An Integrated Solution for Sustainable Care for Multimorbid Elderly Patients with Dementia

CAREPATH

WP3: Foundations of the Clinical Decision Support Services for the management of multimorbid elderly patients with dementia

D3.2: CAREPATH Polypharmacy Management Services

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Executive Summary

In this deliverable we will present the implementation of machine-readable rule base platform for polypharmacy, drug-drug-interaction and adverse conditions. Guidelines were selected based on their prominence in the domain and analysed for their structure to allow for the creation of templates, which can be used in the automatic generation of results. The templates were designed to work with the Drools business rule management system.
Task 3.2 collaborates with WP6 and T3.3 to provide personalized predictions and warnings about the development of patient's health condition. Furthermore, it takes from T3.1 the CIG specification with CDS Hooks (using HL7 CDS Hooks standard interfaces), from which synchronous and asynchronous CDS engines will then be integrated in the Adaptive Integrated Care Platform of the CAREPATH system (Task 3.4).

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Abbreviations

AEWSDT	Advanced Early Warning Smart Decision Tools
AICP	Adaptive Integrated Care Platform
API	Application Programming Interface
BRMS	Business Rule Management System
CAREPATH	An integrated Solution for Sustainable Care for Multimorbid Elderly Patients with Dementia
CDS	Clinical Decision Support
CDSM	Clinical Decision Support Modules
DAIS	Drug To Drug Interaction Service (DIAS) 13
DDI	Drug-Drug-Interaction
DoA	Description of Action
EHR	Electronic Health Record
EWS	Early Warning Services
FHIR	Fast Healthcare Interoperability Resources
H2020	Horizon 2020 Framework Programme
H/HMP	Health/Home Monitoring Platform
I.C.	Intrinsic capacity
MCI	Mild Cognitive Impairment
PEP	Patient Empowerment Platform
PIPs	potentially inappropriate prescribing
PROM	Patient Reported Outcome Measures
REST	Representational State Transfer
SIS	Semantic Interoperability Suite
TIS	Technical Interoperability Suite
WP	Work Package

1 Introduction

1.1 Project information

CAREPATH is a Horizon 2020's funded project (Grant agreement ID: 945169), proposing an ICT based solution for the optimization of clinical practice in the treatment and management of multimorbid older patients with Mild Cognitive Impairment (MCI) or mild dementia. In order to achieve this, CAREPATH will elaborate on a methodology for computer interpretable clinical guidelines and computationally derived best clinical practice for best suitable treatment of this patient group. Thereby, a multidisciplinary care approach is considered, with a focus on the very individual needs of these patients to be translated into personalized care plans for increasing their independence and Quality of Life (QoL).

The CAREPATH project started on July the 1st, 2021 and will end on June the 30th, 2025.

1.2 Document scope

This deliverable provides a description of the prototype of the clinical decision support services for polypharmacy and drug-drug-interaction (DDI) management. It encompasses medication assessment based on an extended set of recommendations regarding drug prescriptions for the elderly as evidence knowledge-based criteria. These criteria work against data from electronic health records, such as age, gender, morbidities, and medication plans. The workflow between all components of the polypharmacy component and the CAREPATH AICP will be described. The DDI is based on knowledge stored in international drug repositories.

1.3 Document structure

The deliverable is organized as follows:
Chapter 1 - provides most importantly information about the scope deliverable
Chapter 2 – provides description of the implementation of the polypharmacy
Chapter 2 – provides description of the implementation of the drug-drug-interaction components
Chapter 3 – concludes on findings from the implementation process
Appendix A – Recommended medications
Appendix B – Not recommended medications
Appendix C – Example of the output of the component

2 Polypharmacy

2.1 Description

Based on efforts done in previous projects, the CAREPATH consortium has continued the work on an approach to represent medication guidelines in a machine-readable form for its use within CAREPATH's ICT based solution for the optimization of clinical practice in the treatment and management of multimorbid older patients with Mild Cognitive Impairment (MCI) or mild dementia. For this purpose, a machine actionable version of standardized medication guidelines was required. Such version was partially available as a result of previous H2020 research projects e.g. the Polycare project[1]. The translation of the polypharmacy guidelines from human readable into machine readable rules and the implementation are complex and pose many challenges e.g. ambiguity of the rules.
Aging population have got greater attention by a multitude of organizations, notably in the World Health Organization (WHO) report" Global Health and Aging" in 2011 [1]. The number of people aged 65 or older is projected to reach 1.5 billion in 2050, from 524 million reported in 2010. Chronic noncommunicable diseases are one of the biggest burdens on health and on the health care systems. Elder patients tend to suffer from so called multi-morbidity illnesses, i.e., the presence of many diseases or disorders that exist concurrently with a primary disease. This is challenging in multiple aspects for health care professionals and leads to increased usage of health care resources [2][3]. This leads to more complicated and/or multiple concurrent treatments, which usually lead to long-term use of multiple drugs in combination [4][5], called polypharmacy. Countermeasures to issues arising from polypharmacy are urgently required, as polypharmacy is common in elderly patients [6] and care at home requires systems to monitor possible complications to ensure patient safety and provide a better medication prescription. Therefore, in this work, we focus on potentially inappropriate prescribing (PIPs), and translated a rule-based system into machine-readable form to detect possible adverse events. Polypharmacy is defined as the concurrent use of multiple (usually more than four) medications or, sometimes, as the unnecessary use of multiple and/or redundant medications [7]. As mentioned before, this is common in adults older than 65 years, which shows that generally more than half of all patients older than 65 years take more than 5 prescription drugs [6]. The situation is complicated further by over-the counter medications. Studies regarding such medications show that, especially in certain communities, 90% of the patients take more than 1 and almost 50% take 2 to 4 of these over-the-counter medications [6][8]. Additionally, because of incomplete case histories and cases of low patient compliance, the medical professionals treating the patient often have incomplete knowledge on which substances the patient is using. Patient safety is a problem area and topic of active research in general, as adverse drug events are a serious problem in modern health care. Multiple studies brought this to attention, notably the report "To Err is Human" in the US, however, adverse events are preventable in many cases [9][10][11]. Multiple clinical guidelines and screening tools have been developed to check for PIPs. Mark Beers et al. created a list of medications that can be considered inappropriate for older patients in long-term care in 1991 [12]. Beers' criteria were updated regularly and are the basis for other criteria sets, most notably" Screening Tool of Older Persons potentially inappropriate Prescriptions" (STOPP) and" Screening Tool to Alert doctors to the Right Treatment" (START). Both are evidence-based lists of criteria, first published in 2008 and developed in Ireland by a round of experts using the Delphi consensus method [13][14]. Version 2 of these criteria was published in 2014 [15]. STOPP/START resulted in much research interest, many countries and institutions support the tools and consider them appropriate for evaluating prescriptions [16]. Here is an example of the STOPP criteria: The following prescriptions are potentially inappropriate to use in patients aged 65 years and older for cardiovascular system:

- Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit).
- Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
- Beta-blocker in combination with verapamil or diltiazem (risk of heart block).

And here is an example of the START criteria for the respiratory system:

- Regular inhaled agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.
- Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50
- Home continuous oxygen with documented chronic hypoxaemia (i.e. pO2 <8.0 kPa or 60 mmHg or SaO2 <89

[1] https://cordis.europa.eu/project/id/690367/results/de

2.2 Methodology

In Bi-Weekly tele conferences work in WP03 was discussed among other the work in Task3.2, where the work for polypharmacy was conducted. Additionally dedicated workshops on polypharmacy were organised to discuss the extension of the guidelines to the CAREPATH patients with mild dementia. Clinical partner studied the guidelines and provided feedback about possible extensions. These efforts resulted in adding many guidelines. The integration of the polypharmacy and AICP was conducted incrementally in many loops to ensure the right output format as FHIR CDS Hooks (see CAREPATH's deliverable D2.3). Only few of the above-mentioned guidelines were available in a machine-readable format that originate from the previous efforts in the Polycare project. These guidelines were indented to be used manually by medical professionals, which can create a considerable workload. The usage of the guidelines out of paper documents is likely unrealistic due to time restrictions of the medical staff. There is an urgent need to translate such rules into machine readable form and integrate them into decision support system as part of the medication prescription process making them in almost real time available for clinicians. So, in the frame of this work a set of machine-readable rules was extended using the Drools rule engine [17]. The target of this work was to translate the extended STOPP/START guidelines into machine readable rules using the Drools format, wrapped them in a prototype service application. The developed prototype is being integrated with the CAREPATH Adaptive Integrated Care Platform (AICP) allowing its extension beyond existing systems' capabilities and approaches especially when combined with real time sensors' data measuring the body vital signs and utilizing machine learning algorithms. Business rule systems have been used together with other technologies in "business rule management systems" since the early 1990s, especially in industries with a lot of rules in everyday operation, such as insurances [18]. The RETE algorithm that optimizes the process of matching conditions to rules by" compiling" a network of conditions and their relation has been designed in the 1980s for such scenarios [19]. Derivatives and improvements of this algorithm are still used in current rule engines, such as Drools [20]. The usage of a decision support system to reduce medication errors shows good results, especially when used at the prescription stage of a medication [21]. A Business Rule Management System (BRMS) is software that creates, supports, and executes decision logic and business rules. Drools is one of the most used BRMSs being utilized by thousands of organizations currently. The object-oriented system is an augmented implementation of the known Rete algorithm tailored for the Java language. It includes both forward as well as backward chaining interference-based rules engine and it provides a framework to allow business logic externalization in a common place. Efforts have been made to compute sets of medical guidelines for using them in applications. One example is STRIPA [22], a rule-based decision support system for medication reviews. It was developed with the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) in mind, a drug optimization process, and aims at making the pharmacotherapeutic analysis step easier and less time-consuming by automation [22]. This system was not available and not targeted to integration in home monitoring systems and was developed as a standalone system. In section 2.2.1, an elaboration on design principles, system design and involved frameworks is given.

2.2.1 DESIGN

This prototype was designed with usability of the clinical guidelines for clinical professional's focus, to have a structured and easily manageable representation of the machine-readable rules, without losing too much precision in detecting rule violations or losing too much flexibility in the addition of rule conditions and the manipulation of rules. With this in mind, we looked at state-of-the-art rule engines with a wide implementation in the industry, such as Drools. Additionally, with the use of the Drools Rule Language (DRL), rules can also be generated from schematic representations, so called decision tables. This confirmed our choice of Drools as the core of the system, as it has also proven itself in similar applications [22].
As shown in Figure 1, the system was designed as a self-contained service, with various possibilities for interoperability with the rest of the CAREPATH system in mind e.g. direct calls or REST API.
It is important to note that Drools is used in a stateless fashion. Stateless Drools sessions can be called like a function, a batch of data is passed to the session and the results of the rule executions are sent back. The production rule system does not keep track of (generated) knowledge and the result of one rule execution will never trigger or influence the execution of other rules. This was the desired operation mode in the use case at hand.

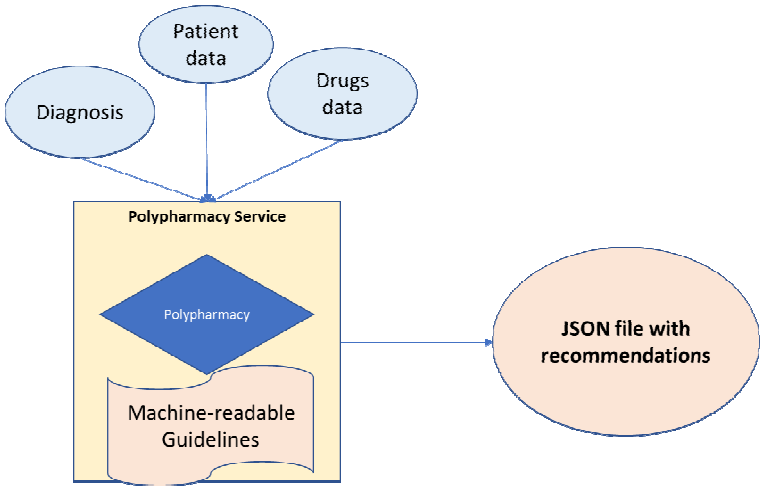

Figure 1: Overview of CAREPATH's polypharmacy service

2.2.2 Analysis of the STOPP/START Guideline Structure

The following parts could be identified in most STOPP rules:

- The rule subject, being a drug or drug family
- A part specifying co-medication that might interact with the subject
- Therapeutic information / information on pharmacotherapy, filtering for special (mis-)use cases of the subject
- A diagnosis / treatment condition, in some cases the subject is only harmful / not harmful if some condition, symptom or treatment is present
- Some "dependent clinical characteristic", an additional condition that can be a diagnosis, symptom or lab value for example that narrows down the execution of the rule (often exceptions to the rest of the rule)
- The outcome: in the case of STOPP rules that is a warning to consider a medication change for the patient (See section 7)

START rules have similar parts that can be identified, but they do not contain a subject in the sense above, meaning a drug or drug group that has to be matched with a drug from the patient's records for the rule to be executed. Instead, they contain a drug that they advise in case the rule is executed successfully, as START aims to recommend initial and/or additional medication that is proven to be beneficial in the case described in the rule (See section 6). The various connective words and phrases used in the plain English statements of the original set of criteria could be reduced to" and"," or" and" not". Statements containing temporal modifiers like" X with concurrent Y" were also reduced to the logical operators above. However, at present the current prototype does not have the required structured data from electronic health records to execute that specific type of rules. The identified rule parts were also further sub-divided into" types". Conditions on drug dosage, time of prescription and co-therapy could be reduced to conditions on intolerance, efficacy, duration, dosage and a check for contraindication. Further time/co-therapy conditions were: "The subject is the first treatment for something"," used as a long-term treatment"," used as secondary prevention"," used when an alternative is available", "used as mono-therapy", "used instead of some other drug" and "used with some other drug of the same class". Similarly, detailed types of symptom / diagnosis conditions were:" Usage of the subject drug with a history of some diagnosis X"," used as a treatment for X", "used for therapy in X" and "used unless concurrent X". Clinical characteristics could be reduced to: Health conditions, physical examination result, interventions, disease history, laboratory results.

2.2.3 DESIGN IMPLICATIONS AND IMPLEMENTATION

In principle, it would have been possible to create conditions in the machine-readable version of the criteria sets for all of these condition types. However, as such a level of detail is not available in the data and is difficult to achieve and use correctly, many types were left out or combined into very basic conditions. Some information is contained in the codes of the classification systems used and a good selection of codes for condition checks allows representation of some of these detailed condition types in their more general parent condition. With more detailed data, additional conditions can be implemented, but some only appear in very few and quite specific rules, it might be better to accept the possibility of false alerts and let the clinical

professionals decide if acting is necessary, instead of trying to make a rule more precise with complicated conditions on unreliable data. This trade-off had to be evaluated throughout the design and development process. It will also be important for future improvements and extensions. For the realization of the concept, proven technologies have been chosen. The requirements fit the use case of a production rule system. Additionally, a general-purpose programming language, such as Java was chosen as a consequence of the choice of the rule engine.

2.2.3.1 Data Model

As Drools is data-driven, the data model is very important. It consists of a typical object-oriented programming class hierarchy: all used objects are plain Java objects. Each type that was used in one of the decision tables is represented by a Java class, which includes objects representing patients, drugs and diagnosis. As shown in Figure 2, the system is currently only using coding systems for both diagnosis and drugs, the presented objects basically only act as a container for these codes with some additional functionality. The defined objects contain methods for matching codes and code prefixes by simple string matching. This way, the rules can easily take advantage of the structure of the mentioned coding system. For example, if a guideline from the STOPP set states that all opioids should never be given together with some other drug, we can take the common prefix for opioids in the Anatomical Therapeutic Chemical (ATC) system and use it for pattern matching in the rule, by just passing it system for evaluation.

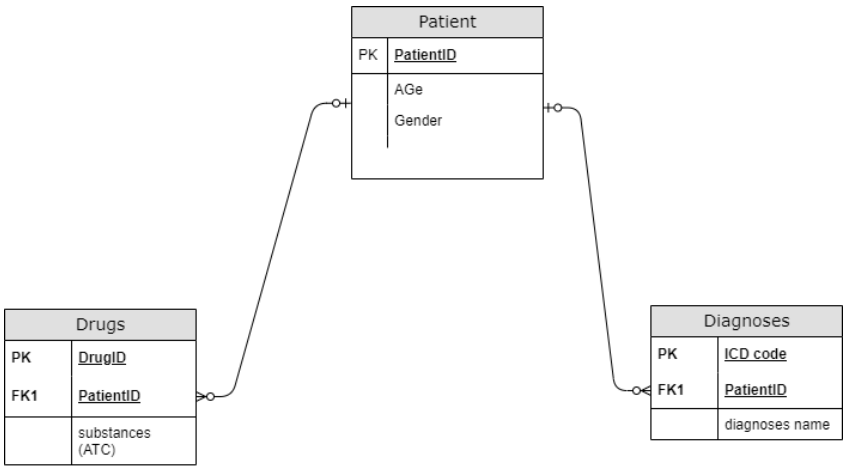

Figure 2: Overview system design

This is easier than compiling lists of drugs manually and less error prone, but not as simple as it may sound, in fact, it is quite difficult in many cases to find a coded representation of what is stated in the original criteria that means exactly the same semantically. Still, we will see how rules make use of the coding systems in detail in the next sections.

2.2.3.2 Rule Structure and Decision Tables

Each rule can be fitted to a schema consisting of conditions. Basically, as mentioned above, the following parts could be identified as a general structure in all STOPP/START criteria: a rule subject, being a drug or drug set, another drug or drug set, representing drugs that might interact with the subject (comedication group), a set of diagnosis and a patient, to which all other objects have to relate.
The co-medication group filters for drug-drug interaction using ATC codes, many STOPP rules state something like:" If the patient is taking drug A and he is also taking drug B at the same time, revoke the prescription for drug B". The assumption was made that drugs supplied to the system are always prescribed at the same time, there is currently no check for concurrency. The rule base will be made more precise during the next phase along with having the available data of better quality, something that will become apparent multiple times and has already been mentioned before. The diagnosis group filters for diagnoses, symptoms, or other information that can be represented by the International Classification of Diseases (ICD) system. This further narrows down the execution of the rule immensely by applying an additional condition that many of the rules have in common. To summarize, the most important criteria and parts of the resulting decision tables are the rule subject, drug interactions, and coded diagnoses, they were the only ones that were selected for implementation. The observation that most of the rules in both STOPP and START follow a certain scheme led to the belief that they can be reduced to a fixed structure, basically a prototype rule with parametric conditions. That is why so-called decision tables were chosen as the source of rules for the system. Drools supports Microsoft Excel spreadsheets with a certain structure as an input and will generate

rules from them. This approach has certain advantages over representing the rules in files using the decision support language described above in certain use cases and the STOPP/START criteria were quite compatible with the approach. Figure 3 represents a first iteration of a STOPP table. Each rule follows the same structure, as it is given by the decision table. First, the knowledge base is checked for the drug that is the subject of the corresponding STOPP guideline. If the subject drug is found, the following columns contain all other tests, but not always all tests for every rule, some are left out, if the guideline does not contain such a requirement. This can be done by leaving the respective cell empty. The conditions check for interacting drugs, for diagnosis and that the patient ID of both objects match the one of the subject drugs. In the current version, we do not verify the patient's age, although the STOPP/START criteria are designed for people above the age of 65, because the rule base will be used in an environment, where only data of such patients will be processed. An additional column contains the negation of the check for interaction drugs. This was necessary for a few rules, which apply only if a certain drug or drug class is not in the medication plan of a patient. This, of course, leads to the logical conjunction turning into a logical disjunction: the condition requires the medication list of a patient to be free of all the mentioned codes or code prefixes. Note that this generally is a first naive table layout and does not take performance optimization into account. The order of the conditions can be optimized for quicker execution, as we will see, but this always affects all rules, one drawback of using decision tables. If the rule is evaluated to be positive, the marked action of the available ones is taken.

RuleTable STOPP

NAME	CONDITION	CONDITION	CONDITI	CONDITION	CONDITION	ACTION
	$s : Drug	$drug : Drug	$drug : Dr	$p : Patient	$d : Diagnosis	
	forall(||){matchATC($)}	getPatientID() == $s.getPatientID(),forall(||){matchATC($)}	forall(&&){matchATC($)}	(id == $s.getPatientID())	getPatientID() == $p.id, forall(||){$}	System.out.println("------ STOPP WARNING ------"); System.out.println("$param"); $s.printDrug(); $p.printPatient(); $d.printDiagnosis(); System.out.println("------ END STOPP ------");
NAME	subject drugs	complication drugs	neg. complication drugs	patient	diagnosis	OutputNoDrug
STOPP B1	"C01AA05"			TRUE	hasICDPrefix("I50")	STOPP B1: No clear evidence of benefit
STOPP B2	"C08DA01","C08DB01"			TRUE	hasICDPrefix("I50.04"),hasICDPrefix("I50.05"),hasICDPrefix("I50.13"),hasICDPrefix("I50.14")	STOPP B2: May worsen heart failure

Figure 3: The template code of the STOPP decision table

In Figure 3, this is one of four very basic output variants. During use of the system later ones, this can be any kind if post-processing or event handling. Decision tables make creating, testing and updating of a larger rule base of similar rules easier. Once the structure of the decision table and the template code is done, only parameters have to be entered into the table. In the case of the rule base presented here, this brings other challenges, mainly in choosing the correct codes for representing the symptoms and illnesses mentioned in the STOPP/START guidelines, but the actual implementation work is reduced. In the case of the" subject drug" test template code, the rule engine will loop over all parameters found in the rules cell for this condition and that the results of the evaluation of each single one should be connected with the" or" operator. The parameter is inserted at the placeholder "$", in this case we pass it to a function. The template code section allows us to call functions of the object specified in the row for types above. In this case, the function "matchATC" is called with the parameter inserted in the rule's cell. We can also see that we can add arrays of parameters to rules by just adding them into the cell, separated with commas, in this case strings representing the ATC code or ATC code prefix we want to match. The method we call is described in the data model section, which we use it to match codes template code for the "complication drugs" condition is the same, but adds an equality check for the patient ID to make sure that only drugs that are actually taken by the patient are considered. The template code for the diagnosis check, basically works in the same way. But instead of inserting a parameter into a method call, we just specify that all parameters should be connected in a disjunctive fashion. The rules' fields of this condition check contain both method calls and equality checks. The same result is achieved in a different fashion. This basically concludes the description of the pre-optimization STOPP table. The complete STOPP rules are listen in section 7.

The decision table for the START criteria works in a similar way as the templates but has different requirements for the number and order of condition checks and for the patient check. This is because we do not have a subject drug in every case that can be used to get all patients taking the drug like in the STOPP decision table. Instead, we now have to look at all patients. In the next step, all drugs with a matching patient ID are checked against the rule's codes and code prefixes, just as in the STOPP table. The diagnosis check is also the same, the number of parameters is just higher in many cases. The complete STOPP rules are listen in section 6.

2.3 Integration of Polypharmacy into CAREPATH's system's workflow

The foundation of this work described in Figure 4, (0) starts with CAREPATH's interoperability service (Technical Interoperability and Semantic Interoperability Suites, namely TIS and SIS), that gathers medication data of the participating patients in the clinical study. The CAREPATH polypharmacy (1) receives a REST API POST call with the patient id, the polypharmacy service (2) reads all relevant information about

a patient and provides feedback about drug interactions and interference while under certain therapies or suffering from certain diseases, as defined in the CAREPATH extended STOPP/START criteria. Depending on whether a START or STOPP condition is detected, an alert is given or a recommendation for therapy will be generated (4) (See an example in section 8). The information is sent back to the AICP to be used for care plan management, as seen in Figure 4.

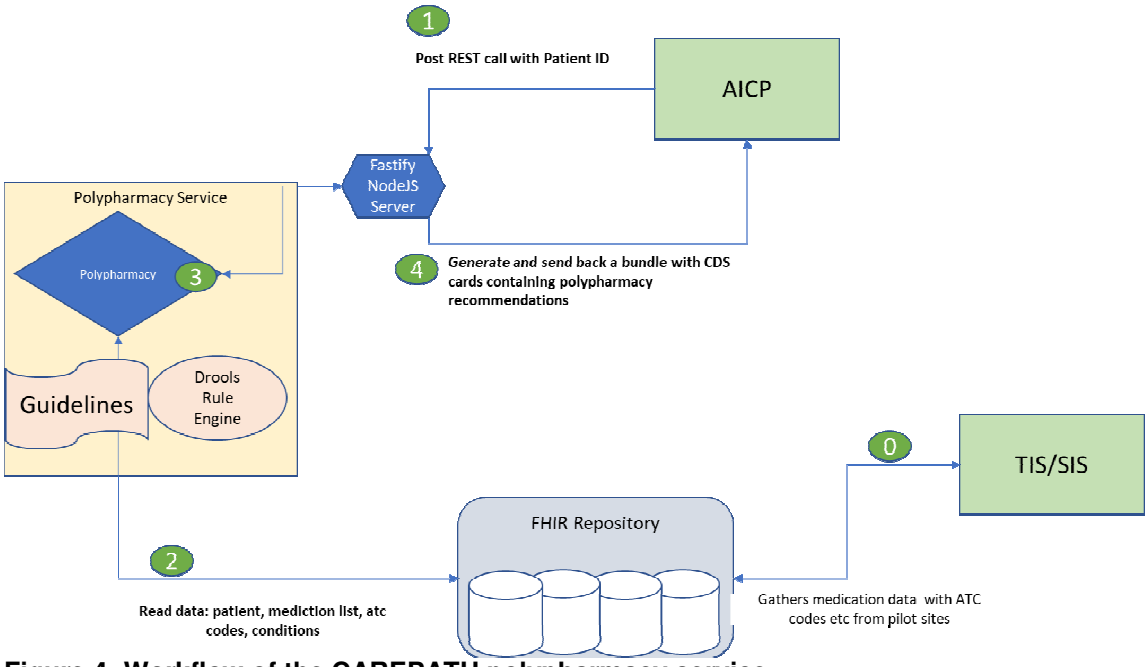

Figure 4: Workflow of the CAREPATH polypharmacy service

Not shown in the workflow diagram is the process of looking up medications' ids, from the electronic health record of a patient is used to get detailed information about a drug (more specifically about the active substance) and its classification in other coding systems such as ATC, which is currently used in the system so far. Finally, information about the medication of the patient and her diagnosis is used. If available, more precise information such as dosage of specific drugs, duration of the treatment and lab values can be used to give better feedback. Technically we utilised a NodeJS CRUD API with Fastify[2] for connecting the loosely coupled services. Fastify is a NodeJS framework for building fast NodeJS servers. With this tool, we were able to create a server with NodeJS, create routes (endpoints), handle requests to each endpoint, and lots more. So, we have built many NodeJS servers with Fastify. These servers have endpoints to Create data, Read data, Update data, and Delete data (CRUD). Our servers support authentication that fits in the ecosystem of CAREPATH.

3 Drug-Drug Interaction (DDI)

3.1 Service Description

Another service of this Task3.2 is a generic CAREPATH drug-drug-interaction service, that just provide drug-drug-interactions or adverse conditions out of information provided by the producers of the drugs or by monitoring authorities. As we have 4 pilot sites in Europe, this service will rely on the drug information repositories that can be accessed programmatically to read drug-drug-interaction and adverse conditions and provide these data sets in a readable format to the clinical professionals.
Another difficulty in providing this service is the fact that the pilot sites are in four different European countries with different languages and drug indexing / coding systems. In Figure 4 we illustrate the drug-drug-interaction ecosystem of CAREPATH for technical details see section 2.3.

As shown

Figure 5 our main strategy is based on (0) TIS/SIS gathering from participating patients in all pilot sites medication data with ATC codes, product information, adverse conditions etc. Additionally, we will use where possible the DIAS service (see section 3.2) and/or publicly available international repositories, that allow API

[2] https://www.fastify.io/

access to the drug information systems as e.g. as compiled by the European Medicines Agency (EMA)[3], most relevant of the for the CAREPATH project are:

- Germany: Drug Information Systems[4]
- Romania: Lista medicamentelor din NOMENCLATOR[5]
- Spain: Medicine Online Information Center of AEMPS - CIMA[6]
- BNF via NICE is only available in the UK[7]

Additional resources are:

- USA: FDA Drug Approvals and Databases[8]
- Canada Vigilance adverse reaction online database[9]

Point (1) in
Figure 5 shows the connection between AICP and the drug-drug-interaction service that will provide the PatientID in REST API POST method call. In step (2) of 5 the drug-drug-interaction service will read all prescribed medications to this patient from the CAREPATH EHR repository along with their substances and ATC codes. In step (3) the DDI will read from internal and external repos any possible adverse conditions or drug interactions. In step (4) the DDI will gather all drug interactions and transform them to CDS hooks cars that will be sent a response to the REST API from step (1).

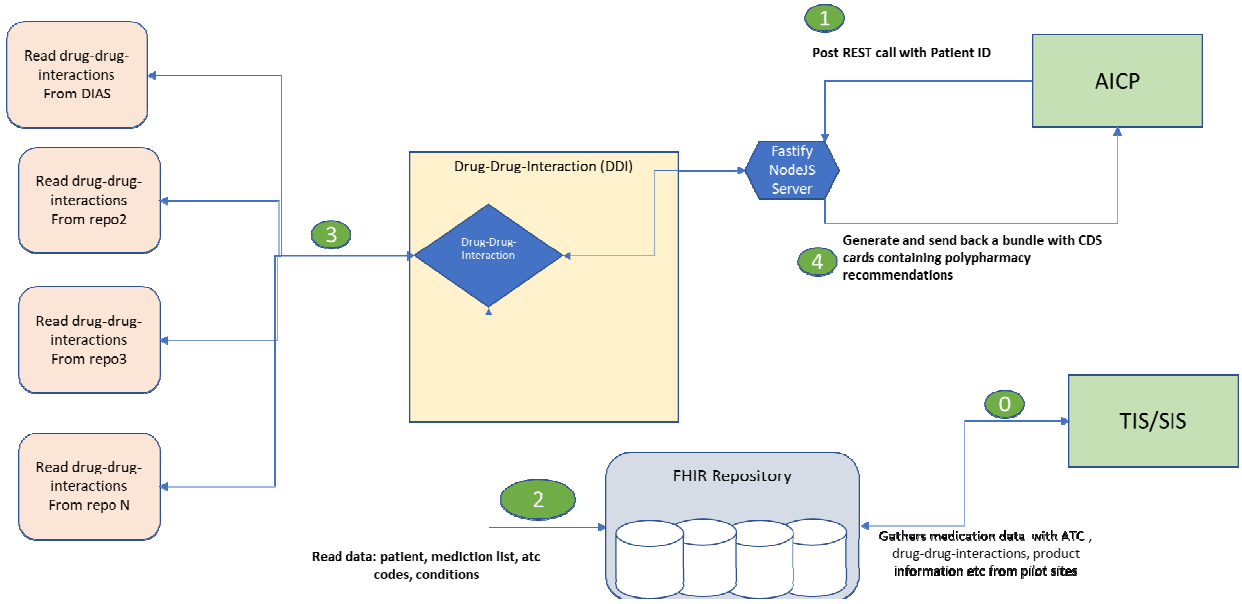

Figure 5: Workflow drug-drug-interaction

3.2 Backend: The CDSS Drug to Drug Interaction Service (DIAS)

[3] https://www.ema.europa.eu/en/medicines/national-registers-authorised-medicines

[4] http://www.pharmnet-bund.de/dynamic/de/arzneimittel-informationssystem/index.html

[5] https://nomenclator.anm.ro/medicamente

[6] http://cima.aemps.es/cima/publico/home.html

[7] https://www.nice.org.uk/bnf-uk-only

[8] https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases

[9] https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html

CAREPATH is an e-health ICT system, offering integrated, patient-centred care, considering all aspects of multi-morbidity, creating a collaborative environment for all involved stakeholders 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. The CAREPATH 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. Medication regimes for combination of conditions may include drugs that when combined, may result in adverse reactions. Drug Interaction Advisory Service (DIAS) is part of the CAREPATH CDSS, offering advisories of potential interactions.

CAREPATH 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 requirements of the service that needs to be offered to patients.

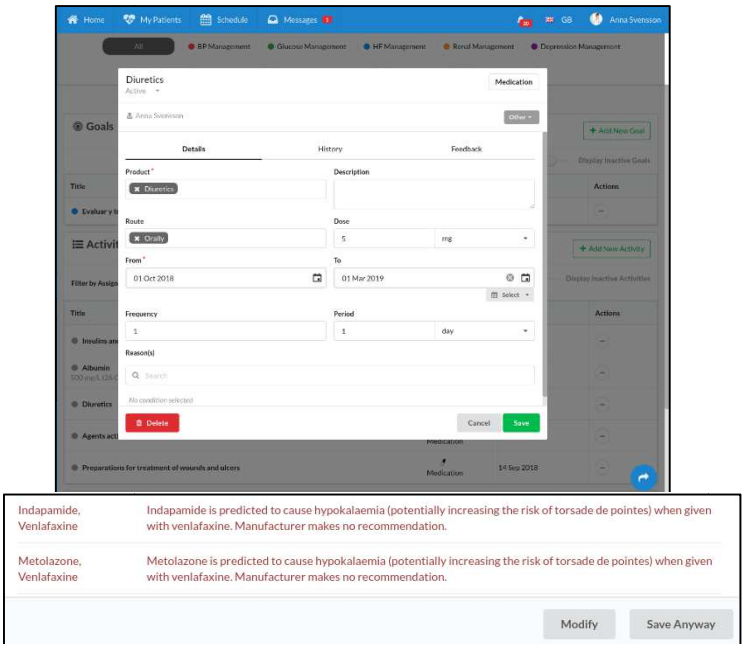

Figure 6: a) Envisioned AICP (care plan) medication prescription view (top) b) test extract from the interactions notification pop-up dialogue (bottom); it gives interactions between diuretics (ATC: C03) and existing medication in the patient's record.

The Patient Empowerment Platform (PEP) provides a dedicated interface module to the patient, adapted to their needs. The Adaptive Integrated Care Platform (AICP), 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 AICP will interact with the Clinical Decision Support (CDS) service, and will receive a number of automated recommendation. All communication amongst CAREPATH components, as well as storage of information is achieved by accessing FHIR resources.

Healthcare professionals can amend a patient's medication via the AICP. When a new medication request is entered the AICP 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. The DIAS database currently includes interactions in 3 languages (English, Spanish and Swedish) at present, but extensions can be made using a semi-automated translation approach.

```
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 7: a) A typical DIAS GET request (top) b) extract from interactions returned in JSON (bottom).

3.3 Drug To Drug Interactions Advisory Service Ontology

DIAS implements the interactions between drugs, as specified by the National Institute of Care Excellence's implementation of the British National Formulary (BNF). 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.

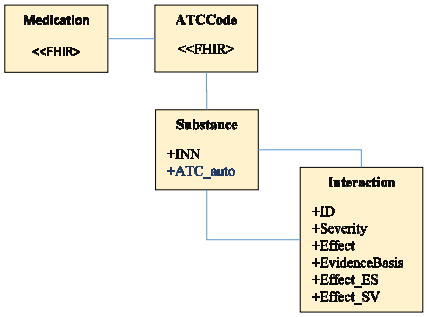

Figure 8: The DIAS Database Model.

For example, Acarbose is a drug active ingredient Alpha-glucosidase inhibitor, 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 mappings, whereas the ATC codes in the patient's care plan have been coded by CAREPATH 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 AICP, 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. For Carepath translations to German and Romanian will be added. Translation was done using an automated translation service, and tested with manual random sampling. AICP 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. 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. The service is able to be extended with further data sources, beyond the NICE BNF interactions. The ontology is suitable for such extension by adding the attribute *+interactionSource* that will maintain the provenance of the data.

4 Technical evaluation

We have conducted technical tests of the above-described services thoroughly. There are technical functioning and generating the correct results, as well performance aspects. Additionally, there is a discussion on how the results presented here fit in within the project infrastructure, what drawbacks exist and what may need more work. An issue is the selection of both ATC and especially ICD codes for the rule's conditions. A first selection was used in this work to demonstrate how such a rule base for the STOPP/START criteria and the accompanying system might work, but there was no guarantee for correctness of the rules from a medical standpoint. Technical evaluation resulted in some key points. Most obviously, as previously mentioned, finding the correct order of condition checks and was part of the task at hand. Still, with more conditions and more complex comparisons can be added to the rules e.g. dosage, time of intake. The diagnosis codes used in CAREPATH polypharmacy were chosen by looking at the ICD-10-CM index and choosing codes that seemed suitable. Choosing ATC codes was easier, as it is pretty clear in most cases which substances are mentioned in the original guideline statements or the drug description record. But as the ATC structure allows one substance to have multiple codes if it can be used for different treatment goals on different physiological systems, one has to choose the correct code or include all variants. Generally, it is always possible to include more codes, especially in the case of diagnosis codes, to catch more rule violations. But this can lead to more false alarms. Working around the coding systems by, e.g., compiling a list of single codes instead of using the hierarchy of the system, is generally more difficult and inefficient than using well-defined codes or the structure of the coding system, but sometimes there is no other way.

5 Conclusion

In this deliverable we described the two main services developed in the frame of Task3.2 (1) Polypharmacy (2) Drug-Drug-Interaction. First, there was a lot of effort spent in the selection of technologies and software available for such a task, with active development and very prominent credentials. The choice of Drools even its features were not fully used. Drools fits in the architecture of CAREPATH system, one can say with Drools that scaling the project will be easily possible. With Drools we can create or read rules from multiple sources with flexible and powerful template coding and accompanying tools that can be used to modify rules even by people who do not know a lot about programming. It allows the use of the knowledge base as a server but can also be integrated into any other form of application. Using decision tables to represent the STOPP/START criteria was the correct choice. The criteria turned out to be surprisingly similar in their structure, allowing the use of template code to generate rules. Drools is also quite efficient in matching and executing rules. Running both the STOPP and START set against 10.000 test records took less than 1 second per case on a consumer grade laptop. While the decision tables are not too complex, the complexity of the problem lies in choosing the correct codes for both drugs and diagnosis. This is not a trivial problem, and it impacts the whole domain. Focussing on international standards for medical data, improved standards for coding and agreements on translating between them and from natural language would help the whole domain immensely. We have seen that choosing codes that precisely represent what was stated in the STOPP/START criteria was difficult. We will continue the consensus process with medical experts to agree on coding to ensure correct results. One of the main conclusions drawn from studies [24] is that the quality of the available data is one of the biggest factors in the success of using such guidelines with a decision support system. With these limitations and problems in mind, the presented rule base can still need monitoring in the process of integration in the entire decision support system of CAREPATH. It will certainly be improved and evaluated further in the next development and integration rounds. Lab values, for example, are mentioned in certain criteria of the STOPP/START criteria and could be compared to lab values from a data source. But again, semantic equality has to be ensured, a variety of abbreviations and codes for lab values have to be translated to match the data source. In general, as the quality of health care data in CAREPATH relies on standardized data formats, workflows and other technologies, it will become easier to build systems giving warning and advice regarding medication that work with data from electronic health records. The consortium will work on many of these extensions and warnings during the integration phase and as a result of the TVU study.

6 Appendix A – START Recommendations

NAME	Diagnosis	complication drugs	Recommendation
START A1	icd == "I48.2"		START A1: Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.
START A2	icd == "I48.2"		START A2: Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.
START A3	hasICDPrefix("I25.1"),hasICDPrefix("I60"),hasICDPrefix("I61"),hasICDPrefix("I62"),hasICDPrefix("I63"),hasICDPrefix("I64"),hasICDPrefix("I65"),hasICDPrefix("I66"),hasICDPrefix("I67"),hasICDPrefix("I68"),hasICDPrefix("I69"),icd=="I73.9"		START A3: Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.
START A4	hasICDPrefix("E08"),hasICDPrefix("E09"),hasICDPrefix("E10"),hasICDPrefix("E11"),hasICDPrefix("E13"),icd=="I10",icd=="R03.0"		START A4: Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.

START A5	hasICDPrefix("I25.1"),hasICDPrefix("I60"),hasICDPrefix("I61"),hasICDPrefix("I62"),hasICDPrefix("I63"),hasICDPrefix("I64"),hasICDPrefix("I65"),hasICDPrefix("I66"),hasICDPrefix("I67"),hasICDPrefix("I68"),hasICDPrefix("I69"),icd=="I73.9"		START A5: Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.
START A6	hasICDPrefix("I50.2"),hasICDPrefix("I50.4"),hasICDPrefix("I20"),hasICDPrefix("I21"),hasICDPrefix("I22"),hasICDPrefix("I23"),hasICDPrefix("I24"),hasICDPrefix("I25")		START A6: Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease.
START A7	hasICDPrefix("I20"),hasICDPrefix("I21"),hasICDPrefix("I22"),hasICDPrefix("I23"),hasICDPrefix("I24"),hasICDPrefix("I25")		START A7: Beta-blocker with ischaemic heart disease.
START A8	icd == "I50.22"		START A8: Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.
START B1	hasICDPrefix("J44"),hasICDPrefix("J45")		START B1: Regular inhaled b2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.

START B2	hasICDPrefix("J44"),hasICDPrefix("J45")		START B2: Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.
START B3	icd == "R09.02",icd=="J96.21",icd=="J96.11"		START B3: Home continuous oxygen with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)
START C1	icd=="G20"		START C1: L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability.
START C2	hasICDPrefix("F32"),hasICDPrefix("F33")		START C2: Non-TCA antidepressant drug in the presence of persistent major depressive symptoms.
START C3	hasICDPrefix("G30"),icd == "G31.82"		START C3: Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).
START C4	hasICDPrefix("H40.1")		START C4: Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.

START C5	icd == "F41.9"		START C5: Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.
START C6	hasICDPrefix("G25.8")		START C6: Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.
START D1	icd == "K21.0",icd == "K21.9",icd=="R12",icd=="K22.2"		START D1: Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.
START D2	hasICDPrefix("K57")		START D2: Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation.
START E1	hasICDPrefix("M05"),icd == "M79.0"		START E1: Disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease.
START E2			START E2: Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.

START E3	hasICDPrefix("M80"),hasICDPrefix("M81")		START E3: Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites).
START E4			START E4: Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).
START E5	hasICDPrefix("M85.8")		START E5: Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).
START E6	hasICDPrefix("M10")		START E6: Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout.
START E7		"L01BA01","L04AX03"	START E7: Folic acid supplement in patients taking methotexate.

START F1	hasICDPrefix("E08"),hasICDPrefix("E09"),hasICDPrefix("E10"),hasICDPrefix("E11"),hasICDPrefix("E13")		START F1: ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.
START G1	hasICDPrefix("N40")		START G1: Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.
START G2	hasICDPrefix("N40")		START G2: 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.
START G3	icd == "N95.2"		START G3: Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.
START H1			START H1: High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.
START H2		"N02A*"	START H2: Laxatives in patients receiving opioids regularly.
START I1			START I1: Seasonal trivalent influenza vaccine annually

STA RT I2			START I2: Pneumococcal vaccine at least once after age 65 according to national guidelines
STA RT I3			START I3: COVID-19 vaccine according to national guidelines

7 Appendix B – STOPP recommendations

OutputNoDiag	OutputNoDrug	OutputFull	OutputBasic
	STOPP B1: No clear evidence of benefit		
	STOPP B2: May worsen heart failure		
STOPP B3: risk of heart block.			
	STOPP B4: risk of heart block, asystole - (Drugs-ATC of group C07)		
	STOPP B5: higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem		
	STOPP B6: Loop diuretic as first-line treatment for hypertension? (safer, more effective alternatives available).		
	STOPP B7: Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).		
	STOPP B8: hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic		
	STOPP B9: may exacerbate incontinence)		
			STOPP B10: unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people)
	STOPP B11:		
			STOPP B12: Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous

			hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).
	STOPP B13: Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse)		
	STOPP C1: . Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).		
	STOPP C2: Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).		
	STOPP C3: high risk of bleeding.		
STOPP C4: Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy)			
		STOPP C5: Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin)	
		STOPP C6: Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary,	

		cerebrovascular or peripheral arterial disease (No added benefit from dual therapy).	
			STOPP C7: Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).
			STOPP C8: Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit).
	STOPP C9: Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).		
STOPP C10: NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding).			
STOPP C11: NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease)			
	STOPP D1: risk of worsening these conditions		
	STOPP D2: Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).		
	STOPP D3: Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).		
	STOPP D4: Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant		

	hyponatraemia i.e. serum Na+ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).		
			Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).
	STOPP D6: Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms)		
			STOPP D7: Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity),
	STOPP D8: Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).		
			STOPP D9: Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other treatments have failed (increased risk of stroke).
			STOPP D10: Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls). (here: Modafinil, sodium oxybate, methylphenidate)
	STOPP D11: Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).		
			STOPP D12: Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of

			prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).
	STOPP D13: Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)		
			STOPP D14: First-generation antihistamines (safer, less toxic antihistamines now widely available).
			STOPP E1: . Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m2 (risk of digoxin toxicity if plasma levels not measured).
			STOPP E2: Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m2 (risk of bleeding)
			STOPP E3: Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2 (risk of bleeding)
			STOPP E4: NSAID's if eGFR < 50 ml/min/1.73m2 (risk of deterioration in renal function).
			STOPP E5: Colchicine if eGFR < 10 ml/min/1.73m2 (risk of colchicine toxicity)
			STOPP E6: Metformin if eGFR < 30 ml/min/1.73m2 (risk of lactic acidosis).
	STOPP F1: Risk of exacerbating Parkinsonian Symptoms		
	STOPP F2: PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).		
	STOPP F3: Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation)		
			STOPP F4: Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day; no evidence of enhanced iron absorption above these doses).
	STOPP G1: Theophylline as monotherapy for COPD		

	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).		
	STOPP G2: Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).		
	STOPP G3: Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).		
	STOPP G4: Non-selective beta-blocker (whether oral or topical for glaucoma) with a history of asthma requiring treatment (risk of increased bronchospasm).		
	STOPP G5: Benzodiazepines with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa (risk of exacerbation of respiratory failure).		
			STOPP H1: Non-COX-2 selective non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).
	STOPP H2: NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).		
			STOPP H3: Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief)
			STOPP H4: Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthrtitis (risk of systemic corticosteroid side-effects).
			STOPP H5: Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).

			STOPP H6: Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).
			STOPP H7: COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke)
STOPP H8: NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease)			
			STOPP H9: Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)
			STOPP I1: Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).
	STOPP I2: Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope)		
	STOPP J1: Risk of prolonged hypoglycaemia		
	STOPP J2: Risk of exacerbation of heart failure		
	STOPP J3: Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).		
			STOPP J4: Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence)
STOPP J5: Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).			
			STOPP K1: sedative, may cause reduced sensorium, impair balance
			STOPP K2: Increases risk of falls in

			older people
			STOPP K3: Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg (risk of syncope, falls)
			STOPP K4: May cause protracted daytime sedation
			STOPP L1: Strong opioids as first line therapy for mild pain?
			STOPP L2: Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).
			STOPP L3: Long-acting opioids without short-acting opioids for break-through pain (risk of non-control of severe pain)

8 Appendix C – Example FHIR CDS Hooks


```
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     "indicator": "info"
    }
  ]
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10 Document History

Date	Changes	Version	Authors
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2022-06-28	Initial - Incremental draft	1v1	Yehya Mohamad, Henrike Gappa, Carlos Velasco
2022-08-10	Contribution to drug-drug-interaction (DDI)	1v2	WARWICK team
2022-08-15	Integration of DDI into the workflow	1v3	Yehya Mohamad, Henrike Gappa, Carlos Velasco
2022-08-24	Internal review of deliverable	1v4	Gökça Banu Laleci Ertürkmen, Robbins Timothy
2022-08-24	Internal review of deliverable	1v4	Gökça Banu Laleci Ertürkmen, Robbins Timothy
2022-08-28	Deliverable D1.5 last editing	1v5	Yehya Mohamad
2022-08-31	Deliverable D3.2 submitted to the EC.	1v6	Angelo Consoli, Jaouhar Ayadi

- End of document -