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Drug Interaction Advisory Service for Clinical Decision Support of Multimorbidity Patient Centric Care Plans in the C3-Cloud System.

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Abstract. C3-Cloud is a project aiming to provide an ICT infrastructure, which will allow patient centric and integrated care, based on best practice guideline, for patients with multi-morbidity. The collaborative cure and care plan lies at the heart of the system, allowing healthcare professionals to manage the patients' conditions. Clinical Decision Support, enhances this capability by offering recommendation based on guidelines, but also checking the patient's record for known adverse interactions when the medication changes. The drug interaction advisory service provides recommendations in the three languages used in the project's pilot sites, for over 1000 substances, based on the UK's NICE BNF body of knowledge. The service can be integrated with any system using its RESTful API and by rendering results in JSON.

Keywords. Drug interactions, pharmacovigilance, multi-morbidity, clinical decision support

1. Introduction

C3-Cloud is an e-health ICT system, offering integrated, patient-centered care, considering all aspects of multi-morbidity, creating a collaborative environment for all involved stakeholders [1]. The navel of the system consists of the patient care plan, a digital shared picture of the patients' needs and care regime. The care plan allows all professionals to review and understand the implications of one condition in the presence of others; this by its nature is complex, containing a considerable amount of diverse information. Navigating, understanding, and interpreting all the information can be confounding. The C3-Cloud Clinical Decision Support service (CDS) offers an automated means of interpreting the available data. CDS connects to the care plan repository, and continuously searches records for relevant data. One of the CDS services focuses on potential drug-drug interactions. The current implementation of C3-Cloud cares for multi-morbidity patients with up to four conditions, including diabetes, renal failure, chronic heart failure, and depression. Medication regimes for this combination of conditions may include drugs that when combined, may result in adverse reactions [2].

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Drug Interaction Advisory Service (DIAS) is part of the C3-Cloud CDSS, offering advisories of potential interactions.

2. Drug Interactions Service Architecture and Integration with C3-Cloud

C3-Cloud has adopted a modular architecture, which can be deployed locally on an organization's intranet, as well as a distributed system; depending on the scale and integrated care model [3] requirements of the service that needs to be offered to patients.

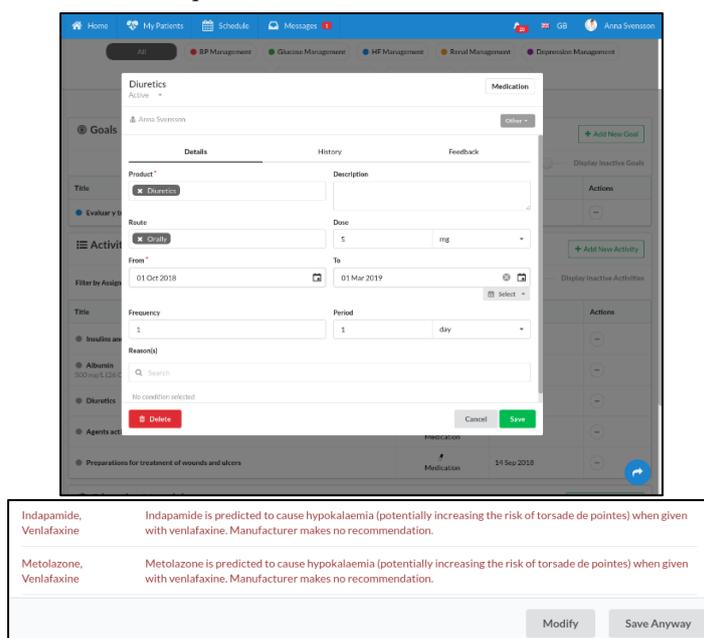


Figure 1. a) C3DP (care plan) medication prescription view (top) b) test extract from the interactions notification pop-up dialogue (bottom); it gives interactions between diuretics (ATC: C03) and existing medication in the patient's record.

The Patient Empowerment Platform (PEP) provides a dedicated interface module to the patient, adapted to their needs. The Coordinated Cure and Care Delivery Platform (C3DP), shown in figure 1a, offers the interface to healthcare professionals, who will create, monitor, negotiate and customize a care plan with the patient. When loading a care plan from the repository, the C3DP will interact with the Clinical Decision Support (CDS) service, and will receive a number of automated recommendation. All communication amongst C3-Cloud components, as well as storage of information is achieved by accessing FHIR resources.

Healthcare professionals can amend a patient's medication via the C3DP. When a new medication request is entered the C3DP will issue a request to DIAS with the ATC codes of the patient's medication. DIAS will then return a list of all the identified interactions amongst the substances that correspond to the ATC codes. The service can check all codes in a record, as well as only potential interactions of a newly prescribed medication. The latter is the default notification method, by a pop-up dialogue, to avoid fatigue alert. DIAS is accessed via a RESTful API using a GET request, and returns the results in JSON. Figure 2 shows an example of a request checking 3 ATC codes (Fig.2a), and an extract in JSON (Fig.2b) from the returned result. The JSON results are then presented in a friendlier format, in a pop-up dialogue (Fig.1b), once the user clicks the

save prescription button, and only if interactions are found. The service returns an advisory and does not make any decisions. Furthermore, users are advised that lack of interactions, may not necessarily mean that there are not any, as this is limited to the knowledge body of the specific database.

```
GET https://DIAS_Service_Host/ATC?code=J01CA04,B01AA03,G03XA01

{
  "DIAS_id": 101762,
  "chemical": "Warfarin",
  "chemical_ATC_code": "B01AA03 ",
  "interactant": "Amoxicillin",
  "interactant_ATC_code": "J01CA04 ",
  "interaction_criticality": "Severe",
  "interaction_effect": "Amoxicillin potentially alters the anticoagulant effect of warfarin.
  Manufacturer advises monitor INR and adjust dose.",
  "interaction_effect_ES_auto": "La amoxicilina altera potencialmente el efecto anticoagulante de la
  warfarina. El fabricante aconseja monitorizar el INR y ajustar la dosis.",
  "interaction_effect_SV_auto": "Amoxicillin förändrar potentiellt warfarins antikoagulerande
  effekt. Tillverkaren rekommenderar att INR kontrolleras och dosen justeras.",
  "interaction_evidence_basis": "Anecdotal"
},
```

Figure 2. a) A typical DIAS GET request (top) b) extract from interactions returned in JSON (bottom).

3. Design of the Drug Interactions Advisory Service

DIAS implements the interactions between drugs, as specified by the National Institute of Care Excellence's implementation of the British National Formulary (BNF) [4]. BNF is a pharmaceutical reference book, used by the UK NHS. The information provided by the service, includes potential adverse interaction between substances, the effects of the interaction, the severity of the interaction, as well as the evidence basis of interaction.

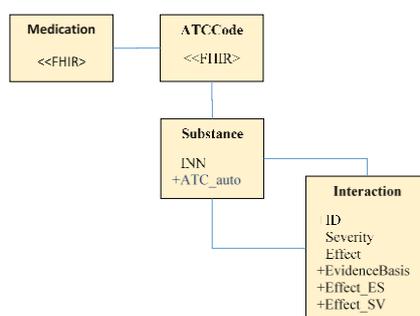


Figure 3. The DIAS Database Model.

For example, Acarbose is a drug active ingredient Alpha-glucosidase inhibitor, commonly used by patients with type 2 diabetes, which reduces the effects of carbohydrates on blood sugar. Acarbose is listed as having a pharmacokinetic interaction with the active ingredient Digoxin used in patients with congestive heart failure to improve quality of life and prevent hospitalisation. The interaction is listed as moderate in criticality, having an effect as decreasing the concentration of Digoxin. The information is encoded as a database using as the international nonproprietary name (INN) of each substance. Substances have been matched to the ATC codes automatically using the NCBO BioPortal's [5] mappings, whereas the ATC codes in the patient's care

plan have been coded by C3-Cloud clinicians. The mapping was tested with random sampling covering 50 substances. The current database contains over 50,000 interacting pairs of substances for over 1,000 substances. Figure 3 shows the logical view of the DIAS database. *Medication* and *ATCCode* are data from the FHIR repository, accessed through the C3DP, whereas *Substance* and *Interaction* are the DIAS entries. *Substances* are associated through an *Interaction*, which serves as an association class. *Severity* of an *Interaction* can have the values *Severe*, *Moderate*, *Mild* and *Unknown*, and *EvidenceBasis* can be a *Study*, *Anecdotal* or *Theoretical*. The effect of an interaction has been translated, in addition to English, to Spanish and Swedish so that can be used in the pilot sites where the system will be deployed. Translation was done using an automated translation service, and tested with manual random sampling. C3DP gives the option to users to access the original language as well as to flag a translation issue.

In the ATC classification, substances are classified in a 5-level hierarchy, which from the higher to the lower level contains: anatomical main group, therapeutic subgroup, pharmacological subgroup, chemical subgroup and chemical substance [3]. The hierarchy of ATC codes allows for further flexibility, offering identification of potential interactions between substance and classes of medication. For example, the service can check for interactions between plain ACE inhibitors (C09AA) which is a chemical subgroup, with blood glucose lowering drugs, excluding insulins (A10B), which is defined at the pharmacological subgroup. Although this trades coverage for accuracy (54 interactions), this was considered a more realistic implementation as in many cases, patient records will contain information that matches a higher ATC level. It was decided that the advisory should be offered to healthcare professionals who could investigate further.

4. Summary

The Drug Interaction Advisory Service is a component of the C3-Cloud integrated care for multi-morbidity, IT infrastructure. It provides the system with over 50,000 interactions between chemical substances, in three languages. DIAS has a RESTful API and returns results in JSON, which are shown during medication changes in a patient's care plan. Future work will extend DIAS to include advisory on probability of side-effects.

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References

- [1] Gokce Banu Laleci Erturkmen, Mustafa Yuksel, Bunyamin Sarigul, Mikael Lilja, Rong Chen, Theodoros N. Arvanitis. "Personalised Care Plan Management Utilizing Guideline-Driven Clinical Decision Support Systems". In: *Studies in Health Technology and Informatics*, 247:750-754. IOS. DOI: 10.3233/978-1-61499-852-5-750. <http://ebooks.iospress.nl/volumearticle/48892>
- [2] Bilici, E., Despotou, G. and Arvanitis, T. N. (2018) 'The use of computer-interpretable clinical guidelines to manage care complexities of patients with multimorbid conditions: A review', *DIGITAL HEALTH*. doi: 10.1177/2055207618804927.
- [3] WHO Regional Office for Europe, *Integrated care models: an overview*, 2016. Last accessed 3/4/19 at: <http://www.euro.who.int/en/health-topics/Health-systems/health-services-delivery/publications/2016/integrated-care-models-an-overview-2016>
- [4] NICE BNF, Last accessed 4/3/19 at: <https://bnf.nice.org.uk/>
- [5] Whetzel PL, Noy NF, Shah NH, Alexander PR, Nyulas C, Tudorache T, Musen MA. BioPortal: enhanced functionality via new Web services from the National Center for Biomedical Ontology to access and use ontologies in software applications. *Nucleic Acids Res.* 2011 Jul;39(Web Server issue):W541-5. Epub 2011 Jun 14.