web services for use in medical informatics and especially in clinical research [32]. These web services can be categorized in four categories:

- RESTful web services for working with LOINC codes
- RESTful web services for working with CDISC controlled terminology and submission data standards variables (CDISC-SDTM)
- A RESTful web service for unit conversions using the UCUM (Unified Code for Units of Measure) [33] system
- A very experimental web service for retrieving machine-readable FDA rules concerning electronic submissions implemented as XQuery scripts ("OpenRules for CDISC" initiative)

The RESTful web service for working with LOINC codes implements the latest version of the LOINC database (December 2016) [34]. It allows to look up the LOINC name (containing the 5-6 components) and the LOINC long name (lab code description), and when applicable the example UCUM units for the given LOINC code. It can be seen as complimentary to the RESTful web service of MedlinePlus Connect [13] which

essentially returns a description for the code and a hyperlink to a web page containing information about the laboratory test which is more suitable as information to patients. Both of these web services have been implemented in the "Smart Dataset-XML Viewer" [11], a review software for use in regulatory submissions to the FDA and PMDA, as will be explained further on in the "discussion" section. We are currently extending our LOINC web services to allow chaining, e.g. for looking up whether a specific test is a member of a panel, and then to provide all other tests of that panel.

We also developed a large number of RESTful web services for use with the CDISC set of standards [35] and especially the submission standard SDTM and the CDISC controlled terminology as published by NCI [36]. These web services have also been implemented in the "Smart Dataset-XML Viewer" [11], but are now also already used by other applications in the pharma industry. These applications typically try to answer concrete questions, like "what is the variable label and data type of SDTM variable XYZ in version ABC of the standard?", or "is CDISC codelist XYZ version ABC extensible or not?". The underlying base of these web services is a set of databases, containing all SDTM information since v.1.2 and all CDISC controlled terminology since version 2014-03-28. The approach here differs from the one use by the CDISC-SHARE API as will be discussed in the "discussion" section.

Furthermore, we developed a RESTful web service for automating unit conversion using the UCUM notation [33]. The service is not based on conversion tables, but is based on the property that any UCUM unit can be broken down into a combination of base units. Doing this for as well the source as target unit allows to calculate the conversion factor between both. The algorithm for this goes beyond the scope of this paper and will be described in a subsequent publication. The service allows client applications to automate unit conversions, not only in medicine and clinical research, but also in other areas.

Furthermore, we developed an experimental RESTful web service to automatically retrieve the latest updates of sets of FDA and PMDA rules for electronic submissions [37]. These rules have been implemented before in software by a vendor [38], but in such a way that the rule implementation is hidden, so that users cannot see how exactly the rule was implemented in the software. The "Open Rules for CDISC" Initiative of a number of CDISC volunteers aims at making these rules implementations transparent, by providing them as machine-readable as well as human-readable scripts. Therefore, they have been rewritten in XQuery, the W3C standard for querying XML [39]. The web service allows client applications to always retrieve the newest version of each of the rules, as the latter are still in development and optimized for speed and efficacy.

4. Discussion

The advantages of web services are obvious:

- No need to "reinvent the wheel": once a (public) web service is established, it can be used by any modern application that can connect to the internet, without the need of a database installation or reading data from local files with information
- Always up-to-date: many applications in healthcare still work with either a local database or with files that are usually not up-to-date. Updating these applications for the newest available information ("please wait for the next release") can be a challenge and is usually not accepted by the end users anymore.

STUDYID	DOMAIN	USUBJID	LBSEQ	LBTESTCD	LBLOINC	LBTEST	LBCAT	LBORRES	LBORRESU	LBORNRLO
CDISCPIL...	LB	01-701-1097	98	PLAT	26515-7	Platelet	HEMATOL...	284	THOU/uL	130
CDISCPIL...	LB	01-701-1097	128	PLAT	26515-7	Platelet	HEMATOL...	266	THOU/uL	130
CDISCPIL...	LB	01-701-1097	158	PLAT	26515-7	Platelet	HEMATOL...	261	THOU/uL	130
CDISCPIL...	LB	01-701-1097	191	PLAT	26515-7	Platelet	HEMATOL...	260	THOU/uL	130
CDISCPIL...	LB	01-701-1097	223	PLAT	26515-7	Platelet	HEMATOL...	293	THOU/uL	130
CDISCPIL...	LB	01-701-1097	253	PLAT	26515-7	26515-7 (LBLOINC)				130
CDISCPIL...	LB	01-701-1097	286	PLAT	26515-7	LOINC Name: Platelets:NCnc:Pt:Bld:Qn				130
CDISCPIL...	LB	01-701-1097	321	PLAT	26515-7	LOINC Common Name: Platelets [#/volume] in Blood				130
CDISCPIL...	LB	01-701-1097	31	RBC	26453-1	Example UCUM Units: 10*3/uL				4
CDISCPIL...	LB	01-701-1097	68	RBC	26453-1	Erythrocytes	HEMATOL...	4.40	MILL/uL	4
CDISCPIL...	LB	01-701-1097	100	RBC	26453-1	Erythrocytes	HEMATOL...	4.30	MILL/uL	4
CDISCPIL...	LB	01-701-1097	130	RBC	26453-1	Erythrocytes	HEMATOL...	4.30	MILL/uL	4
CDISCPIL...	LB	01-701-1097	160	RBC	26453-1	Erythrocytes	HEMATOL...	4.40	MILL/uL	4
CDISCPIL...	LB	01-701-1097	193	RBC	26453-1	Erythrocytes	HEMATOL...	4.40	MILL/uL	4
CDISCPIL...	LB	01-701-1097	225	RBC	26453-1	Erythrocytes	HEMATOL...	4.30	MILL/uL	4
CDISCPIL...	LB	01-701-1097	255	RBC	26453-1	Erythrocytes	HEMATOL...	4.20	MILL/uL	4

Figure 1. Use of the LOINC web services in the "Smart Dataset-XML Viewer".

As an example, the software used by the FDA and PMDA to validate electronic submissions contains a file with NDF-RT (National Drug File Reference Terminology) codes. This list is updated monthly, but the software itself is only updated every 6 months to 1 year. The consequence is that end-users have started complaining that valid, but newer NDF-RT codes are rejected by the software, which may lead to an (automated) rejection of a new drug application by the FDA.

Combined usage of different web services may open completely new perspectives in medical informatics. For example, the "Smart Dataset-XML Viewer" [11] combines different RESTful web services (from different sources) to help validating electronic submissions to the FDA and PMDA. One of the use cases overcomes the difficulty that reviewers at the FDA and PMDA do not know what each LOINC code means. The viewer triggers our LOINC lookup web service when the user points the mouse over a LOINC code, and uses the response to display the basic information (LOINC names and preferred units) as a tooltip (Fig ire1). A right mouse click then triggers another RESTful web service from "MedLinePlus Connect" [13] which returns the address of a static website containing more extensive information about the test. The application then opens a new browser windows with the address provided by the "MedlinePlus Connect" web service.

The UMLS RESTful web services, although still in beta, do already allow to generate "networks of information". Some of our early experiments with these services already allowed us to create mini-networks where lab test codes are related to panel codes and these again to diseases.

Our own RESTful web services can be regarded as "bottom up" web services: they try to answer single questions, like "provide the mandatory variables in SDTM domain XYZ in version ABC of the SDTM standard", or "is term XYZ a valid term in codelist MNO version ABC of the CDISC controlled terminology?", meaning that the responses are always small, very granular pieces of information, which can be used immediately without much parsing effort. They complement other "top down" web services which typically contain relatively large amounts of information (e.g. extensive lists), such as the CDISC SHARE API [5] which is more meant to populate metadata repositories at pharmaceutical companies, which then can of course be queried by … RESTful (intranet) web services within the company itself.

Web services can, as they are easy to implement and prevent "the reinvention of the wheel" considerably contribute to patient empowerment. With the use of public web services, software providers could easily generate systems for patients helping to govern their own health, like helping them to interpret their lab values, or to find information

about different medications for their specific disease, or to find clinical trials they can enroll in. Even in Europe, such applications are already beginning to emerge [40]. Such patient empowerment applications are, however, seriously hindered in Europe by the lack of suitable web services, even for the simplest things, like looking up (and comparing) information for different medications by their medication ID.

5. Conclusions

One of the advantages of RESTful web services is that they are easy to implement, as well on the server side as on the client side. When combining different web services (from different organizations) on the client side, there is of course the difficulty that one needs to deal with different APIs, different authentication mechanisms and different response formats. Even then, developing client applications that combine different web services is relatively easy and straightforward.

Most web services in the area of medical informatics are provided by US based organizations like the National Library of Medicine or the National Cancer Institute (both part of the National Institutes of Health - NIH). In Europe, almost no RESTful web services in this area exist, probably due to fragmentation of efforts, and the difficulty having to deal with different countries and languages. So if Europe wants to make a serious effort in patient empowerment, it needs (among other actions) start creating an infrastructure where information about diseases, medications, lab tests and many others is accessible through the use of RESTful web services. This not only requires a change in mentality among the "information owners", but also a European equivalent of the US National Library of Medicine.

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